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"APPROACH TO"

A GUIDEBOOK FOR STUDENTS, MADE BY STUDENTS

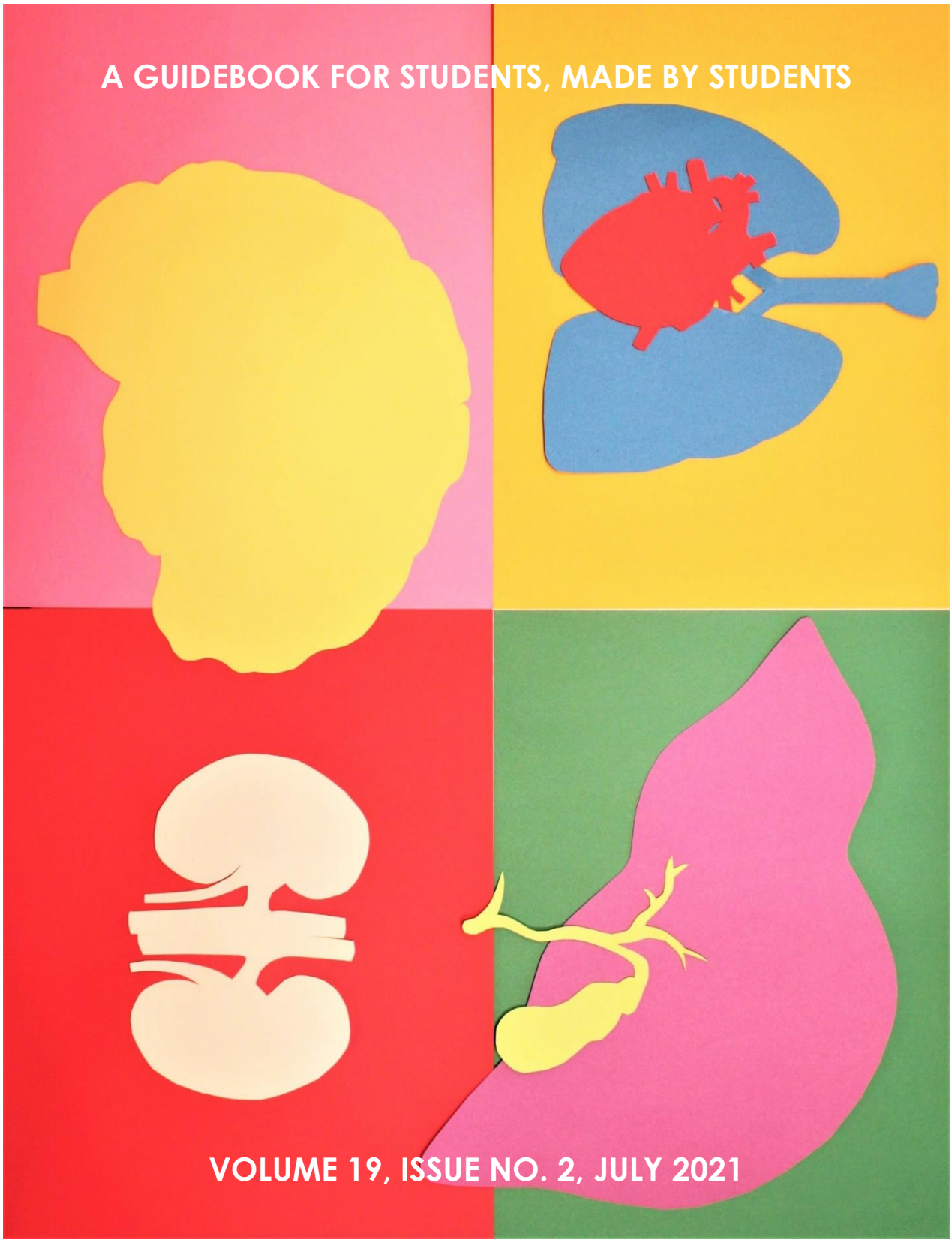

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Table of Contents

**MJM Approaches published between September 2020 and June 2021 have been included in this issue. All manuscripts are internally peer-reviewed. Informed consent practices and any conflicts of interest are specified in the articles if applicable.*

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Letter from the Editors
MJM Approaches - By Students, For Students

We are thrilled to present the first issue of the McGill Journal of Medicine Approaches Series. These articles are meant to offer medical students condensed overviews of the most important things to know about common clinical topics, such as chest pain, chronic obstructive pulmonary disease, red eye, and heart failure. Beyond being a valuable source of information, these articles help students forge their clinical reasoning by offering a structured approach to these problems.

This format was created for several reasons that benefit authors and readers alike. First, the MJM Approaches have offered several medical students the chance to publish their first peer-reviewed article. Beyond the pride associated with this accomplishment, students had the chance to learn more about the topic they were writing about and understand the intricacies of the peer-review process. Furthermore, these articles give our readers the chance to learn about important medical topics in a format that is specifically made for them, with the unique perspective of a peer author who is facing the same challenge of mastering the approach to common clinical presentations seen in a variety of medical disciplines.

In its first year of operation, the MJM Approaches format was a tremendous success for both the MJM and the McGill medical community. Our goals for next year include continuing to help this peer-learning format grow and evolve, while expanding its reach throughout Canada. On behalf of the McGill Journal of Medicine, we thank the editorial board, reviewers, authors, and readers. We look forward to publishing more Approach articles in the future.

Sincerely,

Mack Michell Robinson, MSc.
Co-Editor-in-Chief, McGill Journal of Medicine
MD/PhD Candidate, 2025

Etienne Leveille

Etienne Leveille, MDCM
Co-Editor-in-Chief, McGill Journal of Medicine

Jack Lam, MSc., MDCM
Managing Editor, McGill Journal of Medicine

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Foreword
Approach To… Developing Illness Scripts

Like many of my colleagues at the time, I accomplished an ambitious feat during my residency: I read the principal textbook in neurology from start to finish.

It was a ponderous, two-volume set, a 2500-page compendium of neurological disorders from Alzheimer's dementia to Zellweger syndrome. I spent countless hours poring over Parkinson's disease, soaking up Sydenham's chorea, and delving into Duchenne's muscular dystrophy. I devoured the content of these tomes with the resolve of a participant in a spelling bee who, while preparing for the final contest, studies the Oxford English Dictionary cover to cover.

My clinical rotations followed a similarly sequential pathway. Month by month, I migrated from the Movement Disorders clinic to the Epilepsy unit to the Neuromuscular lab. In each setting, I took patients' histories, examined them, applied my hard-won knowledge, and tendered a final diagnosis.

And more habitually than I care to disclose, I was utterly and decisively wrong.

The problem? It turns out that patients don't read medical textbooks. And they don't give a damn what rotation you're on.

Patients don't come with flashcards or section headings that divulge what afflicts them. Instead, they share stories of suffering and offer observations about what pains them. They report on red eyes and achy backs, not on scleral ulcers and slipped disks. They look to you to make pathophysiological sense of their lived experiences by sifting through, interpreting, and classifying the information their narratives reveal.

Crucially, the lens through which you examine their statements is influenced by – and often negatively biased by – your own prior experiences in learning about disease and illness. When you are reading a chapter on Lung Disorders, for example, you're apt to suspect pulmonary embolism in every patient with chest pain. During your ID rotation, every flushed face is an infection; during your vascular rotation, every crooked smile is a stroke.

Put another way: While textbooks often proceed from diagnosis to symptom, the clinical world generally proceeds from symptom to diagnosis. Viewed in this light, misdiagnosis results from mismatch: the way a patient's story unfolds is often at odds with the way a physician's knowledge is organized, because of the way he or she has acquired it in the first place.

This issue of the McGill Journal of Medicine seeks to help you lay down the fundamental aspects of diseases in a manner that jibes with the way patients recount their experiences of them. The "Approach To…" approach to medical education adopted by the authors in this issue serves to guide you toward building knowledge networks adapted for clinical practice. These bundles of specialized knowledge, sometimes referred to as "illness scripts," are designed to enable you to recognize patterns and irregularities in symptom complexes, identify similarities and differences between disease states, and make predictions about how diseases are likely to evolve.

Illness scripts that closely parallel clinical realities are more likely to be retrieved at the right time and in the right place, allowing you to reason through cases with greater ease and accuracy. So it behooves you to acquire solid mental models of diseases from the outset of your training, and gradually to update and refine them as you continue to grow and gain experience.

Take it from me: It's harder to unlearn than it is to learn.

And what has become of my neurology textbook? I recall that its covers are green. I recall the sense of naive satisfaction I felt when I snapped its back cover shut. I recall little else of what it contains, although perhaps I sell it somewhat short. I'm certain, however, that an appreciation of the vast and rich array of stories and experiences my patients have shared with me over the years, and a sound approach to understanding them, has shaped my ability to be a better doctor.

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APPROACH TO
McGill Journal of Medicine

Ocular Trauma

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ABSTRACT

Ocular trauma can be a common presentation in the emergency department. It is therefore important for a physician to be able to quickly recognize vision-threatening conditions and provide necessary medical management prior to consulting ophthalmology. This article describes the pertinent information that should be gathered during a focused ocular history in a patient with ocular injury, and also provides a systematic approach to evaluating ocular trauma. As an example, a case study of open globe injury is used to illustrate the appropriate pre-ophthalmologic management and common medical errors that must be avoided for a good prognosis. Additional ocular conditions such as traumatic hyphema, traumatic optic neuropathy, traumatic vitreous hemorrhage, orbital compartment syndrome, chemical burns, and eyelid lacerations are also described as differential diagnosis. Ultimately, the aim of this work is to provide medical students with a fundamental understanding in approaching ocular trauma in emergency clinics.

KEYWORDS
Ocular trauma, Ocular chemical injury, Orbital compartment syndrome, Open globe injury, Hyphema, Vitreous hemorrhage, Retinal detachment

1 | QUESTION

A 36-year-old male presents to the emergency clinic with sudden onset of pain, redness, and bleeding from his left eye that started while operating a woodcutter machine three hours ago. He irrigated his eye at home with water and took Tylenol® but noted that the bleeding and pain did not stop. He also reports blurry vision and some sensitivity to light in his left eye. Upon initial inspection you observe a 'teardrop' shaped pupil, conjunctival redness, and three small woodchips protruding out of the corneal limbus and scleral region in the left eye. There is no hyphema, no proptosis, and no apparent deformity of the globe. His past medical and ocular history is unremarkable, and he is currently not taking any medication. He does not wear any glasses or con-

tact lens. No eye protection was worn at the time of injury.

Visual tests

- Visual acuity (VA): 20/25 OD and 20/150 OS
- The text in the entries may be of any length.
- Visual fields by confrontation: normal
- Relative afferent pupillary defect (rAPD): inconclusive (patient did not cooperate)
- Ocular motility: Full range, discomfort with left eye
- Intraocular pressure (IOP): not measured
- Red reflex: visible, symmetrical
- Eye pH: 7.2

What is the next best step in management of this patient prior to consulting ophthalmology?

A. Continue to irrigate with saline

B. Place an eye shield over the affected eye

C. Put tetracaine (anesthetic) eye drops to relieve pain

D. Carefully remove the protruding woodchips

E. Perform an orbital ultrasound to determine extent of injury

2 | ANSWER

B. The 'teardrop' pupil along with protruding foreign body raises suspicion of an open globe injury. The best course of action is to protect the eye with an eye shield and obtain urgent ophthalmology consultation. Removal of foreign body should be deferred to the ophthalmologist, and one should avoid placing any medication (e.g. tetracaine) or diagnostic eye drops (e.g. fluorescein) into the affected eye. Maneuvers that may increase intraocular pressure and risk extrusion of intraocular contents are contraindicated; therefore, eye irrigation, IOP measurements with tonometry, orbital ultrasound, and eyelid retraction should not be performed.

3 | INITIAL APPROACH

Evaluation of a patient with suspected ocular trauma begins by identifying and treating any life-threatening injuries. Once medically stable, the physician should obtain a focused ocular history to identify any vision-threatening conditions. (1) This includes information regarding the injury, such as:

1. Mechanism: high-velocity projectiles, blunt trauma, or chemical exposure
2. Timing: acute or chronic
3. Location: home, work, or motor vehicle accident
4. Symptoms: diplopia, photophobia, pain with eye movement, or facial numbness
5. Past ocular history: pre-injury visual acuity, cataract, glaucoma, or retinal detachment

Other elements to note on history include current medications, drug allergies, tetanus immunization status, and prior anesthesia complications. (1) Next, an organized approach should be utilized to rapidly assess imminent threats to vision (Figure 1). Careful inspection of the ocular and orbital anatomy, along with comprehensive visual examination provides further information on the extent of trauma. (1,2)

In the present case, the patient was suspected to have an open globe injury, which involves a full thickness break of the eye wall composed of the sclera (white outer layer of the eyeball) and the cornea (transparent part of the eye covering the iris and pupil). Caused by sharp or blunt trauma, patients suffering from open globe injury present with acute eye pain that may or may not be accompanied with reduced VA. (3) Inspection with penlight or slit lamp may reveal eccentric or 'teardrop' pupil (Figure 2a), extrusion of vitreous (Figure 2b), possible loss of globe contour, and deep or shallow anterior chamber depth depending on the type and position of injury. (1,4) In this case, the patient presented with pain, bleeding, teardrop pupil, and protruding woodchips from the eye wall, suggesting a high-velocity penetration injury likely from the projectile debris when operating wood-cutting machinery without ocular protection.

Once an open globe injury is suspected, protecting the affected eye with an eye shield and consulting ophthalmology is the first step in management. Avoid fur-

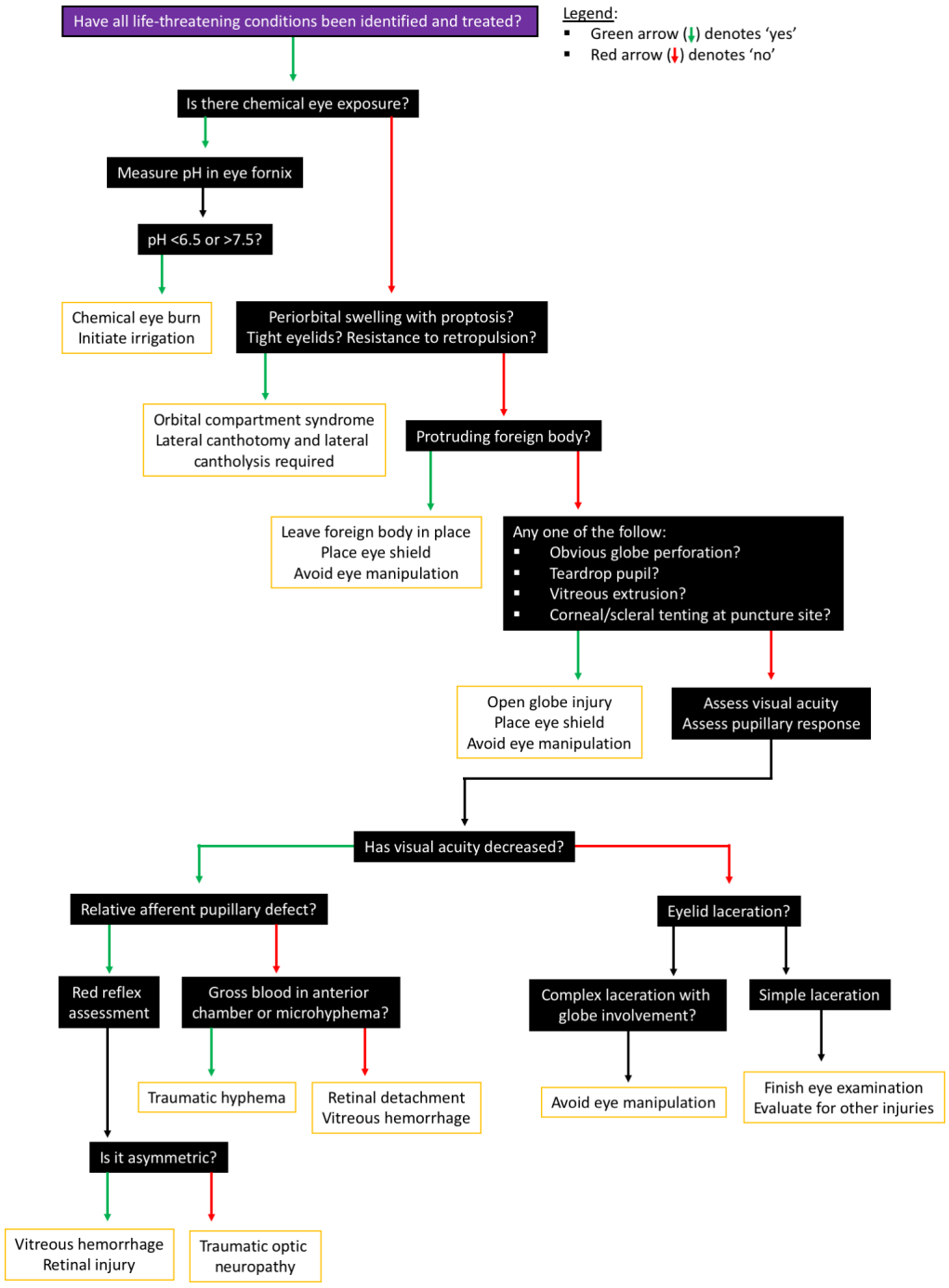

FIGURE 1 Organized approach for the assessment of ocular trauma in emergency department.

Adapted from: Approach to eye injuries in the emergency department, *UpToDate*®
https://www.uptodate.com/contents/ approach-to-eye-injuries-in-the-emergency-department?csi=271f7410-cbe8-407a-883d-1a032c7971cf&source=contentShare

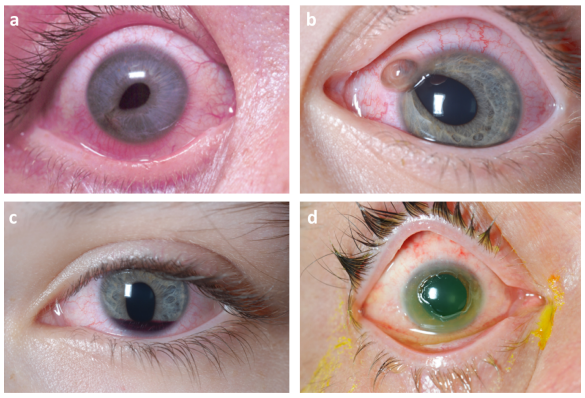

FIGURE 2 Presentation of the affected eye following ocular trauma. (a) Teardrop pupil pointing towards the location of corneal injury and suggestive of open globe injury. (b) Extrusion of intraocular content (iris prolapse) through an open globe defect. (c) Hyphema as noted by the accumulation of red blood cells in the anterior chamber. (d) Severe alkali chemical burn that resulted in a large corneal defect.

Images obtained from: Serrano, F., Stack, L. B., Thurman, R. J., Phillips, L., & Self, W. H. Traumatic eye injuries: management principles for the prehospital setting. JEMS. 2013; 38(12): 56–62. https://www.jems.com/gallery/80545/traumatic-eye-injury-management-principles-for-the-prehospital-setting/

ther examination that may increase IOP such as orbital ultrasound, eyelid retraction or IOP measurements with tonometry, as these maneuvers can extrude intraocular contents (Figure 2b). (3,4) Do not attempt to remove the protruding foreign bodies and refrain from placing any medication (e.g. tetracaine) or diagnostic eye drops (e.g. fluorescein) into the affected eye. Verify patient's tetanus status. Treat any nausea/vomiting and pain with antiemetics (e.g. ondansetron) and analgesics. Broad-spectrum antibiotics can be started to decrease the risk of endophthalmitis. (4) Imaging includes non-contrast orbital computer tomography (CT) to confirm diagnosis, determine the extent of foreign body penetration, and guide the treatment approach.

Several other conditions may occur in isolation or concomitantly with open globe injury following ocular trauma. These should be noted in the differential diagnosis, and can include the following:

3.1 | Traumatic Hyphema

Hyphema is the accumulation of red blood cells in the anterior chamber that can be visualized in a sitting patient with a penlight or slit lamp (Figure 2c). (5) Hyphema should be suspected if the patient presents with decreased VA, pain with pupillary constriction to bright light, anisocoria, iridodialysis, and increased IOP. Hyphema can result from blunt or penetrating trauma that damages the iris or ciliary body vessels. It can be graded from zero (microhyphema) to four depending on the amount of blood present in the anterior chamber. (5,6) Visual prognosis depends on the etiology, grade of hyphema, and ocular complications such as re-bleeding, optic atrophy, synechiae, and corneal blood staining. (7) Patients with sickle cell disease and bleeding disorders are at higher risk for poor outcomes; therefore, solubility testing or hemoglobin electrophoresis is recommended in susceptible population (e.g. African or Mediterranean descent or positive family history). (6)

Initial management includes protecting the eye with an eye shield and bed rest with the head of bed elevated to 30 degrees. (5) Diagnostic imaging with non-contrast orbital CT is considered when open globe injury, intraocular foreign body, or orbital fracture is suspected. If open globe injury is ruled out, IOP can be measured and topical pain medications (e.g. tetracaine, proparacaine) can be administered. Avoid the use of NSAIDs and aspirin for pain control as their platelet-inhibiting properties can increase risk of bleeding; use oral acetaminophen or oxycodone instead. (6) Antiemetic therapy can help control nausea/vomiting and the associated increase in IOP.

3.2 | Eyelid lacerations

It is not uncommon for ocular or facial trauma to be accompanied by eyelid injuries, especially if the etiology includes injury from high velocity projectiles. The eyelids play a crucial role in protecting the eye globe and maintaining tear film distribution and drainage. (8) If eyelid

lacerations are present in a suspected open globe injury, avoid manipulation of eyelid and follow the open globe injury guidelines. Eyelid trauma that requires immediate consultation by ophthalmology includes laceration through full thickness of the lid or the lid margin, laceration with orbital fat prolapse, and laceration involving the tear drainage system. (9) Furthermore, any laceration in the medial one-third of the eyelid should be suspect for having a canalicular laceration and requires ophthalmology consultation. (9) Lid lacerations that do not involve the eyelid margin can be repaired with simple interrupted running sutures within 12-36 hours for good prognosis. In the event of animal bites, prophylactic antibiotics that cover anaerobes and aerobes should be initiated, and prophylaxis for rabies and tetanus may be considered.

3.3 | Traumatic optic neuropathy

While indirect traumatic optic neuropathy (TON) from blunt trauma is more common, it can also occur with a direct penetrating or lacerating trauma from high velocity projectiles. (10) Patients with TON can present with decreased VA, visual field defects, achromatopsia (red colour desaturation), and rAPD (present only in unilateral or asymmetric TON). Diagnostic evaluation requires urgent CT imaging of the optic canal and consultation with the ophthalmologist as treatment is determined by underlying etiology. (10)

3.4 | Orbital compartment syndrome (OCS)

As the orbit is a confined space, a rise in volume in this compartment can occur with intraorbital hemorrhage or soft tissue swelling following penetrating or blunt trauma. OCS occurs when the intraorbital pressure surpasses the arterial perfusion pressure of the optic nerve. (11) Patients present with acute onset of markedly decreased VA, diplopia, rAPD, ophthalmoplegia, proptosis, periocular edema, and evidence of increased intraorbital pressure such as tight eyelids and resistance to retropulsion. If it remains uncorrected, OCS can result in permanent vision loss within hours. As a true emergency, ophthalmology should be immediately consulted. If the IOP is found to be extremely high, emergent decompression of the orbit may be provided by lateral canthotomy and inferior cantholysis. (11,12) Additional management involves bed rest with head elevation, pain control, and prevention of sudden increases in IOP through cough suppressants, stool softeners and antiemetics.

4 | BEYOND THE INITIAL APPROACH

Although the patient presented with open globe injury, in this case, a complete history may reveal other ocular trauma that warrant immediate treatment. For example, construction site hazards can include risk of chemical exposure and head trauma from falling debris. Therefore, other ocular conditions to probe on history include:

4.1 | Ocular chemical injury

The extent of damage caused by chemical burns depends on the type of agent, volume, and duration of exposure. (13) Alkaline agents cause severe injury as they lead to liquefactive necrosis, which allows for deep intraocular penetration (Figure 2d). In contrast, acids cause coagulative necrosis which protects the eye from deeper chemical penetrations. (13) Patients presenting with decreased VA, eye pain, conjunctival redness, blepharospasm (inability to open eyes), and photophobia should be suspected for ocular chemical injury. If a chemical burn is established, irrigation with isotonic saline should be started immediately before conducting further ocular evaluation. Irrigation should continue manually (or with a Morgan lens) with maximal exposure to conjunctiva and cornea until a pH between 7.0 and 7.4 is established (30-60 min) by placing a litmus paper at the conjunctival fornix. (14,15) Once a neutral pH is maintained, the affected eye should be assessed for corneal abrasions, foreign bodies, and globe rupture.

4.2 | Traumatic Vitreous Hemorrhage

Vitreous humor is a clear, gel-like substance that occupies the space between the retina and the lens. (16) Traumatic vitreous hemorrhage occurs when blood leaks into the areas in and around the vitreous humor. (17) While this condition suggests retinal detachment or tear, it can also be observed in patients with subarachnoid or subdural hemorrhage due to head trauma. (16,17) Patients may complain of acute painless visual loss, red hue to vision, and new onset of cobweb-like floaters. (16) Fundoscopy is used to evaluate the optic disc, retina and the surrounding vessels. Decrease in the red reflex can be noted on fundoscopy when blood is present in the aqueous or vitreous humor. (16,17) Diagnostic imaging includes CT of the head in cases of head trauma, and an ophthalmologist provides definitive treatment.

5 | CONCLUSION

Ocular trauma is a common presentation in the emergency department. A focused ocular history should include the mechanism, timing, and location of the injury, along with patient's symptoms and past ocular history. It is crucial to rule out open globe injuries prior to performing any eye manipulation procedures including orbital ultrasound, eyelid retraction, or IOP measurements with tonometry. Careful evaluation of the ocular and periocular structures should be followed by assessment of VA, rAPD, confrontational visual fields, red reflex, and IOP. Depending on the diagnosis, medical management could be initiated to reduce patient's pain, nausea/vomiting, and anxiety. Ultimately, it is important to familiarize oneself with early recognition and preophthalmologic management of vision threatening conditions.

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APPROACH TO
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Red Eye

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ABSTRACT

Red eye is a common symptom that presents in primary care practice, and may be accompanied by pain, irritation, or discharge. It is a sign of ocular inflammation, often involving the anterior segment of the eye. Most causes of red eye are benign; however, the primary care physician must identify when urgent referral to an ophthalmologist is required. This may be achieved through targeted questioning regarding the chronicity, intensity of pain, vision changes, and associated symptoms. The following article outlines an approach to identifying the cause of red eye using history and physical exam findings. Common features of red eye disorders and their respective treatment modalities are discussed.

KEYWORDS
Red Eye, Hyperemia, Ocular Inflammation, Conjunctivitis, Infection

1 | QUESTION

A 35-year old man presents to your office with a two-day history of persistent, diffuse left-eye redness. He notes watery discharge from the left eye and a mild burning sensation in both eyes with no ocular pain or foreign body sensation. Associated symptoms include rhinorrhea over the past two days.

The patient has no significant past medical history, does not take medication, and has no known allergies. He does not report increased exposure to dust, animals, or pollen. His daughter has had similar symptoms since starting daycare a few days ago.

Upon examination, both eyelids and surrounding structures are unremarkable. Examination of the left eye shows diffuse hyperemia of conjunctival vessels, scant watery secretions, and dried crusting of the eyelid. The right eye contains minimal watery secretion but is otherwise unremarkable. There is absence of corneal opacity bilaterally. Vision testing reveals no change in visual acuity. Penlight examination reveals pupils that are equal, round, and reactive to light (PERRL) and a normal anterior chamber depth. Extraocular movements are normal in all cardinal directions of gaze. Preauricular

and submandibular lymph nodes are enlarged.

What is the most appropriate next step in management of this patient?

A. Obtain a bacterial culture

B. Refer to an ophthalmologist

C. Prescribe broad-spectrum antibiotic eyedrops

D. Instruct the patient to apply cool compresses and avoid sharing personal items with others (i.e. towels)

E. Prescribe steroid eye drops to reduce inflammation

2 | ANSWER

D. The two-day diffuse hyperemia, mild burning sensation, and associated rhinorrhea suggest conjunctivitis. A viral conjunctivitis is differentiated from bacterial conjunctivitis based on its watery rather than purulent discharge consistency and the presence of lymphadenopathy. Further, viral conjunctivitis generally lasts longer than bacterial conjunctivitis. Therefore, the patient does not require either a bacterial culture or antibiotic eyedrops. Cool compresses are helpful in reducing itching and inflammation. Viral conjunctivitis is highly contagious and transmission between individuals can arise from sharing personal items and close contact. In this scenario, the virus was likely transmitted to the patient by his daughter. Referral to an ophthalmologist is necessary if symptoms do not resolve within seven days, there is corneal involvement, or there is presence of conjunctival pseudomembranes/true membranes. Conjunctival pseudomembranes appear as thin yellowish-white membranes in the fornices of the eye. Steroid eye drops are useful in treating ocular inflammation; however, they should only be given in severe cases of conjunctivitis and under direct supervision of an ophthalmologist.

3 | INITIAL APPROACH

Red eye refers to hyperemia of conjunctival or episcleral vessels secondary to disease of almost any part of the eye. Most cases can be treated by a primary care physician, although a subset require urgent ocular referral. Evaluation of a patient with red eye should begin with a thorough history of ocular-related symptoms followed by a complete review of systems.

The following details are important to elicit on history. (1):

1. The onset and duration of hyperemia, unilateral or bilateral eye involvement, whether it has been stable or progressively worsening, and whether it is present constantly or intermittently
2. Ocular pain and its quality and severity. Ocular pain should be differentiated from itchiness or irritation
3. Foreign-body sensation
4. Changes in vision or photophobia
5. The presence of epiphora, discharge (type and amount), pus, or blood in the eye
6. Other associated symptoms (e.g. rhinorrhea, sore throat)
7. Environmental exposures, close contacts with similar symptoms, and recent trauma
8. Past medical history including ocular disorders, systemic disorders, sexually transmitted infections, clotting/vascular disorders, allergies, contact lens use, surgical history, and medication history

The physical examination should be completed on both eyes. Start with inspection of the eyelids and surrounding structures, assessing for swelling, erythema, or deformities. The tarsal conjunctiva should be screened for papillae or follicles, which are characteristic of allergic conjunctivitis or chlamydial conjunctivitis respectively. (2) If a foreign body is suspected, evert the eyelid using a cotton swab for further assessment. Next, the qualitative characteristics of the ocular hyperemia should be described as diffuse, localized with poorly demarcated borders, localized with well-demarcated borders, or ciliary/limbal injection. If discharge is present, it should be quantified and characterized as purulent (characteristic of bacterial conjunctivitis or keratitis), watery (characteristic of viral or allergic conjunctivitis), or mucoid (characteristic of chlamydial conjunctivitis). (1-3) The presence of pus (hypopyon) or blood (hyphema) in the anterior chamber should prompt immediate ophthalmologic referral. (1)

Visual acuity may be measured using a Snellen chart for distance acuity or a reading sample to measure near acuity (with correction). Extraocular movements are evaluated by directing the patient to look in the cardinal directions of gaze. Next, the penlight exam can reveal whether pupils are equal, round, and reactive to light (PERRL). Tonometry may be used to measure intraocular pressure; however, this should be avoided if ocular trauma is suspected. Normal intraocular pressure is 10-21 mmHg. (4) Next, opacities of the cornea may be assessed. Corneal epithelial dysfunction can be evaluated using fluorescein stain and a Wood's or cobalt blue lamp.

Once the ocular exam is complete, an infectious disease process should be ruled out by inspection of the nose and throat and evaluation of regional lymph nodes. The remainder of the physical exam may be tailored based on suspicion of systemic or other disease.

4 | BEYOND THE INITIAL APPROACH

This section covers a selected number of diseases that may present with red eye, organized by the duration of symptoms and presence or absence of pain. Acute presentation is defined as a duration of symptoms for seven days or less. (3)

4.1 | Acute, painful disease

Corneal abrasion occurs when there is a scratch to the cornea from contact with small particles such as dust or dirt, or direct injury from an object. (3) The patient often presents with eye pain, epiphora, and a foreign-body sensation. (3) Removal of a corneal foreign body should be completed with slit-lamp examination to avoid further corneal damage. (6) Management includes analgesics, cycloplegics, and prophylactic antibiotic therapy. (3) Individuals with chemical penetration should irrigate the eye with sterile water or saline for 20 minutes prior to emergent ophthalmologic referral. (7) Keratitis refers to infectious or non-infectious corneal inflammation. Infectious organisms may be found in contact lenses or contaminated water, and individuals with ocular injury or prolonged topical corticosteroid use are at heightened risk of infection. (1, 8) Herpes simplex keratitis is an infection caused by the HSV strain. (4, 8) Symptoms of keratitis include ocular pain and/or irritation, blurred vision, photophobia, redness, and discharge. (1) In viral keratitis, watery discharge may be present and corneal staining may reveal a dendritic pattern of the epithelium in HSV-specific keratitis. (1) In bacterial keratitis, a mucopurulent discharge is present often with corneal opacification. (1, 4) Keratitis may be treated with artificial tears for mild cases, with possible antimicrobial therapy depending on the cause. (8) Infection of the cornea may lead to a corneal ulcer, whereby there is loss of corneal tissue. (8) This finding should be immediately referred to an ophthalmologist.

Scleritis is inflammation of the sclera and may present with nocturnal ocular pain, redness, blurring of vision, photophobia, and epiphora. (3) Scleritis is often associated with underlying systemic disease such as rheumatoid arthritis or granulomatosis with polyangiitis. Management includes administration of oral non-steroidal anti-inflammatory drugs (NSAIDs), while severe cases may require treatment with oral corticosteroids. (3, 9) Episcleritis is associated with mild pain and occurs due to inflammation of the superficial episcleral vessels. (4) Episcleritis can be treated with supportive therapy such as lubricating drops, while recurrent cases can be managed with oral NSAIDs. (4, 9) Anterior uveitis refers to inflammation of the iris and ciliary body. (3) Its characteristic features include severe photophobia and engorgement of the anterior ciliary vessels which result in a "ciliary flush". (3)

Acute angle-closure glaucoma (AACG) is a ocular emergency referring to the closure of the angle between the cornea and the irisThis impairs drainage of the aqueous humor resulting in increased intraocular pressure. (10, 11) Patients often present with severe eye pain and redness, headache, nausea, vomiting, coloured halos, mid-dilated and poorly reactive pupils, and photophobia. (4, 10) AACG treatment is directed at relieving symptoms and decreasing intraocular pressureusing oral or topical carbonic anhydrase inhibitors, topical beta-

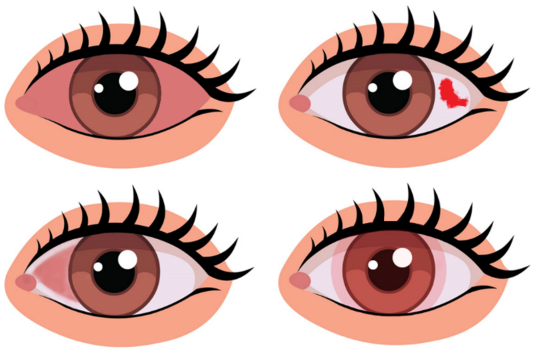

FIGURE 1 Patterns of injection in red eye disorders.
A) Diffuse injection, seen in conjunctivitis
B) Localized, well-demarcated injection, seen in subconjunctival hemorrhage
C) Localized, poorly-demarcated injection, seen in scleritis and episcleritis
D) Ciliary or limbal injection, seen in iritis, corneal conditions, or acute angle-closure glaucoma
Clipart modified from Classroom Clipart. (5)

blockers, and topical alpha-2 adrenergic agonists. (4, 10) If a pupillary block is suspected, a cholinergic agent may be used. (10) After the acute attack is resolved, a laser peripheral iridotomy is completed to allow the aqueous fluid to bypass the pupil. (10)

Eyelid-related entities, such as a stye or chalazion, may result in ocular irritation and subsequent red eye. (1) A stye is the infectious inflammation of a lash follicle. (1), while a chalazion is non-infectious. (7) Both conditions are treated with a warm compress applied multiple times a day and massages of the affected eyelid. (7).

4.2 | Acute, non-painful disease

Subconjunctival hemorrhage is the bursting of a conjunctival blood vessel, which causes blood to leak between the conjunctiva and sclera. (3) Patients present with a bright red spot in the sclera. (12) Subconjunctival hemorrhage may occur in response to a Valsalva maneuver (coughing, straining) and is more common in individuals with cardiovascular disease or bleeding disorders. (3, 11)

Conjunctivitis refers to dilatation of the small blood vessels within the conjunctiva. (3, 12) It may be due to infection, allergy, or irritants. (3) The most common form of conjunctivitis is caused by adenovirus and is contagious. (3) Viral conjunctivitis generally starts unilaterally and progressively infects the other eye. (2) Laboratory tests are warranted in resistant cases of bacterial conjunctivitis or in immunocompromised patients. (7, 12) Both viral and bacterial conjunctivitis are treated with rigorous hygiene and the application of a cool compress. (7) Bacterial conjunctivitis is additionally treated with antibiotic eyedrops. (3) Allergic conjunctivitis generally presents with bilateral tearing and causes eye itchiness. (3) It may be treated with an over-the-counter antihistamine. (3).

4.3 | Chronic, painful/irritating disease

Keratoconjunctivitis sicca, or dry eye, can be caused by multiple etiologies, including decreased tear production, increased tear evaporation, or imbalances in the mixture of water, oils, and mucus in the tear film. (3) Patients may feel a foreign body sensation and generalized ocular irritation with paradoxical tearing. Precipitating factors include anticholinergic and antihistamine medications, increased age, and medical conditions such as rheumatoid arthritis, diabetes, and Sjogren's syndrome. (3) Mild keratoconjunctivitis sicca may be treated with artificial tears, lubricant ointments, and the usage of humidifiers. (3)

Blepharitis is a chronic inflammation of the eyelid. The patient presents with itchy, inflamed, crusted eyelids with misaligned eyelashes. (13) Anterior blepharitis may occur due to staphylococcal infection or seborrheic dermatitis. (13) Posterior blepharitis, the more common presentation, may occur due to clogging of the meibomian glands or inflammatory skin conditions such as rosacea. (13) Both are treated through eyelid hygiene using eyelid wipes, a warm compress, an eyelid scrub, diluted baby shampoo, and, in select cases, an antibiotic ointment. (7, 13) Ectropion is eversion of the eyelid which renders the eye prone to irritation. (14) Entropion is inversion of the eyelid which can cause the eyelashes to strike the cornea. (14) Symptoms of ocular irritation

are generally treated using eyedrops; however, surgery is required for complete correction. (14).

As a non-specialist, it is important to recognize immediate referral is required. These include reduced visual acuity, severe ocular pain, photophobia, corneal opacification or epithelial dysfunction, pupillary abnormalities, hypopyon, and hyphema. (2, 7) Timely referral is crucial in preventing sight-threatening complications.

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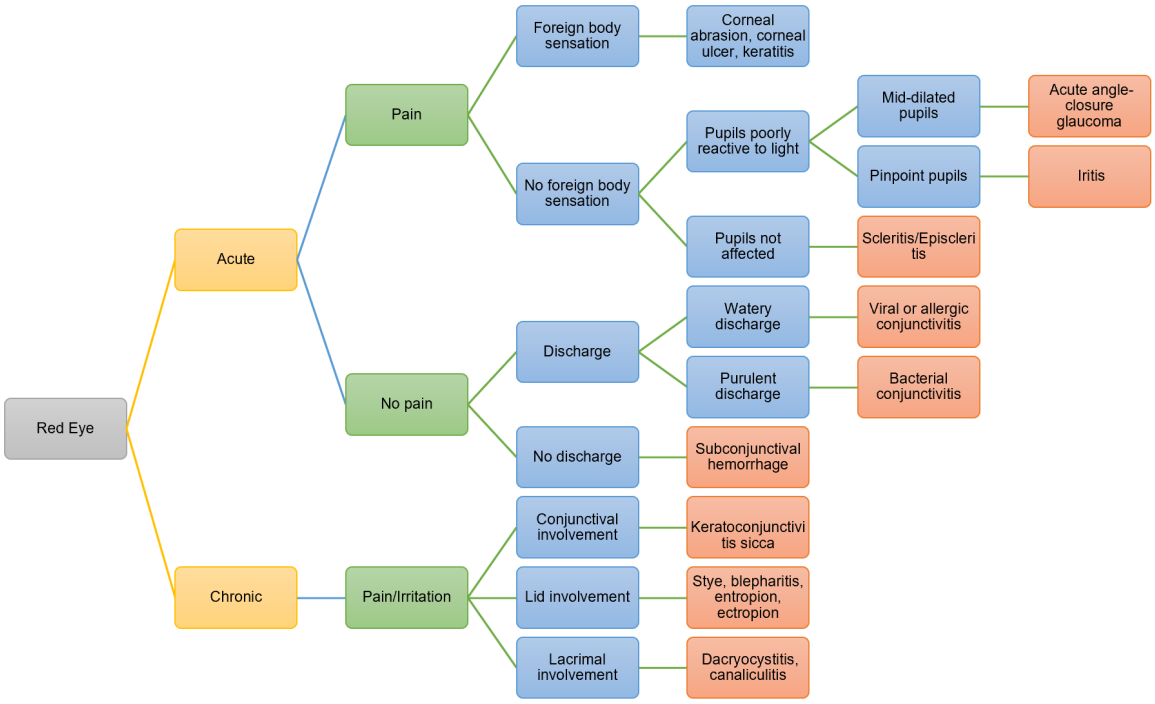
5 | TABLES & FIGURES



FLOWCHART 1 Approach to Red Eye. Algorithm for the diagnosis of red eye, based on history and physical exam findings. (3).

Disease	Severe pain	Irritation	Foreign body sensation	Epiphora	Discharge	Photophobia	Reduced acuity
Acute angle-closure glaucoma	X			X		X	X
Conjunctivitis		X			X		
Corneal abrasion	X	X	X	X		X	
Corneal ulcer	X		X	X	X	X	X
Episcleritis		X		X			
Iritis	X					X	X
Keratitis	X			X	X	X	X
Keratoconjunctivitis sicca		X	X	X			
Scleritis	X			X		X	X
Subconjunctival hemorrhage							

*Symptoms may vary on a case-by-case basis and with varying severity.

X = Presence of the stated characteristic (4, 11, 12)

TABLE 1 Presence of ocular signs in red eye disorders

APPROACH TO
McGill Journal of Medicine

Acute Vision Loss

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ABSTRACT

Acute vision loss is the temporary reduction of visual acuity or visual field, lasting from a few minutes to a few days. The etiologies of acute vision loss may be divided into anterior segment disease, retinal disease, optic nerve disease, or neurovascular disease. It is recommended to refer all presentations of acute vision loss for ophthalmologic consultation; however, the primary care physician plays an important role in determining the urgency of referral. The following article describes an approach to narrowing the differential diagnosis of acute vision loss, using relevant ocular history and physical exam findings. The features of common eye disorders relating to acute vision loss and their treatments are also discussed.

KEYWORDS
Vision loss, Amaurosis fugax, Retinal vascular occlusion

1 | QUESTION

A 69-year old man presents to your office with a 5-day history of sudden, transient episodes of left-eye vision loss. He describes the vision loss as a curtain being pulled over his eye, with each episode lasting approximately 20 minutes. The patient denies ocular pain, discharge, change in color vision, or photopsia (flashes of light). He also denies involvement of the right eye.

His past medical history is significant for hypertension and hypercholesterolemia, which is poorly controlled using perindopril and atorvastatin. He has no history of ocular trauma or ocular surgery. Upon examination, both eyelids and surrounding structures are unremarkable. There is an absence of conjunctival hyperemia or corneal opacity bilaterally. On examination, best-corrected visual acuity is 20/20 in the right eye (OD) and hand motion in the left eye (OS). Confrontational visual field testing reveals a full visual field OD, but an inability to detect movement in any quadrant OS. Extraocular motility is normal bilaterally in all directions. Penlight examination reveals absent pupillary constriction with direct light OS, but the consensual response is normal. The swinging flashlight test reveals a left rela-

tive afferent pupillary defect. Funduscopic exam reveals a diffusely opaque retina, apart from a small red spot at the location of the macula. There is generalized vascular narrowing, and pallor of the optic disc without swelling is noted.

Which condition is most consistent with the clinical presentation? A. Retinal detachment

B. Retrobulbar optic neuritis

C. Ischemic optic neuropathy

D. Central retinal artery occlusion

E. Central retinal vein occlusion

2 | ANSWER

D. The sudden episodes of painless vision loss, history of hypertension and hyperlipidemia, and the funduscopic findings suggest central retinal artery occlusion (CRAO). The absence of photopsia makes the diagnosis of retinal detachment less likely. Optic neuritis is an unlikely cause as ocular pain and change in color vision were absent. Ischemic optic neuropathy typically presents with optic disc pallor, swelling, and splinter hemorrhages; the latter two findings were not present in this case. Central retinal vein occlusion also presents with optic disc swelling, venous engorgement, cotton-wool spots (due to the accumulation of axoplasmic material), and diffuse hemorrhages throughout the retina. Funduscopic findings characteristic of CRAO include the narrowing of arterial blood vessels and segmental blood flow, termed "box-carring". There is subsequent pallor of the optic disc and retina, with the exception of a "cherry red spot" in the macular region which reveals the underlying choroidal circulation.

3 | INITIAL APPROACH

Acute vision loss is the temporary reduction of visual acuity or visual field, developing over a few minutes to a few days. (1) This symptom can be worrisome for many patients, and evaluation by an ophthalmologist is warranted to prevent permanent vision loss. (2) The role of the primary care physician is to determine whether the acute vision loss requires emergent, urgent, or non-urgent care.

Obtaining a comprehensive past medical history can help delineate a potential etiology. An initial characteristic to elicit is whether there is unilateral or bilateral eye involvement. Unilateral involvement suggests an ocular pathology whereas bilateral eye involvement suggests a neurologic etiology. Next, the physician should identify whether the vision loss is transient or persistent. Transient vision loss lasts less than 24 hours. The patient may describe the vision loss as blurry, indicative of a media-related ocular issue; dimming of vision, indicative of a vascular-related issue; or a reduction in visual field, suggesting an optic disc or neurologic issue. Associated flashes of light are suggestive of retinal detachment. Ocular pain and photophobia are usually present in corneal pathologies. Pain specifically on ocular movement is suggestive of, retrobulbar optic neuritis. Severe pain accompanied by tearing, nausea, and vomiting, is usually indicative of acute angle-closure glaucoma (AACG).

Visual acuity and visual fields should be assessed to confirm extent of vision loss. Additionally, pupillary reaction can be an important indicator of neurologic function. The swinging-flashlight test evaluates direct and consensual pupillary reflexes and may reveal a relative afferent pupillary defect (RAPD), indicative of monocular optic nerve disease. (2) Fundus examination of the retina may reveal retinal hemorrhaging, retinal whitening, cotton-wool spots (indicative of vascular disease), arteriolar narrowing, tortuosity, or venous engorgement. (3, 4, p. 56) The fundus exam may also reveal optic disc swelling, pallor, or an increase in the cup-to-disc ratio. The remainder of the physical exam may be tailored based on suspicion of cardiovascular, neurologic, or other disease.

4 | BEYOND THE INITIAL APPROACH

Diseases that present with acute vision loss can be divided into monocular and binocular involvement. Of

monocular diseases, the presence of ocular pain is generally indicative of an optical media or fundus abnormality. The anterior segment plays an important role in light refraction; therefore, pathology in this region may lead to blurry vision. Keratitis refers to corneal inflammation, which may occur due to infection, injury, or allergy. (1) On examination, clouding of the cornea and severe irritation are characteristic. (1) Corneal staining may be used to evaluate epithelial defects. Uveitis refers to inflammation of the iris, ciliary body, and/or choroid. (7) Uveitis may present with ocular pain and redness, and photophobia if the iris is involved. (7) Both anterior and posterior uveitis may occur due to infection; however, anterior uveitis is also associated with systemic disease. (7) The mainstay of treatment for anterior segment inflammation is topical steroids, mydriatic eyedrops, and topical or oral antimicrobial agents where appropriate. (7)

AACG is a painful eye disease that occurs as aqueous fluid is insufficiently drained, leading to increased intraocular pressure and subsequent optic nerve damage. (14) Symptoms include vision loss, eye pain and headache, nausea/vomiting, and seeing halos around lights. (5, 14, 15) Signs include a fixed, mid-dilated pupil, a closed anterior chamber angle upon slit-lamp examination, and optic disc pallor and cupping (cup-to-disc ratio of 0.6 or greater). (5) Tonometry demonstrates an increased intraocular pressure ranging from 40 to 80mmHg. (1) Treatment is focused on the reduction of intraocular pressure, aqueous fluid production, and inflammatory damage. (15) Laser peripheral iridotomy may relieve anterior chamber blockage after the acute attack is resolved. (15)

Painless monocular disease may also be divided into pathologies of the media or fundus. Fundus involvement may be further subdivided into retinal or optic disc abnormalities. Visual field defects generally suggest a retinal or neurologic pathology. Retinal vascular occlusion should be suspected in a patient with cardiovascular disease. (5) Funduscopic examination can pinpoint the subtype and extent of vascular occlusion. Further evaluation with optical coherence tomography and fluorescein angiography may assist with clinical decision making. Central retinal artery occlusion is an ocular emergency in which fleeting vision loss occurs, termed amaurosis fugax. (8) RAPD may be seen on examination. Initially, fundoscopy shows arterial narrowing and segmental blood flow (boxcarring). (3) After several hours, the fundus appears opaque apart from a “cherry-red” spot in the macular region. (8) The most common cause of CRAO is carotid atherosclerosis, seen on carotid artery imaging. (9) Immediate treatment is warranted and involves ocular massage, paracentesis and IV acetazolamide to reduce intraocular pressure, carbogen inhalation to induce vasodilation, and laser embolectomy for clot lysis. (1) Central retinal vein occlusion is an urgent event presenting similarly to CRAO, in which venous engorgement occurs. However, funduscopic examination shows optic disc swelling, diffuse retinal hemorrhage, and cotton-wool spots which are representative of the axoplasmic material. (3) Branch artery and branch retinal vein occlusion may produce partial vision loss, but if central vision is not affected, they may also go unnoticed. (8) Retinal detachment is a non-vascular retinal pathology that may result in acute vision loss, due to oxygen and nutrient-deprived retinal tissue. (1) Symptoms include floaters, photopsia, and visual field loss. (1) Funduscopic examination may reveal dulling of the red reflex and an elevated portion of the retina. (1) Retinal imaging with ocular sonography and indirect ophthalmoscopy can be used to further evaluate the peripheral retina. (2) Ophthalmologic treatment should be sought immediately and includes pneumatic retinopexy, scleral buckling, and vitrectomy. (10) Optic neuritis refers to optic nerve inflammation, and is most commonly caused by multiple sclerosis, but may also occur due to infection or autoimmune disease. (13) Symptoms include loss of red-green color discrimination, pain with eye movement, and temporary vision loss. (1) A RAPD is typically present. (1) Funduscopic examination may reveal a swollen optic disc; however, retrobulbar optic neuritis often results in a normal fundus exam. (13) Vision loss often recovers completely without treatment, but steroid treatment may be used in refractory cases. (13)

Causes of binocular vision loss may be subdivided into transient and persistent vision loss. Similar to

monocular diseases, the transient and persistent binocular diseases may be further subcategorized based on fundus involvement. Papilledema refers to the non-painful swelling of bilateral optic nerves seen on fundoscopy, occurring due to increased intracranial pressure. (9) Symptoms include mild persistent blurred vision or visual disturbances that alter with change in position, headache, and nausea/vomiting. (9) Papilledema is differentiated from optic neuritis with normal pupillary reflexes and bilateral presentation. (1) Neuroimaging may pinpoint the cause of increased intracranial pressure, such as a mass or hemorrhage. (9) If no fundus abnormality is present, the possibility of migraine, seizure, or transient ischemic attack (TIA) should be considered. Migraines may present with a temporary loss of vision lasting several minutes, with photopsias/scintillations progressively worsening as the headache worsens. (6) Conversely, the visual obscurations seen in seizures are typically maximal at onset. (9) There may be multiple episodes of vision loss relating to the recurrence of migraines or seizures. In the setting of a stroke, the visual field is affected if the occipital lobe is involved. (9) In a transient ischemic attack, the ocular symptoms disappear within 24 hours. In a stroke, however, vision loss may be permanent. (6)

If binocular vision loss persists for greater than 24 hours, ischemic optic neuropathy should be considered. Giant cell arteritis is a form of vasculitis affecting elderly individuals, commonly involving branches of the carotid artery. (9) Symptoms include a temporal headache and jaw claudication. (11) A potentially devastating complication is arteritic-anterior ischemic optic neuropathy (AAION), where blood flow to the optic nerve is interrupted and visual field loss occurs. (11) A temporal artery biopsy confirms the diagnosis. (10) Corticosteroid therapy is provided immediately to prevent permanent vision loss. (5) Non-arteritic anterior ischemic optic neuropathy (NAION) may also result in the blurring or loss of vision. (11) Systemic risk factors include hypertension, diabetes mellitus, and hyperlipidemia. (12) There is no specific treatment for NAION. (12)

In the absence of fundus abnormality with persistent vision loss, a lesion further than the optic disc should be considered. As the optic nerve travels towards the brain, a portion of the nerve fibres responsible for temporal vision decussate, forming the optic chiasm. A lesion in this area, caused by a disease process such as a pituitary tumor, may result in bitemporal hemianopia. (6, 9) Post-chiasmic (optic tract) lesions present with vision loss in one side of the visual field, termed homonymous hemianopia. (2) This may occur due to a stroke, infection, or surgery. (6) Of the aforementioned diseases, the more common presentations of acute vision loss include cornea-related pathologies, retinal vascular occlusion, and trauma. (2, 7) Although all etiologies of acute vision loss require ophthalmological referral, the following conditions warrant emergent care: acute central retinal artery occlusion, ischemic optic neuropathy, AACG, and suspected cerebral vascular accidents. (6)

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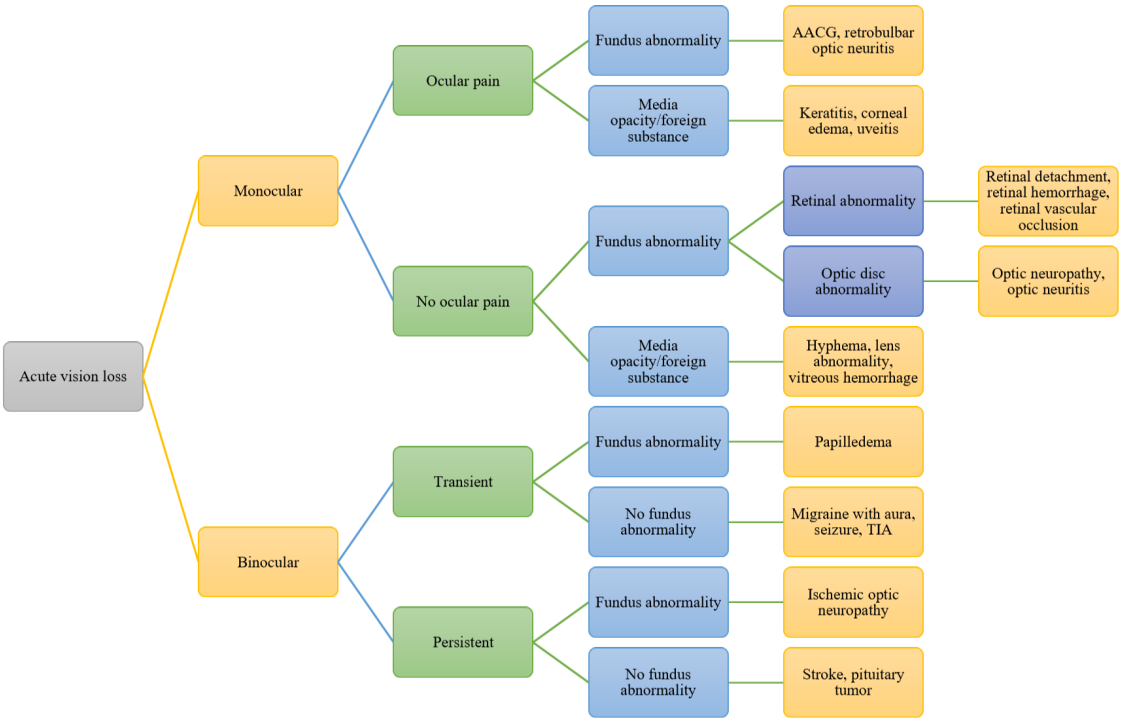
5 | TABLES & FIGURES



FLOWCHART 1 Approach to Acute Vision Loss. Algorithm for the diagnosis of acute vision loss, based on history and physical exam findings.
AACG: acute angle-closure glaucoma, TIA: transient ischemic attack
Adapted from (6) and (7)

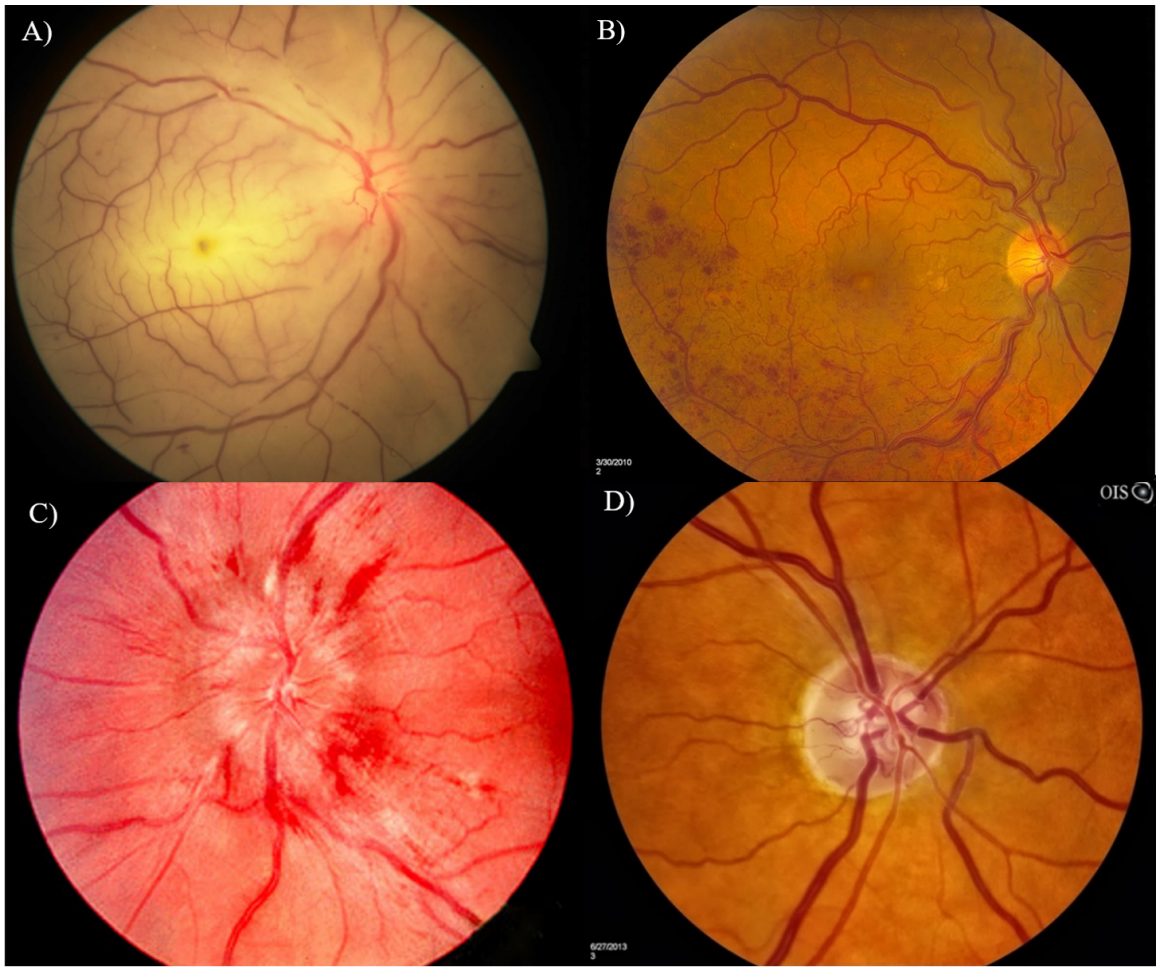


FIGURE 1 Funduscopic images of selected eye disorders
A) Central retinal artery occlusion, image obtained from (17)
B) Branch retinal vein occlusion, image obtained from (18)
C) Papilledema, image obtained from (19)
D) Glaucoma, image obtained from (20)

APPROACH TO
McGill Journal of Medicine

Febrile Seizures

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ABSTRACT

This approach article provides pre-clinical students and students preparing for rotations in pediatrics with an approach to the evaluation, diagnosis and management of patients with febrile seizures. Febrile seizures are the most common childhood neurological disorder. They are most commonly defined as a seizure occurring in a child 6-months to 6-years of age with a fever in the absence of an intracranial infection or other identifiable cause. The vulnerability of a child's central nervous system to fever is thought to be responsible for febrile seizures. They can be categorized as either simple or complex, depending on seizure duration, characteristics and recurrence. This categorization directs the necessary diagnostic investigations. While the majority of febrile seizures are benign, students must learn to differentiate benign febrile seizures from other dangerous causes of seizure, such as a central nervous system infection, and identify the life-threatening condition of status epilepticus.

KEYWORDS
Pediatrics, Seizure, Neurology, Infectious Disease, Febrile Illness

1 | QUESTION

You are a third-year medical clerk working in the pediatric emergency room. Layla, an 18-month-old, presents with a history of a 3-minute seizure. After speaking to her parents, you find out that preceding the seizure, Layla had been experiencing a 12-hour history of gastrointestinal symptoms. Layla was born at 40 weeks via spontaneous vaginal delivery. Her mother's maternal history was unremarkable and screening for group B strep at 37-weeks was negative. At birth, Layla weighed 3.9 kg (8.6 lb.) with APGAR scores of 7 and 9 at 1 and 5 minutes respectively. Layla has reached her developmental milestones at appropriate times with first words spoken at 8 months, crawling beginning at 9 months and walking at 13 months. Layla was breast-fed exclusively for 6 months before transitioning to formula feeds. She was introduced to solid foods at 9-months of age. Her growth charts indicate that she has been following the 85th percentile for weight and length. Layla has no pre-

vious medical history; no known allergies and all her immunizations are up to date. Layla currently lives with her mother and father who both work full time as secondary school teachers. Layla has been attending daycare since she was 6-months of age and her parents report that she enjoys her time there. Layla's parents deny recent travel or exposure to sick contacts.

You observe the following findings on physical exam:

General Appearance: An irritable but alert infant with no signs of dehydration and normal capillary refill.
Vital Signs: HR: 110, RR: 26, BP: 90/50, Temp: 39.5 °C, O2 Sat: 98% on room air
Growth Parameters: Weight: 13.4kg (85th percentile), Height/Length: 86cm (85th percentile), Head Circumference: 47cm (50th percentile)
Head: Fontanelle are soft and non-protruding.
ENT: Normal temporomandibular joints bilaterally, pharynx/palate normal
Neck: No cervical adenopathy, neck is supple, negative Kernig and Brudzinski signs
Respiratory: Good air entry bilaterally, no adventitious lung sounds
Cardiovascular: Normal S1, S2, no S3 or S4, no murmurs on auscultation, radial, brachial and femoral pulses normal, no signs of cyanosis, normal capillary refill
Abdomen: No scars, abdomen soft and non-distended, no organomegaly, no tenderness or guarding, no palpable mass
Neurological: Pupils equal and reactive, extraocular movements intact, no facial asymmetry, normal tone and reflexes, moving all limbs symmetrically, normal gait, normal cerebellar exam

Which one of the following investigations are indicated in the acute management of Layla?
a) Lumbar puncture
b) EEG
c) Brain MRI
d) CBC, serum glucose, urea nitrogen and electrolytes
e) No further investigations are needed, provide reassurance to parents

2 | ANSWER

E. From the history that has been gathered from Layla's parents, it appears that she had a simple febrile seizure as a result of a recent gastrointestinal illness. As Layla's vitals, neurological exam and general physical exam are normal apart from fever, no specific diagnostic workup is required. As Layla's neurological exam was normal, intracranial infection or underlying structural mass is unlikely. As a result, lumbar puncture is not warranted. As she is not exhibiting any signs of dehydration and is generally appearing well, CBC, serum glucose, urea nitrogen and electrolytes should not be routinely ordered. Furthermore, MRI and EEG are not routinely recommended in the evaluation of children with simple febrile seizures. Since Layla appears wells, her management includes discharge and close follow-up with her primary care physician as needed.

3 | INITIAL APPROACH

Febrile seizures are the most common neurological condition of childhood. Approximately 3-4% of children in North America will experience an episode prior to the age of 5. (1) Febrile seizures are defined as seizures occurring in childhood after one month of age, associated with febrile illness without any evidence of intracranial infection or other identifiable cause. Febrile seizures most commonly occur between 6-months to 6-years of age. (1)

3.1 | Clinical Presentation

A thorough medical history and examination is crucial in the evaluation of a child with a suspected febrile seizure. (2) Key elements include description of the onset, duration and characteristics of the episode. Examples include loss of consciousness, foaming at the mouth, tongue biting, difficulty breathing, cyanosis, and rhythmic repetitive movements of both arms and legs. (2,3) These details will help distinguish true seizures from seizure mimickers. Elements that are suggestive of

seizure activity include unresponsiveness, tongue biting, lip smacking, rolling back of the eyeballs and flickering eyelids. (3) Mimickers of seizure include breath-holding spells, rigors, pseudo-seizures and syncope. Breath holding spells are often triggered by emotional distress or pain and can be distinguished from seizure activity. (4) Rigors are not typically associated with a loss of consciousness. (2) Although syncope may be associated with muscular twitching events, there is usually a prodrome of pallor and perspiration, which distinguishes it from a seizure. (4)

3.2 | Past Medical History, Physical Exam and Red Flags

It is important that the child's caregivers provide a history of recent respiratory or gastro-intestinal illness. It is also important to ask caregivers about recent vaccinations or medication use such as antibiotics. The majority of children who experience a febrile seizure experience it on their first day of illness. However, a febrile seizure may also be the first indication of infection. (3) A complete general physical exam should be done to identify the underlying cause of fever. Furthermore, it is vital to ascertain a history of red flags from caregivers as these will alter the management of the child. Red flags in a child presenting with febrile seizure include a history of developmental delay, lethargy or head injury. A complete neurological examination of the child is also necessary to identify red flags associated with an acute neurological problem such as central nervous system infection. (5) Red flags suggestive of meningitis include irritability, altered level of consciousness, positive Brudzinski and Kernig's signs, neck stiffness, photophobia, petechial rash, hypotension and bulging fontanelles. (3)

3.3 | Classifications

Febrile seizures can be categorized as either simple or complex depending on seizure duration, characteristics and recurrence. The type of seizure a child experienced will dictate how the condition of the child is managed. Simple febrile seizures account for approximately 80% of all febrile seizures. (1) They are typically generalized and associated with tonic-clonic jerking of bilateral limbs that last between several seconds to 15 minutes. (2) On presentation, a child with a simple febrile seizure is typically alert as post-ictal symptoms generally resolve within 10-15 minutes. Simple febrile seizures should not reoccur within a 24-hour period. In contrast, complex febrile seizures are often focal, last longer than 15-minutes, may reoccur more than once in a 24-hour period and are associated with a prolonged period of post-ictal drowsiness or hemi-paresis known as Todd's Palsy. (2) Status epilepticus is the most serious form of febrile seizure and is defined as 5 minutes or more of continuous or intermittent seizure activity without the regaining of consciousness between seizures. Prolonged seizure activity, typically defined as longer than 30 minutes, can cause neuronal injury and death. (6)

3.4 | Investigations

Diagnostic investigations for a child experiencing a febrile seizure is dependent on whether the seizure was simple, complex or status epilepticus. In cases of simple febrile seizure with normal neurological exam findings, no further investigations are necessary. (5) Evaluations should instead focus on identifying the underlying cause of fever. (2) A complete blood cell count, urea nitrogen, serum glucose and electrolytes should be considered in children with a history of vomiting or diarrhea or if signs of dehydration are present. (2) While a lumbar puncture is not necessary for well-appearing children after a simple febrile seizure, it is recommended for children under the age of 12-months as physical exam signs of meningitis are extremely subtle in this age group. (5) Lumbar puncture with cell counts, gram stain and culture, protein and glucose should also be performed in a child with concerning neurological examination findings as CNS infection must be ruled out. (5) Furthermore, lumbar puncture should be considered in un-immunized children or children with recent antibiotic use as this increases suspicion of an underlying bacterial infection. (2) It is important to note, however, that in a child with a neurolog-

ical exam suggestive of a space-occupying lesion, neuroimaging must be immediately performed and lumbar puncture is contraindicated due to suspected increased intracranial pressure. (7) Electroencephalography (EEG) is of limited value and therefore not recommended in children with a first presentation simple febrile seizure. (5)

Children presenting with complex febrile seizures warrant further evaluation to identify any potential structural or metabolic causes, particularly if this is their first episode. EEG is indicated in the evaluation of a complex febrile seizure as there is a risk of an underlying epileptic syndrome. (1) Neuroimaging with MRI or CT should be considered in children with neurological abnormalities on physical exam, history of head injury, signs of increased intracranial pressure or suspected intracranial abnormality. (3)

3.5 | Management

Children presenting in status epilepticus require immediate resuscitative efforts. (8) It is critical that the child's airway is maintained, supplemental oxygen is provided, and cardiac monitoring is established (CABs). (6) Administration of benzodiazepines to terminate seizure activity is a priority five minutes after seizure onset. (6) As intravenous access in an actively seizing child may be difficult, benzodiazepines may be administered rectally, intranasally, buccally or intramuscularly. It is important to recognize that some patients require further doses of benzodiazepines. Status epilepticus is a life-threatening emergency situation which rarely stops spontaneously and often requires several doses of anticonvulsants to control. (2) Children with status epilepticus require an extended period of observation as seizure activity may recur. Long-term management of patients should include EEG and neuroimaging.

4 | BEYOND THE INITIAL APPROACH

4.1 | Risks of Recurrence and Epilepsy

The etiology of febrile seizures is not fully understood and likely thought to be multifactorial. Theories suggest that febrile seizures may be due to the vulnerability of the developing child's central nervous system to the effects of fever in combination with genetic factors. (3) Identified risk factors for febrile seizure include age, prematurity, developmental delay, viral infection, daycare attendance, prenatal exposure to nicotine and/or alcohol and a family history of seizures. (3,17) Furthermore, no single causative gene has been identified, although a familial association has been demonstrated as the risk of febrile seizure is 25% if one sibling is affected and 33% if both parents or more than one sibling is affected. (11) Recurrence of febrile seizures in the future is also relatively common with approximately 33% of children having a second febrile seizure during early childhood. (12) Seventy percent of reoccurrences occur within the first year following a febrile seizure and 90% within 2 years. (12) Risk factors for recurrent febrile seizures include first seizure occurring prior to 18 months of age, family history of febrile seizure, seizure associated with a fever below 39 degrees. (12) Furthermore, children experiencing a simple febrile seizure have a 1% risk of developing epilepsy compared to the 0.5% incidence in the general population. (15) Children with a complex febrile seizure have a 4-6% risk of future epilepsy. (3,16) Risk factors for the development of epilepsy include previous neurodevelopmental impairment, family history of epilepsy and complex febrile seizures.

4.2 | Caregiver Counselling

A febrile seizure can be an extremely frightening experience for caregivers, particularly if the seizure is prolonged. Parents may be terrified that their child will experience long-term brain damage as a result of their seizure or have epileptic syndrome. It is important to reassure caregivers that the majority of febrile seizures

are harmless and are not associated with complications of long-term brain damage or intellectual disability. (13) Caregivers should be informed that their child may experience another febrile seizure in the future and be counselled on steps they can take to ensure their child's safety. This includes placing the child on their side to prevent aspiration, removing or loosening tight-fighting clothing, ensuring that the child is on a soft surface with all nearby objects removed and tracking the length of the seizure. (12) Parents should also be instructed to call emergency medical services should a recurrent seizure last longer than five minutes, if the child looks cyanotic or appears to have difficulty breathing, if the seizure is focal or if the child experiences a second seizure within 24 hours. While febrile seizures occur as a result of a fever, the rapidity of fever onset has not been found to be associated with an increased risk of seizure.

As such, antipyretics should not be given as they have not been shown to reduce the risk of febrile seizure prophylactically. (9,10) While the majority of febrile seizures are harmless, children that experience recurrent febrile seizures are at an increased risk of delayed language and memory development. (14) Caregivers of children with recurrent febrile seizures should therefore be informed so that adequate developmental support can be put in place.

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5 | TABLES & FIGURES

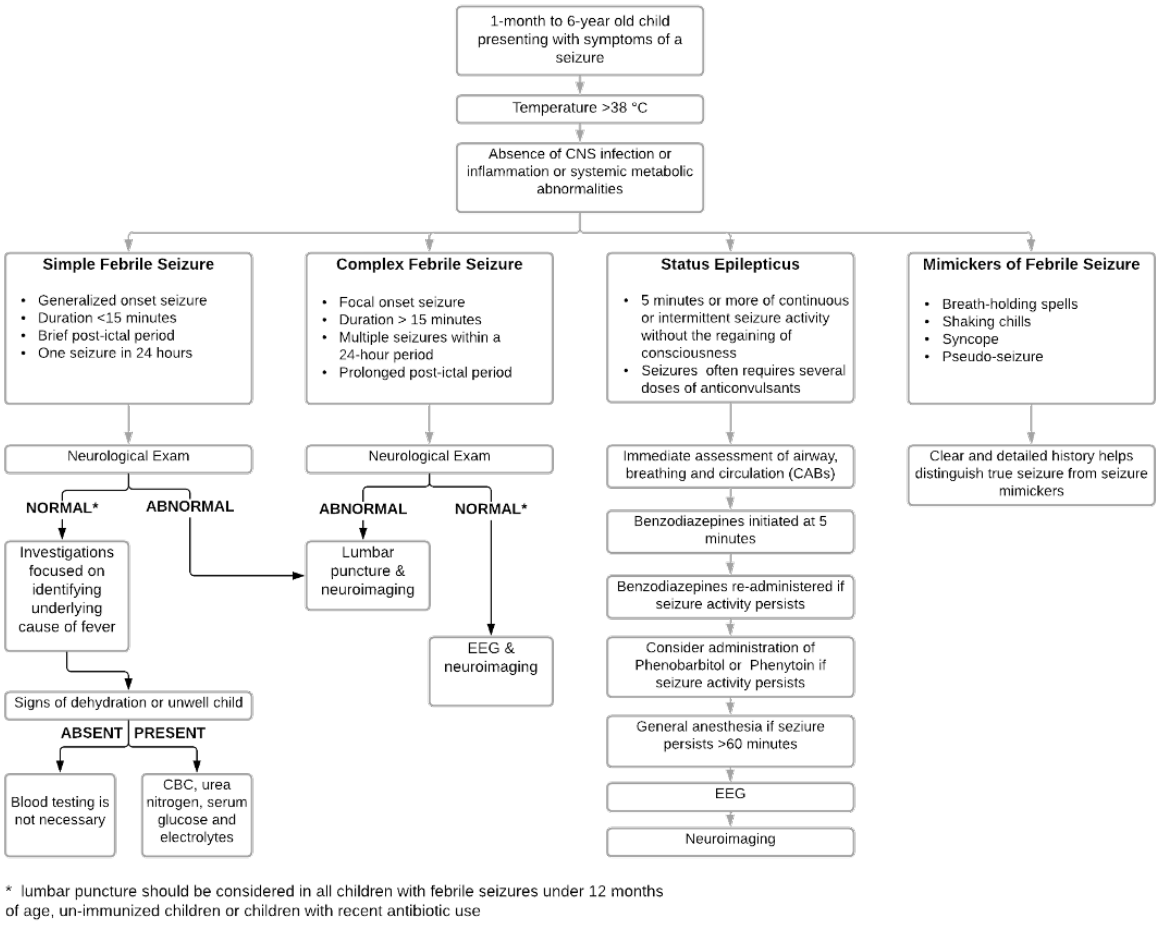

FIGURE 1 Approach to Febrile Seizures

	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Blood Pressure (mmHg)
Neonate	90-205	30-53	67-84/ 35-53
1-12 Months	90-190	30-53	72-104/ 37-56
1-2 Years	80-140	22-37	86-106/ 89-112
3-5 Years	65-120	20-28	89-112/ 46-72
6-11 Years	58-118	18-25	97-120/57-80
12-15 Years	50-100	12-20	110-131/ 64-83

Adapted from Dr. Chris Novak & Dr. Peter Gill for www.pedscases.com

TABLE 1 Pediatric Vital Signs Normal Ranges

APPROACH TO
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Chest pain

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ABSTRACT

The diagnosis of chest pain is not always due to a cardiac cause such as a myocardial infarction. In fact, non-cardiac causes of chest pain may present with similar signs and symptoms. This article delves into the differential diagnosis of chest pain using an anatomical approach and describes how a thorough history, physical examination as well as specific tests are required to confirm each diagnosis.

KEYWORDS
Acute chest pain, Anatomical approach, Diagnosis

1 | QUESTION

An overweight 55-year-old man presents to the emergency department with sudden, sharp, and severe interscapular chest pain. The pain began about 30 minutes ago and the patient also reports weakness, diaphoresis, and dyspnea. The patient has Marfan syndrome and has had hypertension for the past 10 years, for which he is taking telmisartan. He does not smoke. On physical exam, there is an increased respiration rate and pulse of 88 beats per minute (bpm) that was weaker in his right arm. Blood pressure of both arms were the following: 165/80 (left) and 120/70 (right). Electrocardiogram revealed ST-segment elevation in leads II, III, and aVF. What is the next best step?

A. Exercise stress test
B. Thrombolytic therapy
C. CT angiogram
D. Transthoracic echocardiogram
E. Percutaneous coronary intervention

2 | ANSWER

C. The patient presents with an aortic dissection that needs to be urgently diagnosed before further steps are

taken. The sudden, sharp, ripping/tearing pain radiating to the back, accompanied with diaphoresis, pulse and blood pressure asymmetry, and weakness are typical signs noted in aortic dissection. Additionally, Marfan syndrome is a common risk factor, as is hypertension (the most common risk factor). In fact, an acute rise in blood pressure may cause an aortic dissection, specifically in the case of cocaine drug use. Other physical exam findings include aortic regurgitation and focal neurological deficits. If there is compression on other structures such as the superior cervical ganglion, superior vena cava, or esophagus, patients may also present with Horner's syndrome, superior vena cava syndrome, and dysphagia, respectively. Furthermore, extension of the dissection flap may cause obstruction of the branching vessels off the aorta, increasing the risk of complications and death.

In this case, the next best step is to diagnose an aortic dissection then follow up with management. A CT angiogram is the gold standard for the diagnosis of aortic dissection and is useful in the pre-operative planning to potentially rule out distal arterial involvement such as renal artery dissections. Following diagnosis, the blood pressure should be reduced with beta-blockers or nitroprusside to reduce shear forces on the aortic wall/intima. Depending on the type of aortic dissection (Stanford classification), management differs. Type A (involving the ascending aorta and the arch) is treated surgically whereas type B (involving the descending aorta) is generally managed medically or endovascularly.

Aortic dissections can develop with a concomitant myocardial infarct, specifically occlusion of the right coronary artery (RCA) resulting in an ST-segment elevation pattern in the inferior leads. (1) A misdiagnosis can result in fatality as treatment with a thrombolytic or anticoagulant could result in severe bleeding.

3 | INITIAL APPROACH

Chest pain can be divided into cardiac vs non-cardiac origin. Non-cardiac chest pain can be further subdivided using an anatomical approach: gastrointestinal (GI), pulmonary, musculoskeletal (MSK), and psychogenic/neurogenic pain (Figure 1). (2–5) When evaluating chest pain, it is pertinent to first stabilize the patient and rule out any life-threatening conditions that require immediate treatment such as an acute coronary syndrome (ACS), aortic dissection, pericarditis/cardiac tamponade, pulmonary embolism, pneumothorax, and esophageal rupture (Flowchart 1).

3.1 | History

For an adequate medical history, the following information should be gathered: onset (abrupt or gradual), palliation/provocation, quality (sharp, dull, squeezing, pleuritic, tightness, ripping), radiation, intensity, positioning, and timing of the pain (recurrent/intermittent, new). With this information, one can begin to use the anatomical approach to identify the cause of the chest pain.

Cardiac chest pain is a visceral type of pain; hence it is poorly localized. Patients complain of squeezing, aching, dullness, pressure, tightness, ripping, and burning pain that tends to radiate to the arms or jaw. (2–5) An ACS can be categorized as either an ST-segment elevation myocardial infarct (STEMI), non-ST-segment elevation myocardial infarct (NSTEMI), or unstable angina. Importantly, the retrosternal chest pain from ACS typically lasts longer than 30 minutes, is exacerbated by activity, and is relieved by rest/nitroglycerin. ACS symptoms described by women, elderly, and diabetic patients may differ slightly from those listed above as there can be atypical symptoms such as diaphoresis, dyspnea, epigastric pain, back pain, nausea and vomiting, unusual fatigue, and indigestion. (6) For chest pain that a physician deems appropriate for ACS workup, the HEART score can be used to predict the risk of major cardiac events over 6 weeks in order to facilitate diagnosis and therapeutic choices for a patient displaying cardiac chest pain. Moreover, the T-MACS decision aid is helpful in ruling out an ACS using more regimented descriptors which can ultimately help medical learners to differentiate between high, medium, and low suspicion of ACS. In the event of an unstable angina or NSTEMI, the TIMI/GRACE score may be used to estimate patient's

mortality and can correlate with the risk of adverse outcomes as well as to guide early invasive vs medical management.

Another example of cardiac pain is an aortic dissection, which presents with a ripping, intense pain that radiates to the back. An ADD-RS score and D-Dimer are useful in ruling out an aortic dissection in low to moderate-risk patients. Pericarditis is unique in that it presents with substernal pain with concomitant pleuritic pain. Moreover, the pain is usually positional (relieved when leaning forward). In pericarditis, the substernal pain often radiates to the shoulder and can sometimes be mistaken for ACS.

GI pain is visceral and tends to be related to food intake and recumbency, and can often be relieved by antacids. However, certain diagnoses are difficult to differentiate from cardiac such as an esophageal spasm or rupture. (2,5,7,8) Nonetheless, it is better to rule out an ACS by performing diagnostic investigations than to misdiagnose. Interestingly, studies have shown that patients with gastroesophageal reflux disease (GERD) are at a higher risk of developing an acute myocardial infarct (MI); thus, GERD diagnoses do not necessarily rule out an ACS but in fact may increase the likelihood of an ACS event. (9,10) Upper GI pathologies such as cholecystitis and pancreatitis may also exhibit some pulmonary-type symptoms as diaphragmatic irritation may occur. Esophageal rupture is a life-threatening cause of chest pain that is most commonly caused by increased intra-esophageal pressure (such as forceful vomiting) leading to a barogenic esophageal rupture. The chest pain in esophageal rupture is typically associated with vomiting and subcutaneous emphysema, termed Mackler triad. (11)

Pulmonary pain is described as pleuritic, meaning that the pain is enhanced or sharpened on inspiration or following a cough. A pneumothorax has an acute onset of pleuritic pain with dyspnea. (2,8) Pulmonary embolism (PE) typically presents with dyspnea, chest pain, cough, and fever and if suspected, the risk and pre-test probability can be estimated using Well's criteria. The PERC rule can be additionally used to rule out PE in patients who are deemed low risk with a pre-test probability <15% to ultimately avoid any further unnecessary testing. Depending on the scores, further testing may be required such as a D-dimer or CT angiogram to rule out a PE.

MSK pain is a somatic pain rather than visceral and tends to be darting, sharp, very well localized, positional, and worsens with movement; the pain can be reproduced upon palpation, specific movements, and positions. Some examples include rheumatic disease, costochondritis, fibromyalgia, and fractures secondary to trauma. (8)

Psychogenic pain such as panic attack is much harder to diagnose as the symptoms may overlap with the other subtypes. However, a good psychosocial history and GAD-7 screening is helpful in the primary care setting. (8,12) Neurogenic pain is typically described as burning, tingling, electrical shock-like, stabbing pain that tends to follow dermatomes.

A history of past medical illness should be acquired, especially history of hypertension, diabetes, dyslipidemia, lung disease, and genetic disorders. Social history (specifically smoking, alcohol, and other illicit drugs including cocaine) and other associated symptoms such as fever, nausea, vomiting, syncope, dyspnea, and palpitations could additionally help narrow down the cause of the chest pain. A family history of cardiovascular disease, cardiomyopathy, and sudden or unexplained death are also pertinent in identifying potential genetic risk factors for concerning cardiac causes.

3.2 | Physical Exam

Next, a systems approach for physical examination is employed, starting with vital signs. For instance, unequal pulse and pressure between both limbs suggest an aortic dissection and hypotension may indicate a vascular etiology, a pneumothorax, anxiety, or PE.

A targeted cardiac exam should identify heart sounds and murmurs: a fourth heart sound can indicate ischemia (due to impaired relaxation of the ventricle leading to acute diastolic dysfunction), a pericardial rub can indicate pericarditis, and a murmur is a typical finding of valvular disease – for instance, aortic regurgitation is

particularly concerning for aortic dissection. Low blood pressure, muffled heart sounds, and jugular vein distension (also termed Beck's triad) are indicative of cardiac tamponade and warrant immediate intervention. Volume status and leg edema should also be assessed to identify any cardiac etiology of chest pain such as volume overload indicating heart failure. Of note, jugular venous distension has a high negative predictive value for heart failure. Additionally, POCUS (Point-of-care ultrasound) is useful in the context of pericardial effusion.

The pulmonary exam should include auscultation of all lung lobes, listening for wheezes, rales, rhonchi, rubs, and bronchial breath sounds. Percussion of the lungs should assess for hyperresonance and decreased fremitus in the case of a pneumothorax or dullness if consolidation or pleural effusion is present. Rales and dullness may also suggest left-sided congestive heart failure. POCUS may also be used to rule out a pneumothorax if suspected: one must look for the absence of lung sliding and B lines, and the boundary/margin of the pneumothorax can be identified by the lung point.

An abdominal exam should also be performed to assess for abdominal tenderness, specifically in the right upper quadrant (suggesting liver or gallbladder pathologies). POCUS may also be used to better diagnose pathologies such as choledocholithiasis and cholecystitis; however, a good history and physical exam is more relevant. Furthermore, a formal ultrasound may be required prior to surgical management, if deemed necessary.

Finally, the Vancouver Chest Pain Rule may be used to identify patients who are low-risk and safe for an early discharge. This tool allows one to quickly discharge patients based on medical history, physical exam (especially reproducible palpable chest pain), electrocardiogram (EKG), and cardiac biomarkers.

4 | BEYOND THE INITIAL APPROACH

In an academic hospital setting, 12-lead EKG and troponin levels are the first steps in diagnosing possible acute coronary syndrome. If pulmonary disease is suspected, a chest x-ray (CXR) can be ordered. (2,13,14)

When evaluating an EKG, one should be aware of the many different pathologies. Although not always the case, ischemia typically presents with an ST-segment depression whereas an ST-segment elevation indicates infarction or pericarditis. Furthermore, T wave abnormalities could also indicate ischemic disease or infarction. Signs of right heart strain, such as right axis deviation and right bundle branch block, could indicate pulmonary diseases such as PE. Electrical alternans and low EKG voltages suggests cardiac tamponade, which warrants pericardiocentesis or pericardiotomy as treatment modalities. (15)

The presence of cardiac biomarkers (particularly troponins) is helpful in differentiating active myocardial infarction from unstable angina. If valvular disease is suspected, an echocardiogram is helpful. Additionally, echocardiography is useful in diagnosing cardiac tamponade via cardiac chamber collapse, septal "bounce", and inferior vena cava (IVC) dilatation. An MI can be identified by echocardiogram since regional wall motion abnormalities can be observed. (15,16) CT coronary angiogram can be useful for risk stratifying coronary artery disease which can subsequently be diagnosed via cardiac catheterization and treated with coronary stenting or coronary artery bypass grafting depending on disease severity and contraindications to therapies. A myocardial perfusion imaging test (MIBI) may also be used to identify areas of ischemia by comparing cardiac perfusion under rest and stressed conditions. (17) MIBI is extremely useful in identifying ischemic areas that can be salvaged by reperfusion.

For diagnosing life-threatening aortic dissection, a CT scan is utilized; alternatively, depending on the resources available a transesophageal echocardiography (TEE) is just as useful especially when a patient is hemodynamically unstable. Type A aortic dissections (which involve the ascending aorta and the arch; also the most common type) are typically repaired surgically whereas type B (involving the descending aorta) are managed medically with beta blockers and calcium channel blockers or endovascularly. (18) A CT scan may also be useful

in diagnosing an MSK etiology secondary to a trauma. (5,8)

If a patient complains of pleuritic pain, a CXR is a rapid modality to rule out pneumothorax, pneumonia, and rib fractures which are treated with a chest tube, antibiotics, and analgesics, respectively. Furthermore, a CXR is useful in identifying an aortic dissection as a widened mediastinum may be present. If a PE is suspected, a CT pulmonary angiogram (gold standard) or a ventilation-perfusion scan (V/Q; used when CT is contraindicated such as in renal failure) may be used to diagnose and treatment entails either anticoagulation, thrombolytics, or catheter-directed thrombolysis. (2,8,19)

An esophagography may be useful in diagnosing esophageal etiologies such as an esophageal rupture which often warrants immediate surgical repair. Endoscopy and manometry are pertinent in diagnosing esophageal etiologies such as achalasia and esophageal spasms.

In conclusion, a thorough history, physical exam, and the use of predictive tools and diagnostic modalities are critical in diagnosing chest pain using an anatomical approach. Importantly, life-threatening causes should be ruled out and treated, since these etiologies progress quickly.

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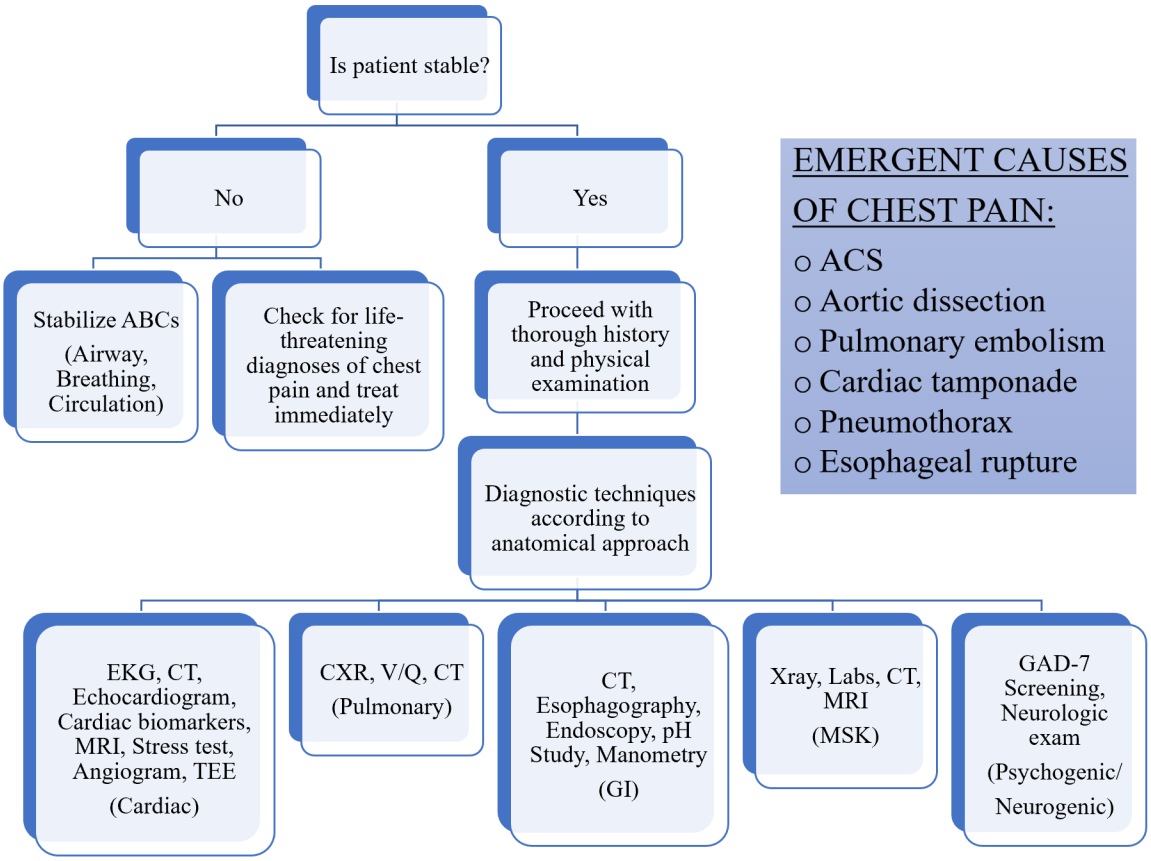
5 | TABLES & FIGURES



FLOWCHART 1 Approach to chest consists of first stabilizing the patient and identifying and treating any life-threatening conditions (noted in the grey box to the right). Following a thorough history and physical examination, diagnostic techniques should be utilized according to the anatomical system identified.

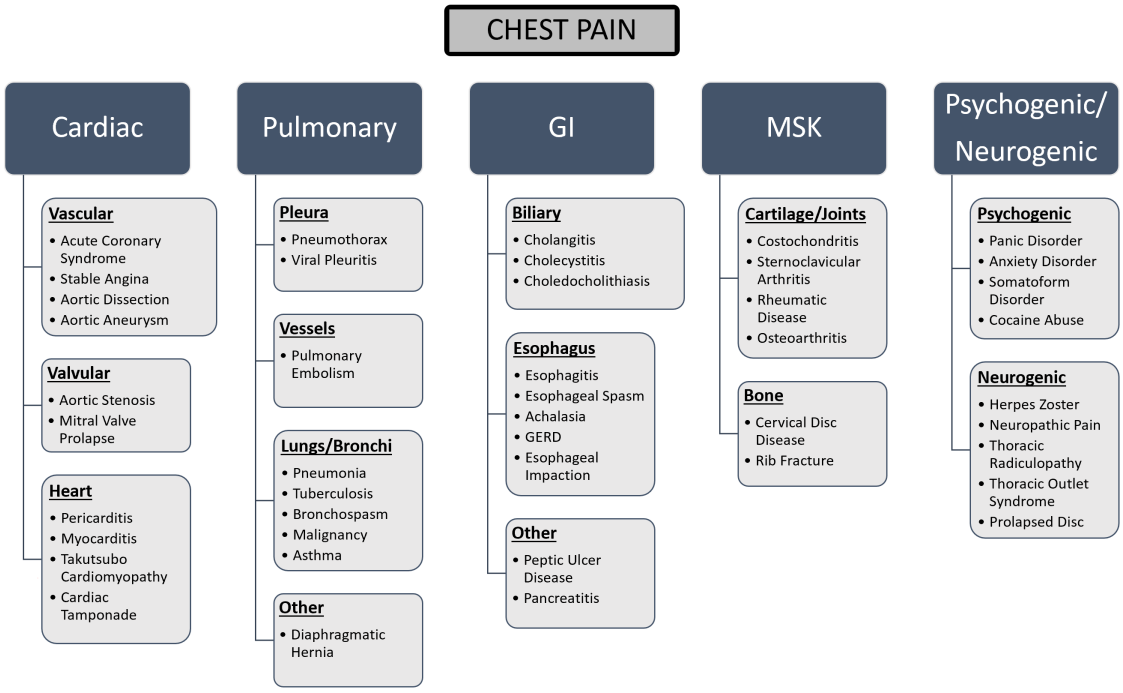


FIGURE 1 An anatomical approach to diagnosing chest pain. This includes cardiac, pulmoary, gastrointestinal (GI), musckuloskeletal (MSK), and psychogenic/neurogenic chest pain. The causes of pain are listed under each of the subcategories. History is important for identifying which anatomical structure is affected and to ultimately treat the underlying cause of the pain.

APPROACH TO
McGill Journal of Medicine

Heart Failure

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ABSTRACT

Heart Failure (HF) affects more than 650,000 Canadians (3.6% of Canadian adults above age 40). Even with recent advances in the diagnosis and treatment of this disease, HF remains among the five most common causes for hospitalization in Canada, with a readmission rate above 30% at the 1-year mark. Despite the significant economic and clinical burden of this disease, there is limited awareness among healthcare providers, healthcare system managers, and governments regarding the current HF epidemic and available therapies. This article reviews the definition of HF and the approach to evaluating a patient with suspected HF, focusing on the different presentations of HF, the clinical significance of ejection fraction, and the usefulness of BNP as a marker of cardiac function.

KEYWORDS
Heart Failure, Ejection Fraction, Dyspnea, Pulmonary Edema, Brain Natriuretic Peptide (BNP)

1 | QUESTION

A 61-year-old male presents to the Emergency Department with a 4-month history of progressive exertional dyspnea and fatigue. He reports frequently waking up due to a feeling of breathlessness. He complains of a 10-pound weight gain in the past month. Past medical history is significant for hypertension, coronary artery disease (CAD), dyslipidemia, and obesity—for which he takes atorvastatin and perindopril. He has a 40 pack-year history of cigarette smoking. On cardiopulmonary auscultation, there are diffuse bilateral crackles in the lower third fields of the lungs and a third heart sound (ventricular gallop). Vital signs are: pulse of 118, respiratory rate of 26, blood pressure of 164/93, O2 saturation 92%, and body temperature of 36.9°C. On physical exam, you note mildly laboured breathing, a distended jugular vein, and bilateral edema of the lower extremities.

Which of the following statements is true regarding this patient?

A. This patient should be started on a short-acting

bronchodilator, a long-acting bronchodilator, and a corticosteroid to improve respiratory status.

B. Measurement of brain natriuretic peptide (BNP) is the gold-standard diagnostic tool for this patient's condition.

C. If the heart echocardiogram shows a left ventricular ejection fraction (LVEF) < 40%, a triple therapy consisting of an ACE inhibitor (ACEi), a beta-blocker (BB) and a mineralocorticoid receptor antagonist (MRA) should be started to decrease this patient's risk of mortality.

D. If the heart echocardiogram shows a LVEF > 50%, the likelihood of a diagnosis of heart failure is low.

2 | ANSWER

C. This patient's clinical presentation is highly suggestive of heart failure (HF). The three classes of medication proven to reduce HF mortality with reduced LVEF are ACEi, BB, and MRA, thus constituting the basic initial triple therapy for patients with this condition. (1)

A. False. This pharmacotherapy would be indicated for a patient with chronic obstructive pulmonary disease (COPD). Although both COPD and HF can present with dyspnea, dyspnea in HF is more likely due to pulmonary edema and should be treated with diuretics, not inhalers.

B. False. HF is a clinical diagnosis that should be confirmed with an echocardiogram.

D. False. HF can present with a preserved ejection fraction.

3 | OVERVIEW OF HEART FAILURE

3.1 | What is Heart Failure?

Heart failure is a clinical syndrome characterized by signs and symptoms of reduced cardiac output and/or pulmonary and systemic volume overload. (2,3) Signs and symptoms include dyspnea, orthopnea (dyspnea in an inclined or supine position), paroxysmal nocturnal dyspnea (dyspnea most severe at night, often leading to nighttime awakening), fatigue, weakness, exercise intolerance, dependent edema, cough (particularly in the decubitus position), weight gain (due to water retention), abdominal distension, nocturia, and cool extremities. (3)

3.2 | Etiologies and Risk Factors

HF often results from a previous insult or disease process in the heart. The most common causes include CAD, hypertension, idiopathic cardiomyopathy, and valvular heart disease. Less frequent etiologies include arrhythmias, connective tissue diseases such as lupus, endocrine and metabolic disorders such as diabetes or thyroid disease, myocarditis, and pericarditis. (2) Other risk factors for HF include heavy alcohol or substance use, smoking, physical inactivity, obesity, diabetes, chemotherapy or radiotherapy, and lower socioeconomic status. (1,2)

3.3 | Epidemiology

HF affects more than 650,000 Canadians (3.6% of Canadian adults aged 40 and above). Prevention, diagnosis, and treatment of HF are paramount because the all-cause mortality for Canadians living with this disease is four to six times higher than those living without the condition. (4)

4 | INITIAL APPROACH

Evaluating a patient with suspected HF begins with a thorough medical history and physical examination. It is important to remember that **symptoms** suggestive of HF include exertional dyspnea, intolerance to exercise, edema, fatigue, orthopnea, paroxysmal dyspnea, and weight gain. **Signs** suggestive of HF include elevated jugular venous pressure, large abdomen (may include ascites and hepatojugular reflex), cool extremities, dependent edema, and labored breathing (with or without rales). (1-5)

On cardiac auscultation, both bradycardia and tachycardia can be found, as well as a third heart sound (ven-

tricular gallop). (1,5) Finally, in a patient with a clinical presentation suggestive of HF, attention should be given to signs and symptoms suggestive of a particular HF etiology: chest pain or recent myocardial infarction (CAD), skin, joint or eye lesions (sarcoidosis), recent fevers, viral infection, history of IV drug use (endocarditis, myocarditis, pericarditis), syncope (bradycardia, heart block, or other arrhythmias). (2,5)

Initial investigations in suspected HF are aimed at gathering evidence suggestive of the diagnosis, ruling out other possible causes for the symptoms, determining potential etiologies, and identifying complications and comorbid illnesses (see Table 1).

There is no gold standard diagnostic test for HF. One of the most widely accepted diagnostic aid scores is the Framingham Diagnostic Criteria for Heart Failure (available at: https://www.mdcalc.com/framingham-heart-failure-diagnostic-criteria). (2,6) Even though many scores exist to determine the likelihood of HF, it remains a clinical diagnosis where one must consider clinical presentation, scores, and investigations (See Flow chart 1). (2,3,7,8)

If clinical suspicion of HF remains high after the initial work-up, echocardiography should be ordered to confirm the diagnosis and determine ejection fraction. (1,2,5,8)

5 | BEYOND THE INITIAL APPROACH

5.1 | Many Presentations for the Same Disease

HF covers a wide variety of presentations, ranging from gradual lower extremity edema to rapid-onset respiratory distress. HF can present with acute or chronic symptoms. Acute or "decompensated" HF presents as an exacerbation of symptoms with or without a previous HF diagnosis. Severe acute HF can present with flash pulmonary edema and even cardiogenic shock. Chronic HF refers to patients with a diagnosis of HF whose condition and symptoms are currently stable. (7)

In a patient diagnosed with acute-on-chronic HF, precipitating factors should be investigated. The most common precipitating factors of acute exacerbations of HF are de novo or paroxysmal atrial fibrillation, acute my-

Investigation	Rationale
Chest X-Ray	Rule out pulmonary disease (e.g. pneumonia, pulmonary mass) Assess for pulmonary edema, cardiomegaly and pleural effusions
Electrocardiogram (ECG)	Rule out arrhythmias, acute or previous MI Determine if patient needs concurrent referral to cardiology (for example, presence of a heart block necessitating a pacemaker)
Complete blood count (CBC)	Rule out concomitant anemia or an infectious process
Electrolytes, including magnesium, phosphate, and calcium	Rule out electrolyte imbalances which can cause arrhythmias (particularly if the patient is on diuretics)
Renal function	Rule out renal causes of volume overload Assess renal function (may influence the choice of treatment)
Urinalysis	Rule out renal causes or infection
Glucose	Rule out hyperosmolar state
Thyroid function	Rule out concomitant thyroid disorder
Brain natriuretic peptide (BNP)	Rules out HF if low Can raise suspicion for HF if high Can be used as a baseline value for monitoring purposes during treatment

Adapted from King M, Kingery J, Casey B. Diagnosis and Evaluation of Heart Failure. Am Fam Physician [Internet]. 2012 Jun; 85(12):1161-1168. Table 4, Laboratory Evaluation for Heart Failure and Selected Alternative Causes; [Cited 2020 Oct 22]. Available from: https://www.aafp.org/afp/2012/0615/p1161.html#afp20120615p1161-t4

TABLE 1 Suggested initial investigations for suspicion of heart failure

ocardial infarction or ischemia, non-adherence to medication, new prescriptions impairing myocardial function (e.g., a calcium channel blocker), increased sodium and fluid intake, and physical overexertion. (7)

Pulmonary edema is defined as an abnormal buildup of fluids in the extravascular compartments of the lungs. In terms of pathophysiology, pulmonary edema is caused by severe left ventricular failure that leads to retrograde pulmonary venous hypertension. The chest X-ray findings suggestive of pulmonary venous congestion include cardiomegaly, interstitial edema, air bronchograms, Kerley B lines, and pleural effusions (see Figure 1). (7,8,9,10

Cardiogenic shock is defined as a clinical state with evidence of tissue hypoperfusion and a systolic blood pressure <90 mm Hg. (7)

5.2 | Preserved and Reduced Ejection Fraction

HF can be divided into two categories: HF with **reduced** ejection fraction (HFrEF) and HF with **preserved** ejection fraction (HFpEF). HFrEF and HFpEF are also sometimes referred to as systolic and diastolic HF, respectively. A reduced EF is defined as a LVEF of less than or equal to 40%. A preserved EF is defined as an LVEF of greater than or equal to 50%. An LVEF of between 40-50% is considered a “mid-range” or “borderline” EF and remains scarcely studied. (11) Nearly half of patients with HF have a preserved ejection fraction; it is therefore not a rare presentation. (5, 12, 13) HFpEF tends to be more common in women, older patients (> 65 years old), and in patients without a history of CAD. (5,6) EF cannot reliably be determined based on clinical presentation because signs and symptoms can be similar for both types of HF. (6)

Determination of EF has a two-fold purpose. Firstly, it is a strong predictor of the severity and prognosis of the disease. (2,14) The risk of all-cause mortality, as well as cardiovascular and congestive HF-related death, declines with increasing EF until around 45%. (10) Secondly, HFpEF and HFrEF do not share the same treatment. Therefore, adequate characterization of fraction ejection is essential to determine appropriate interventions.

5.3 | Overview of Heart Failure Treatment

Heart failure treatment depends on ejection fraction. First-line treatment for HFrEF is a triple pharmacological therapy consisting of ACEi (or an angiotensin II receptor blocker (ARB) if ACEi intolerant), BB, and MRA. (1,2) Doses should be titrated to either evidence-based target doses or a maximum tolerated dose. In conjunction, diuretics should be prescribed and titrated to the lowest dose needed to maintain euvolemia. Non-pharmacological interventions include dietary sodium and fluid restriction; weight tracking; weight loss in obese patients; avoidance of alcohol, recreational drugs and tobacco; regular exercise; and seasonal vaccination. (15) Best practice also involves a discussion with the patient about their goals of care and their desired level of intervention. (1)

In the case of HFpEF, studies have shown no medications to be effective for a long-term reduction in mortality. (8,9) Thus, the main pillars of HFpEF management are centered on symptomatic treatment of fluid overload, comorbidities management, and tertiary prevention. Diuretics can be prescribed to reduce volume overload symptomatology. Non-pharmacological interventions can be recommended similarly to HFrEF. Blood pressure should be treated according to local guidelines. CAD and atrial fibrillation should be properly investigated and treated if present. Patients who can tolerate exercise should be referred to endurance and resistance training or cardiac rehabilitation. (12)

Acute HF should be treated similarly regardless of ejection fraction with O2 supplementation targeting saturation above 92%, intravenous furosemide (bolus or perfusion) for treatment of volume overload, and vasopressors if the patient has indications of shock. (1)

5.4 | Judicious Use of BNP in HF

BNP is a hormone secreted by the ventricles of the heart in response to increased stretching or pressure. (16) It is often used as a marker for cardiac function. In the diagnosis of HF, BNP use is limited by its poor specificity despite its high sensitivity. Apart from HF, BNP levels can also be elevated due to acute or chronic renal failure, pulmonary embolism, acute respiratory distress syndrome, myocardial infarction, atrial fibrillation, sepsis, chemotherapy, and many more medical conditions. As such, BNP has a better negative than positive predictive value and should be used to rule out HF from the differential diagnosis rather than to rule it in. (11,12)

Once a diagnosis of HF is established, BNP can be used for monitoring purposes. While BNP often remains chronically high in patients with HF, a sudden rise can be a diagnostic clue to an exacerbation of the disease, especially if >30% of the patient's baseline levels. (5)

Finally, the BNP level is a strong predictor of the risk of death and cardiovascular events in patients with HF. (11)

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6 | TABLES & FIGURES

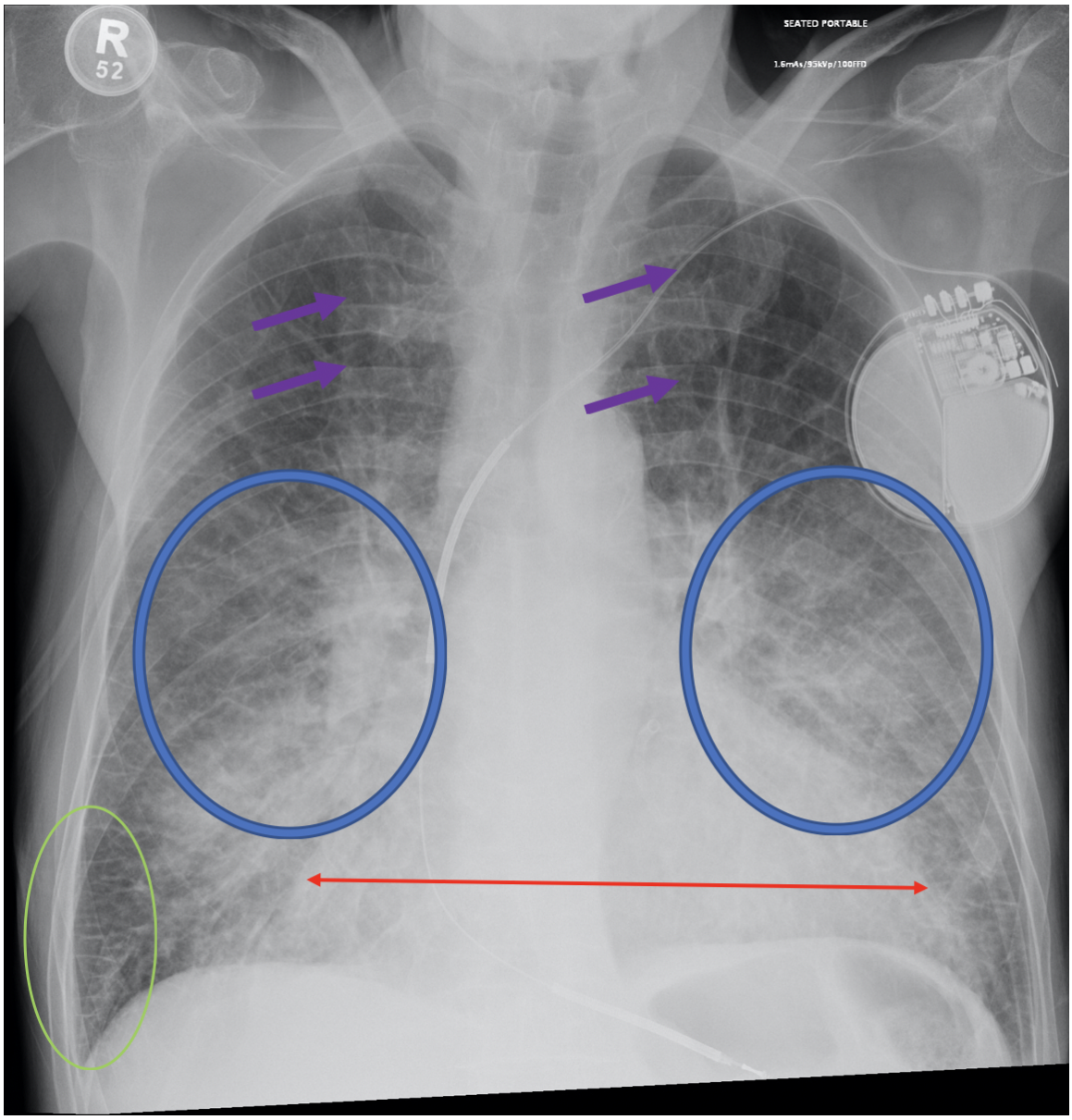
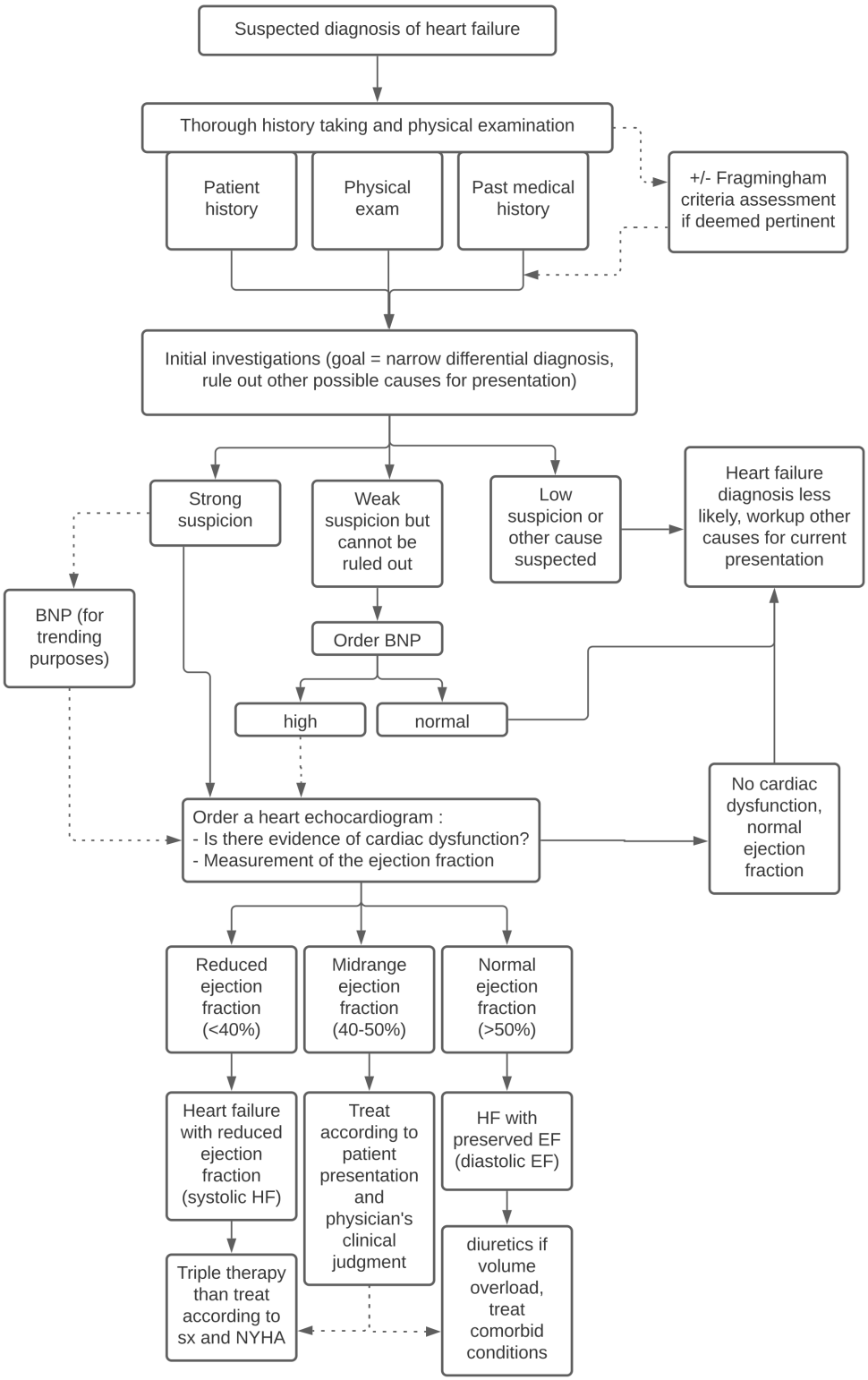


FIGURE 1 Annotated Chest X-Ray demonstrating signs of Pulmonary Edema. Chest X-Ray of a 60 year-old male who presented with shortness of breath. Note the pacemaker in the left hemithorax.
Purple arrows: upper lobes vascular redistribution, suggestive of pulmonary edema
Blue circles: increased interstitial lung markings suggestive of interstitial edema
Green circle: Kerley B-lines suggestive of interstital edema
Red arrow: cardiomegaly (increased cardiothoracic ratio)
Note this particular case does not display pleural effusions (costophrenic angles are clear)

Adapted from Radiopeda. Pulmonary Edema [Image on Internet]. Radiopedia; 2005-2020. Case courtesy of Dr Abeer Ahmed Alhelali; [cited 2020 Nov 6]. Available from: https://radiopaedia.org/cases/pulmonary-oedema-7



FLOWCHART 1 Approach to the Diagnosis of Heart Failure. Adapted from Canadian Cardiovascular Society. Pocket Guide: Is it heart failure and what should I do? [Internet]. 2017 Updated Ed. Canada: Canadian Cardiovascular Society; 2017. Algorithm for the Diagnosis of Heart Failure (HF) in the Ambulatory Setting; [cited 2020 Oct 22]; p.4. Available from: https://www.ccs.ca/images/Guidelines/Pocket Guides_EN/HF_Gui _2017_PG_EN_web.pdf

APPROACH TO
McGill Journal of Medicine

Type 2 Diabetes Mellitus Management

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a chronic and insidious disease that is on the rise worldwide. Diabetes pharmacotherapy is complex and varied, and recent studies of novel antihyperglycemic drugs have raised important considerations for the management of T2DM. This review provides an overview for the diagnosis of T2DM, glycemic targets for individuals with a T2DM diagnosis, and outlines a general approach to the management of T2DM, with an emphasis on how to select the appropriate pharmacotherapy using a fictional case as an example. Hypoglycemia, a complication of pharmacotherapy, macrovascular and microvascular disease resulting from T2DM, and other forms of diabetes mellitus are also briefly reviewed.

KEYWORDS
approach to, type 2 diabetes, guidelines, hyperglycemia, pharmacotherapy

1 | QUESTION

Mrs. S is a 34-year-old woman diagnosed with type 2 diabetes mellitus (T2DM) six months ago. At the time of diagnosis, her HbA1C was 7.4%. She started metformin and began walking for 30 minutes thrice a week. Three months later, her blood pressure (BP) was 125/80 mmHg, weight was 73.2 kg, and height was 161 cm (BMI 28.2); you increased the dose of metformin since her HbA1C was unchanged since her diagnosis. Today, her BP was stable, and she lost 2 kg, about which she is ecstatic. Her laboratory results are:

HbA1C: 7.3% (target in diabetes < 7.0%)
Plasma glucose, fasting: 9.2 mmol/L (normal: 3.0 - 6.1 mmol/L)
Creatinine: 58 µmol/L (normal: 53 - 106 µmol/L)
Estimated glomerular filtration rate (eGFR): 97 mL/min/1.73m ^{2} (normal: 90 mL/min/1.73m ^{2})
Triglycerides, fasting: 1.80 mmol/L (normal: < 1.70 mmol/L)
Total cholesterol, fasting: 6.56 mmol/L (normal: 3.00 - 5.20 mmol/L)
High-density lipoprotein (HDL), fasting: 1.22 mmol/L (normal: > 1.20 mmol/L)
Low-density lipoprotein (LDL), fasting: 2.11 mmol/L (target for diabetes < 2.00 mmol/L)

What is the next best step in managing this patient?
A. Refer to a registered dietician (RD), start insulin ther-

apy and follow-up in 3 months.
B. Counsel on diet, start a sulfonylurea and follow-up in 3 months.
C. Counsel on diet and increasing exercise, start insulin therapy and follow-up in 3 months.
D. Refer to a RD, start a glucagon-like peptide-1 receptor agonist (GLP1-RA) and follow-up in 3 months.
E. Refer to a RD, counsel on increasing exercise, start a sodium-glucose cotransporter-2 inhibitor (SGLT2i) and follow-up in 3 months.

2 | ANSWER

E. Mrs. S is above her glycemic targets (HbA1C < 7.0% for adult diabetes). All patients with T2DM must be counselled on healthy behavior changes, and benefit from working with a RD and a personal trainer. Mrs. S lacks symptoms of hyperglycemia and does not need insulin therapy. Since she is happy with her weight loss, has an overweight BMI and elevated serum triglycerides and LDL, her weight and cardiovascular (CV) function are considered when selecting a drug.

Sulfonylureas are associated with weight gain and no CV benefits. GLP1-RAs and SGLT2is are associated with CV benefits and weight loss, but GLP1-RAs with CV benefits are injected while SGLT2is are given orally. Mrs. S should thus be counselled on exercise, referred to a RD and start a SGLT2i. A follow-up in 3 months is indicated to monitor therapeutic effectiveness, CV status and side effects.

3 | INITIAL APPROACH

Diabetes mellitus is a chronic and insidious disease requiring frequent screening. Diabetes Canada has thorough guidelines with an approach to screening not covered here. (1) Evaluation of a patient with suspected T2DM begins with a complete history and physical examination. Patients can be asymptomatic, but signs and symptoms of hyperglycemia include polyuria, polydipsia, dehydration, blurry vision, headaches, fatigue, weakness, weight loss despite caloric intake, numbness or tingling in the extremities, and frequent infections. Cardiovascular disease (CVD) and microvascular disease affecting the eyes, kidneys and peripheral nerves are common at diagnosis.

3.1 | Diagnosis

The diagnosis of diabetes is established by two confirmatory lab tests reflecting hyperglycemia or one lab test with symptoms of hyperglycemia. The diagnostic criteria are: 1) fasting plasma glucose (FPG) 7.0 mmol/L, where patients have no caloric intake for 8 hours preceding the test, 2) plasma glycated hemoglobin (HbA1C or A1C) 6.5%, considering factors affecting hemoglobin, 3) 2-hour plasma glucose (2hPG) in a 75 g oral glucose tolerance test (OGTT) 11.1 mmol/L), or 4) a random plasma glucose (PG) 11.1mmol/L, regardless of caloric intake timing (Flowchart 1). (2) Hemoglobinopathies and altered red cell turnover (e.g. hemolytic anemia) may affect A1C measurement.

3.2 | Glycemic targets

Treatment of T2DM includes patient education, evaluation for macro- and microvascular complications, glycemic control, and reduction of cardiovascular risk factors and microvascular complications. (3,4) Targets for glycemic control are individualized depending on factors like age, kidney function, risk of hypoglycemia, functional dependence, and other comorbid conditions (Table 1). (1) In most cases, the target is an A1C 7.0%, which is correlated with reduced long-term micro- and macrovascular complications. (5,6)

3.3 | Healthy behaviour interventions

Healthy behaviour interventions (or intensive lifestyle interventions (ILI)), such as diet, physical activity and smoking cessation, are a first-line intervention recommended in all patients with T2DM where reducing complications is a priority. (7) ILI implementation benefits from a multi-disciplinary approach, including RDs and certified fitness instructors. ILI is most effective in pre-

A1C%	Targets for Glycemic Control
6.5	Adults with diabetes to reduce risk of CKD and retinopathy if at low risk of hypoglycemia (for e.g. those with T2DM on oral hypoglycemic agents without risk of hypoglycemia).
7.0	Most adults with diabetes
7.1 → 8.5	Functionally dependent: 7.1-8.0% Recurrent severe hypoglycemia and/or hypoglycemia unawareness; limited life expectancy; frail elderly and/or with dementia: 7.1-8.5%
>8.5	Avoid higher A1C to minimize risk of symptomatic hyperglycemia and complications

T2DM = type 2 diabetes mellitus; A1C = glycated hemoglobin; CKD = chronic kidney disease.

Adapted from: Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada, Canadian Journal of Diabetes. http://guidelines.diabetes.ca/docs/CPG-2018-full-EN.pdf

TABLE 1 Glycemic Control Targets for Type 1 and Type 2 Diabetes Mellitus

diabetes or new-onset T2DM to reduce mortality and slow or reverse disease progression. (7) It can also contribute to a recommended 5-10% weight loss for overweight individuals, which can decrease insulin resistance, hyperglycemia, hypertension and dyslipidemia. (7,8) Principles of diet in T2DM include choosing low glycemic index carbohydrates, reducing refined carbohydrates, increasing dietary fibre, and following the Eating Well with Canada's Food Guide. (9) Many dietary approaches, like the Mediterranean diet, have established benefits, but a patient's ethnocultural background should be considered. (10) Each diet must be individualized, regularly re-evaluated, and reinforced. It is also recommended that patients with T2DM reduce sedentary behaviour by engaging in 150 minutes of aerobic exercise and two resistance training sessions per week. (6,7)

3.4 | First-line antihyperglycemic – Metformin

Due to the heterogeneity of T2DM, there are many classes of antihyperglycemics with varying mechanisms of lowering blood glucose (BG). Antihyperglycemics can be evaluated by characteristics according to the Safety, Tolerability, Effectiveness, Price, and Simplicity (STEPS) approach published by the American Academy of Family Physicians (Table 2). (11) Combining drugs with different mechanisms is common and preferred. Biguanides, or metformin, are a class of antihyperglycemics that lower BG by activating AMP-activated protein kinase to enhance insulin sensitivity in the liver and peripheral tissues. (12) Metformin is a first-line antihyperglycemic and can be prescribed at diagnosis regardless of A1C level. It has a good safety profile with low risk of hypoglycemia when given as monotherapy, a neutral effect on weight, and is less expensive relative to other antihyperglycemics. (13) However, metformin is contraindicated in chronic kidney disease (CKD) with eGFR < 30 mL/min. (13)

3.5 | Second-line antihyperglycemics

A patient with symptoms of hyperglycemia and/or metabolic decompensation, such as dehydration, weight loss, diabetic ketoacidosis (DKA), and a hyperosmolar hyperglycemic state, should be started on insulin immediately, regardless of A1C status. (13) A patient likely to respond to lifestyle changes will require metformin initiation or escalation if they have not attained targets within 3 months (Flowchart 1). A non-insulin and non-metformin antihyperglycemic should be considered in all patients who do not attain targets within 3 to 6 additional months. A patient with an A1C 1.5% above target should be concurrently started on metformin and a second antihyperglycemic. (13) In the presence of atherosclerotic cardiovascular disease (ASCVD), CKD, heart failure or an age > 60 years,

and two CV risk factors (Flowchart 1), patients should start antihyperglycemics with demonstrated cardiorenal benefits. (14) These include SGLT2is, such as empagliflozin and canagliflozin, and GLP1-RAs, such as liraglutide, semaglutide or dulaglutide. Patients without ASCVD, CKD or risk factors can start an additional antihyperglycemic according to their clinical needs (Table 2). (11,14) If avoidance of weight gain and hypoglycemia are priorities, dipeptidyl peptidase-4 inhibitors (DPP-4is), GLP1-RAs and/or SGLT2is are recommended. The A1C value tends to decrease by 0.5% to 1.5% on monotherapy, usually achieving maximal effects by 3 to 6 months. (15) Beta cell function declines over time, often leading BG levels to rise insidiously despite treatment adherence; thus, treatment regimens are frequently adjusted and tailored.

3.6 | Insulin therapy

Insulin therapy is effective for individuals with significant hyperglycemia and can lead to partial recovery of beta cell function in patients with metabolic decompensation. (13,16) Insulin is primarily delivered via injection and is rarely associated with lipodystrophy at the injection site. Long-acting or intermediate-acting insulin analogue injections are used for basal glycemic control while bolus injections at mealtimes are used for prandial glycemic control. Combining insulin with other antihyperglycemics can lead to better glycemic control with less insulin and fewer side effects compared to insulin alone. (13) Risk of hypoglycemia is high with insulin; thus, regimens must be adjusted to reduce risk, especially in the elderly. Reduction of A1C is directly correlated with the dose and number of daily injections.

4 | BEYOND THE INITIAL APPROACH

This section covers special considerations for further evaluation and management of T2DM, as well as distinctions from other forms of diabetes mellitus.

4.1 | Hypoglycemia

Hypoglycemia is defined by a plasma glucose of < 4 mmol/L and the presence of autonomic or neuroglycopenic symptoms that resolve with the administration of carbohydrates. Some symptoms include trembling, palpitations, sweating, anxiety, nausea, confusion, weakness, and vision changes. Hypoglycemia is potentially dangerous if it occurs while driving or operating machinery. Prolonged hypoglycemia can result in coma, paresis, convulsion, and encephalopathy, while repeated episodes can lead to hypoglycemia unawareness and mild intellectual impairment. (17) The best management for hypoglycemia is prevention and patients must be counselled on how to recognize and manage symptoms. This includes awareness of BG levels, especially before driving, as well as preparing and carrying 20 g of fast-acting sugar. (17)

4.2 | Cardiovascular disease

Diabetes significantly accelerates the natural history and development of CVD; therefore, special attention must be given to CV health in T2DM. BP should be < 130/80 mmHg and LDL < 2.0 mmol/L or a > 50% reduction from baseline. (18) Additional pharmacotherapy may be initiated in individuals with high risk or presence of CVD. Drugs include angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), statins, aspirin, GLP1-RAs and SGLT2is. Statins are indicated in patients with clinical CVD and 1) age 40 years, or 2) age > 30 with diabetes > 15 years, or 3) age < 40 with microvascular disease. (18)

4.3 | Microvascular disease

Annual screening is critical to detect and treat microvascular complications like diabetic retinopathy, neuropathy, and nephropathy. In all cases, BG and BP management is the best way to prevent or slow progression of these pathologies. Referral to a specialist is usually warranted. Retinopathy may be treated by laser therapy or vitrectomy and may benefit from statins or fenofibrate.

(19) Neuropathy is screened by 10 g monofilament or vibration perception tests and managed with analgesics or other medications like anti-depressants. CKD is defined as an eGFR < 60 mL/min or the presence of microalbuminuria or proteinuria (a random urine albumin to creatinine ratio 2.0mg/mmol in 2 of 3 samples over 3 months). Low eGFR is associated with a high risk of CVD. ACE inhibitors, ARBs and SLGT2is should be considered for the management of BP and to slow the progression of CKD. (19) SGLT2is have been shown to be effective in early CKD. (14)

4.4 | Other forms of diabetes mellitus

Although T2DM is the most common form of diabetes mellitus, its management differs greatly from that of gestational diabetes mellitus (GDM) and type 1 diabetes mellitus (T1DM). GDM, defined as diabetes with onset during pregnancy, is screened for during the second trimester. First-line therapy focuses on healthy behaviour interventions, followed by insulin +/- metformin if targets are not met. (20) T1DM is an autoimmune condition where pancreatic beta cells are attacked by one's own immune system, resulting in the absence of insulin production. Exogenous insulin therapy is therefore required for these patients to avoid metabolic decompensation. Diagnosis of T1DM usually occurs in the first two decades of life; management of hyperglycemia requires continuous BG monitoring and insulin delivery, either by insulin pump or multiple daily injections.

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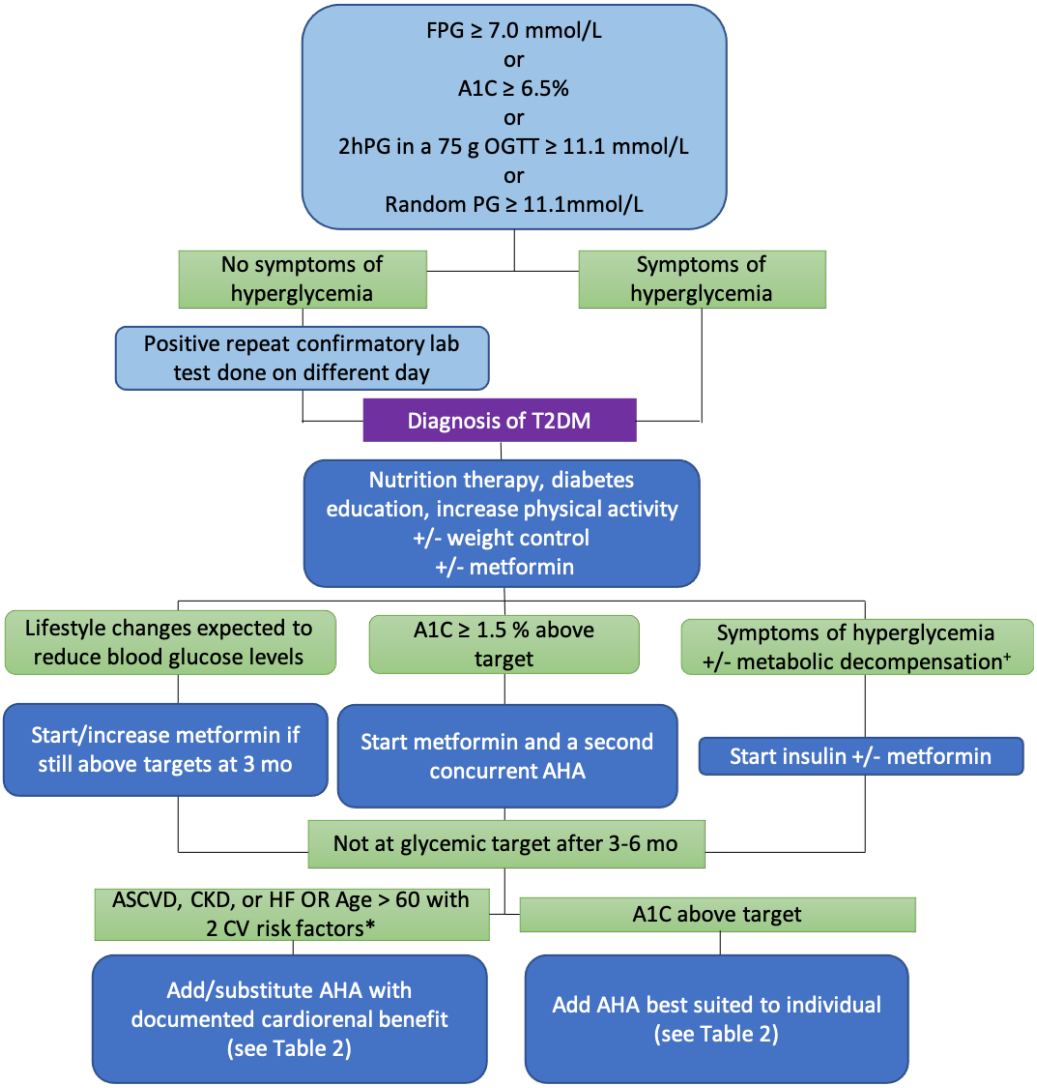
5 | TABLES & FIGURES



FLOWCHART 1 Approach to Type 2 Diabetes Mellitus

Basic algorithm for the management of type 2 diabetes mellitus in adults. Endpoints include meeting targets for glycemic control (see Table 1).

FPG = fasting plasma glucose; A1C = glycated hemoglobin; 2hPG = 2 hour plasma glucose; OGTT = oral glucose tolerance test; T2DM = type 2 diabetes mellitus; mo = months; AHA = antihyperglycemic agent; CKD = chronic kidney disease; HF = heart failure; CV = cardiovascular; ASCVD = atherosclerotic cardiovascular disease

+dehydration, diabetic ketoacidosis, hyperosmolar hyperglycemic state

*tobacco use; dyslipidemia (use of lipid-lowering agents, OR untreated low-density lipoprotein (LDL) 3.4 mmol/L, OR high-density lipoprotein (HDL) <1.0 mmol/L for men and <1.3 mmol/L for women, OR triglycerides >2.3 mmol/L); hypertension (use of antihypertensive therapy or untreated blood pressure 140/95); central obesity.

Adapted from: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults 2020 Update, Canadian Journal of Diabetes. https://www.canadianjournalofdiabetes.com/action/showPdf?pii=S1499-2671%2820%2930228-8

Class	Mechanism	Safety	Tolerability	Effectiveness			Price	Simplicity
				Cardio-renal	Weight (kg)	A1C		
Biguanides metformin	↑ insulin sensitivity by activating AMP kinase	Vitamin B12 deficiency, contraindicated in CKD, hold if risk of AKI	GI effects	↓CVD	neutral	1.0%	$-$$	Oral 1-2x/day
GLP-1 receptor agonists -tide	↑ glucose-dependent insulin release, slow gastric emptying, inhibit glucagon release	Contraindicated with Hx or FHx of medullary thyroid cancer or MEN 2, caution Hx of pancreatitis or pancreatic cancer, risk of retinopathy	GI effects, headache	↓CVD*	↓1.1-4.4	0.6-1.4%	$$$$	S.c. injection 2x/day, 1x/day or 1x/week
DPP-4 inhibitors -liptin		Risk of HF with saxagliptin, caution Hx pancreatitis or pancreatic cancer	Rare: joint pain, pancreatitis	Neutral CVD	neutral	0.5-0.7%	$$$	Oral, 1x/day
SGLT-2 inhibitors -liflozin	Inhibits SGLT-2 to prevent glucose reuptake by kidney	Hypotension, rare DKA, caution with low carb eating or insulin deficiency, dapagliflozin contraindicated in bladder cancer, caution foot care (amputation risk), hold if risk of AKI	UTI, genital tract infections	↓CVD ** ↓ renal disease ***	↓2-3	0.5-0.7%	$$$	Oral, 1x/day
Insulin	Activates insulin receptors	Hypoglycemia	Lipodystrophy	Neutral CVD	↑1-3.5	0.9-1.2% or >	$ to $$$$	S.c. injection 1-4x/day
Thiazolidinediones -glitazone	↑ insulin sensitivity by activating peroxisome proliferator-activated receptors	CHF, fracture, possible increased risk MI with rosiglitazone, pioglitazone contraindicated in bladder cancer	Edema, rare: macular edema	neutral or ↑CVD	↑2.0-2.5	0.7-0.9%	$$$	Oral, 1x/day 6-12 weeks for max effect
α-glucosidase inhibitors acarbose	Inhibits pancreatic α-amylase and intestinal α-glucosidase	Contraindicated in cirrhosis or CKD	GI effects	?	neutral	0.7-0.8%	$$	Oral, 3x/day
Meglitinide repaglinide	Activates sulfonylurea receptors on β-cell to stimulate insulin secretion	Hypoglycemia, contraindicated when combined with clopidogrel or gemfibrozil	GI effects, dizziness	?	↑1.4-3.3	0.7-1.1%	$$	Oral, 3x/day
Sulfonylurea -zide, -ride		Hypoglycemia, caution in G6PD deficiency	-	?	↑1.2-3.2	0.6-1.2%	$	Oral, 1-2x/day

TABLE 2 A STEPS Approach to Antihyperglycemic Agents

CR = cardiorenal; A1C = glycated hemoglobin; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium/glucose cotransporter-2; DPP-4 = dipeptidyl peptidase-4; CKD =chronic kidney disease; AKI = acute kidney injury; Hx = history; FHx = family history; MEN = multiple endocrine neoplasia; HF = heart failure; DKA = diabetic ketoacidosis; CHF = chronic heart failure; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; UTI = urinary tract infection; CVD = cardiovascular disease; s.c. = subcutaneous; x/day = times per day.

* no proven CV benefit with lixisenatide or short-acting exenatide; in established atherosclerotic cardiovascular disease (ASCVD), CKD OR >60 years with CV risk factors

** in established ASCVD, CKD, HF, OR >60 years with CV risk factors

*** in established ASCVD, CKD, OR >60 years with CV risk factors

Adapted from: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults 2020 Update, Canadian Journal of Diabetes. https://www.canadianjournalofdiabetes.com/action/showPdf?pii=S1499-2671%2820%2930228-8 and Type 2 Diabetes Therapies: A STEPS Approach, American Academy of Family Physicians. https://www.aafp.org/afp/2019/0215/p237.html

APPROACH TO
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Hyponatremia

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ABSTRACT

Hyponatremia is a common laboratory finding in numerous patients. It is defined as a serum sodium concentration <135 mmol/L and represents an excess of water in the extracellular compartment. The severity of this electrolyte abnormality ranges from asymptomatic to seizures, coma and death as a consequence of cerebral swelling. There are multiple medical conditions, medications and disease states that can cause hyponatremia. This article summarizes the important pathophysiological pathways involved in the development of hyponatremia, describes an approach to common causes and reviews the initial steps in management.

KEYWORDS
Hyponatremia, Syndrome of Inappropriate Anti-Diuretic Hormone, Vaptans

1 | QUESTION

A 72-year-old man, previously well, presents to the emergency department with a 5-day history of fever, productive cough and dyspnea. His past medical history includes type 2 diabetes mellitus, gastroesophageal reflux disease and dyslipidemia. His medications include metformin, pantoprazole and atorvastatin. On physical exam, the patient appears well. He is hemodynamically stable with a temperature of 38°C. His exam is remarkable for crackles and decreased air entry in the right middle lobe. He has no pitting edema, no ascites, no jugular venous distension, and his mucous membranes are moist. His laboratory results are as follows (normal values in brackets):

- Hemoglobin 137 (125-170 g/L)
- Mean corpuscular volume 83 (80-100 fL)
- White blood count 13 x 10^9/L (3.5-10.5 x 10^9/L)
- Platelets 200 x 10^9/L (130-380 x 10^9/L)
- Absolute neutrophil count 9 x 10^9/L (2-7.5 x 10^9/L)
- Na 129 (136-146 mmol/L), K 4 (3.5-5.1 mmol/L), Cl 107 (98-107 mmol/L)
- Bicarbonate 24 (21-32 mmol/L)
- Blood urea nitrogen 7.9 (2.1-8 mmol/L), Creatinine 81 (49-93 µmol/L)

- Glucose random 6.7 (4-11 mmol/L)
- Thyroid- stimulating hormone 1.16 (0.34-5.60 mIU/L)
- AM cortisol 550 (185-624 nmol/L)
- Plasma osmolality: 273 (275-295 mmol/kg)
- Urine sodium: 50 mmol/L (elevated)
- Urine osmolality: 480 mOsm/ kg (38-1400 mOsm/kg H_2O)

Given the most likely cause of this patient's hyponatremia, what is the next step in management?

A. IV infusion of 3
B. Vaptans
C. IV infusion 0.9
D. Start diuretics
E. Fluid restriction

2 | ANSWER

E. The patient in this scenario most likely has SIADH (syndrome of inappropriate anti-diuretic hormone) secondary to his pneumonia. This is evidenced by the patient's euvolemic hypo-osmolar hyponatremia, with a reduced plasma osmolality, concentrated urine, and elevated urine sodium. Other causes, such as hypothyroidism and adrenal insufficiency, have been ruled out with the normal laboratory values. The first step in managing SIADH is to restrict the patient's fluid intake (E). Hypertonic saline is used in cases of severely symptomatic hyponatremia, whereas this patient has no evidence of symptoms secondary to his hyponatremia (A). Vaptans would be considered for refractory hyponatremia (B). The use of normal saline is appropriate when the patient has evidence of volume depletion, which is not the case for this patient (C). If normal saline were to be given, it would be expected that Na would decrease in the case of SIADH. Diuretics would be prescribed to a patient with congestive heart failure, which this patient is not presenting with (D).

3 | DEFINITION AND PATHOPHYSIOLOGY

Hyponatremia is defined as a measured serum sodium concentration less than 135 mmol/L. Hyponatremia is a pathophysiological process representing an excess of water in the extracellular compartment relative to the amount of sodium. (1)

Water exists throughout the body in two distinct compartments: intracellular and extracellular. The extracellular compartment can be subdivided into the plasma and interstitium. Water is able to move freely between the intracellular and extracellular compartments. (2)

In addition to water, there are solutes in these two compartments which contribute to the osmolality. The plasma osmolality (P_{osm}) is one of the main factors that contributes to water regulation as it must remain constant (between 280-295 mOsm/kg) and equal to the intracellular osmolality. (2) P_{osm} can be measured or calculated with the following equation: P_{osm}= 2[Na+] + [glucose] + [blood urea nitrogen].

Osmoreceptors in the hypothalamus detect the plasma osmolality. If P_{osm} >285 mOsm/kg, osmoreceptors stimulate the release of anti-diuretic hormone (ADH) from the posterior pituitary into the circulation, as well as stimulate thirst. ADH release is also stimulated in states of low effective circulating volume. (1, 2) Circulating ADH binds to receptors on the principal cells of the collecting duct in the kidneys and activates a cellular pathway which ultimately results in water reabsorption. This results in a decrease in the serum osmolality and an increase in the urine osmolality (U_{osm}). (2) In certain states, ADH can be released inappropriately or ectopically, meaning that ADH is released without an osmotic or hemodynamic stimulus. (3) When ADH is suppressed, water is renally excreted. (2)

Another important physiological pathway is the renin-angiotensin-aldosterone system (RAAS). This pathway is activated in states of low effective circulating volume and/or when there is reduced sodium in the renal tubules. These conditions stimulate the release of renin from the juxtaglomerular cells, which are part of the afferent arterioles. The activation of RAAS

ultimately results in increased sodium reabsorption, arteriolar vasoconstriction and release of ADH from the posterior pituitary. (4) Measured urine sodium concentration (U_{Na}) is a reflection of intravascular volume; U_{Na} is elevated with volume expansion and reduced with volume depletion. (3)

Hyponatremia is a common laboratory finding in the inpatient and outpatient settings. (5) As a result of low sodium concentration in the extracellular fluid, water will freely move intracellularly to maintain osmotic equilibrium, resulting in cellular swelling. Hyponatremia can be classified as acute (<48 hours) or chronic (>48 hours) and by severity, as mild (130-134 mmol/L), moderate (125-129 mmol/L) and severe (<125 mmol/L). (1) When hyponatremia develops chronically (>48 hours), cells can adapt by losing cellular electrolytes and organic osmolytes (6), ultimately resulting in less cellular edema. When cells do not have time to adapt (<48 hours), cerebral swelling could ensue and result in neurological symptoms ranging from headache, nausea, and vomiting, to altered mental status, seizures, brain herniation, and coma. (2, 7)

4 | INITIAL APPROACH

The etiology of hyponatremia includes a wide range of medications, medical conditions, and other disease states. Therefore it requires a thorough, stepwise approach to ensure the correct diagnosis is made and the most appropriate treatment can be provided.

4.1 | Is this a "true" hyponatremia?

First, determine if the patient has hypo-osmolar hyponatremia, also known as "true hyponatremia." If measured plasma osmolality is <275 mOsm/kg and the serum sodium is <135 mmol/L, then the patient has "true hyponatremia". (1)

If a patient with hyponatremia is found to have a plasma osmolality in the normal range (280-295 mOsm/kg) or above normal range (>295 mOsm/kg), then the patient has "iso-osmolar hyponatremia" (also known as "pseudohyponatremia") or hyper-osmolar hyponatremia, respectively. In these cases, additional osmoles are contributing to the plasma osmolality, such as glucose, lipids, or proteins. (1) Nowadays, pseudohyponatremia is less commonly seen as laboratories can correct for these additional osmoles. (8)

This article will focus on hypo-osmolar hyponatremia.

4.2 | Is ADH suppressed or secreted?

4.2.1 | ADH is suppressed (U_{osm} <100 mOsm/kg)

Hyponatremia can result in the context of excess water intake relative to solutes consumed. In these situations, ADH activity is absent and the kidneys excrete water to produce a maximally dilute urine (U_{osm} <100 mOsm/kg). (1) However, there is a maximum amount of water that can be excreted, which can result in excess water in the extracellular compartment relative to sodium. Etiologies include "tea and toast" diet, beer drinkers' potomania, or primary polydipsia. (1) Excess water consumption is considered drinking approximately > 1L/hour. (3)

4.2.2 | ADH is secreted (U_{osm} >100 mOsm/kg)

When ADH is secreted, the kidneys reabsorb water, resulting in a concentrated urine. Once known that U_{osm} >100 mOsm/kg, the next step is to determine the intravascular volume by assessing the urine sodium concentration.

4.3 | What is the intravascular volume: U_{Na} 30 mmol/L or U_{Na} >30 mmol/L?

In states of low effective arterial blood volume, RAAS is activated and increased sodium is reabsorbed from the urine, resulting in a U_{Na} 30mmol/L. (4) With normal or elevated effective circulating volume, U_{Na} >30 mmol/L. (1)

4.4 | What is the patient's volume status?

Once U_{Na} is known, patients must be evaluated clinically to determine their overall volume status.

4.4.1 | Hypovolemia

Patients who are hypovolemic may have non-specific symptoms, such as fatigue, weakness, thirst, and postural dizziness. (2) On exam, they may have decreased jugular venous pressure (JVP), orthostatic tachycardia, orthostatic hypotension, dry mucous membranes, decreased skin turgor, and decreased urine output (unless on a diuretic). Their laboratory values may show an elevated creatinine, blood urea nitrogen or hematocrit. (2, 6)

In patients with U_{Na} <30 mmol/L, hypovolemic hyponatremia can be caused by gastrointestinal fluid loss (e.g. diarrhea), excessive sweating, or extravasation of fluid (previously known as third spacing), in which the intravascular volume is depleted leading to the activation of ADH and thus free water retention. (1, 6, 9)

In patients with U_{Na} >30 mmol/L, hypovolemic hyponatremia is often due to renal loss of sodium and water. This includes any cause of hypoaldosteronism (e.g. primary adrenal insufficiency), salt-wasting nephropathies, diuretic use (especially thiazides) and osmotic diuresis. (2)

4.4.2 | Euvolemia

Etiologies of euvolemia with U_{Na} >30 mmol/L include syndrome of inappropriate ADH (SIADH), hypothyroidism, and secondary adrenal insufficiency. SIADH should only be diagnosed once renal disease, hypothyroidism, adrenal insufficiency, and thiazide use have been ruled out. (1) SIADH is the most common cause of euvolemic hyponatremia, in which ADH is secreted despite normal P_{osm} and normal circulating volume. There are many known causes of SIADH, including lung diseases (e.g. pneumonia), pain, nausea, CNS lesions, and drugs (selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotic medications, etc.) (2, 6). Certain cancers, such as small cell lung cancer and olfactory neuroblastoma, can give rise to ectopic ADH production. (10)

Criteria for diagnosing SIADH is found in Table 1.

4.4.3 | Hypervolemia

Patients who are hypervolemic may have an elevated JVP, inspiratory crackles, S3 (third heart sound), ascites, or edema. Laboratory results may show a decreased hematocrit and serum protein. (6)

In patients with U_{Na} <30 mmol/L, hypervolemic hyponatremia can be caused by congestive heart failure (CHF), cirrhosis, or nephrotic syndrome. Patients with these illnesses can be in states of low effective circulating volume but clinically appear hypervolemic. (1, 11)

Hypervolemic hyponatremia in the context of U_{Na} >30 mmol/L can occur in renal failure, due to impaired free water excretion. (7)

5 | BEYOND THE INITIAL APPROACH

The management of hyponatremia is based on its acuity, severity, volume status, and etiology. The approach above helps to determine the most likely diagnosis, which will then guide the most appropriate management. The main principle of treating hyponatremia is to treat the underlying cause.

Acute, severe or symptomatic hyponatremia should be managed immediately to reduce the risk of cerebral edema, seizure, and brain herniation. It should be initially treated with 3% hypertonic saline. (11) Rates of correction should not exceed 6 to 8 mmol/L per day to avoid the risk of developing osmotic demyelination syndrome, a complication that results in paraplegia, dysarthria, dysphagia, diplopia, "locked-in syndrome", or loss of consciousness. (2, 12) Patients must be closely monitored with serial blood tests to evaluate the correction rate.

In hypovolemic hyponatremia, the effective circulat-

Effective serum osmolality	<275 mOsm/kg
Urine osmolality	>100 mOsm/kg
Urine sodium	>30 mmol/L (with normal salt and water intake)
Clinically euvolemic	No evidence of volume overload or volume depletion (i.e., hemodynamically stable, no postural symptoms, normal JVP, normal mucous membranes, no crackles, no S3, no ascites, no edema)
No other contributing illness	Rule out adrenal, thyroid, pituitary or renal insufficiency No recent use of diuretics

TABLE 1 Essential criteria to diagnose syndrome of inappropriate antidiuretic hormone

Adapted from Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Intensive Care Med. 2014;40(3):320-31.

ing volume must be restored with an intravenous infusion of normal saline. Once intravascular volume is restored, ADH will be suppressed, resulting in renal excretion of water and rapid correction of the hyponatremia. (11) Urine output should be monitored, as an output >100 ml/hour can be a sign of correcting too rapidly. (9) Serial blood tests should be ordered to monitor the correction rate.

Euvolemic hyponatremia can be due to several underlying conditions, including low solute intake or excess fluid intake. These conditions can be addressed by increasing the patients' solute intake or restricting fluid intake. If the hyponatremia is secondary to hypothyroidism or adrenal insufficiency, the management plan should include fluid restriction as well as treatment to address the underlying disease. (11)

SIADH, a cause of euvolemic hyponatremia, is initially managed with fluid restriction in addition to investigating and treating the underlying etiology. Increasing solute intake may be helpful in order to increase electrolyte-free fluid excretion. Vaptans, a medication that antagonizes the effects of ADH, can be added to the management plan if the above methods fail. (11)

Hypervolemic hyponatremia is generally managed with fluid restriction. When caused by CHF or cirrhosis, patients tend to respond to fluid and salt restriction. In CHF, and cautiously in cirrhosis, loop diuretics should also be started as part of the first-line management. A second-line option could include vaptans. (11)

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6 | TABLES & FIGURES

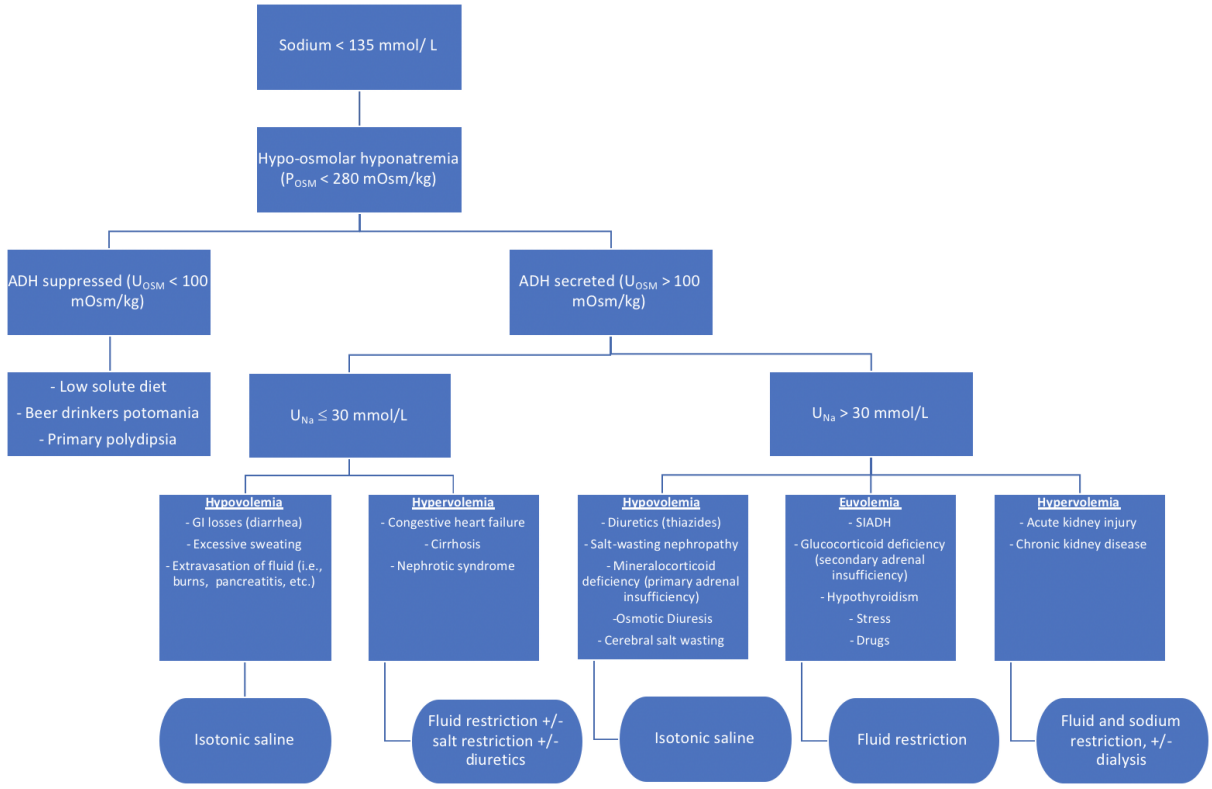

FIGURE 1 Approach to Hyponatremia
Basic algorithm to hyponatremia in order to determine the etiology and the first-line in management.

Abbreviations:
P_{osm} = plasma osmolality
ADH= antidiuretic hormone
U_{osm} = urine osmolality
U_{Na} = urine sodium
CHF= congestive heart failure
SIADH= syndrome of inappropriate antidiuretic hormone
AKI= acute kidney injury
CKD= chronic kidney disease

Adapted from

Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Intensive Care Med. 2014;40(3):320-31.
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APPROACH TO
McGill Journal of Medicine

Amenorrhea

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ABSTRACT

This article provides an approach to amenorrhea and is intended for pre-clinical and clerkship medical students. Primary amenorrhea refers to the absence of menarche by 15 years or 3 years post thelarche while secondary amenorrhea is the cessation of menses for 3 months in women with a previously regular cycle or for 6 months in women with previously irregular menses. While amenorrhea can be physiological it can also reflect an anatomical or more complex hormonal problem that students must learn to identify and investigate.

KEYWORDS
Anatomical defects, Hypogonadism, Primary amenorrhea, Secondary amenorrhea

1 | QUESTION

A 15-year-old girl presents to your office. Her primary concern is that she is shorter than her classmates. She mentions she has had hearing difficulties since childhood, and is known for a heart defect and scoliosis. She is concerned about being the only one in her not having had her period yet. On physical exam, the patient is short in stature with no physical signs of pubertal development. You also notice that she has low set ears and a low hairline. Initial laboratory results are as follows:

Beta Human Chorionic Gonadotropin (hCG): 1mIU/mL (normal value in non-pregnant women <5mIU/mL)

Follicle-stimulating Hormone (FSH): 50mIU/mL (normal value between 5-20mIU/mL)

Luteinizing Hormone (LH): 48mIU/mL (normal value between 5-20mIU/mL)

Prolactin (PRL): 27µg/L (normal value in non-pregnant women 2-29µg/L)

Which of the following would not be indicated as the next step in the diagnosis of this patient's amenorrhea?

a) Karyotype
b) Thyroid function tests
c) Pelvic ultrasound (US)
d) Testosterone and 17-OHP levels

2 | ANSWER

D. The patient's presentation is consistent with primary amenorrhea, most likely due to Turner Syndrome (TS). The elevated FSH and LH levels are representative of hypergonadotropic hypogonadism, most likely caused by gonadal dysgenesis in this case. (1) The physical appearance of this patient as well as the implication of other organ systems are also suggestive of TS, but the diagnosis can only be confirmed by karyotype. Many patients with TS also suffer from hypothyroidism which should be investigated when detected on laboratory testing for amenorrhea. (1) In this case, the amenorrhea is caused by the gonadal dysgenesis and not the hypothyroidism per se. Pelvic US should always be included in the initial investigation of primary amenorrhea to confirm the presence of a uterus and vagina. In TS, ovaries will appear as fibrous streaks without any follicles. (1) Testosterone and 17-OHP testing are not useful in the initial diagnosis of TS and would be more relevant if the patient had signs of hyperandrogenism or high LH/FSH ratio to rule out malignancy, congenital adrenal hyperplasia or polycystic ovary syndrome (PCOS). Note that TS can be characterized by monosomy or mosaicism and that the manifestations of this condition can vary dramatically from one person to another.

3 | INITIAL APPROACH

The initial investigation of a patient presenting with amenorrhea begins with a thorough history and physical examination. First, it is important to differentiate between primary and secondary amenorrhea. (2) The former refers to the absence of menarche by 15 years or 3 years post-thelarche, while the latter is the cessation of menses for 3 months in women with a previously regular cycle. (3) For primary amenorrhea, a complete growth history as well inquiry as to the onset and progression of puberty is crucial. In addition to the history of present illness, a review of the patient's previous menstrual patterns, gynecologic instrumentation and general health status are important to ask for on history when secondary amenorrhea is suspected. (4, 5) On physical examination, the clinician should look for the presence of secondary sexual characteristics, signs of virilization, presence of dysmorphic features, and signs of thyroid disease. (4, 5) Abdominal and pelvic examinations should also be performed. While investigating the cause of amenorrhea may be necessary, it is important to keep in mind that constitutionally late menarche or early menopause can also explain these clinical manifestations.

3.1 | Beta Human Chorionic Gonadotropin

The first step in the evaluation of amenorrhea is to exclude pregnancy because it is the most common cause of amenorrhea in women of reproductive age. (5) Measurement of serum or urine hCG levels are the most common laboratory tests ordered to evaluate pregnancy. hCG is produced by syncytiotrophoblast cells and rises exponentially during the first trimester of pregnancy. (5) Serum testing is very sensitive and can detect hCG amounts as low as 1-2mIU/mL. (6) Normally, hCG levels are insignificant in non-pregnant women but high levels can occur in the presence of malignancies producing very high levels of ectopic hCG such as choriocarcinoma, germ cell tumors and hydatidiform moles. (5, 6) If the hCG laboratory testing is positive, US should be performed next to evaluate the presence of an intrauterine or ectopic pregnancy. (2)

3.2 | Prolactin

Hyperprolactinemia is the most common cause of secondary amenorrhea after pregnancy and is diagnosed when serum levels of PRL exceed 25µg/L. (7, 8) Elevated PRL disrupts gonadotropin-releasing hormone (GnRH) pulsatile secretion which results in hypogonadotropic hypogonadism (HH). PRL levels of 20-200µg/L are often due to the use of prescription drugs or lactotroph microadenomas, while a PRL level of more than 200µg/L is mostly caused by a macroprolactinoma. (7, 8) The presentation of a prolactinoma depends on its size; rang-

ing from symptoms of hyperprolactinemia such amenorrhea, loss of libido and galactorrhea to mass effect occurring with macroprolactinomas. (7) If hyperprolactinemia cannot be explained by the use of medications, a physiologic cause or dysfunction of another organ system, an MRI should be ordered to investigate the possibility of a pituitary gland tumor. (7, 8)

3.3 | Thyroid Stimulating Hormone

Menstrual irregularities are frequent consequences of thyroid dysfunction. (9) Amenorrhea can be caused by hypothyroidism or hyperthyroidism. Once pregnancy has been ruled out, thyroid stimulating hormone (TSH) level should be measured as the initial investigation of a thyroid disorder. TSH is low in hyperthyroidism, which leads to an excess of sex hormone-binding globulin (SHBG). (9, 10) The result is a reduction of the free fraction of estrogen and testosterone available in the circulation, causing anovulation and amenorrhea. (9, 10) Amenorrhea can also be a symptom of hypothyroidism, which also causes a reduction in serum SHBG, resulting in a decrease in total circulating estrogen and testosterone. (9, 10) Ovulatory dysfunction may also be caused by hyperprolactinemia from long-standing increases in thyrotropin-releasing hormone levels seen in hypothyroidism. (9, 10) The underlying cause of thyroid dysfunction should be investigated further if abnormal TSH levels are found on initial investigation of amenorrhea.

3.4 | Pelvic Ultrasound

Anatomical defects should always be considered in the differential diagnosis of primary amenorrhea. Women presenting with primary amenorrhea should be evaluated for the presence of a uterus and vagina by pelvic US. (3, 4) Observation of a shortened vaginal canal or absent uterus should prompt investigation for Müllerian agenesis and androgen insensitivity syndrome (AIS). (3, 11) These two conditions can be differentiated by karyotyping or measuring serum testosterone (Figure 1, Table 1). Outflow tract obstructions such as an imperforate hymen or a transverse vaginal septum often present with cyclic pain and may be the cause of amenorrhea in the presence of a normal uterus. (3, 11) Pelvic US is also relevant in the investigation of secondary amenorrhea to assess for ovarian pathology as well as PCOS. Intrauterine adhesions and cervical stenosis resulting from endometrial instrumentation and cervical procedures also need to be considered in the differential diagnosis of secondary amenorrhea. (3, 11)

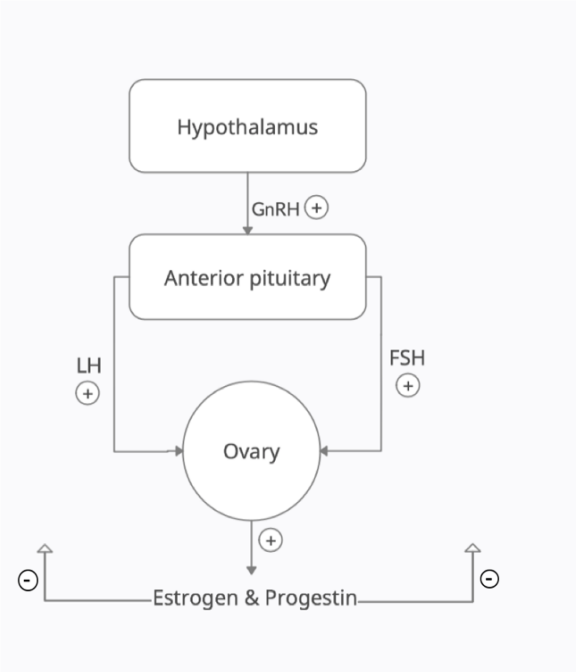


FIGURE 1 Hypothalamic-pituitary-ovarian axis. Depending on the level of dysfunction within the HPO axis, the serum levels of FSH and LH will be different. When the defect is downstream at the level of the ovaries, FSH and LH levels will be elevated in the absence of negative feedback from the gonads (hypergonadotropic hypogonadism). When the defect is more upstream (hypothalamus or pituitary), the patient will suffer from HH and the serum levels of FSH and LH will be low.

Adapted from: Naftolin F., Khafaga A., Nachtigall M. (2019) The Hypothalamic-Pituitary-Ovarian Axis and Regulation of the Menstrual Cycle. In: Berga S., Genazzani A., Naftolin F., Petraglia F. (eds) Menstrual Cycle Related Disorders. ISGE Series. Springer, Cham. https://doi.org/10.1007/978-3-030-14358-9_

Type of amenorrhea		FSH	LH	LH/FSH	PRL	Testosterone	17-OHP
Hypergonadotropic Hypogonadism	**Ovarian Failure** *Gonadal dysgenesis* *Premature ovarian insufficiency*	↑		↓	↔	↔ or ↓	↔
Normogonadotropic Hypogonadism	Outflow tract obstruction	↔		↔	↔	↔	↔
	PCOS			↑	↑	↑	↔
	Adrenal or ovarian malignancy			↔	↔	↑↑	↔
	Late-onset congenital adrenal hyperplasia			↑	↔	↑	↑
Hypogonadotropic Hypogonadism	Hyperprolactinemia	↓		↑	↑	↔	↔
	Hypothalamic amenorrhea			↔	↓	↔ or ↓	↔

TABLE 1 17-OHP: 17-hydroxyprogesterone
↔: Normal levels
↑: High levels
↑↑: Very high levels
↓: Low levels

Adapted from: Amenorrhea: A Systematic Approach to Diagnosis and Management, AAFP. https://www-aafp-org.proxy3.library.mcgill.ca/afp/2019/0701/afp20190701p39.pdf

3.5 | Follicle-stimulating Hormone, Luteinizing Hormone and Estradiol

Independent of the classification of the patient's amenorrhea as primary or secondary, the remaining causes can be divided into normogonadotropic, hypergonadotropic or HH, depending on FSH and LH serum values (Table 1). FSH, LH and estradiol levels will be increased or decreased depending on which component of the hypophyseal-pituitary-ovarian (HPO) axis is dysfunctional (Figure 2). Normal values of FSH and LH are between 5-20mIU/mL, but LH levels can increase up to 40mIU/mL during the LH surge 24h prior to ovulation (11, 12). Normal values of estradiol vary between 30-400pg/mL in premenopausal women and 0-30pg/mL in postmenopausal women. Elevated levels of FSH and LH with low estradiol are characteristic of ovarian failure, while low levels of these hormones are a feature of hypothalamic or pituitary dysfunction. (11, 12) It is also important to note that pregnant women or women taking exogenous estrogens would have high estradiol with low FSH and LH. Specific causes of each category are discussed below, and further management depends on the diagnosis. When there is evidence of hyperandrogenism, PCOS should be considered as well as the possibility of malignancy and late-onset congenital adrenal hyperplasia (CAH). (13, 14)

4 | BEYOND THE INITIAL APPROACH

In this section, important causes of amenorrhea are discussed in more detail, including further steps in patient management and treatment.

4.1 | Polycystic Ovary Syndrome

PCOS is the most common cause of infertility in women and is a major cause of hyperandrogenic amenorrhea. (13) It should be considered in every patient presenting with amenorrhea and signs of virilization, such as hirsutism and acne. Diagnosis of PCOS requires two out of three of the following criteria: clinical or laboratory evi-

dence of hyperandrogenism, oligo or amenorrhea, and polycystic ovaries on US. (13) Other causes of hyperandrogenism and menstrual irregularities must also be excluded to make a diagnosis of PCOS. These include androgen secreting tumors and CAH. Often, the criteria for hyperandrogenism are met on physical examination but biochemical measurement of androgens should be included in the initial investigation as it helps differentiate PCOS from an androgen secreting tumor (13). The first step in the management of patients with PCOS is diet and exercise. Given that PCOS is associated with insulin resistance, metabolic screening is also recommended and treatment with metformin may be beneficial. Finally, since chronic anovulation is associated with an increased endometrial cancer risk, patients can be managed with cyclic progesterone every 3 months if there is no spontaneous menses or with the use of combined oral contraceptives to ensure regular menstrual bleeding if pregnancy is not being pursued. (13)

4.2 | Anatomical defect: Müllerian agenesis vs Androgen Insensitivity Syndrome

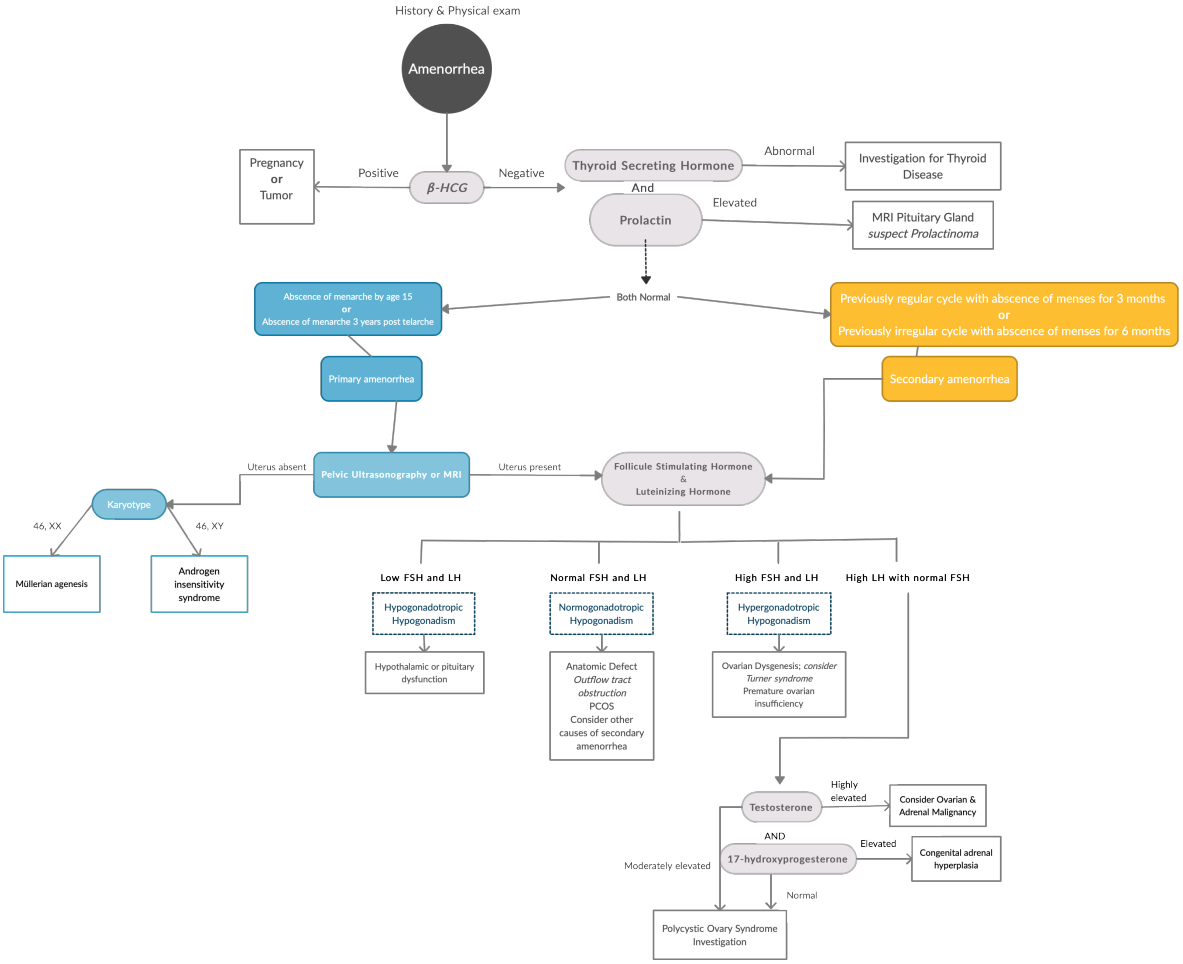
Müllerian agenesis and AIS both cause primary amenorrhea. Patients with either pathologies will have an absent or hypoplastic uterus and upper vagina which can be initially observed on US. (14, 15) It is important to distinguish the two entities by karyotype to direct management. Patients with Müllerian agenesis have a 46XX karyotype and the HPO axis remains unaffected. (15) The ovaries are functional, and the patient will have female secondary sexual characteristics. Patients with AIS have a 46XY karyotype but have a defect in the androgen receptor preventing external male genitalia development. (14, 15) Excess aromatization of their male-levels of androgens to estrogen allows for the development of female secondary sexual characteristics. (14) Management of both pathologies should address functional, sexual and psychologic issues. (14, 15) Gonadectomy after puberty is recommended for patients with AIS because of their high risk of cancer when gonads are left in the abdominal cavity. (14, 15) Other anatomical causes of primary amenorrhea that can be corrected surgically include imperforate hymen and vaginal septum.

4.3 | Hypergonadotropic hypogonadism: Turner Syndrome and Premature Ovarian Insufficiency

TS can be found in about 1/3 of patients with gonadal dysgenesis. (1) It should be suspected in women presenting with primary amenorrhea and hypergonadotropic hypogonadism and can be confirmed by karyotyping (usually 45X0 or mosaic). (1, 14) In TS, the ovaries degenerate during fetal life or early childhood, explaining the decreased level of estradiol and the absence of pubertal development. (1) Considering the involvement of many organ systems and the possibility for complications, patients should be managed by a multidisciplinary team and hormone replacement therapy is usually recommended. (1) Premature ovarian insufficiency can also be the cause of secondary amenorrhea. While chemotherapy in young children can lead to primary amenorrhea, autoimmune diseases or iatrogenic causes such as surgery, chemotherapy and radiation are often the culprit for acquired ovarian failure occurring later in life. (11) The diagnosis is often suspected on history and management depends on the cause.

4.4 | Hypogonadotropic hypogonadism: Functional hypothalamic amenorrhea

HH affects upstream levels of the HPO axis, either the hypothalamus or the pituitary gland (Figure 2). Another common cause of secondary amenorrhea is functional hypothalamic amenorrhea (FHA). (9, 12) FHA is characterized by dysfunction in the pulsatile release of GnRH by the hypothalamus, resulting in abnormal levels of FSH and LH and reduction of estradiol production by the ovaries. (9, 12) FHA can often be confused with pituitary dysfunction as a cause of HH but will respond to a GnRH stimulation test unlike the latter. (12) Major causes of hypothalamic disturbances include stress, weight loss and exercise, however organic causes should also be ruled out by imaging. (12) Particular attention



FLOWCHART 1 Approach to amenorrhea. Systematic approach to the evaluation of amenorrhea. The differential diagnosis of amenorrhea can be divided into two broad categories; primary and secondary amenorrhea. It is important to note that etiologies of secondary amenorrhea can also be the cause of primary amenorrhea. If the patient has a uterus, the evaluation of primary and secondary amenorrhea is similar following history and physical examination. Note that in real life, FSH and LH levels are often measured with TSH and PRL not to delay diagnosis.

Adapted from: Amenorrhea: A systematic Approach to Diagnosis and Management, AAFP.
https://www-aafp-org.proxy3.library.mcgill.ca/afp/2019/0701/afp20190701p39.pdf
Using an algorithmic approach to secondary amenorrhea: Avoiding diagnostic error, Clinica Chimica Acta.
https://pdf.sciencedirectassets.com/271330/1-s2.0-S0009898113X00075/1-s2.0-S0009898113001411/main.pdf

should be placed on the presence of underlying anxiety or mood disorders and a bone density scan may be indicated for women with amenorrhea lasting for more than 6 months. (12) Amenorrhea is usually reversible, and treatment depends on the cause but mostly relies on adequate nutritional status, stress reduction and treatment of underlying psychiatric disorders.

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Pediatric urinary tract infection (UTI)

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ABSTRACT

Urinary tract infections (UTIs) are prevalent in the children. Presentation of UTI vary in children of different ages. In infants, who cannot localize symptoms, UTI can present with a fever whereas in older children a UTI can present with urinary symptoms (dysuria, urinary frequency, incontinence). It is important to establish a clear diagnosis in order to treat and resolve the infection with antibiotics therapy to prevent bacteremia, pyelonephritis, and long-tern renal disease. Urine is collected through a mid-stream urine sample, in toilet trained children, via urethral catheterization, suprapubic aspiration and pediatric urine collection bags. Urine analysis and culture are the first-line investigations in children with suspected UTI. Goals of treatment include elimination of infection, relief of acute symptoms, and prevention of recurrent and long-term complications. The Canadian Pediatric Society recommends initial treatment with oral antibiotics for nontoxic children with febrile UTIs. Imaging, such as a renal/bladder ultrasound, may be used.

KEYWORDS
Pediatric, Urinary Tract Infections, Clinical Approach

1 | QUESTION

Angela is a 10-month old girl presenting to your community emergency department. Past medical history includes a febrile urinary tract infection (UTI) at 6 months of age. She presents with a 2-day history of fever without diarrhea, vomiting or other symptoms. Her 6-year-old sister attends daycare and had a self-limiting febrile illness 1 week ago.

Angela is fussy but alert and consolable. On examination, she does not appear toxic. Her temperature is 39.1°C. She is tachycardic with a heart rate of 155 beats/min with no audible murmur. Her respiratory rate is 34 breaths/min and she does not demonstrate laboured breathing or retractions, nor is she in distress. Bilaterally, her lungs are clear. She has no cough or congestion. Her abdomen is soft. Her tympanic membranes are normal and present with no nuchal rigidity. She does

not have any rashes. Her genital examination findings are normal, with no erythema or labial adhesions. Identify the next best step in Angela's care:

A. Obtain a urine sample via catheterization for urinalysis and urine culture

B. Obtain a urine sample via bag collection for urinalysis and urine culture

C. No further investigations are required at this time, however a follow-up in 1 week is recommended if fever persists

D. Perform a voiding cystourethrogram (VCUG)

2 | ANSWER

A. Angela requires a urine sample and further investigation. The appropriate next step is to obtain a urine sample through catheterization and send this urine sample for urinalysis and urine culture. Alternatively, one can use the bag method to obtain a sample for urinalysis, however it is **not** recommended to use bag-obtained samples for culture due to high contamination rates. Angela is 10 months old and presents with risk factors for UTI. Her risk factors include febrile illness without an identifiable source, young age, a history of UTI, and a temperature of greater than 39.0°C for 2 days. This presentation requires further investigation as a UTI is high on the differential diagnosis. A VCUG can be discussed with the family if vesicoureteral reflux (VUR) is suspected, however a renal bladder ultrasound (RBUS) is the recommended first-line investigation.

3 | INITIAL APPROACH

3.1 | Pathogenesis and Classification

UTIs frequently occur when bacteria invade and ascend up the urinary tract. Hematogenous spread to the urinary system is a rare cause of UTI that primarily occurs in neonates and immunodeficient children. (1) Lower UTIs are limited to cystitis, where the infection results in an inflammatory response in the bladder. Upper UTIs occur when the infection ascends to the ureters and kidneys resulting in pyelonephritis. (2) In previously healthy children who have not recently taken antibiotics, *Escherichia coli* account for the majority of UTIs. (3) Other common causative pathogens are *Klebsiella*, *Proteus*, and *Enterococcus*. (2-4) This approach to article discusses the diagnosis and management of uncomplicated UTIs in infants and children; uncomplicated UTIs are infections that are not an associated condition or structural abnormality.

UTIs are common bacterial infections in childhood that frequently cause acute illness in the pediatric population. (3) Occurrence rates among infants and children vary depending on age, sex, race, and circumcision status in males. (5) It is helpful to divide children into age groups to conceptualize approaches as clinical presentations, urine collection methods, and guidelines vary among children of different ages.

3.2 | Infants and Toddlers 2 Months to 3 Years of Age

3.2.1 | Clinical presentation

Approximately 7% of infants aged 2 to 24 months that present with fever without a source are diagnosed with a UTI. (5) Infants and toddlers frequently present late in the course of the infection with fever since they are unable to localize pain and urinary symptoms. When an infant or toddler presents with fever and no localizing symptoms (respiratory symptoms or rash suggestive of a viral etiology), the clinician must consider UTI as a cause. Recurrent UTIs should be further investigated as they can be indicative of complicated UTIs and associated with an underlying urinary tract abnormality, such as obstructive uropathies and VUR.

3.2.2 | Recommendations

The Canadian Pediatric Society (CPS) recommends that a urinalysis and urine culture be obtained from children less than 3 years of age who present with a fever (>39.0°C rectal) with no apparent source. (4) Children under 3 years of age who present with a fever greater than 39.0°C for more than 48 hours and without a lo-

calizing source of fever are highly likely to have a UTI. Risk factors for UTIs can also be considered to calculate a pretest probability of UTI and determine which children require further investigation (Figure 1). It is important to consider other factors, such as the ability of the physician to follow up with the patient and the patient's history of UTIs. Additionally, the family unit should be included in the decision-making process.

3.3 | Children 3 Years of Age and Older

3.3.1 | Clinical presentation

Older children are able to localize pain and describe symptoms. Symptoms such as dysuria, urinary frequency, new daytime incontinence, and suprapubic discomfort are common in cystitis and warrant testing for UTI. (3, 6) Prepubertal girls can present with dysuria and vulvovaginitis due to poor hygiene or exposure to irritants. History and physical exam are necessary to rule out non-UTI causes of dysuria. (3, 4) Urologic symptoms accompanied by systemic symptoms, flank pain, costovertebral tenderness, abdominal pain, and fever are suggestive of upper UTIs such as pyelonephritis. (7)

3.3.2 | Recommendations

The CPS states that the presence of urinary symptoms in verbal children, children usually greater than 3 years of age, can be used as a criterion for requesting further analysis and culture. (8) Children in this age group can generally submit to spontaneous urine samples for analysis and culture. (3)

3.4 | Diagnosis

In children presenting with a possible UTI, it is important to establish a clear diagnosis in order to treat and resolve the infection with appropriate antibiotic therapy. This prevents the spread of infection to the kidneys, long-term renal scarring and disease. UTI is diagnosed based on the results obtained from urine analysis and cultures. (3)

3.4.1 | Urine collection

In children who are toilet-trained, a mid-stream urine sample should be collected. In young children and those who cannot submit spontaneous samples, other means to obtain urine samples are required. Urethral catheterization, suprapubic aspiration (SPA) and pediatric urine collection bags are typically used. (9) It is important to consider that urine collection bags, although convenient and non-invasive, are at a high risk of contamination and are therefore not recommended for culture. (10) SPA is the gold standard for UTI diagnosis; any growth from a sterile SPA is diagnostic for a UTI. Table 1 summarizes advantages and disadvantages of available urine collection methods.

3.4.2 | Urine Analysis

Urine analysis is the physical, chemical (dipstick), and microscopic examination of urine. Urine dipsticks can be used to detect the presence of leukocyte esterase, a marker for white blood cells (WBCs) in the urine, and nitrites, a marker of gram-negative bacteria. The urine

	Advantages	Disadvantages
Urethral catheterization	Sterile urine sample Less discomfort than SPA	Invasive and uncomfortable
Suprapubic aspiration	Gold standard for diagnosis of UTI Sterile procedure	Less commonly used Invasive and painful
Bag Specimen	Non invasive Does not rely on technical skills	Not sterile, potential for contamination Not recommended for culture
Clean catch void sample	Non invasive Does not rely on technical skills	Not sterile Difficult to obtain in children who are not toilet-trained

TABLE 1 Advantages and Disadvantages of Urine Collection Methods (3, 4, 9)

Parameter	Sensitivity %, (range)	Specificity %, (range)
Leukocyte esterase test	83 (67-94)	78 (64-92)
Nitrite test	53 (15-82)	98 (90-100)
Leukocyte esterase or nitrite positive result	93 (90-100)	72 (58-91)
Microscopy, white blood cells	73 (32-100)	81 (45-98)
Microscopy, bacteria	81 (16-99)	83 (11-100)
Leukocyte esterase test, nitrite test, or microscopy, positive finding	99.8 (99-100)	70 (60-92)

TABLE 2 Sensitivity and Specificity of Urine Analysis Components (3, 11)

sample can be analyzed under a microscope to quantify the WBC concentration; 5 WBCs per high-power field is considered pyuria. (11) Infants empty their bladder more frequently, therefore gram-negative bacteria do not have the 4 hours required to form nitrites. For this reason, the nitrite test has a lower sensitivity in infants. The absence of nitrites does not rule out a UTI, however the test has a high specificity, thus the presence of nitrites is suggestive of UTI. Collecting information on the presence of WBCs and nitrites, as well as the WBC concentration, improves diagnostic testing for UTIs. Table 2 summarizes the sensitivities and specificities of urine analysis components.

3.4.3 | Urine Culture

Urine collection for culture must occur prior to starting antibiotics as a single dose of effective antibiotics can sterilize the urine. (4, 8) Bag collection methods are not reliable for culturing. For a clean catch specimen, 10^5 colony forming units (CFU)/mL is indicative of a UTI. In a catheter specimen, 5 x 10^4 CFU/mL is indicative of a UTI. In these specimens, mixed growth is usually indicative of contamination and a repeat sample is recommended. Finally, in SPA, any growth is suggestive of a UTI as this is a sterile procedure. (4) It is important to consider the clinical presentation and the child's age when interpreting a culture result. 10^4 – 5 x 10^4 CFU/mL may represent UTI in neonates, children with immunodeficiency, or children who have recently taken antimicrobial therapies. (3)

3.5 | Management

Goals of treatment include the elimination of the infection, relief of acute symptoms, and prevention of recurrent and long-term complications including hypertension, renal scarring, as well as impaired renal growth and function. (3) The CPS recommends initial treatment with oral antibiotics for nontoxic children with uncomplicated febrile UTIs (no structural abnormality) who can tolerate each dose. (4) Furthermore, the child should be treated empirically for the most likely bacterial pathogens while awaiting susceptibility test results, regardless of age. (3, 4) Therapy must be narrowed to the least broad-spectrum antibiotic when susceptibility results become available. Cefixime is a common antibiotic choice for outpatients presenting with their first febrile UTI. (4) Other common oral antibiotics are amoxicillin, amoxicillin/clavulanate, co-trimoxazole, cefprozil, and cephalexin. Other options include ampicillin, ceftriaxone, cefotaxime, gentamicin, and tobramycin. (11) Note that for complicated UTIs associated with a structural abnormality, IV antibiotic therapy is recommended. (4)

4 | BEYOND THE INITIAL APPROACH

4.1 | Infants Less than 2 Months of Age and Ill-appearing children

In the neonatal period, symptoms and signs are nonspecific. It is important to consider this age group carefully as children presenting with respiratory symptoms may

have an appreciable risk of UTI. (3) Furthermore, in ill-appearing children with no other symptoms, the clinician should consider bacteremia and sepsis, as well as their appropriate work-ups. (4)

4.2 | Role of Imaging and Other Investigations

Imaging is not routinely used in children with cystitis. The objectives of imaging in the context of children with a UTI is to confirm pyelonephritis and identify VUR or other structural abnormalities of the urinary tract. (4) Currently, RBUS is commonly used in children and it is recommended as a standard tool in children <2 years of age with a first febrile UTI as it is non-invasive and inexpensive. (12) Previously, a VCUG was recommended in this age group. A VCUG is optimal for diagnosing and staging suspected VUR. A dimercaptosuccinic acid scan is the best tool for identifying an upper UTI and renal scarring, however it exposes patients to radiation and is therefore not routinely performed unless results may alter treatment. (13) Laboratory tests such as procalcitonin and C-reactive protein can be measured; if elevated, they can suggest renal involvement.

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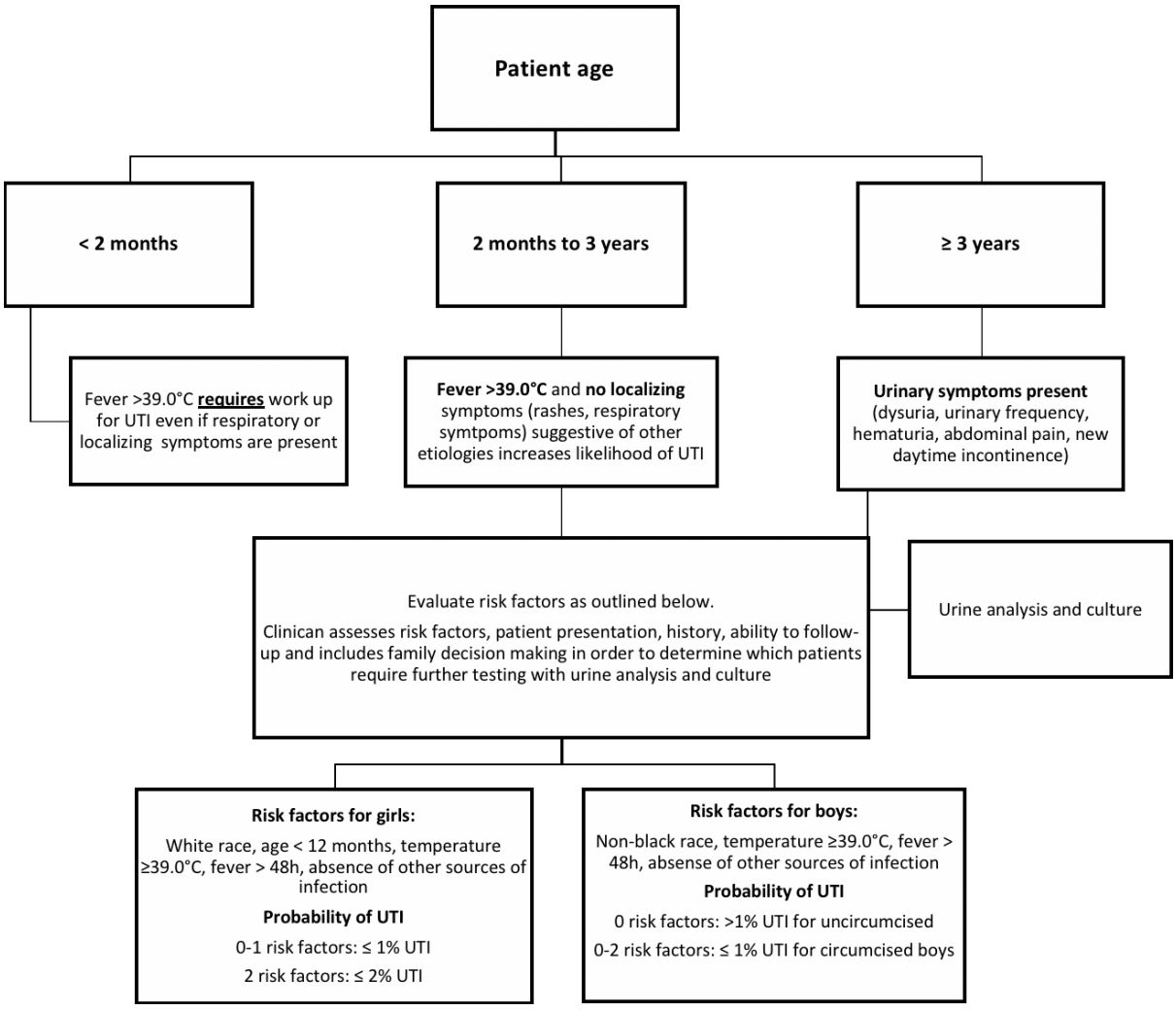
5 | TABLES & FIGURES



FLOWCHART 1 Approach to UTIs in infants and children of different ages

APPROACH TO
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Acute Lower Back Pain (LBP) in the Primary Care Setting

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ABSTRACT

Between 50 and 80% of adults will experience lower back pain during their life. (1) This condition is responsible for a significant portion of emergency room and primary care consultations and it creates a significant burden on the healthcare services and costs. Even if lower back pain causes a significant impact on the quality of life of the patients most causes are benign. This article presents a systematic approach to identifying the cause of lower back pain, summarizes the indications for further workup and presents current evidence for the management of this condition.

KEYWORDS
Lower back pain, Physical treatment, Pharmacology, Family medicine, Orthopedic Surgery

1 | QUESTION

Miss M. is a 55-year-old female who works as a cashier in a grocery story. She has hypertension, dyslipidemia and diabetes. She takes Lipitor, Metformin and Ramipril. describes herself as physically inactive. She presents to her family doctor complaining of a diffuse pain localized in her lower back. Although she is unable to put a finger on the pain, she tells you that it's worse at the end of her workday and has been going on for the last 2 weeks. She is taking Tylenol for the pain which seems to help. She denies any incontinence, saddle anesthesia, leg weakness or numbness.

On physical examination she has no point tenderness on palpation of her back, a normal range of motion, strength of the lower extremities is 5/5 on both sides, and her sensation to light touch over dermatomes L2-S2 is normal and symmetrical. She has 2+ reflexes at her patellar and Achilles tendon bilaterally. Examination of her gait is normal and a straight leg raise reveals minor pain on the right side throughout the range of motion.

She tells you that her sister has a herniated disk. She

is worried that she may have the same condition and requests an MRI.

As the family doctor, what is the next best step?

A. Order an MRI to rule out neural compression or malignancy

B. Prescribe two weeks of muscle relaxants and narcotics for the pain

C. Give her a medical leave from work and recommend bedrest for three days.

D. Reassure her that she does not need an MRI as this is likely benign and self-limited.

E. Urgent referral to a neurosurgeon.

2 | ANSWER

D. This is a physically inactive patient that has started a new job which requires a significant amount of standing. She does not report trauma, is not known for risk factors of pathological spine fracture, and has no history of cancer. She comes in complaining of symptoms that correspond to this new physical demand. The description of her symptoms are localized to her lower back with no radiation, and appears with fatigue at the end of the day. The physical examination is completely normal and she has no signs or symptoms of cauda equina syndrome. This case represents an uncomplicated mechanical back pain without worrisome features. This condition is common, requires no investigations and is self-limited. Reassurance is the mainstay of treatment, but physical treatment, non-steroidal anti-inflammatory medications might help the symptoms.

3 | INITIAL APPROACH

When a patient presents with lower back pain, we are interested in understanding the mechanism of injury, onset of the symptoms, location and radiation of the pain, provoking factors, associated neurologic deficits and systemic manifestations to determine whether the cause of the symptoms is worrisome or not (Fig. 1). Common causes are described later and summarized in Table 2. The next step is to provide expert referral and further workup when a serious etiology is suspected. In cases of benign causes of lower back pain, the three key components of management are described later in the text.

Trauma
History of cancer
Systemic symptoms (weight loss, fever…)
Urinary or fecal incontinence
Steroid use
Progressive neurologic deficit
Saddle anesthesia
Immunosuppression
IV drug use

TABLE 1 Red flags of lower back pain

3.1 | Red flags of lower back pain

While questioning the patient, the clinician must keep in mind that their main goal is to differentiate benign from potentially dangerous and devastating causes of lower back pain. Cauda equina syndrome is the most time-sensitive and potentially catastrophic cause of lower back pain. To assess the risk of the patient having a serious cause for their symptoms, it is imperative to look for red flags (Table 1).

3.2 | Physical Examination

A pertinent physical examination includes the inspection of the back for deformities, bruises or skin changes. Palpation of the spine and paravertebral soft tissues can allow the clinician to elicit a focal area of tenderness which might help in differentiating a skeletal from a muscular etiology. Examination of the range of motion and gait will give the examiner an estimation of the functional deficit and may hint to inflammatory causes, infectious causes, or neurologic impairment. A quick distal neurologic examination is essential and should include testing light touch sensation, strength of the L2 to S2 myotomes, and testing the reflexes of the patellar and Achilles tendons.

	Benign	Dangerous
Mechanical	Muscle strain	Fracture (potentially)
	Degenerative back pain	
	Sacroiliac symptoms	
Malignant		Metastasis
		Multiple myeloma
Neurogenic	Radicular back pain (sciatica)	Cauda equina syndrome

TABLE 2 Summary of causes of lower back pain

3.3 | Common and less common causes of lower back pain

3.3.1 | Mechanical causes

Muscle strain: This is the most common cause of back pain. It often appears in the context of rapid movement or physical activity. The pain is usually acute and associated with reproducible tenderness on paravertebral palpation. It is characterized by stiffness and difficulty bending the spine. It is self-resolving and improves with rest, ice, and analgesia.

Fracture: Vertebral compression fractures account for 4% of patients that present to a primary care setting complaining of back pain. (1) In the context of high energy trauma and is likely to be pathological when no trauma is involved. The index of suspicion of fractures should be high in patients with cancer and osteoporosis. Spine fractures are potentially unstable and might lead to neural compromise if not treated appropriately. Fractures require consultation with a spine surgeon.

Degenerative back pain: It is caused by facet degeneration. This cause is more common in older adults and is worse with physical activity such as standing for long periods of time or lifting objects. It is not associated with trauma. Patients will describe it as dull, worse at the end of the day, and worsened by exertion.

Sacroiliac symptoms: The pain is located in the lower back overlying the sacroiliac joint. It is often bilateral, worse when standing still and with activity.

3.3.2 | Malignancy

The clinician should have a high index of suspicion in patients with a history of cancer. The patient often describes an insidious onset and systemic symptoms such as weight loss, anorexia, and night pain. These patients are at high risk for complications and pathologic fractures. When cancer is suspected as the cause of back pain, an expert consultation is warranted.

3.3.3 | Infectious

Infectious causes of back pain are often associated with fever and systemic symptoms. It is common in a patient who recently underwent a spine surgery, is an IV drug user, or has had a recent bacteremia. An epidural abscess is an urgent infectious cause that requires timely diagnosis and immediate treatment with intravenous antibiotics as well as a surgical consultation for possible drainage. Patients coming from a tuberculosis endemic region of the world that present with multi-level back pain should raise the suspicion of tuberculous spondylitis.

3.3.4 | Neurogenic

Radicular pain: It is a condition more common in older adults and is associated with unilateral leg pain in a dermatomal distribution. It is called sciatica when the radiating pain follows the course of the sciatic nerve (posterior or lateral leg extending to the foot or ankle) due to irritation of the L5-S1 spinal roots. The patient might have a positive straight leg raise test and their symptoms are usually not acute. Symptomatic disk herniations or spinal stenosis account for 3-4% of cases of back pain seen in primary care. (1)

Cauda Equina syndrome: This syndrome is caused by the neural compression of the cauda equina. This is a

surgical emergency. Worrisome findings on history or physical exam such as bilateral leg pain, lower extremity weakness, saddle anesthesia, bowel or bladder symptoms warrant further worker and urgent neurosurgical or orthopedic surgery consultation. Cauda equina syndrome is most commonly due to disk herniation, ankylosing spondylitis, lumbar puncture, trauma or malignancy. (2)

3.4 | Working up lower back pain

After having considered the demographics of the patient, taking a history and conducting a focused physical examination, the clinician will be able to determine which investigations, if any, are relevant.

79% of asymptomatic adults between 50 and 65 have radiological abnormalities of the spine which do not warrant any intervention. (3) For this reason, there is no indication for any imaging or work-up in the first 6 weeks for a patient presenting with low back pain without worrisome features (Table 1). (4)

It is indicated to image the patient starting with an X-ray in cases of trauma, worsening neurologic deficit, or when an infection or a malignancy is suspected. (3) Further imaging such as a computed tomography (CT) or a magnetic resonance imaging (MRI) may be the next step if an X-ray does not allow a diagnosis or if a pathology involving the spinal canal is suspected.

If an evident fracture is identified, expert consultation is warranted to rule out instability and the need for surgery. If a CT or MRI reveal an infection, neural compression, malignancy or infection, urgent expert consultation is necessary.

The role of laboratory tests in lower back pain is to identify infectious and malignant causes. An elevated c-reactive protein (CRP), white blood cell count (WBC), and erythrocyte sedimentation rate (ESR) and the presence of fever are suggestive of an infective etiology. (5) In cases where a multiple myeloma is suspected, the best initial test is a serum protein electrophoresis. (6)

4 | BEYOND THE INITIAL APPROACH

4.1 | Managing Lower back pain

In 75% to 90% of patients, acute lower back pain improves within a month. (7) Initial management of the patient suffering from lower back pain without worrisome features includes three key spheres of intervention: reassuring and educating the patient, pharmacological interventions, and physical interventions.

It is important to explain to the patient with simple lower back pain that the condition is likely to improve by itself and to reassure them of the benign and widespread nature of the condition. Immobilization should be discouraged, and the patient should be recommended to stay active and limit time off from work in order to reduce long-term disability and accelerate recovery. (8)

Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen seem to offer a mild effect in short-term pain reduction and disability. (9) (10) Muscle relaxants and narcotics offer no benefit in short-term pain relief compared to NSAIDS and acetaminophen, and multiple studies have raised concerns with regards to their side effects and risks. (11)

Physical treatment modalities proven to improve lower back pain and increase function include physical therapy, spinal manipulation by trained specialists (12), and active mobilization exercises such as tai chi, yoga or any other prescribed exercises. All these methods are safe and effective, but spinal manipulation appears to offer a larger benefit than mobilization in regards to pain reduction and functional improvement in chronic lower back pain patients. (13) Application of cold or warm compress to the painful region is safe and may result in a mild improvement in symptoms. There is insufficient evidence to favor the use of one over the other. (14) Acupuncture for non-specific lower-back pain remains unproven. (15) In summary, physical treatment modalities should be used as often as possible as they are safe, cost efficient, and associated with high patient satisfaction and symptom improvement. (16)

5 | CONCLUSION

A recent systematic review estimated the global point prevalence of activity-limiting low back pain lasting for more than one day was 12% and the one-month prevalence was 23%. (17) This common condition accounts for many primary-care consultations and is self-limited in most cases. Due to the high number of asymptomatic individuals with radiological anomalies, imaging is reserved for cases of trauma or when malignancy, infection, or neural compromise are suspected. Treatment of lower back pain focuses on alleviating the acute symptoms and preventing chronicity by educating the patient, favoring physical treatments, and providing symptom management with NSAIDS and/or acetaminophen while limiting the use of narcotics or muscle relaxants.

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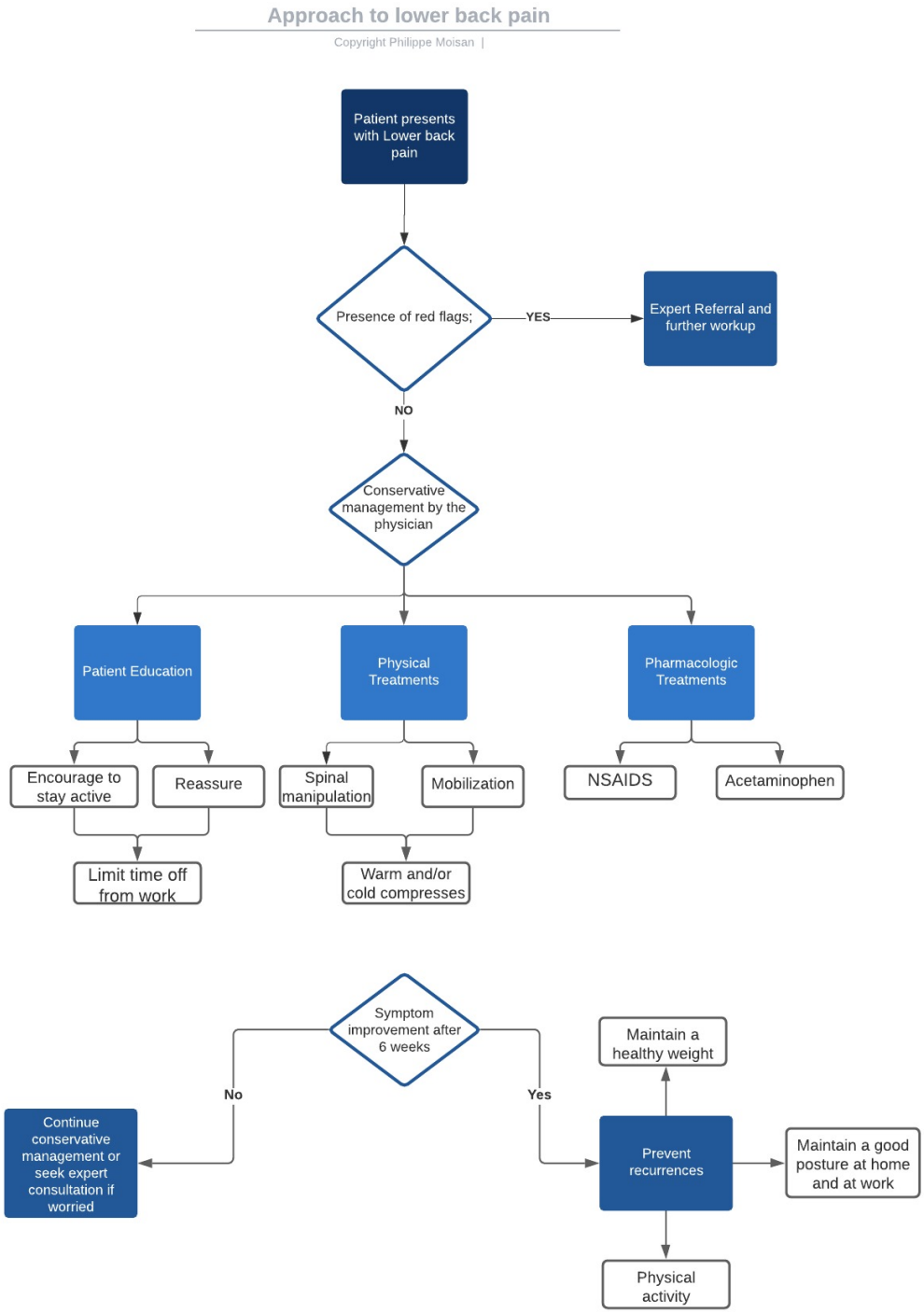
6 | TABLES & FIGURES



FLOWCHART 1 Flowsheet summarizing the approach and management of lower back pain

APPROACH TO
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Approach to fall in an elderly patient

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ABSTRACT

25% of elderly adults fall every year. As most of disease entities seen in Geriatrics, falls are often multifactorial. A systematic approach is therefore key to identify causes and address them. This review summarizes the main causes of falls in the geriatric population, an approach for work-up, and key aspects for its management and prevention.

KEYWORDS
Geriatrics, Fall, Elderly

1 | QUESTION

An 80-year-old man who did not seek medical attention for several years presents to the Emergency Department for recurrent falls at his house. His past medical history includes hypertension, dyslipidemia, ischemic stroke (2 years ago), COPD, diabetes, and BPH with a history of urinary retention 6 years ago. He had cataract surgery in his left eye 1 year ago. He weighs 80 kg and measures 1.65 m tall. His medications are:

- Perindopril 4 mg + Indapamide 2.5 mg PO daily
- Rosuvastatin 40 mg PO daily
- ECASA 80 mg PO daily
- Inspiolto 2.5 mcg + 2.5 mcg INH daily
- Pantoprazole 40 mg PO daily
- Metformin 850 mg PO BID
- Glyburide 10 mg PO BID
- Tamsulosin 0,8 mg PO daily
- Dutasteride 0,5 mg PO daily
- Lorazepam 1 mg po QHS regular
- Vitamin D 10,000 units qweek
- Acetaminophen 650 mg PO QID regular

Physical examination shows BP 110/70 and HR 95 bpm when sitting and BP 89/62 with HR 108 bpm

when standing. As he was standing up, the patient reported transient blurry vision and dizziness. The tongue is swollen and tender to palpation. A 2/6 systolic murmur is heard. Multiple ulcers are observed on both feet and decreased sensation is present. The patient has difficulty standing up from the chair and an unstable gait is noticed.

Lab results are:

- Hb 100 g/L (normal 130-170)
- MCV 115 fL (normal 80-100)
- Platelets: 380x109/L (normal 130-400)
- WBC: 7x109/L (normal 4-10)
- Na 141 mmol/L (normal 136–146 mmol/L)
- K 4.0 mmol/L (normal 3.5–5.1 mmol/L)
- Urea 8.1 mmol/L (normal 2.1–8.0 mmol/L)
- Cr 99 mol/L (normal 49–93 µmol/L)
- Cl 100 mmol/L (normal 98–107 mmol/L)
- Ca total 2.40 mmol/L (normal 2.12–2.52 mmol/L)
- Mg 0.65 mmol/L (normal 0.74–1.03 mmol/L)
- PO4 1.41 mmol/L (normal 0.81–1.58 mmol/L)
- HCO3 26 mmol/L (normal 21–32 mmol/L)
- Glucose 6.0 mmol/L (normal 4.0–11.0 mmol/L)
- CK 320 IU/L (normal 30–250 IU/L)

What is the best next step in management?

A. Measure serum vitamin B12 level
B. Perform EKG
C. Perform CT head without contrast
D. Start IV fluids
E. All of the above
F. All of the above except c

2 | ANSWER

Based on the clinical presentation, multiple diagnoses can be suspected. The patient has orthostatic hypotension since his systolic BP drops over 20 mm Hg and his heart rate increases over 20 beats per minute when standing from a seated position. It might be caused by polypharmacy including his antihypertensive medication and -1 blocker, as well as by dehydration, which is reflected in the elevated CK, Cr and urea. Other medications, such as benzodiazepines, can also cause falls. Therefore, medication review and IV fluids can be helpful. A systolic murmur has been identified and warrants further investigation with ECG as the first step. The macrocytic anemia with signs of peripheral neuropathy suggests vitamin B12 deficiency, so serum levels should be measured. In this situation, a CT head is not absolutely indicated, given the absence of focal neurological deficit and normal level of consciousness.

3 | INITIAL APPROACH

Falls, like any geriatric syndrome, is often multifactorial. It is often the result of several predisposing factors, which puts the patient at increased risk of falls, and of a precipitating factor, which is commonly an environmental hazard or an acute or worsening medical condition. (1-5) Therefore, evaluation of a patient with falls starts with a complete history and physical examination.

3.1 | History of previous fall(s) and near-falling

For each fall, the following components should be covered: time (year, month), any medical visits or hospitalizations, activity of the patient at the time of fall, prodromal symptoms (e.g. light-headedness, difficulty breathing), location of the fall (indoors? outdoors? anything on the floor that precipitated the fall?), mechanism of fall (e.g. whole body on the ground? outstretched hands?), loss of consciousness, and change in medication. Loss of consciousness suggests orthostatic hypotension, cardiac and/or neurological disease, and potentially serious injuries from the fall. (1-4)

3.2 | Environmental hazards

These hazards are defined as any item or situation in the environment that puts one at risk of falls. One can ask about rugs, slippery or uneven floors or bath tub, or dif-

ficult stairs. (1-5)

3.3 | Activities of daily living (ADLs) and instrumental activities of daily living (iADLs)

Asking about ADLs and iADLs are essential when assessing any elderly patient. They portrays the functionality of a patient and reflect his/her social environment. Limitations in ADLs and iADLs points to some impairment (e.g. cognitive, mobility) and helps to guide management, such as the involvement of other health professionals including an occupational therapist, physiotherapist, or social worker. ADLs include bathing, dressing, eating, urinary/fecal continence, and mobility. iADLs include cooking, shopping, managing medications, managing finances, housework, and transportation. (1-4)

3.4 | Orthostatic hypotension

Orthostatic hypotension should be evaluated for any patient presenting after a fall. It is a quick, easy, and readily available test that can be performed in virtually any setting. It constitutes an important and reversible cause for falls. To evaluate for orthostatic hypotension, the patient should be supine for 5 minutes before blood pressure and heart rate are measured. Then, the patient stands up and vital signs are measured once more within 2 minutes of standing. A patient meets criteria for orthostatic hypotension if the systolic blood pressure drops 20 mm Hg, the diastolic blood pressure decreases 10 mm Hg, or the heart rate rises 20 beats per minute. Once a diagnosis has been established, clinicians should look for its cause, which is commonly autonomic dysfunction, medications, or dehydration. Medications that frequently cause orthostatic hypotension include tricyclic antidepressants, anxiolytics, levodopa, diuretics. Autonomic dysfunction can be screened by asking for symptoms of dizziness, loss of consciousness, incontinence, constipation, and impotence. It can take place in the context of diabetes, vitamin B12 deficiency, stroke, multiple system atrophy, or Parkinson's disease. (1-6)

3.5 | Gait, balance, and lower extremity strength

Assessment for these components should start with a thorough history. The clinician should ask questions about difficulty with balance/walking, use of assisting devices, level of mobility (e.g. bed-bound? chair-bound? regular exercise?), and environmental hazards (e.g. carpets). Then, on physical exam, the following components are routinely assessed: a) observation of gait (asymmetry, wide base, slow, shuffling, posture, arm swinging), b) Romberg, c) Timed Up and Go, d) 30-second chair stand, e) 4-stage balance. (1-4)

3.6 | Vision

Decreased visual acuity, defined as a visual acuity of 20/40 and less, impairs the sensory part of balance and can prevent one from adequately assessing the environment. Visual acuity can be assessed with a Snellen chart. Patients wearing glasses at the time of fall should keep them on during the assessment. Each eye should be evaluated separately. Visual fields should also be assessed. Interestingly, multifocal lenses, or lenses containing multiple prescriptions, are not recommended when walking outdoors and going up/down the stairs as they are found to increase the risk of falls. (1-5)

3.7 | Audition

Impaired hearing capacity may suggest a deficit in the vestibular system. Hearing can be tested via the whisper test: the examiner stands at arm length behind the patient and while the opposite ear is occluded, the examiner orates some words or numbers that the patient has to repeat. If the test is abnormal, Rinne and Weber tests can be performed to distinguish sensorineural from conductive hearing loss. (1,3,4)

3.8 | Feet and footwear

Foot deformities (e.g. callouses, arthritic deformities) and inappropriate footwear impair the contact between

the feet and the floor. Poorly-fitted footwear, high heels, and unlaced shoes are associated with an increased risk of falls. Additionally, sensory function in the feet should be tested, as proprioception can be impaired in diabetes, vitamin B12 deficiency, and other diseases. (1-5)

3.9 | Cognition

Dementia can impair environmental awareness and/or create neurological deficits. Cognition can be assessed with Folstein's Mini Mental State Examination. An abnormal score is 25. If a patient scores well but dementia is still suspected, a MOCA can be performed to test executive function. (1-5)

3.10 | Medication review

Polypharmacy, defined as the daily intake of 5 medications, particularly affects elderly individuals. It is important to pay close attention to medications causing sedation, confusion, or orthostatic hypotension, and to medications that interact with alcohol and other medications. To help with medication selection, the American Geriatrics Society developed Beers Criteria. Medications strongly linked with falls include SNRIs, opioids, benzodiazepines, and "Z-drugs" (Eszopiclone, Zaleplon, Zolpidem). Over-the-counter drugs should also be considered (e.g. dimenhydrate, diphendramine).

Patient compliance should also be evaluated. Poor patient compliance can lead to exacerbation of medical illness and precipitate falls. Notably, elders are recommended to take vitamin D supplements, especially in Northern countries where exposure to sunlight is limited. Deficiencies in vitamin D cause neuromuscular dysfunction, decreased muscle strength, and increased risk of osteoporosis. (1-7)

3.11 | Investigations

There is no consensus on lab tests and imaging modalities that should be performed in the setting of falls. The following are investigations commonly ordered:

- **CBC**: Hemoglobin can help support the diagnosis of anemia or of hemoconcentration, suggesting dehydration. If anemia is diagnosed, the mean corpuscular volume can be helpful in determining the cause of anemia. For patients presenting after a fall, special consideration should be given to macrocytic anemia associated with vitamin B12 deficiency as it can cause peripheral neuropathy. (2)
- **Creatinine kinase (CK)** : CK is an essential enzyme for muscle contraction. Elevated CK can be seen in rhabdomyolosis, dehydration, and with use of statins. Serum CK level can help to estimate the timing of falls, especially if the patient lost consciousness or was unwitnessed. (8)
- **Chem10**: Abnormalities in electrolytes can reveal renal injury. Hypoglycemia may precipitate a fall, and hyperglycemia may hint diabetes and the possibility of peripheral neuropathy. (2)
- **CT head**: This investigation is not routinely performed for elders presenting after a fall. The indications are decreased consciousness, focal neurological deficits, and history of post-traumatic lesion. The use of antiplatelet or anticoagulant is not an absolute indication but should be considered. (9)
- **EKG**: EKGs can help to identify arrhythmias that might have caused a syncope-associated fall. (1-5)

4 | BEYOND THE INITIAL APPROACH

This section covers special considerations for the management of important causes of falls in the elderly population.

- **Orthostatic hypotension**: Educate patients to rise slowly from bed or chair and to take a pause prior to walking. Elastic stockings and adequate hydration (i.e. 1.5-2L/day with adjustments based on the patient's medical conditions) are recommended. The clinician should discharge any non-essential medication or reduce dosage if possible. If hypotension is persistent despite these interventions, patients can be started

on midrodrine (an adrenergic 1-agonist) or fludrocortisone (a synthetic mineralocorticoid). (1-6)

- **Difficulty with gait or balance**: Involve physiotherapists and occupational therapists to help patients with mobility reconditioning and to assess patients' needs in terms of living environment. (1-4)
- **ADLs and iADLs**: If a patient requires regular assistance, lives in a setting that is inappropriate for their needs, or is suspected of suffering from abuse or neglect, social workers should be involved. Close family members can also be consulted. (1-4)
- **Vision**: An eye exam every 1-2 years is recommended. If cataract is suspected, refer to an ophthalmologist. (1-5)
- **Audition**: If vestibular dysfunction is suspected, refer to an otolaryngologist. (1,3,4)
- **Feet and footwear**: Counsel patients to not walk barefoot or in stockings as these modalities are more slippery and the risk of infection/injury is higher. Recommend foot care with a podiatrist. (1-5)
- **Medication review**: A medication review should be done for every patient and if available, pharmacists can be consulted. If discontinuation of a medication is chosen, gradual tapering down might be required to prevent withdrawal. If there are issues with patient compliance, dispills can be helpful and local community centers can also provide assistance with medication administration. (1-6)
- **Environmental hazards**: Involvement of an occupational therapist is recommended for a complete assessment of environmental hazards. Night lights are suggested. Consider involving social work if the patient's living situation is not considered appropriate for his/her needs. (1-5)
- **Elevated CK**: Generous hydration is recommended, whether oral or intravenously. (8)
- **Hypoglycemia**: Ensure appropriate food intake and adjust diabetic medications if needed. (10)
- **Hyperglycemia**: Measure HbA1c and adjust medication if needed.
- **If abnormal CT head**: Consider consultations with Neurology and Neurosurgery. If a bleed is observed (see Figure 1), arrest antiplatelet and anticoagulation therapies. (9)

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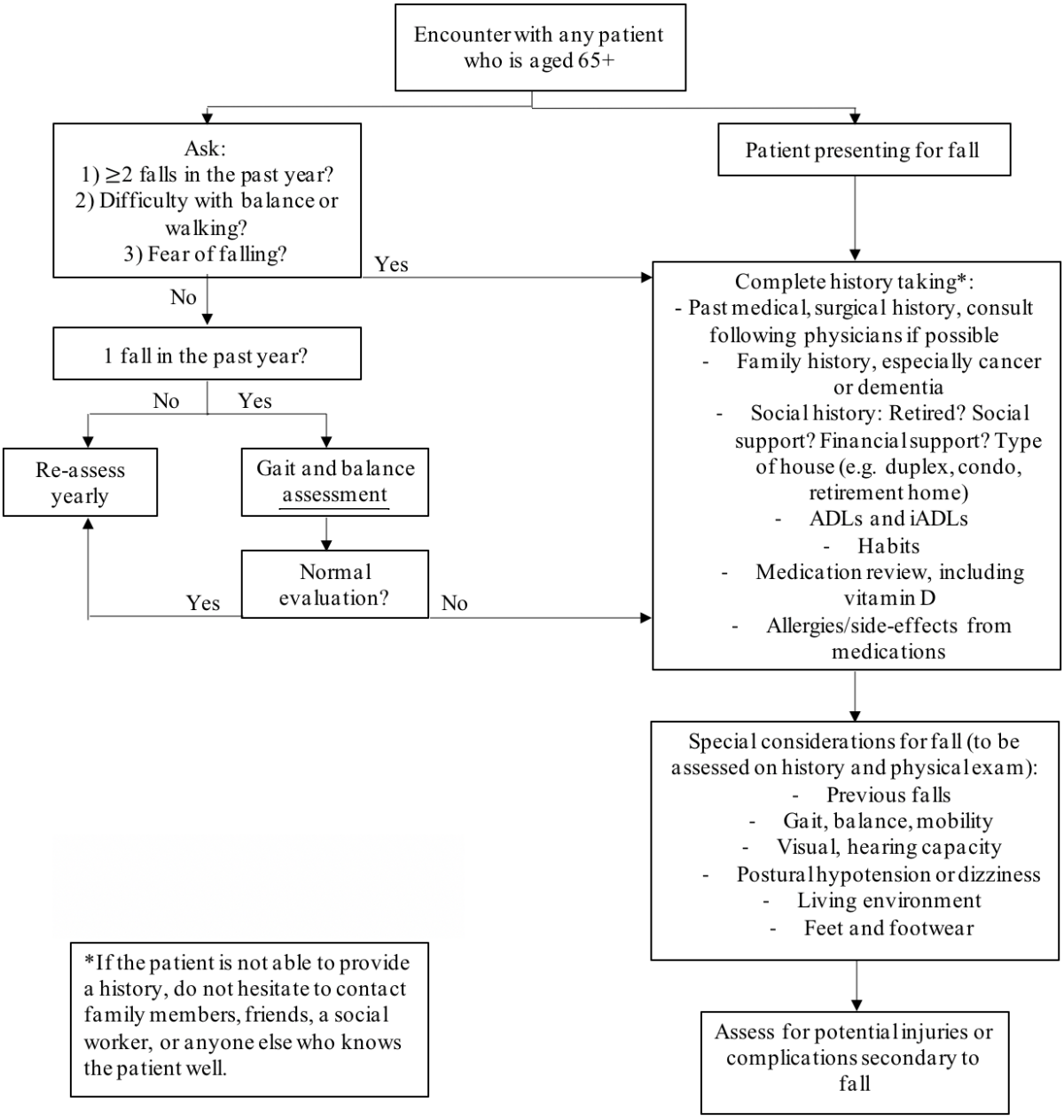
5 | TABLES & FIGURES



FLOWCHART 1 Approach to fall in an elderly patient. Basic algorithm for the diagnosis of fall.

Adapted from: Summary of the updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. (4)

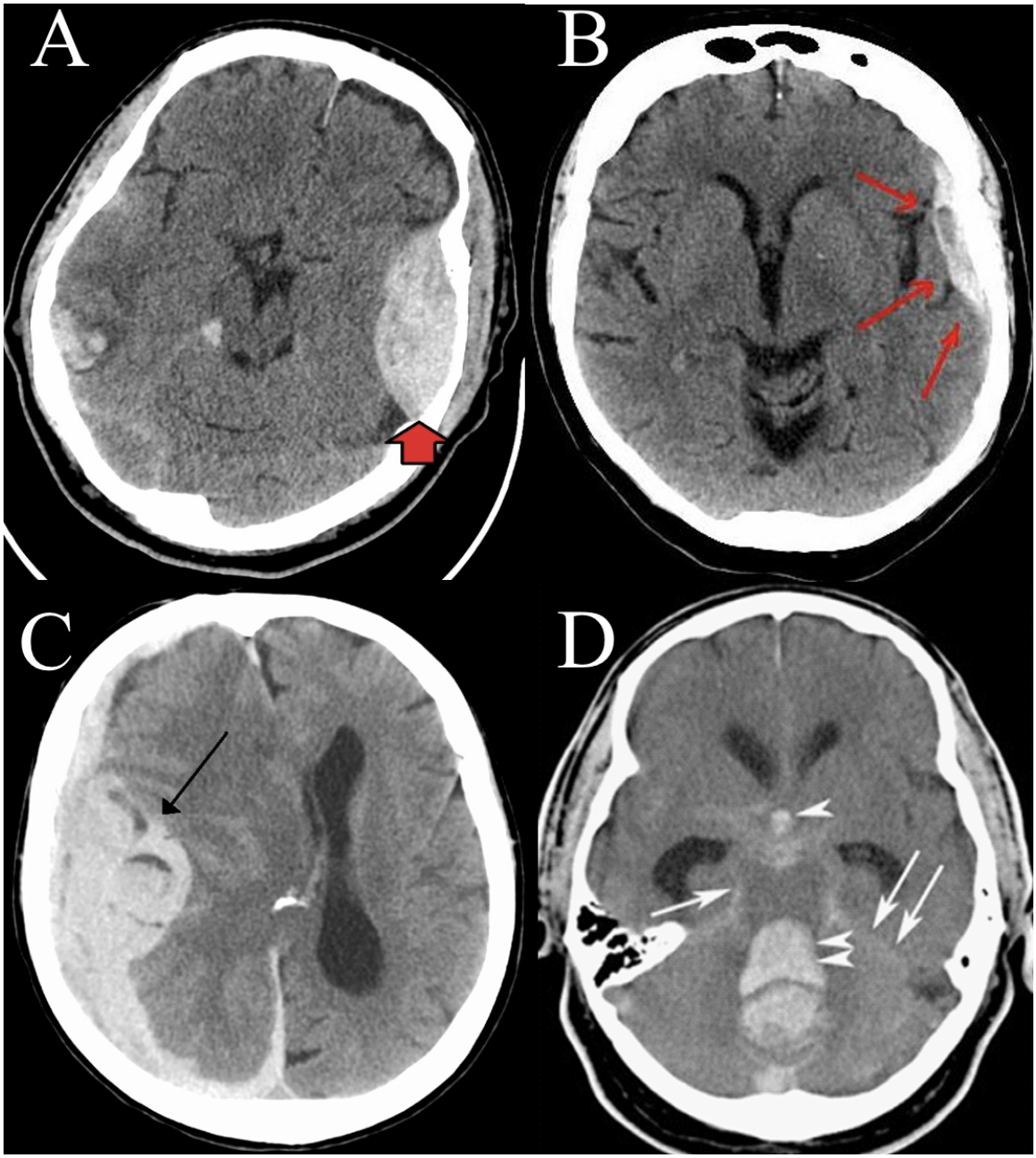


FIGURE 1 Different types of cranial hematomas on CT head.
A) Epidural hematoma. (11)
B) Subdural hematoma. (12)
C) Intracranial hematoma. (13)
D) Subarachnoid hematoma. (14)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