Missing a Malignancy in Unexplained Anemia

When a patient of mine has unexplained anemia, I'm always concerned that I may be missing a malignancy. Can you advise on the proper work-up and when to reassure the patient?

Question submitted by:  
Dr. Mitch Rubin  
North Vancouver, British Columbia

Anemia is defined as a hemoglobin level below the laboratory reference specific to a man or woman. There are numerous causes that should be considered of which an underlying malignancy is only one. The work-up should begin with the mean corpuscular volume, or mean cell volume (MCV). An anemic patient with a MCV that is low, normal, or high is said to have microcytic, normocytic, or macrocytic anemia, respectively.

Common causes of microcytic anemia include iron deficiency anemia, thalassemia, anemia of chronic inflammation (previously called anemia of chronic disease), and sideroblastic anemias (including lead poisoning). The most common anemia is iron deficiency anemia, which requires both repleting the iron stores and correcting the underlying cause of the condition. There may be an underlying gastrointestinal malignancy or, in postmenopausal women with spotting, an underlying gynecological malignancy may be present. In normocytic anemia, causes, such as acute blood loss and hemolysis, can be separated from bone marrow failure states and anemia of chronic inflammation by a reticulocyte count, which will be high with the former cause and low or normal in the latter. There may be underlying bone marrow malignancies for marrow failure states or other malignancies that can contribute to an underlying chronic inflammatory state. Macrocytic anemia can be caused by vitamin B12 or folate deficiencies, medications that impair DNA synthesis, liver disease, alcohol misuse, hypothyroidism, reticulocytosis, or underlying bone marrow failure states.

Unfortunately, there is no set protocol that can apply to all patients that can rule out all forms of cancer. The proper work-up and reassurance has to be made on a case-by-case basis and determined by the proper history and physical exam.

Answered by:  
Dr. Cyrus Hsia and  
Dr. Kang Howson-Jan
**Thumb-sucking in Infants**

**Please comment on thumb-sucking in infants. Should we discourage it? Should we substitute with a soother?**

**Question submitted by: Dr. C. Littlejohn, Burlington, Ontario**

Infants often suck their thumb when falling asleep or during sleep. Thumb sucking normally ends by the second- to third-year-of-life.¹ ² During this period, no treatment is necessary, provided that the child is receiving sufficient oral gratification through nursing or feeding. Forceful attempts to stop the habit may create more serious neurotic symptoms and personality problems.³ A pacifier may be offered if the child has a strong need to suck. However, one should not dip a pacifier in sugar, honey, or other sweeteners before giving it to an infant.³ The use of a pacifier is an easier habit to break.³ ⁴

Malocclusion in both primary and permanent dentition may result from thumb sucking if the habit persists beyond six-years-of-age.³ Malocclusion usually resolves spontaneously if thumb sucking ceases before eruption of the permanent teeth.¹ ² Other potential complications include blisters, calluses, irritant eczema, paronychia, herpetic whitlow, digital deformities, dysfunction of the temporomandibular joints, narrowing of the maxillary arch, ulceration of the sublingual mucosal, and atypical apical root resorption.¹ ²

In a three- to four-year-old child, thumb sucking may occur during periods of tiredness, boredom, frustration, insecurity, hunger, maternal deprivation, emotional stress or illness.¹ ² In such cases, treatment should be directed at correcting the underlying problem. The child should be provided with ample opportunity and space to play, and play materials should be suited to the child’s age of development. Threats or punishment should not be used to stop the thumb sucking. Rather, positive reinforcement, such as praise, should be given when the child is not sucking the thumb.³ Parents should maintain a sympathetic, patient, and understanding attitude toward the child at all times. Parents should also be instructed to gently remove the thumb from the child’s mouth, provide immediate emotional support in the form of a hug or compliment, and then proceed to distract the child with another activity.

**References**


**Answered by:**

Dr. Alexander K.C. Leung
Elevated Serum Ferritin — Diagnosis and Management

A patient has a high ferritin level (> 600 ug/L) but normal serum iron, total iron binding capacity, and transferrin level; there is no evidence of infection or malignancy. What is the diagnosis and management?

Question submitted by: Dr. V. Poon
Toronto, Ontario

Elevated serum ferritin is often found incidentally in patients on routine work-up for other reasons. Iron overload (referred to as hemochromatosis) can result in an elevated serum ferritin. Unfortunately, serum ferritin is an acute phase reactant that can be elevated for other reasons, such as with infections, inflammation, or malignancy. Hence, a work-up for different causes of an elevated ferritin is warranted.

The gold standard for assessing iron overload is a liver biopsy. However, this is invasive and often not necessary. A transferrin saturation is considered a better surrogate marker of iron overload than the serum ferritin and less invasive than a liver biopsy. Often, if the serum ferritin is elevated but the transferrin saturation is normal, then the patient most likely does not have iron overload and a work-up for other causes should be sought as described above. A simple first step after a thorough history and physical examination is completed is to determine if there is a historical ferritin level for comparison. Should this value continue to increase on repeating the test, one should consider these other tests and work-up.

In a patient with an elevated serum ferritin but normal transferrin saturation with no evidence of infection or malignancy, one should look for occult infections, liver disease, connective tissue disease, and other inflammatory conditions. A number of patients who consume alcohol, have a metabolic syndrome, or have an underlying fatty liver may have an elevated ferritin level. Management then consists of treating the underlying cause, encouraging abstinence from alcohol and weight loss, and reducing other CV risk factors that may lead to a metabolic syndrome or fatty changes in the liver.

Answered by:
Dr. Cyrus Hsia and Dr. Kang Howson-Jan
How does one investigate prolonged, unconjugated hyperbilirubinemia in a breastfed neonate who is two-months-of-age?

Question submitted by: Dr. Anne Monty LaSalle, Québec

Unconjugated hyperbilirubinemia is produced by three basic pathophysiologic mechanisms:

1. Bilirubin overproduction, which occurs mostly with hemolysis (i.e., sickle cell disease, thalassemia, glucose-6-phosphate dehydrogenase deficiency, and spherocytosis)
2. Impaired hepatic bilirubin uptake, which can be caused by certain drugs or reduced hepatic blood flow, and
3. Impaired bilirubin conjugation, which occurs in disorders such as Gilbert’s syndrome, Crigler-Najjar syndrome, hyperthyroidism, and chronic liver disease.

Of these causes, hemolytic processes are the most common.

The work-up for unconjugated hyperbilirubinemia should begin with a thorough history and physical examination to assess for the presence of inherited conditions and liver disease. Next, a reasonable laboratory work-up should include a CBC, peripheral blood smear, reticulocyte count, and lactate dehydrogenase to assess for the presence of hemolysis. Alanine transaminase and Aspartate transaminase tests should also be done to look for the presence of liver disease. If the patient is found to be anemic with evidence of hemolysis, then a more specific work-up can be done to determine the cause of this condition. Likewise, if liver enzymes are abnormal, a more thorough work-up can be completed to look for the presence of specific liver disease. Therefore, these initial screening tests can provide reassurance or point in the correct direction for further investigation.

Answered by: Dr. Krista Helleman
Diagnosing Different Types of BCC

How do you diagnose different types of basal cell carcinoma, and when is Mohs surgery performed?

Question submitted by: Dr. Nicolas Boudreault
Lac-Etchemin, Québec

The different types of basal cell carcinoma are nodular, cystic, cicatricial (morpheiform), infiltrative, micronodular, superficial, pigmented, and Fibroepithelioma of Pinkus. They all have distinct clinical appearances, but biopsy is the best way to be sure of which variant you are dealing with.

Mohs surgery involves immediate biopsy analysis of excised tissue so there is clear confirmation of complete removal.

All recurrent tumours or high-risk primary tumours with one or more of the following features are candidates for Mohs micrographic surgery:

1. Aggressive histologic growth pattern: sclerosing, infiltrating contiguous tumours; multicentric, clinically ill-defined micronodular BCC; perineural and perivascular growth patterns; and deep tissue or bone involvement
2. Location in anatomic sites at which conventional treatment modalities have a higher potential risk of recurrence: periorbital and canthal regions, central-third of the face, nasofacial sulcus, and perinasal region
3. Location at anatomic sites that require tissue conservation for optimal reconstruction: nasal tip and alae, lips, eyelids, auricular helix and canal, hands and feet, genitalia
4. Other characteristics: large size (> 2 cm); history of incomplete removal; rapid growth, or aggressive clinical behaviour; tumours in patients with immunosuppression; tumours arising in patients with a history of previous radiation therapy; patients with basal cell nevus syndrome

Answered by:
Dr. Scott Murray
What Is the Risk of Performing a CT Scan during Pregnancy?

How safe is a CT in pregnancy (before pregnancy is diagnosed)?

Question submitted by: Dr. N. Dhiraj
Milton, Ontario

Generally, radiologic imaging is avoided during pregnancy, but this must be balanced with the need to make an accurate diagnosis for a condition to be treated. If a pregnant patient requires a CT scan to the lower abdomen and pelvis, effort should be taken to minimize the radiation dose by limiting the areas imaged, the thickness and number of slices taken, and added elements, including preliminary “scout” films.

The effects of radiation differ throughout a pregnancy. During the first 14 days of pregnancy, before a period is missed, the conceptus is the most susceptible to the deleterious effects of radiation. Radiation will damage a percentage of pluripotent cells and the embryo will either continue through pregnancy unharmed or abort spontaneously, depending on the percentage of cells killed. The higher the dose of radiation, the greater the number of cells killed.

Embryogenesis occurs during the first 56 days of pregnancy, and radiation during this time can lead to congenital anomalies or disturbances with development and growth, such as microcephaly. This can occur until 25 weeks gestation; a fetus is more resistant to the effects of radiation in the following weeks.

The deleterious effects from radiation are not seen at radiation doses less than 5 cGy. An abdominal/pelvic CT scan can deliver a radiation dose from 1 to 10 cGy with doses estimated at 2.4 cGy in the first trimester and 4.6 cGy in the third trimester. CT scans of the head and chest with shielding pose little radiation risk to the conceptus. In general, teratogenesis is not a major concern after a diagnostic pelvic CT scan in pregnancy and it is “exceptionally unlikely” than any single diagnostic radiology exam would have a radiation dose sufficiently high to consider termination.¹,²

References

Answered by:
Dr. Cathy Popadiuk
Does Revascularization Improve Survival in CAD?

Remember that coronary artery revascularization was developed to treat symptoms of angina, for which it is very successful. None of the early studies were powered to detect a decrease in mortality. The baseline risk of death for people with stable angina is 0.9 to 1.4% per year — to detect a 25% reduction would require a study with over 2,000 subjects per group.

Yusuf et al., published a meta-analysis on CAD and revascularization in 1994. The 10-year mortality in the medically treated group was 15.8%, and in the coronary artery bypass grafted (CABG) group it was 10.2%. The absolute risk reduction was 5.6%, resulting in a number-needed-to-treat of about 18 to prevent one death in 10 years. Patients with left main (or equivalent) CAD and triple vessel CAD had a higher risk of death and a greater absolute risk reduction with CABG. A 2005 Cochrane review comparing CABG with angioplasty and stenting found no mortality difference but a considerably increased need for repeat revascularization at one year in the angioplasty/stented group. Greenhalgh, et al., compared results using bare metal stents with drug eluting stents. They found no difference in total mortality.

Finally, it’s known that many myocardial infarctions arise from lesions that occlude less than 50% of the lumen — the “vulnerable plaque.” These lesions would not ordinarily be targeted for revascularization.

References

Answered by:
Dr. Thomas W. Wilson
Biliary Sludge Treatment

What is the treatment for biliary sludge (bile)? Does hydration help?

Question submitted by: Dr. Nicolas Boudreault
Lac Etchemin, Québec

Biliary sludge is a mixture of cholesterol crystals, calcium bilirubinate pigment, and other calcium salts that compose a particulate solid precipitate of bile. Development has been associated with a variety of conditions including pregnancy, rapid weight loss, medications (e.g., ceftriaxone and octreotide), bone marrow/solid organ transplantation, critical illness with minimal oral intake, the use of total parenteral nutrition, and bariatric surgery. A clinical association has been established with choledolithiasis and choledocholithiasis. Management of biliary sludge has been poorly defined, as the clinical course of this condition can be variable and unpredictable (ranging from complete resolution to precipitation of choledolithiasis and clinical biliary obstruction). Asymptomatic patients with sludge require no specific therapy, whereas symptomatic patients with or without related complications should be managed with cholecystectomy. Elderly patients or those at risk from surgery (e.g., endoscopic sphincterotomy) may prevent recurrent episodes of related pancreatitis. To date, there is no clearly defined medical therapy for this condition.

Answered by:
Dr. Theodore Xenodemetropoulos
9. Connection between DMPA and Osteoporosis Development?

What is the mechanism of developing osteoporosis from medroxyprogesterone acetate? How many doses are safe?

Question submitted by: Dr. B. Leonard Chandrarajan Kingston, Ontario

Long-acting, injectable depot medroxyprogesterone acetate (DMPA) is a useful contraceptive option. It suppresses pituitary gonadotropin secretion thus inhibiting ovarian function and estradiol production. This may result in a measurable decline in bone mineral density (BMD). Bone loss mainly occurs in the first two years; it then stabilizes somewhat afterwards. This bone loss is especially concerning in young women who have yet to achieve their maximum bone density, perimenopausal women who are losing bone density, and those with risk factors, such as decreased mobility or steroid use.

However, studies show that after discontinuation of DMPA, there is recovery of BMD, even after many years of use. There is no good evidence that fracture rate increases in DMPA-treated women. Thus, there is little concern in limiting the duration of the use of DMPA. Nevertheless, this information should be discussed with the patient prior to initiating DMPA, and other measures should be considered for the promotion of bone health.

Resources

Answered by: Dr. Bernard Corenblum
Advising Family Members of Patients with LQTS

What advice do you have for family members of patients who have long QT syndrome (LQTS) that does not fit the known familial types?

Question submitted by: Dr. Margaret Culliton
Corner Brook, Newfoundland

The most common of the genetic arrhythmia syndromes is the long-QT syndrome (LQTS), which is characterized by abnormal repolarization of the heart and manifested by QT-interval prolongation on the surface ECG (QT interval corrected for heart rate exceeding 500 msec); this confers an increased risk of sudden death, usually secondary to torsade de pointes or ventricular fibrillation.¹ While there are some well-defined familial subtypes of this potentially fatal disease, LQTS comprises a large group of genetic disorders involving hundreds of mutations in a variety of genes producing abnormal cardiac potassium-ion or sodium-ion channels.²

Guidelines for management of the LQTS have been established with the major therapeutic options for high-risk patients, including β-blocker therapy and implantable cardioverter-defibrillators.³ However, identifying patients at high risk for sudden cardiac death can be problematic, since half of mutation carriers are asymptomatic, and one-third have QT interval corrected values that overlap those of normal persons.⁴ Therefore, in addition to clinical review with a screening ECG for family members of patients with LQTS, education about the risks associated with certain drugs must be clearly integrated into the strategy of fatal-arrhythmia prevention. Avoidance of QT-prolonging therapies can be facilitated by accessing the International Registry for Drug-induced Arrhythmias (www.crediblemeds.org) where there is a regularly updated list of these drugs.

References

Answered by: Dr. Theodore K. Fenske
Regular Exercises for Parkinson’s Patients

Are regular exercises useful in Parkinson’s disease?

Question submitted by:  
**Dr. Guy Frenette, Cap-Santé, Québec**

Yes. A recent Cochrane study found physiotherapy to be beneficial on measures of gait velocity and other mobility measures, while another systematic review found benefit from resistance training. However, the long-term benefit (whether the effect is sustained over time) is not known.

Resources


Answered by:  
**Dr. Sarah A. Morrow**
Medications for Alzheimer’s Patients with Hallucinations

What medications can help Alzheimer’s patients with hallucinations?

Question submitted by: Dr. Daniel Dodek, Vancouver, British Columbia

Alzheimer’s disease is the most common form of dementia, accounting for 60 to 80% of dementia cases. The dementia spectrum includes vascular dementia, Lewy body dementia (LBD), mixed dementia, and frontotemporal dementia.

As Alzheimer’s is a progressive disorder, symptoms usually begin with patients finding it challenging to remember the names of people and objects and difficulty recalling recent events. Neuropsychiatric symptoms start with apathy and depression at the earliest stages and progressing to impaired judgement, behavioural changes, hallucinations/delusions (especially in LBD), and agitation/aggression.

With respect to cognitive impairment, it is essential that commonly distressing symptoms for the patient and caregivers (e.g., hallucinations and depression) are effectively managed. Medications with anticholinergic side effects (e.g., tricyclic antidepressants) should be avoided, as they may worsen cognition and psychotic symptoms.

Hallucinations and delusions in the early stages of dementia differentiate between patients with LBD and those with Alzheimer’s disease. Published as early as 2002 by Bullock et. al., a root-cause analysis showed that treatment of the underlying disease using rivastigmine, a cholinesterase inhibitor, provided benefits in patients with hallucinations.

From an antipsychotic perspective, typical or atypical antipsychotics may be considered. Typical antipsychotics may not be safer versus atypicals, but they do not carry the burden of a black box warning. As the atypicals may be more effective for the negative symptoms of the disease, an agent with a low anticholinergic load may be considered. Low-dose quetiapine is often used in patients with Alzheimer’s disease, but consideration of the incidence of orthostasis and anticholinergic effects is essential. Perhaps the best-studied option would be low-dose haloperidol, which has demonstrated efficacy as a typical antipsychotic. A starting dose of 0.5 to 1 mg/day with an upward dose titration, pursuant to patient response, may be indicated.

References

Answered by:
Professor Joel Lamoure
Unfortunately, varicella antibody titres are not of much use in determining the need for, or benefit from, the zoster, or shingles vaccine. First of all, since shingles represent the reactivation of latent varicella infection, everyone at risk of shingles would have varicella antibodies present. For those who grew up in North America or Europe before the widespread use of the similar varicella (or chickenpox) vaccine, infection was almost universal. In theory, those who never had chickenpox (i.e., they are antibody negative) could develop classic varicella after exposure, but they would normally not get shingles. However, it is presumed (though it has never been demonstrated) that the shingles vaccine would also protect those individuals from acquiring chickenpox indirectly from shingles at a later time. It should also be noted that younger adults who received the chickenpox vaccine during childhood might not develop antibodies detectable by current commercial techniques, even though they are still protected. This may lead to even greater confusion in the future, because those who are antibody negative could be naïve to the infection, be immune due to vaccination, or be at risk of infection because the vaccine’s protection has faded.

Answered by:

Dr. Michael Libman
What Conditions Are Associated with Restless Leg Syndrome?

**14. Is restless leg syndrome associated with any vitamin deficiencies?**

Restless leg syndrome is known to be associated with renal insufficiency, pregnancy, iron deficiency anemia, diabetic neuropathy, and Parkinson’s disease.

Answered by:

Dr. Sarah A. Morrow

Question submitted by:

Dr. Adele Belliveau

Dartmouth, Nova Scotia

Oxygen Therapy during Exertion for Emphysematous Patients

**15. Is intermittent oxygen therapy good for emphysematous patients with severe dyspnea exacerbation at exertion?**

Long-term oxygen therapy has only been validated as a means to prolong life for patients with chronic obstructive pulmonary disease (COPD) who are hypoxemic at rest. The use of oxygen therapy to relieve dyspnea during exercise is a widespread practice that lacks an evidence base.

In some jurisdictions, patients with COPD who become hypoxemic on exercise have been offered a clinical trial where oxygen or air through nasal prongs is provided while a six-minute walk test is completed. In a very small group (less than 10% of those tested), there was a measurable and meaningful improvement in the distance walked with oxygen compared with that walked with air. In that strict circumstance, a case could be made for the use of oxygen during exercise.

Reference


Answered by:

Dr. Robert Cowie
Treatm ent for Young W om en w ith C hronic C ystitis

Please comment on prophylactic treatment for recurrent (< 4 years) cystitis in young women on contraception who are allergic to sulfa.

Question submitted by: Dr. S. Gill, Sorel-Tracy, Québec

Cystitis that occurs at least twice in six months or three times in a year is considered a recurring or chronic problem for which prophylactic antibiotics can be prescribed. Once investigations confirm that there is no anatomical or physical cause for the cystitis, it can be attributed to bacterial infection from individual predisposition, which is sometimes exacerbated by sexual activity and colonization at the urethra. In a patient with a sulfa allergy, several antibiotics are available, such as cotrimoxazole, nitrofurantoin, cephalaxin, trimethoprim alone, or a quinolone. The antibiotics can be given continuously over a 6 to 12 month period and re-evaluated or, if the cystitis is associated with intercourse, post-coitaly (see Table 1). The latter minimizes the number of pills taken and, thus, cost and possible side effects.

For recurrent cystitis associated with intercourse, spermicides can exacerbate the problem and another form of birth control should be considered. The OCP may be a better option. Rifampin and griseofulvin increase liver enzyme activity, decreasing the effectiveness of OCP through accelerated estrogen and progesterone metabolism. It has been traditionally thought that many antibiotics negatively impact the effectiveness of OCPs, but the evidence suggests this is not the case and contraceptive failure is a result of real-life use, pill delays, missed pills, or other drug interactions. Nonetheless, to prevent any concern or anxiety, another form of contraception, such as the NuvaRing® or progesterone IUD or patch could be suggested in younger women with cystitis who require contraception.

<table>
<thead>
<tr>
<th>Continuous Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim</td>
</tr>
<tr>
<td>Nitrofurantoin monohydrate/macrocrytall</td>
</tr>
<tr>
<td>Nitrofurantoin macrocrystals</td>
</tr>
<tr>
<td>Cephalexin</td>
</tr>
<tr>
<td>Cefaclor</td>
</tr>
<tr>
<td>Norfloxacin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Cinoxacin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postcoital Prophylaxis (Single Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin macrocrystals</td>
</tr>
<tr>
<td>Cephalexin</td>
</tr>
<tr>
<td>Cinoxacin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Norfloxacin</td>
</tr>
<tr>
<td>Ofloxacin</td>
</tr>
</tbody>
</table>

Resource

Answered by: Dr. Cathy Popadiuk
The optimal treatment of rectal bleeding due to radiation proctitis remains unclear. A wide variety of medical therapies have been investigated, including oral or topical 5-aminosalicylic acids (5ASAs), short-chain fatty acids, oral metronidazole, rectal steroids, sucralfate, and hyperbaric oxygen. Unfortunately, given heterogeneous data generated from small, largely single-centre, uncontrolled, and unblinded studies, the evidence supporting these therapies is poor. Numerous endoscopic therapies have also been described, including argon plasma coagulation (APC), endoscopic formalin application, as well as radiofrequency ablation and cryoablation. Repeated sessions of treatment with APC have been shown to reduce bleeding as well as blood transfusion requirements in patients with mild to moderate radiation proctitis. Patients with more severe or refractory bleeding may benefit from treatment with intrarectal formalin application, radiofrequency ablation, or cryoablation, although the data supporting the efficacy of these modalities is limited.

References

Answered by:
Dr. Theodore Xenodemetropoulos