Expediting the Diagnosis of Hypertension
CAMPBELL ET AL.

Non-Alcoholic Fatty Liver Disease:
From Obesity to Liver Transplant
ANYANE-YEBOA AND STEWART
2 companies

1 vision

0 compromise

Anticoagulant Alliance
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Taking Every Opportunity to Reduce Cardiovascular Risk

In North America, heart disease is the leading cause of death for both men and women; accounting for approximately 1 in every 4 deaths. Coronary heart disease (CHD) is the most common type of heart disease and two of the key risk factors for CHD are hypertension and diabetes. After smoking cessation programs, the detection and management of hypertension, and of diabetes, may be the next most important interventions that physicians can offer to reduce the risk of cardiovascular morbidity and mortality.

In this issue of the *Canadian Journal of General Internal Medicine* there are two important articles that relate to this topic. The article by Campbell et al discusses the new recommendations (2015) of the Canadian Hypertension Education Program that are designed to expedite the diagnosis of hypertension. This is particularly important in light of the significant problem of undiagnosed, and undertreated, hypertension. With so many therapeutic options for managing hypertension it is unacceptable to have patients suffer the consequences of untreated hypertension.

In the second article, Gilmour and Yu review the clinical practice guidelines of the Canadian Diabetes Association (2013). Beyond the change in diagnostic criteria, and discussing the choices for second line therapy in type 2 DM, the guidelines also emphasize the need to address vascular protection in this “at risk” population.

Both hypertension, and diabetes, are extremely common conditions among patients that internists see, either occurring as the primary problem or, more commonly, as a co-morbidity. It is in the latter situation that we need to ensure that clinical management is optimal, and evidence based, and when the patient returns to the care of their primary health care provider that this path will continue. So while the patient’s presentation may be, for example, an acute exacerbation of COPD, or for the investigation of an unusual arthropathy, we need to see these clinical situations as opportunities to improve (where necessary) the management of the two important co-morbidities. These clinical encounters are potential teachable moments for the patients and for the referring physician. Therefore implementing, and communicating, the clinical guidelines for hypertension and diabetes management, will be important in all circumstance.

Réduire le risque cardiovasculaire : chaque occasion compte!

En Amérique du Nord, les maladies du cœur causent environ un décès sur quatre chez les hommes et les femmes et constituent ainsi la principale cause de mortalité\textsuperscript{1,2}. La cardiopathie la plus courante est la coronaropathie. Deux de ses principaux facteurs de risque sont l’hypertension et le diabète. Hormis les programmes d’abandon du tabac, la détection et la prise en charge de l’hypertension et du diabète représentent la meilleure intervention qu’un médecin peut offrir pour réduire le risque de morbidité et de mortalité cardiovasculaires.


Dans le deuxième article, Gilmour et Yu examinent les lignes directrices de pratique clinique de l’Association canadienne du diabète (2013). En plus d’apporter des changements aux critères diagnostiques et d’analyser les choix disponibles comme traitement de deuxième intention dans les cas de DT2, les lignes directrices soulignent également la nécessité de se préoccuper de protection vasculaire chez cette population « à risque ».

L’hypertension et le diabète sont des affections extrêmement courantes chez les patients que les internistes rencontrent, soit en tant que trouble principal ou, plus fréquemment, en tant que maladie concomitante. C’est dans ce deuxième cas que nous devons nous assurer, d’une part, que la prise en charge clinique est optimale et basée sur des données probantes et, d’autre part, que cette voie est maintenue lorsque le patient retourne sous les soins de son fournisseur de soins de santé principal. Ainsi, quand un patient présente par exemple une exacerbation aiguë d’une BPCO ou lors de l’investigation d’une arthropathie inhabituelle, nous devons voir ces situations cliniques comme des occasions pour améliorer (le cas échéant) la prise en charge des deux importantes maladies concomitantes. Ces rencontres cliniques sont des occasions d’enseignement au patient et au médecin orienteur. Pour cette raison, il est important d’appliquer et de diffuser les lignes directrices cliniques concernant la prise en charge de l’hypertension et du diabète en toute circonstance.

Mitch Levine

Acute Care SINS: Surgical Insights for the Non-surgeon
Chapter 12: Brain Surgery SINS

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Summary
“Surgical Insights for the Non-surgeon,” or SINS, is composed of several short chapters intended to cover fundamental surgical knowledge for non-surgeons. The authors focus on surgical pearls, operative insights, and applied anatomy. In Chapter 12 of this series, the authors address the brain and neurosurgery Part One.

Résumé

“I would like to see the day when somebody would be appointed surgeon who had no hands, for the operative part is the least part of the work.”
—Harvey Cushing, Father of Neurosurgery
Anatomy

First, the disclaimer: brain anatomy can be daunting, and what takes a moment to describe can take a career to master. Moreover, there are variations in our "brain wiring," such that cerebral insults (whether strokes, trauma, or tumours) affect people differently. However, a basic knowledge of neuroanatomy means that pinpointing the injury usually explains the deficit, and informs the prognosis.

The cerebrum (Figure 1) has four primary lobes: frontal, temporal, parietal, and occipital. It contains folds that i) increase its surface area (two-thirds of the brain is hidden in the folds), and ii) increase its ability to grow (a smooth brain’s growth would be limited). These folds, in turn, are called i) sulci: depressions or grooves, the singular of which is sulcus; ii) gyri: the intervening up-swelling, the singular of which is gyrus, and iii) fissures: larger grooves separating the brain into primary lobes and into two hemispheres. The lateral fissure (a.k.a. the lateral sulcus or the Sylvian fissure) separates the frontal and parietal lobes (above) from the temporal lobe (below). The midline interhemispheric fissure separates the brain into left and right hemispheres. The central sulcus/fissure (a.k.a. the Rolandic fissure) divides the frontal and parietal lobes.

The pre-central gyrus (i.e. the frontal lobe area in front of the central fissure) is responsible for motor output, and the post-central gyrus (i.e. the parietal lobe area behind the central fissure) is responsible for sensory input from the body. Regarding speech, the left hemisphere is “dominant” (meaning it mediates speech) in > 95% of right-handed individuals and approximately 85% of left-handed individuals. This means that approximately 1 in 7 people will control speech from their non-dominant right hemisphere or have significant bilateral speech representation. Within the frontal lobe, Broca’s area is responsible for speech expression. Within the posterior temporal lobe, Wernicke’s area is responsible for speech comprehension. Damage will cause, respectively, an expressive aphasia (and the inability to utter expressions such as, “no ifs, ands, or buts”), versus a receptive aphasia (fluent but non-comprehensible speech).

The thalamus (from the Greek for "chamber") is a bilateral, midline symmetrical structure, located between the cortex and the midbrain. It relays sensory and motor signals and helps regulate consciousness, sleep, and alertness. Laterally, the basal ganglia comprise the striatum (caudate nucleus and putamen), globus pallidus, substantia nigra, nucleus accumbens, and subthalamic nucleus. The basal ganglia help mediate such diverse behaviours as voluntary motor movements, procedural learning, eye movements, and cognition. These diverse functions help explain why midline (or deep cortical) damage is so serious.

The brain’s ventricles contain cerebrospinal fluid (CSF) (Figures 2a and 2b). The two lateral ventricles are composed of frontal (or anterior) horns, a body, an atrium, temporal (or inferior) horns, and occipital (or posterior) horns. CSF is produced within those lateral ventricles by the choroid plexus. Benign calcifications within the choroid plexus are common and are visible on CT as small hyperdensities—these are not small intraventricular bleeds! CSF drains into a single third ventricle via the interventricular foramen of Monro, then via the cerebral aqueduct of Sylvius to the fourth ventricle. Thereafter, it leaves the ventricular system via the foramen of Luschka laterally and via the midline foramen of Magendie (“lateral Luschka, midline Magendie”). CSF enters the subarachnoid space and is reabsorbed into the superior sagittal sinus through arachnoid granulations. We produce 500 mLs of CSF daily, but the ventricles have capacity for only 150 mLs. This means that CSF is produced and continually reabsorbed. Inability to drain CSF causes hydrocephalus, increased intracranial pressure (ICP), and tissue damage.

Brain herniation (Figure 3) is frequently deadly and occurs when part of the brain squeezes outside of its usual confines. The two categories of herniation are i) supratentorial
Brain SINS

The ventricles of the brain.

Fourth ventricle lateral aperture (foramen of Luschka)

Figure 2A. The ventricles of the brain.

Foramen of Magendie

Foramen of Luschka

Figure 2B. Mid-sagittal illustration of the brain identifying areas of cerebrospinal fluid (CSF) production, flow and reabsorption.

Structures above the tentorial notch and ii) infratentorial (below the tentorial notch). “Tentorial” refers to the tentorium cerebelli, which is the dura mater separating the cerebellum from occipital lobes. Supratentorial herniation can be subdivided into uncal (transtentorial), central, cingulate (subfalcine), and transcalvarial. Infratentorial herniation is of the cerebellum and can be upward (a.k.a. upward cerebellar or upward transtentorial) or downward (tonsillar herniation). Now, on to more clinical matters . . .

Head Trauma

General Comments

- Predictors of good outcome:
  - Younger age
  -prompt surgical treatment of mass lesions
- Predictors of bad outcome:
  - Better neurologic status on arrival
  - i.e. Higher Glasgow Coma Score (GCS)
  - (see Trauma SINS chapter)

Epidural (a.k.a. Extradural) Hematoma (EDH)

- Typically follows trauma to the middle meningeal artery (MMA)
  - The MMA runs in a groove on the inner surface of the thin temporal bone
  - Therefore, it can be torn when the skull is fractured

(transstructures above the tentorial notch) and ii) infratentorial (below the tentorial notch). “Tentorial” refers to the tentorium cerebelli, which is the dura mater separating the cerebellum from occipital lobes. Supratentorial herniation can be subdivided into uncal (transtentorial), central, cingulate (subfalcine), and transcalvarial. Infratentorial herniation is of the cerebellum and can be upward (a.k.a. upward cerebellar or upward transtentorial) or downward (tonsillar herniation). Now, on to more clinical matters . . .
Might be the explanation for how David beat Goliath with just a slingshot!

Bleeding causes the dura mater to separate from the skull’s inner table, filling the epidural space

- **Classic clinical presentation**
  - Brief loss of consciousness (LOC)
  - Followed by a ‘lucid interval’ which is usually brief but can last hours
  - Lucid interval followed by obtundation (due to symptoms of mass effect)
    - Mass effect on ipsilateral motor strip causes contralateral hemiparesis
    - Further mass effect causes uncal herniation (see above)
    - *Which causes ipsilateral pupillary dilatation (a.k.a. “a blown pupil”)*
      - Due to pressure on the ipsilateral third cranial nerve
  - **Evaluation**
    - CT head:
      - Hyperdensity due to acute blood
      - ‘Biconvex’ or lens-shaped hematoma in the epidural space
      - Epidural blood may not spread past bony suture lines
        - This is because the dura mater adheres to the suture lines
        - This contrasts with subdural bleeds (SDH) (see below)
      - Following an EDH, also look for skull fracture on the CT
  - **Medical management**
    - Small volume EDH can be followed (albeit frequently)
      - If no neurological deterioration/focal signs, then no surgery
      - Admit to hospital for observation
      - OPERATE EARLY if patient deteriorates (i.e. if GCS drops)
  - **Surgical management**
    - For symptomatic patients
      - Craniotomy for hematoma evacuation
      - Cauterize any bleeding arteries
    - Simple burr hole is ineffective for an acute epidural hematoma
      - Because acutely clotted blood is too thick to aspirate
  - **Outcomes**
    - Mortality is reduced substantially with surgery
    - Earlier intervention yields better outcomes
      - ‘Time is brain’

**Subdural Hematoma (SDH)**

**Acute Subdural Hematoma**

- **Etiology**
  - Most commonly from tearing of the bridging veins
    - These extend between the cortex and the dural sinuses
  - More common in an atrophied brain
    - (alcohol; advanced age)

  - Bridging veins more likely to tear because of enlarged subdural space
  - i.e. veins are under tension
  - SDH often results from severe acceleration-deceleration head movement
    - This acceleration/ deceleration motion can mean significant injury to the underlying brain

- **Clinical presentation**
  - Patients often more obtunded than those with EDH
  - Also no lucid interval following SDH (versus EDH)

- **Evaluation**
  - CT head shows crescent-shaped hematoma
    - Compared to lens-shaped for EDH
  - Usually over the convexity of the entire hemisphere
    - Compared to blood restricted by suture lines after an EDH
  - Appearance of blood on CT (density) changes over time
    - Acute (first few days)
      - Hyperdense to the brain (white blood; grey brain)
    - Subacute (week to month)
      - Isodense to the brain (grey blood; grey brain)
    - Chronic (greater than 1 month)
      - Hypodense to the brain (black ‘blood’; grey brain)

- **Treatment**
  - If a small bleed (<1 cm, 5 mm midline shift) and a stable/asymptomatic patient,
    - Frequent observation but no automatic need for surgery
  - If large clots: mass effect
    - Typically need a craniotomy for evacuation
  - Bleeding vessels are rarely sought out or found, so rarely need to cauterize
    - In contrast to EDH

- **Outcomes**
  - All surgical decisions should be individualized
    - The decision to operate depends on premorbid state, extent of disease, and patient’s wishes
  - However, mortality following SDH increases with age
  - Therefore, some surgeons are reluctant to operate on those aged over 65 years
  - Therefore, more surgeons are reluctant to re-operate on those aged over 65 years

**Chronic Subdural Hematoma**

- Typically occurs in elderly patients
- Ask about minor head trauma in the preceding weeks
  - Though only recalled in 50% of patients
- Also likely due to tearing of bridging veins
  - But requires less and less head motion as the brain ages
  - Due to the increased stretch on these veins in an atrophied brain
- Often present with several weeks of headache
- Can be confused with meningitis/alcoholism, etc.
• Undiagnosed, this can progress to confusion and focal neurologic deficits
• Most of the blood is old and liquefied
  o Consistency is like ‘motor-oil’ when removed
• In symptomatic patients
  o Evacuate via a burr hole
  o Wash out the blood
  o Plus/minus insert a subdural drain
• Majority of symptomatic patients improve within hours of surgery

Traumatic Subarachnoid Hemorrhage (SAH)
• Blood in the SA space
  o From trauma to small cortical vessels (usually veins)
• More common (and different) than aneurysmal SAH (see below)
  o Less clinically concerning than aneurysmal SAH
• Traumatic SAH has minimal clinical significance in isolation, but serves as marker of a more significant head injury
  o Does not require specific treatment, other than observation
  o Treatment focuses on managing any other associated head injury
• No surgical treatment required
  o Neurologically intact patients managed with observation
  o Repeat imaging, based on GCS
  o Patients may have concussion symptoms during the recovery phase

Intraparenchymal Contusion and Hematoma
• CT appearance is mixed-density following contusion
• CT appearance is high-density following hematoma
• Small contusions in asymptomatic patients can be observed
  o Repeat imaging only if clinical deterioration
• When symptomatic from mass effect, contusions and hematoma may require surgery
  o Via craniotomy
    ▪ Remove blood and dead brain to minimize swelling
  o Via craniectomy
    ▪ Leave bone flap off to give extra room for cerebral edema
• In patients without trauma
  o Intraparenchymal hematomas are usually hypertensive hemorrhagic strokes
  o Typically managed by the stroke neurology team, rather than neurosurgeons
  o Hydrocephalus from posterior fossa blood warrants a neurosurgical opinion

Diffuse Axonal Injury
• Diffuse damage to the brain (as opposed to focal damage from bleed, etc.)
• Shearing of axons
• At the junction of grey and white matter and in the deep white matter
• Patient’s injury may be neurologically devastating, despite CT scan looking relatively innocuous
• MRI can help determine the extent of injury
• Surgical management is limited
  o After all, there are no focal lesions to evacuate
  o Rare decompressive craniectomy (see below) for elevated ICP if medical management fails
• Long-term outcome may be acceptable, even if low GCS initially
  o So, life support may be maintained for longer than following other head injuries

Management of Increased Intracranial Pressure (ICP)

Pathophysiology
• Monro-Kellie doctrine
  o Intracranial volume is constant
  o Therefore, any increase in any one of its contents (brain, CSF, blood, space-occupying lesion) must be offset by an equal decrease in one of the others
  o If not, then ICP increases
    • Increased brain pressure ➤ increased brain swelling ➤ increased brain injury
      ▪ Higher pressure means CSF is displaced through the foramen magnum and venous blood is shunted extracranially
      ▪ Further increased brain pressure obstructs arterial flow
        • Mean arterial pressure (MAP) must increase to maintain status quo
        ▪ If unable to compensate:
          ▪ Decreased oxygenation of cerebral tissue occurs
          ▪ Neuronal hypoxia, anoxia, and death
• Cerebral perfusion pressure (CPP) – and therefore cerebral blood flow (CBF) – depends on MAP (forward flow) minus ICP (obstruction to forward flow)
  o CPP = MAP – ICP
  o CBF = CPP/Resistance
    ▪ BUT resistance cannot be easily measured, so we target CPP
• Normal adult ICP in adults is <10–15 mmHg; sustained >20 mmHg is pathologic
• Cushing’s response
  o Increased ICP causes increased pressure on the brain stem
  o This causes irregular respirations, increased systolic blood pressure, and bradycardia
  o A “Cushing’s response” indicates the body is trying to compensate for higher ICP
    ▪ By increasing systolic blood pressure (SBP) via the sympathetics in order to increase CPP
    ▪ This increased SBP causes reflex bradycardia
  o Cushing’s response indicates that ‘the brain is not happy’
Medical Management of High ICP

- Raise head off bed to 30 degrees to enhance venous outflow
  - Beware, however, because raising the head also decreases cerebral arterial perfusion
  - Therefore, compensate by placing your arterial transducer at the tragus (level with the ear/circle of Willis)
    - Rather than usual phlebostatic axis (level of the heart)
    - Because you want to know the perfusion pressure in the brain
      - Not in the major systemic vessels
    - Or do not move transducer, but instead target a higher CPP
      - i.e. 70 rather than 65 mmHg, to compensate for the raised head
- Mannitol
  - Causes an osmotic diuresis: flow of fluid out of a swollen brain
  - Decreases intravascular volume and raises serum sodium
  - This (hopefully) decreases brain edema, improves blood rheology, and increases CBF
  - Mannitol comes only in 20% solution; 250 mL and 500 mL bags
    - Dose is 0.5–1.0 g / kg; given as an intravenous (IV) bolus
    - Give approximately one large bag for a large person (i.e. 100 g)
    - Give approximately one small bag for a small person (i.e. 50 g)
- Hypertonic saline – same osmotic mechanism as mannitol
  - Currently an alternative to mannitol
  - May lead to less volume depletion, compared to mannitol
  - Dose for 3% hypertonic saline is 150–250 mLs IV
- Hyperventilation – decrease arterial CO₂
  - End Tidal CO₂ can be used to estimate PaCO₂
    - End Tidal CO₂ is usually 5 mmHg less than arterial PCO₂
  - Lower PaCO₂ leads to cerebrovascular vasoconstriction (CVV)
  - CVV leads to decreased intracranial volume
  - HOWEVER, PaCO₂ reduction is a temporary measure
    - New equilibrium will be reached and vessels return to normal calibre
    - Will also decrease brain oxygenation (bad in an injured brain!)
    - Therefore, do not target low PaCO₂ until you need to
    - Also, only hyperventilate to temporize
    - While coordinating definitive management, such as decompression of clot or craniectomy
- Osmotic agents and hyperventilation are used in emergency situations, such as:
  - Acutely elevated ICP
  - Patient arriving in the Emergency Room with un-reactive dilated pupils
  - En route to the OR for emergency surgery
  - Sedation/paralysis/analgesics/anesthetics
    - Given to reduce sympathetic tone
    - Given to reduce ICP effect of voluntary muscle movements
    - Given to reduce cerebral metabolic demands
  - Therapeutic hypothermia
    - Not universally applied, as little evidence of benefit
      - Benefit may just be from avoidance of hyperthermia
    - Theory is that it reduces cerebral metabolic demands
      - Which protects against injury from increased ICP
    - Some believe the lack of benefit is because hypothermia is started too late
- Other
  - Prompt treatment of seizures
  - Avoid hyperglycemia and hypoglycemia

Surgical Management of High ICP

- An intraparenchymal pressure monitor
  - Inserted through the skull and rests in superficial brain tissue
  - Measures ICP, but does not drain CSF
  - For obtunded patients
    - Where serial examinations won’t help determine increased ICP
  - Used for monitoring only (and to direct other treatments)
    - For ventricles that are too small to access with external ventricular drain (EVD)
    - For patients with normal ICP but at risk of increased ICP
    - Potentially for coagulopathic patients
    - If ICP rises despite medical management, definitive management required
      - EVD or surgical decompression
- Use of an EVD (see Surgical Pearls, one through three)
  - Inserted through the skull and rests in the lateral ventricle
  - Monitors ICP and also removes CSF
    - Requires a CSF drainage unit
  - Source control
    - Craniotomy for evacuation of space-occupying lesion/hematoma
  - Decompressive craniectomy
    - Remove a large area of cranium and open the dura to allow intracranial volume expansion
    - Bone flap is left out and re-implanted weeks later
      - When cerebral volume has returned to normal
    - Studies have not conclusively shown a benefit
      - The alternative is death without decompression
    - But almost certain significant disability with
Therefore, decompression is not automatic
- Debate rages on
- If it is done, it is better to do it early

**Aneurysmal Subarachnoid Hemorrhage**

**Presentation**
- Classic sign is the “thunderclap” headache
  - Acute onset of the worst headache (10/10) of a patient’s life
- May be accompanied by meningism
  - Irritation of the meninges from blood, manifesting as neck pain and stiffness
- May be accompanied by obtundation
  - Increased ICP, widespread damage from ischemia/hemorrhage, seizure
- Death before even reaching medical care as high as 10%
  - Overall case fatality is 40% (in a recent series)

**Evaluation**
- Unenhanced CT head is the initial test of choice
  - Will see subarachnoid blood (white/hyperdense) in most cases
    - If done using a third-generation scanner within 6 hours of the ictus
  - Sensitivity declines significantly after 12–24 hours
  - Distribution of blood depends on the location of aneurysm
    - Can also get intraparenchymal or intraventricular blood
- If > than 6 hours from presentation, and CT head negative, perform a lumbar puncture if safe to do so
  - Test is to detect CSF blood
    - Usually > 100,000 RBC/mm³ in SAH
  - If lower count/less discoloration in sequential tubes
    - Suggests traumatic tap rather than SAH
  - Look for xanthochromia
    - Yellow discoloration of CSF following centrifugation of cellular components
    - Due to breakdown products of hemoglobin
    - Decreased sensitivity (70% sensitivity) at 3 weeks
- If SAH is confirmed, or if CT scan/lumbar puncture negative but clinical suspicion is high
  - Perform a CT-angiogram (CTA)
    - To determine the presence and location of aneurysm
    - 97% sensitive in diagnosing an aneurysm
  - Cerebral catheter angiogram is still the gold standard for ruling in, or ruling out, an aneurysm
    - Indicated if aneurysmal suspicion high and CTA negative
    - Also used to characterize the morphology of the aneurysm in planning treatment

**Management Considerations**
- Following a ruptured cerebral aneurysm, the goals are to prevent and treat three major causes of morbidity and mortality:
  1. Aneurysm re-rupture
    - Re-rupture most likely in the first 24 hours following initial rupture
    - Decreases but remains a concern for several months
    - Mortality is higher with re-ruptured aneurysms
  2. Hydrocephalus and increased ICP
    - May be acute (over hours/days) or chronic (over weeks/months)
  3. Vasospasm
    - Major cause of post-rupture brain ischemia/infarction
    - Onset day 3; may last for 3 weeks
- Also, there is the risk of seizures
- Also, sodium abnormalities
  - Diabetes insipidus: high sodium
  - Syndrome of inappropriate anti-diuretic hormone (SIADH): low sodium

**Medical Management of Unsecured Aneurysms**
- Blood pressure management
  - Treating headache will often help in managing blood pressure
  - Target systolic blood pressure (SBP) <140 mmHg in patients with normal GCS or treated ICP (ventricular catheter)
  - Use labatolol/hydralazine
    - 5–20 mg IV q30 mins prn
  - Exercise caution in the obtunded patient
    - They may have elevated ICP
    - Therefore, aggressive BP lowering can compromise cerebral perfusion
- Sedation
  - Can prevent re-rupture by decreasing spikes in SBP
  - Can also be helpful in managing ICP
- ICP management
  - As outlined above
- Nimodipine for treatment of vasospasm
  - A calcium channel blocker shown to improve outcome
  - But no significant reduction in rates of radiographic vasospasm
  - Also, does not cure vasospasm once it has occurred
  - Patient should remain on this medication for 21 days
    - Or until discharge, whichever is sooner

**Surgical/Endovascular Management (i.e. Securing an Aneurysm)**
- If symptomatic hydrocephalus is present
  - Place an EVD for ICP control
- Surgical clipping
  - Involves craniotomy and surgical clipping
    - The clip is placed across the base of the aneurysm)
An open procedure, with associated surgical risk
If successful, the risk of recurrence/re-bleed is effectively removed
Endovascular treatment (“coiling”)
Via a catheter placed through the femoral artery
Metal coils then placed into the aneurysm under fluoroscopy
- To occlude the lumen from the inside
- Lower risk than open procedure
- But higher risk of aneurysm recurrence
- And may need long-term monitoring

Vasospasm

Definition/Presentation
- Delayed onset of focal neurological deficits due to narrowed cerebral vessels
- Due to ischemia and often distal to location of spasm

Pathophysiology
- Spasm risk is proportional to the amount of blood in the SA space
  - An EVD does not remove blood from the SA space
  - Therefore, an EVD is to drain CSF and prevent hydrocephalus, not spasm
- Amount of blood is expressed by the Fisher Grade (FG)
  - FG1: no hemorrhage
  - FG2: < 1 mm thickness in layering of blood on CT
  - FG3: > 1 mm thickness in layering of blood on CT
  - FG4: intra-parenchymal blood/intra-ventricular extension
- Highest spasm risk is from post-rupture day 3 to day 14
  - However, spasm can occur (and reoccur) up to day 21
  - Beware: some patients have delayed presentation
  - Therefore, post-rupture day not always the same as post-admission day
- Clinical examination
  - Suspicion means the need for frequent neurological examination
  - Physical exam testing of the major arterial supplies
    - Face/arm weakness for middle cerebral artery
    - Leg weakness for anterior cerebral artery
    - Level of consciousness/cerebellar testing for posterior circulation
- Screening and confirmatory testing
  - Formal (dye) angiography remains the gold standard, but has increased risks
    - Risk of stroke (albeit low)
    - Also not practical for repeat testing
  - Transcranial Doppler (TCD)
    - Finicky (but safe) procedure: learn to love your TCD technician
    - Ultrasound performed via acoustic windows in the skull
    - Requires volume-based competence
    - Measures mean flow velocity (FV) (and also resistance)
  - The trend in FV is more important than the absolute number
  - ‘Normal’ < 120 cm/s; ‘moderate’ spasm 120–200; ‘severe’ > 200
  - Abnormal TCDs numbers are confirmed by CTA, CT perfusion, angiography

Vasospasm Management
- Nimodipine is started on admission to prevent (not treat) vasospasm
  - Goal is to relax the smooth muscle of the cerebral vasculature
- Hyperdynamic (“Triple-H”) therapy previously used to prevent and treat vasospasm
  - “Triple H” refers to hypertension, hypervolemia, hemodilution
  - Only hypertension (i.e. with a noradrenaline infusion) shown to effectively treat vasospasm
  - Therefore, hypervolemia and hemodilution no longer widely recommended
- Intra-arterial drug injections to treat vasospasm
  - Vasodilators act locally at site of spasm to induce vessel wall relaxation
    - Papaverine, verapamil, milrinone
  - Mechanical arterial dilatation to treat vasospasm
    - Cerebral balloon angioplasty
    - Performed in angiography suite with anesthesia back-up
  - Risky procedure:
    - Concerns of arterial occlusion or rupture
    - Families should provide informed consent

Intracranial Tumours

Basic Nomenclature
- “Intra-cranial” denotes anywhere within the bony cranium
- “Intra-axial” denotes within the brain parenchyma
- “Extra-axial” denotes outside the brain parenchyma
- “Intra-ventricular” denotes (you guessed it!) within the ventricular system

Common Tumours
- Most common intracranial tumour is the pituitary adenoma
  - Divided into microadenoma (< 1 cm) or macroadenoma (> 1 cm)
  - Also classified as functioning (hormone-producing) or non-functioning
    - Non-functioning microadenomas common but rarely require surgery
    - Usually just followed
  - Non-functioning macroadenomas
    - Require surgery if enlarging or causing neurologic symptoms
Most common neurologic symptom is bi-temporal hemianopsia (no lateral vision on either side)
  - Due to pressure on the optic chiasm
    - Functional adenomas require treatment according to the hormone they secrete
    - Options include medical therapy, radiation, and surgical excision
    - Prolactinomas are, by far, the most common and respond very well to medical therapy
      - Most commonly a dopamine agonist (bromocriptine, cabergoline)
      - Even large prolactinomas can be treated without surgery
  - Next most common is the meningioma
    - Homogenous enhancing dural-based extra-axial tumour leading to mass effect
      - In everyday English: grows under the dura, then presses on the brain
    - 20% of all intracranial tumours
    - Present in 3% of autopsies in patients aged over > 60 years
    - Typically benign
      - Therefore, can become large before symptoms of mass effect noted
    - Good prognosis with complete excision
  - Most common intra-axial tumour is a metastatic tumour
    - Often multiple lesions present on imaging
    - Common sites of primary lesion (in order of prevalence):
      - Lung, breast, melanoma, GI tract, renal
    - Tumour of origin predicts how aggressive/treatable a cerebral metastasis is
    - Oncology (not neurosurgery) manages the majority of workup and treatment
  - Most common primary intra-axial tumour is an astrocytoma, the most aggressive form of which is glioblastoma multiforme (GBM)
    - An aggressive glial tumour arising most commonly from astrocytes
    - Therefore, also known as a Grade IV Astrocytoma
    - Appearance can be similar to metastatic lesion, though rarely more than one present
    - Typically requires surgical resection and adjunct chemo/radiation therapy
    - Prognosis is not good
      - About 40% die within one year
      - About 80% die within three years

Surgical Pearl 1: Troubleshooting a Blocked EVD
  - Ensure all stopcocks are open to the collection bag
  - Ensure no disconnections or breaks have occurred
  - Drop the collection system to the floor
    - To see if the drain is patent and rule out that flow stopped because of low ICP
    - If patent, then CSF drains when the bag is lowered
  - Working from most proximal (patient) port, you flush distally (towards the bag)
    - Flush particulate matter through the tubing toward collection bag
    - Use sterile saline
    - Observe for flow after each flush
  - If all distal flushes fail
    - Call neurosurgery to consider a proximal flush
      - With the stopcock open to the patient
      - Neurosurgery may attempt to aspirate
      - They may gently inject a few mLs sterile saline through the proximal port
      - Then, once again, check for flow
  - If no flow after any of the above and EVD still necessary
    - Consider removing drain/inserting a new catheter and repeating the CT
    - Neurosurgery definitely should be involved by this point

Surgical Pearl 2: Removing Cranial Catheters
  - Ensure all stopcocks are closed to the patient and that CSF is not flowing
  - Apply sterile gloves and clean/drape area
  - Infiltrate the exit site with lidocaine
    - This step is not always necessary, particularly if only one stitch to be placed
  - Cut the sutures that hold the drain in place
    - Then remove the catheter
  - Close the incision/exit site with 1 or 2 interrupted sutures
  - If patient is awake, have them do a Valsalva and observe for any CSF leakage from exit site
    - Apply another stitch if any leakage observed
Surgical Pearl 3: Inserting an EVD (a right frontal approach is usual to minimize damage)
(Requires experience and precise positioning: usually reserved for neurosurgery)

**Equipment:** Personal protective equipment, sterile towels, EVD tray and drill, hair clippers, ICP transducer, sterile occlusive dressing (Tegaderm®), suture, IV pole.

**Preparation:** Head is elevated to 30 degrees, immobilized, and in a neutral position. Hair is clipped and scalp is infiltrated with lidocaine plus epinephrine.

**To determine the site at which to drill:** Draw a backwards line 11 cm from the nasion in the mid-line (nasion = top of the nasal bone, just under the brow ridge). Then draw a lateral line 3 cm from midline and make a mark. This is Kocher’s point (KP): just anterior to the coronal suture and in the midpupillary line.

**To determine where to aim the catheter:** Draw a line from KP to the ipsilateral medial canthus. Draw a second line from KP to 1 cm anterior to the ipsilateral tragus.

**Insertion technique:**
- 2-cm scalpel incision at KP and down to the skull
- Clear the periosteum and insert a small retractor
- Use a manual twist drill aimed perpendicular to the skull (to penetrate the skull)
- A stop guard prevents plunging into the brain parenchyma
- Introduce a probe/18-gauge needle to ensure the drill penetrated the bone
- Use probe/18-gauge to score and puncture the dural surface
- Direct catheter toward the ipsilateral medial canthus (in sagittal plane) AND 1 cm anterior to the tragus (in the coronal plane)
- Catheter should be advanced 5 cm below the dura (6–7 cm below the skull surface)
- This will place the tip of catheter close to the foramen of Monro
- A "pop" is felt at about 3–4 cm, indicating entry into the ventricle
- Egress of CSF also confirms entry and the height of the column approximates ICP

**Set up the drain:**
- Distal end is tunnelled under the scalp posteriorly and laterally (to decrease infection)
- This is secured with 2-0 nylon suture, connected to the EVD drainage system
- Then the EVD is zeroed at the tragus, and (usually) left open to 10 cm (to allows drainage, but not over drainage)
The diagnosis of hypertension is fundamental to the practice of medicine. Increased blood pressure (BP) is the second leading global risk factor for death and disability (behind unhealthy diets), accounting for 18% of global deaths (>9 million deaths per year). Contemporary guidelines recommend assessing BP at every care visit; thus, BP measurement is probably the most commonly performed diagnostic maneuver in medicine. Importantly, evolving technology is making the diagnosis of hypertension more accurate, reliable, and rapid.

Although accurate when performed in standardized fashion, auscultatory BP is consistently incorrectly and, hence, inaccurately performed in clinical practice. Provider education programs have failed to produce consistent and sustained improvements in accuracy. Electronic (oscillometric) BP measurement removes or minimizes many (but certainly not all) measurement errors, such as those due to impaired hearing, missed auscultatory gap, rapid cuff deflation, and terminal digit preference. Furthermore, oscillometric readings (in studies with home, ambulatory, and automated office readings) are more closely related to vascular risk than are auscultatory readings, when the latter are performed in a routine manner, which they are most of the time. Hence in 2014, the World Hypertension League and, in 2015, the Canadian Hypertension Education Program (CHEP), endorsed preferential use of electronic (oscillometric) BP assessment. One commonly used means of electronic measurement is a fully automated BP device (automated office BP or AOBP) that can be deployed to take multiple readings, usually while the patient is alone in an exam room, thereby reducing white coat effect. Readings with AOBP devices of 135/85 mmHg and above should be considered high enough to initiate a full assessment to confirm the presence of hypertension, while electronic devices that require manual initiation of each measurement, which is termed office blood pressure measurement (OBPM), or auscultatory blood pressure readings (OBPM) still use a 140/90 mmHg threshold (Figure 1). Important to all methods of BP assessment is the need to follow standardized protocols to ensure accuracy.

CHEP has also made a second major change to its diagnostic algorithm to recommend that out-of-office measurement (ambulatory blood pressure measurement [ABPM] or home blood pressure measurement [HBPM], with ABPM preferred) be performed to confirm that an elevated AOBP or OBPM truly represents a diagnosis of hypertension (Figure 1). Out-of-office measurement should be performed early in the evaluation of patients with elevated BP readings (after the first hypertension visit) to expedite the diagnosis of hypertension.
and identify patients with white-coat hypertension. A revised protocol with detailed procedures is also provided in the new CHEP recommendations. As before, people with markedly elevated BP (≥180/110 mmHg) or hypertensive emergencies and urgencies can be diagnosed immediately.

After out-of-office measurement is performed, patients identified as having high—normal (130–139/85–89 mmHg) or white coat should be counselled to optimize their health behaviours and followed annually, as they have a high rate of progression to overt hypertension. Patients with white-coat hypertension do not require pharmacologic management for their BP. For clinicians who continue to measure office blood pressure using an auscultatory technique (not recommended), CHEP continues to advise that up to five visits will be required to diagnose hypertension in patients who have initial office readings in stage 1 hypertension range (140–159/90–99 mmHg).

These new CHEP recommendations are important for clinicians to understand, as they will optimize hypertension care delivery. It is vital that these recommendations be incorporated into undergraduate and post-graduate curricula/OSCE, as well as in continuing medical education programs. Further resources for training and education can be found at www.hypertension.ca. The greatest proportion of undiagnosed hypertension occurs in young Canadians (aged under 40 years), hence screening is important in this subgroup. Nevertheless, the transition from normal to hypertension occurs at all ages. Canada leads the world in its high rate of hypertension awareness and in treatment and control rates, but still too many are undiagnosed or uncontrolled.

**References**

CM Tools and Pearls: The Canadian Diabetes Association 2013 Clinical Practice Guidelines

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Summary
Diabetes is common in Canada, and over the last decade, the incidence of diabetes has grown rapidly. The Canadian Diabetes Association (CDA) released the 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (CPGs) in April 2013. These internationally recognized guidelines provide recommendations on screening, prevention, diagnosis, education, and management of diabetes. This article summarizes four key messages in diabetes care, including diagnosis, glucose lowering, vascular protection, and organization of care. Information on how to access the CDA’s interactive online and mobile applications is also provided.

Résumé
Introduction
Diabetes is common in Canada, and over the last decade, the incidence of diabetes has grown rapidly. Between 1998 and 2009, there was a 230% increase in the number of individuals with diabetes, and it is estimated that by 2019, 3.7 million people in Canada will be living with diabetes.1

The Canadian Diabetes Association (CDA) released the 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (CPGs) in April 2013.2 These internationally recognized guidelines provide recommendations on screening, prevention, diagnosis, education, care, and management of diabetes.

In this article, we highlight four key messages and refer to useful tools from these guidelines: diagnosis, glucose lowering, vascular protection, and organization of care.

What’s New in the Diagnosis of Diabetes?
Glycosylated hemoglobin (hemoglobin A1C) has now been incorporated into the diagnostic criteria for diabetes, in addition to the traditional criteria, outlined in Table 1. A1C should not be used for diagnosis in individuals suspected of having type 1 diabetes, or in situations that can falsely alter its value, such as hemoglobinopathies.

How Will I Remember this?
The CDA has created a suite of online tools, including one for screening and diagnosis. This can be accessed through the CDA website, as well as on the mobile application.3

What A1C Should I Target?
The CDA CPG recommends that glycemic control targets should be individualized (Figure 1). Many individuals will have an A1C target of ≤ 7%. This target is based on randomized control trial (RCT) data from the landmark United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT), both of which showed the beneficial effects of improved glycemic control on the prevention of microvascular complications.4,5 Furthermore, the 10-year follow-up study from the UKPDS demonstrated a legacy effect of earlier glucose control, with a 15–33% reduction in myocardial infarction (MI) and a 13–27% reduction in all-cause mortality.6 In the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study of the DCCT, there was a 42% reduction in cardiovascular (CV) outcomes.7

New in these guidelines, a less stringent A1C target (7.1–8.5%) has been suggested for individuals with limited life expectancies, high levels of functional dependency, extensive coronary artery disease at high risk of ischemic events, multiple comorbidities, a history of recurrent severe hypoglycemia, and longstanding diabetes for whom it is difficult to achieve an A1C ≤ 7%, despite effective doses of multiple anti-hyperglycemic agents (including intensified basal and bolus insulin).

In contrast, a more aggressive A1C target can be considered in some patients with type 2 diabetes, to further reduce their risk of nephropathy and retinopathy. In the Action in Diabetes and Vascular Disease: Preterax and DiaMicon MR Controlled Evaluation (ADVANCE trial), there was a 21% relative reduction in nephropathy in those undergoing intensive

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### Table 1. Diagnosis of Diabetes

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Dysglycemia category</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mmol/L)</td>
<td>6.1–6.9</td>
<td>IFG</td>
</tr>
<tr>
<td>• No caloric intake for at least 8 hours</td>
<td>≥ 7.0</td>
<td>Diabetes</td>
</tr>
<tr>
<td>2hPG in a 75-g OGTT (mmol/L)</td>
<td>7.8 – 11.0</td>
<td>IGT</td>
</tr>
<tr>
<td>Random PG (mmol/L)</td>
<td>&gt; 11.0</td>
<td>Diabetes</td>
</tr>
<tr>
<td>• Any time of the day without regard to the interval since the last meal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1C (%)</td>
<td>6.0–6.4</td>
<td>Pre-diabetes</td>
</tr>
<tr>
<td>• Standardized, validated assay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• In the absence of factors that affect the accuracy of A1C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Not for suspected type 1 diabetes</td>
<td>≥ 6.5</td>
<td>Diabetes</td>
</tr>
<tr>
<td>FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test; PG = plasma glucose.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Yu and Gilmour
glycemic control. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study also confirmed this finding of reduced microvascular complications with tighter glycemic control, especially with respect to retinopathy.

How Will I Remember This?
The CDA website and mobile application has a helpful interactive application that allows health care providers to create a target A1C based on each individual’s history and key characteristics.

What Is the Next Agent After Metformin in Type 2 Diabetes?
There are many exciting treatment options for managing type 2 diabetes. The CPG encourages individualization of treatment, based on specific clinical factors, such as presence of renal dysfunction or heart failure and baseline A1C.

New to these guidelines, it is recommended that a baseline A1C of ≤ 8.5% should be immediately treated with metformin (assuming no contraindications), without an initial 2–3 month period of lifestyle-only management. If an individual presents with symptoms of hyperglycemia and signs of metabolic decompensation, insulin should be the initial management strategy.

How Do I Decide Which Agent to Start?
The CDA has an interactive tool that provides guidance regarding selection of a second-line treatment option, based on the patient’s comorbidities, degree of hyperglycemia, risk of hypoglycemia, agent’s cost, and impact on weight.

What’s New in Vascular Protection?
Diabetes and its complications significantly impact the individual, their family, and the health care system. Vascular complications can cause severe morbidity and are the leading cause of death in people with diabetes.

The most recent CPGs continue to recommend a comprehensive and multifaceted approach to reduce cardiovascular risk, including lifestyle interventions, optimal glycemic control, and blood pressure management, with a target of < 130/80. In addition, vascular protection medications, including statins, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and aspirin are recommended, depending on the overall cardiovascular risk of the individual.

If My Patient Has a Low-Density Lipoprotein (LDL) of < 2.00 mmol/L, Does This Mean They Don’t Require Statin Therapy?
No, this is not true. Statin therapy should be used to reduce CV risk in adults with diabetes and macrovascular disease. Based on the Cholesterol Treatment Trialists’ (CTT) collaboration meta-analysis, for every 1 mmol/L reduction in LDL-cholesterol (LDL-C), an associated 20% risk reduction in CV events can be seen, regardless of the baseline LDL. If statin therapy is initiated, the goal LDL-C is ≤ 2 mmol/L, or if this target is already met, a 50% or greater reduction. Statin therapy is recommended to all individuals aged 40 years and over who have type 2 diabetes. The evidence is less compelling in type 1 diabetes, though therapy should be considered.
Should I Use a Statin In a Patient Aged Under 40 years?
The use of statins in individuals under 40 without macrovascular
disease is an area of controversy. The 2013 CPGs suggest statin
therapy can be considered in this group if they meet one of the
following criteria: 1) they have had diabetes for more than 15
years and are aged over 30 years, 2) they have microvascular
complications, or 3) therapy is based on the presence of other
risk factors, according to the 2012 Canadian Cardiovascular
Society Guidelines. These recommendations stem from
knowing the presence of CVD is higher in people with diabetes
of longer duration, presence of retinopathy, higher albumin
excretion rates, and other traditional Framingham risk factors,
such as elevated LDL-C.

When Should I Start an ACE Inhibitor or ARB?
Based on data from the Heart Outcomes Prevention Evaluation
(HOPE) and Ongoing Telmisartan Alone, and in Combination
with Ramipril Global Endpoint Trial (ONTARGET) trials,
angiotensin-converting-enzyme (ACE) inhibitors or angiotensin
receptor blockers (ARBs) are recommended to all patients with
diabetes and macrovascular disease and to those aged 50 years
and over with at least one traditional CV risk factor or end organ
damage (including microalbuminuria).12-13 ACEI/ARBs can be
considered in all individuals aged 55 years and over, as well as in
those aged under 55 years with microvascular disease; however,
the evidence is scant in these populations. Whether the CV
benefits from ACI inhibitors are independent from their blood
pressure lowering effect continues to be hotly debated.

Should I Prescribe Aspirin (ASA) to All of My Patients
With Diabetes?
No, ASA should not be used for primary prevention in
diabetes. Meta-analyses looking at diabetes cohorts have
shown an overall lack of benefit of ASA in reducing coronary
artery disease events and stroke for primary prevention, with
an important 50–70% relative increase in gastrointestinal
bleeding.14

ASA use may be considered for secondary prevention in
people with established CV disease. If aspirin is not tolerated,
an alternate anti-platelet (such as clopidogrel or ticagrelor) can
be initiated instead.

How Will I Remember This?
The CDA website has an interactive “vascular protection”
application that allows health care professionals to
individualize vascular protection medications based on patient
age, comorbidities, and duration of diabetes (Figure 3).3

How to Organize Diabetes Care in Clinical Practice
To successfully implement these recommendations into
clinical care, care must be effectively organized around the
person living with diabetes. Adoption of the chronic care
model has been demonstrated to improve quality of care and
disease outcomes. The chronic care model consists of delivery
systems design, self-management support, decision support,
clinical information, and linkage with the community and
health system.
It can be operationalized through various quality improvement (QI) strategies; this can be summarized with the “five Rs” as follows: 1) recognizing diabetes risk factors with appropriate screening, 2) developing a registry of patients with diabetes, 3) having the appropriate resources available (inter-professional team), 4) relaying information, and 5) creating the opportunity for regular reassessment. Checklists on how to implement these QI strategies can be accessed on the CDA website.  

**Final Words**  
Over the last century, advances in research have transformed diabetes from a condition that inevitably led to death to a chronic condition that can have exceptional outcomes with optimal management. The 2013 CDA guidelines, online interactive tools, and mobile applications allow physicians to deliver the highest quality of diabetes care, by making it easy to put the evidence into practice.

**References**
A Review of Non-Alcoholic Fatty Liver Disease: From Obesity to Liver Transplant
Adjoa Anyane-Yeboa MD, Charmaine A. Stewart MD, FACP, AGAF

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Summary
Non-alcoholic fatty liver disease (NAFLD) is becoming an increasingly common etiology of liver disease in the United States. As the prevalence of diabetes and obesity continues to increase, it will soon surpass hepatitis C as the most common etiology of end stage liver disease in the western world. NAFLD like many liver diseases can progress to cirrhosis, and patients often suffer morbidity secondary to the complications of portal hypertension. The exact percentage of hepatocellular carcinoma (HCC) that occurs in NAFLD patients is unknown, however, unlike many other liver diseases there is small potential for development of HCC independent of cirrhosis. Various conservative and pharmacologic therapies have been studied with varying degrees of efficacy including lifestyle modifications, bile acids, insulin sensitizers, vitamin E, and bariatric surgery. However, the only curative treatment for NAFLD cirrhosis is liver transplant. As the epidemic that is NAFLD continues to grow, more studies will need to be done to develop new therapies and curative treatments.

Résumé
La stéatose hépatique non alcoolique est une hépatopathie de plus en plus courante aux États-Unis. Au vu de la hausse continue de la prévalence du diabète et de l’obésité, elle surpassera bientôt l’hépatite C au rang de principale cause d’hépatopathie terminale dans la population occidentale. La stéatose hépatique non alcoolique, à l’instar de nombreuses affections hépatiques, peut évoluer vers la cirrhose, et les patients présentent souvent des affections concomitantes secondaires aux complications de l’hypertension portale. Le pourcentage exact de carcinome hépatocellulaire apparaissant chez les personnes atteintes de stéatose hépatique non alcoolique est inconnu, mais il faut savoir que, à l’encontre d’autres maladies hépatiques, il y a un faible risque de carcinome indépendant de la cirrhose. Divers traitements conservateurs et pharmacothérapies ont été étudiés, dont la modification des habitudes de vie, les acides biliaires, les insulinosensibilisateurs, la vitamine E et la chirurgie bariatrique; ils sont d’efficacité variable. Le seul traitement curatif de la cirrhose secondaire à la stéatose hépatique non alcoolique demeure la greffe de foie. L’épidémie de stéatose hépatique non alcoolique prenant de l’ampleur, la recherche devra se poursuivre pour aboutir à la mise au point de nouveaux traitements, notamment des traitements curatifs.
Non-alcoholic fatty liver disease (NAFLD) is becoming an increasingly prevalent etiology of liver disease in the United States. Surveys conducted by the National Health and Nutrition Examination Survey (NHANES) show the prevalence of other chronic liver diseases such as hepatitis B virus (HBV) and hepatitis C virus (HCV) has remained stable over the years, while the prevalence of NAFLD has been steadily increasing.1 NAFLD is present in approximately 30% of adults and is reported as the etiology of asymptomatic liver enzyme elevation in approximately 45–90% of patients.2,3 The increasing prevalence of NAFLD mirrors the increase in the percentage of obesity, diabetes, hypertension, and the metabolic syndrome in our population. Today NAFLD is considered the hepatic equivalent of the metabolic syndrome.4 NAFLD is rapidly becoming the most common diagnosis prior to liver transplant; thus it is important to recognize the risk factors and natural history of this disease.

NAFLD includes a wide spectrum of liver pathology ranging from steatosis without inflammation to non-alcoholic steatohepatitis (NASH), advanced fibrosis, liver failure, and cirrhosis.5 Histologically, NAFLD is difficult to distinguish from alcohol-induced liver injury; thus it is necessary to ensure that individuals diagnosed with NAFLD are consuming less than 30 grams (gm) per day for men and less than 20 gm per day for women.5,7

There is a proposed “two hit” hypothesis for the development of NAFLD. The “first hit” is insulin resistance, which leads to steatosis of the liver. The “second hit” is oxidative stress induced by development of reactive oxygen species from fatty acid oxidation, which, in combination with insulin resistance, leads to NAFLD. The exact mechanism by which oxidative stress and insulin resistance predispose to NAFLD remains uncertain.8,9 However, it has been proposed that visceral adiposity and adipokines, as well as cytokines such as IL-6 and TNF-alpha, may play a role.10 Genetic susceptibility might also contribute, as shown by the increased prevalence of NAFLD in patients with the PNPLA3 polymorphism.11

Risk Factors for NAFLD
The main risk factors associated with development of NAFLD are diabetes mellitus (DM) type II, obesity, and hyperlipidemia. In a review, Miyake and colleagues noted that high body mass index, elevated alanine aminotransferase (ALT), low total bilirubin, hyperuricemia, elevated hemoglobin A1c, insulin resistance, and elevated ferritin were all associated with increased probability of developing NAFLD.12 However, others have reported the principal associated risk factors for NAFLD to be obesity and hyperlipidemia.6

Approximately 18.5% of obese individuals have been found to have histologic evidence of steatohepatitis, compared to 2.7% of lean individuals.13 Also, DM type II and obesity have been demonstrated to be associated with increasing severity of NAFLD.13,14 Other risk factors for progression to fibrosis include advanced age and inflammation on initial biopsy.15

In addition, it has been shown that patients found to have steatosis on liver biopsy tend to follow a more benign course, whereas patients with advanced fibrosis or steatohepatitis have a much poorer prognosis. The finding of steatohepatitis on histology often predicts development of cirrhosis and its liver-related complications.5,15

NAFLD and Cirrhosis
Approximately 3–15% of patients with NAFLD develop cirrhosis; however, this progression of NAFLD to end-stage liver disease can take decades.6,17,18 Several studies have looked at the risk factors for progression to NASH cirrhosis. In a multi-centre cross-sectional study of 1365 patients, Nakahara found poor glucose control and age to be directly associated with advanced stages of fibrosis.19 Another study cited age over 45 years, diabetes, and obesity as risk factors for progression to advanced fibrosis and cirrhosis, as well.5

Patients with NAFLD-related cirrhosis may be asymptomatic until they present with findings of advanced-stage cirrhosis, including hepatic encephalopathy, ascites, and/or variceal bleeding.20 It is often difficult to diagnose NAFLD once it has progressed to NASH cirrhosis, as steatosis frequently disappears with progression of disease. Consequently, in advanced disease, NAFLD-associated cirrhosis may be indistinguishable from other etiologies of cirrhosis.18 However, once other causes of advanced liver disease have been excluded, it is reasonable to presume that cirrhotic patients with features of the metabolic syndrome including obesity, diabetes, and hyperlipidemia have NAFLD-related cirrhosis.21

We now know that a large proportion of chronic liver disease of unknown etiology or “cryptogenic cirrhosis (cc)” is actually NAFLD-related cirrhosis.20,21 One study found that patients with cryptogenic cirrhosis have a prevalence of diabetes and obesity that is similar to patients with NASH and higher than that of patients with cirrhosis due to autoimmune or viral liver disease.20 In a study of patients who had undergone liver transplant for cryptogenic cirrhosis, NAFLD was diagnosed as the etiology of liver disease in approximately 66% of cases.22 These studies indicate the estimated percentages of NAFLD-related cirrhosis might be underestimated, since cases of cryptogenic cirrhosis are often not taken into consideration.

Similar to other causes of cirrhosis, NAFLD-related cirrhosis is associated with hepatocellular carcinoma (HCC). Therefore, it is important to perform routine surveillance...
imaging to screen these patients for the development of HCC.

NAFLD and HCC
Traditionally, hepatocellular carcinoma (HCC) has been described predominantly in patients with cirrhosis from alcohol-induced liver injury and hepatitis B and C (with and without cirrhosis). The incidence of HCC in the US has increased approximately 80% in recent decades. Half this increase has been attributed to new cases of hepatitis C; however, it is speculated that the remainder may be due to NAFLD.27 The exact percentage of HCC that occurs in NAFLD cirrhosis is unknown. However, the risk factors for development of HCC in NAFLD have been identified as male sex and age over 50 years.28 There is growing evidence that NAFLD, without cirrhosis, is also a risk factor for HCC.25

Multiple studies have shown that some patients with NAFLD can develop HCC in the absence of cirrhosis. Ertle et al looked at 162 patients with HCC and found that approximately 42% (p < 0.005) of patients with NAFLD-associated HCC developed HCC in the absence of cirrhosis. These patients typically had features of the metabolic syndrome, including hyperlipidemia, type 2 DM, and obesity, compared to non-NAFLD patients with HCC. The authors hypothesized that the metabolic syndrome is an independent risk factor for developing HCC in NAFLD patients.26 Although NAFLD might be an independent predictor of HCC, patients with NAFLD-related cirrhosis had a higher incidence of HCC (approximately 10–13%), compared to patients with NAFLD who did not have cirrhosis (0.5%) after a mean follow-up of 7.5 years.27,28 Compared to other etiologies of liver disease, the overall risk of HCC in NAFLD is still lower than that of HCC from other causes, specifically hepatitis-c related cirrhosis.27

Treatment
There are no proven therapies for NAFLD at this time; treatment is focused on management of comorbid conditions; lifestyle modifications; pharmacotherapy, including bile acids, insulin sensitizers, and vitamin E; and bariatric surgery.

Lifestyle Modification
As NAFLD is frequently associated with diabetes, obesity, and the metabolic syndrome, it should be no surprise that lifestyle modification, including weight loss, diet, and exercise remain the cornerstone of management. One study randomized obese individuals with biopsy proven NASH to an intensive lifestyle intervention group, versus a control group, and observed them over 48 weeks. The participants who lost more than 7% of their weight were shown to have significant improvements in liver histology, including improvements in steatosis, lobular inflammation, and ballooning injury. Overall, the study showed that weight reduction significantly impacts liver histology with important implications for progression of disease.29 These findings were further supported by a meta-analysis that demonstrated the effect of weight loss on liver histology in NAFLD.30 In comparison, exercise alone benefits liver steatosis but not transaminases.31 The current AASLD guidelines state that 3–5% of weight loss can improve steatosis, but up to 10% may be necessary for improvement in necroinflammation.32

Pharmacotherapy
Currently no pharmacologic therapy has been approved for use in NAFLD or NASH. Medications for weight loss, agents for hyperlipidemia, glucose-lowering agents, and antioxidants have all been investigated.

Insulin Sensitizers
Insulin sensitizers, such as metformin and the thiazolidinediones, have been proposed for treating NAFLD. Metformin is an oral biguanide used to treat DM type 2. The mechanism of action is to increase insulin sensitivity by decreasing hepatic glucose production, decreasing intestinal absorption of glucose and improving peripheral insulin uptake.33 An open-label study on metformin use in NASH patients found an initial improvement in transaminases, but only a modest improvement in hepatic steatosis and inflammation at one year (33% and 20%, respectively).34 Similarly, a randomized-controlled trial found no significant difference in liver histology between metformin and placebo in patients with biopsy proven NAFLD. However, the study did find that metformin led to overall improvements in weight, low-density lipoprotein (LDL) cholesterol, blood glucose levels, and hemoglobin A1c.35

Thiazolidinediones, such as pioglitazone and rosiglitazone, are peroxisome proliferator activated-receptor gamma agonists (PPAR-gamma agonists). They activate the PPAR-gamma receptor to alter the transcription of several genes involved in lipid and glucose metabolism.36 Thiazolidinediones decrease insulin resistance by increasing glucose use by tissues and decreasing glucose production.37 A meta-analysis looking at the effects of current treatments in NAFLD found that thiazolidinediones slowed progression of fibrosis and showed improvements in histologic activity and inflammation, though weight gain was a side effect in up to 75% of patients.38 Other studies found improvements in hepatic steatosis with thiazolidinediones, as well, yet they also re-demonstrated the side effect of weight gain similar to the previous study.15,20

A meta-analysis comparing thiazolidinediones and metformin in the treatment of NASH determined that the thiazolidinediones led to significant improvements in hepatic
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steatosis, hepatocyte ballooning, and alanine aminotransferase (ALT) levels, but had no significant effect on fibrosis or inflammation in patients with diabetes. However, in patients without diabetes, the thiazolidinediones showed improvement in all categories, including fibrosis. In contrast, metformin did not show any histologic or biochemical benefit. Metformin is currently not recommended as a treatment of liver disease in NAFLD. Pioglitazone can be used in biopsy proven NASH; however, most studies of its effectiveness were done solely in non-diabetic patients.

Bile Acids
Bile acids have also been used to treat NAFLD. It has been hypothesized that dysregulation of bile acid transport and signalling may play a role in the pathogenesis of NAFLD. One study showed that ursodeoxycholic acid reduced ALT to normal levels in approximately 24.5% of patients. However, a systematic review from the Cochrane Review determined there is currently not enough evidence to support the use of ursodeoxycholic acid for the treatment of NAFLD; therefore, it is currently not recommended for treatment of NAFLD or NASH.

Vitamin E
Vitamin E has also been studied in the treatment of NAFLD. Vitamin E is a fat-soluble antioxidant that interferes with lipid oxidation and the production of reactive oxygen species. Reactive oxygen species play a central role in the “two hit” hypothesis and the development of NASH, as discussed. The PIVENS trial found that vitamin E was associated with a significant improvement in NASH when compared to placebo. Treatment with vitamin E resulted in improvements in aspartate aminotransferase (AST) and ALT levels, hepatic steatosis, and lobular inflammation without change in fibrosis. At this time, vitamin E has only been found to be effective in patients who do not have diabetes. The American Association for the Study of Liver Diseases (AASLD) guidelines state that vitamin E improves histology in non-diabetic patients with NASH and can be used at a dose of 800 IU/day in this population. However, the use of vitamin E remains controversial, as several studies have shown an increased risk of all-cause mortality when vitamin E is used in doses greater than 400 IU/day. Thus it should be used with caution.

Bariatric Surgery
The effects of bariatric surgery in the treatment of NAFLD have also been assessed. Klein et al found that patients who lost approximately 29% of their initial body weight after gastric bypass surgery had a decrease in adipose tissue lipolysis, endogenous glucose production, secretion of very-low density lipoprotein and steatosis, as well as a decrease in the mediators associated with the development and progression of fibrosis. Another study evaluated 18 patients two years after undergoing Roux-en-y gastric bypass and discovered resolution of steatosis in 84% and resolution of fibrosis in 75% of those who lost over 60 percent of their weight. Weight loss after gastric bypass surgery has been associated with improved blood glucose control, steatosis, lobular inflammation, and fibrosis, as well as resolution of liver disease in approximately 89%. Nevertheless, for patients with NAFLD who have progressed to cirrhosis with decompensation, liver transplant is the treatment of choice.

Liver Transplant in NASH
As the number of patients with NAFLD who progress to cirrhosis rises, liver transplant is becoming an increasingly important intervention. End-stage liver disease from cryptogenic cirrhosis accounts for approximately 7–14% of liver transplants. The assessment of patients with NAFLD for liver transplant involves most of the same workup as in other liver diseases. However, some pre-transplantation considerations are specific to NAFLD patients. For instance, as previously described, most NAFLD patients have diabetes and obesity. Diabetes mellitus has been found to be an independent predictor of poor survival after transplant. Multiple studies also found patients with pre-transplant diabetes to have higher morbidity and mortality than their non-diabetic counterparts, likely secondary to higher frequency of cardiovascular complications, renal failure, and infections. One case-control study found an increased incidence of complications involving cardiovascular, ophthalmologic, renal, musculoskeletal, hematologic, respiratory, and neurologic systems in diabetic patients with NAFLD who underwent liver transplant. They also found a higher rate of minor and major infections and malignancies post-transplant in diabetic patients. Given the risk of significant morbidity and mortality in diabetics, these patients should undergo thorough pre-transplant cardiovascular evaluation and close evaluation of other comorbid conditions. The amount of steatosis in the donor liver must also be considered prior to transplantation of a patient with NAFLD. Donor livers with severe steatosis (approximately > 60%) have a larger risk of primary non-function in the allograft. Marsman et al performed a prospective study evaluating the outcomes of patients transplanted with livers with up to 30% steatosis. They found a significant decrease in four-month graft survival and two-year patient survival in patients transplanted with the steatotic livers. Limited graft survival in these patients was attributed to primary graft dysfunction or non-function. In the study, fatty infiltration was an independent predictor of poor survival.
outcome after transplantation. In addition, steatosis of the donor liver has been shown to be associated with development of de novo NAFLD after liver transplant. Despite these findings, due to the shortage of donor organs, it is often necessary to allow some degree of steatosis in the donor in order to use as many potential donor livers as possible. Most transplant surgeons perform a biopsy of cadaveric livers prior to transplantation to determine degree of steatosis; however, this practice is controversial in living donors, as there are risks associated with the procedure. Currently, most transplant centres allow for approximately 10–30% steatosis in the donor liver prior to transplantation.

It is speculated that, with the rising proportion of patients with NAFLD, liver transplants for NASH cirrhosis would surpass that of hepatitis C cirrhosis related liver transplant. However, it appears patients with NAFLD-induced cirrhosis have lower associated MELD scores, which could therefore affect the number of patients eligible for liver transplantation.

**Outcomes After Liver Transplant**

Overall, mortality after liver transplant for NAFLD patients is comparable to liver transplants due to other indications. The assessment of 54,687 liver transplant recipients from the UNOS registry found that graft survival at 1, 3, 5, and 10 years for NASH patients was comparable to liver transplants for cholestatic liver disease and hepatitis B and better for alcoholic liver disease, hepatitis C, and hepatocellular carcinoma. Moreover, patient survival at 1, 3, 5, and 10 years post-transplant was 89%, 85%, 84%, and 84%, respectively. Survival was similar to that of cholestatic disease and HBV and better than alcoholic liver disease, HCV, and HCC. Another study by Aafzali et al evaluated 53,738 liver transplant recipients from the UNOS registry and found better survival for liver transplants due to NASH, compared to alcoholic liver disease, HCV, and HCC and poorer survival than transplants due to cholestatic disease, HBV, and autoimmune hepatitis.

There are varying data on recurrence of NAFLD after liver transplant; nevertheless, most studies agree that NASH patients do not frequently require re-transplantation. Patients who develop recurrence of steatosis and NAFLD typically have a higher average BMI in comparison to those who do not develop recurrence. One single center study of 88 patients with NAFLD-related liver transplant found recurrence in 34 (39%), isolated steatosis in 9, steatohepatitis in 25, and advanced fibrosis in 3 patients. Factors associated with recurrence included higher pre and post-transplant body mass index (BMI) and elevated post-transplant triglyceride levels. Patients with recurrence in this study were also on higher doses of steroids. In addition, patients with the genotype PNPLA3 rs738409-G who have undergone liver transplant have an increased likelihood of developing graft steatosis and recurrence as well.

De novo NAFLD after liver transplant has been described in up to 31% of patients who have undergone liver transplantation. One multicentre retrospective study found a prevalence of 31.1% of NAFLD and 1.6% of NASH after liver transplantation. As discussed, pre-transplant steatosis is a risk factor for the development of NAFLD in post-transplant patients. Other risk factors for de novo NAFLD after transplant include use of tacrolimus, hyperlipidemia, post-transplant diabetes, and obesity. Unfortunately, many immunosuppressants, including corticosteroids and calcineurin inhibitors such as tacrolimus, promote development of the metabolic syndrome, which in turn can lead to the development of NAFLD.

**Conclusion**

NAFLD is becoming an increasingly common etiology of liver disease in the US. As the prevalence of diabetes, obesity, and metabolic syndrome are increasing in our population, the frequency of NAFLD is steadily increasing as well. In certain patients, NAFLD can progress to NASH cirrhosis and place patients at risk of developing complications of end-stage liver disease. There is currently no approved medical therapy for NAFLD, and liver transplant is the only curative treatment. Therefore, more studies on NAFLD are needed in order to develop novel therapies.

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How to Maximize Bedside Teaching in Our Busy World

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Summary
Bedside teaching is becoming less frequent. A lack of attending physicians’ time and perceived teaching skill, as well as concerns regarding the impact of bedside teaching on the relationship with patients have been cited as barriers to bedside teaching. The purpose of this paper is to offer some tips on how to increase the frequency and quality of bedside teaching in light of these barriers. The main recommendations are to 1) be explicit about the competencies around which you are teaching; 2) incorporate bedside teaching into your daily workflow, allowing the available cases and patients to dictate the learning competencies; and 3) use a framework that incorporates published teaching tools to guide your bedside teaching.

The first step of this framework is preparation, which involves choosing the most appropriate teaching competency (history-taking, physical exam, clinical reasoning, or decision-making) based on the learner, case, and patient. Next is delivery, including orienting learners and patients to the task, choosing the instructional modality that fits the competency (such as One Minute Preceptor, SNAPPS, or Mini-CEX), and then debriefing and providing feedback. The final step is reflection on the teaching session, which can include peer observation.

Résumé
L’enseignement clinique est de moins en moins fréquent. Le manque de temps et d’aptitudes pour enseigner du côté des médecins, ainsi que certaines préoccupations quant aux répercussions de l’enseignement clinique sur la relation avec les patients sont des éléments que l’on pointe comme étant des obstacles. Cet article a pour but d’offrir des conseils permettant d’augmenter la fréquence et la qualité de l’enseignement clinique en tenant compte de ces obstacles.

Voici les principales recommandations : 1) soyez clair et précis quant aux connaissances enseignées; 2) intégrez l’enseignement clinique au quotidien dans votre travail en saisissant les occasions de cas et de patients qui se présentent pour enseigner; et 3) dotez-vous d’une structure qui intègre des outils pédagogiques officiels pour guider votre enseignement clinique.

La préparation constitue la première partie de cette structure. Elle repose sur le choix des connaissances les plus indiquées à enseigner (l’anamnèse, l’examen physique, la résolution des problèmes cliniques ou la prise de décision) selon l’apprenant, le cas et le patient. La partie suivante est celle de la transmission des connaissances. C’est à cette étape que l’on oriente l’apprenant et le patient au regard de l’exercice, que l’on choisit l’outil pédagogique à utiliser selon les connaissances à transmettre (comme One Minute Preceptor, SNAPPS ou Mini-CEX), puis que l’on fait un compte rendu oral de la séance et que l’on procure de la rétroaction. La dernière étape consiste en une réflexion sur la séance d’enseignement, qui peut s’accompagner d’une évaluation par des pairs.
Introduction
I am walking onto our medicine wards to start a two-week stint attending on the clinical teaching unit. I have already heard a bit about the new patients in morning report, so when the team gathers to review the patients admitted overnight, I say, “Let’s head to the bedside to review the case and do some teaching.” As is often the case, the senior resident looks up from the chart and asks, “You want to go to the bedside?” Sound familiar?

There are many barriers to bedside teaching. Williams and colleagues1 conducted focus groups of trainees at Boston University and identified the following main barriers: lack of time from attending physicians due to busy clinical and non-clinical duties, lack of teaching skill among attending physicians, overreliance on technology, possible lack of respect for patients during the teaching process, and possible threat to patient confidence in the trainee when mistakes are pointed out. The purpose of this paper is to offer some tips on how to increase the frequency and quality of bedside teaching in light of these barriers. The three main recommendations are as follows: 1) to be explicit when doing bedside teaching, 2) to make bedside teaching part of one’s routine workflow, and 3) to use a framework when approaching bedside teaching.

Bedside Teaching – What It Is and Which Competencies Are Best Addressed With It
Bedside teaching can be thought of as any teaching that relates to direct patient care. With this definition, the following four competencies could be the focus of bedside teaching: history taking (including communication, attitudes, and professionalism), physical examination skills, clinical reasoning (incorporating the data into a diagnosis and differential diagnosis), and clinical decision-making (based on the diagnosis and differential diagnosis, how to further investigate or manage the patient). Although some might define bedside teaching as just history taking and physical examination, we will use this broader definition to help us understand the purpose of some published techniques to bedside teaching.

Be Explicit When Doing Bedside Teaching
How often have you engaged your trainees in a discussion around an interesting case and then later overhear them say, “We never get any teaching”? For whatever reason, trainees do not always perceive that, when attending physicians model history taking or discuss clinical reasoning, this is bedside teaching, and can be a very effective method. A powerful impact can be made when a teacher says, “This is a tough case. Let’s do some teaching on clinical reasoning to work through it.” or “Seeing the JVP is not easy and comes with practice. Let’s do some physical exam teaching.” First, the teacher admitting the difficulty of clinical medicine can put a trainee at ease. Second, the trainees become primed and engaged. Finally, when done often enough, teachers can monitor the competencies they like to teach. If a teacher is explicit about “teaching on clinical reasoning” every day for a week, they might quickly realize it is time to focus on another competency, such as observing a learner take a patient’s history or perform a physical examination.

Make Bedside Teaching a Part of Routine Workflow
Although many programs institute dedicated bedside teaching rounds to ensure that bedside teaching occurs, there are two problems with this. First, the addition to routine workflow adds to the workload of already busy physicians. Second, it is...
one of the foundational pedagogical principles that skills are best learned in the context in which they will later be applied. Physicians use the physical examination to augment the history when diagnosing the patient. Therefore, it is best to learn the physical examination of heart failure in the context of a patient presenting with suspected heart failure. For these reasons, bedside teaching should be incorporated into routine workflow; that is, in tandem with reviewing a case with a trainee.

Framework For Bedside Teaching

Ramani² published a set of 12 tips to improve bedside teaching and divided them into activities before, during, and after the teaching session. Rather than reiterate the 12 tips, I will summarize each of the three stages.

Before

Preparation involves knowing the case and the trainee and considering the fit between these and the learning competency (see Figure 1). For example, if you have an orthopedic resident with you, bedside teaching could involve history or physical examination of a patient with heart failure, or clinical reasoning of a patient with delirium; it would be less ideal to use a case of tricyclic antidepressant overdose for this particular trainee. After considering the fit between the case, the trainee, and the competency, the attending needs to orient the trainees and the patient to the focus and objectives of the session and must obtain consent from the patient. As previously mentioned, the lack of respect for patients was identified as a barrier to bedside teaching, due to concerns that patients do not like being practiced on or having sensitive issues discussed in front of others. However, a survey at a Veterans Affairs hospital found that 68% of patients preferred to have the case presentations done at the bedside, and only 6% disliked bedside teaching.³ Hence, most, but not all, patients are willing to have their case presented in front of them and participate in bedside teaching, but this must be confirmed with each patient.

During

Once the bedside teaching session begins, there are three broad approaches to teaching: instruction, modelling clinical skills, and observation. Instruction is likely the most common approach and involves probing the learners with questions, engaging all learners, and capturing teachable moments. This approach tends to focus on clinical reasoning and clinical decision-making. The One-Minute Preceptor⁴ and SNAPPS⁵ are two published techniques that use this approach while reviewing a case. The One-Minute Preceptor involves five steps: 1) Get a commitment from the trainee stating the diagnosis or plan; 2) Probe the trainee to present supporting evidence; 3) Teach some general rules or “take-home points” that are learning issues from the case that can be applied to other cases; 4) Reinforce what the trainee has done well; and 5) Provide constructive feedback.⁴

SNAPPS is a different approach and outlines what the trainees do during a case review. It stands for the following: summarize history and findings (S), narrow the differential (N), analyze the differential (A), probe the preceptor about uncertainties (P), plan management (P), and select case-related issues for self-study (S). Both One-Minute Preceptor and SNAPPS involve summarizing the case, discussing the key features that support or refute a diagnosis, and discussing the management plan. The One-Minute Preceptor is preceptor driven and requires no orientation for the trainee. SNAPPS is learner driven, with the learner probing the preceptor for areas of uncertainty and then selecting a case-related issue to review; this method requires orienting both the preceptors and the trainees.

In a small study of two videotaped case reviews, the One-Minute Preceptor approach increased the ability of the preceptor to diagnose the medical condition and increased his/her confidence in rating the trainee’s presentation skills, clinical reasoning skills, and fund of knowledge pertaining to a case, compared to the traditional case review.⁴ In a study of SNAPPS, learners who were taught this technique discussed a broader differential, justified it more, and verbalized far more questions and uncertainties about the case.⁵ Hence, these two approaches are excellent for teaching and testing clinical reasoning and decision-making.

The second approach to bedside teaching involves the clinical teacher intentionally modelling their interactions with the patient or modelling clinical reasoning as a form of instruction. Breaking bad news is an important part of a general internist’s practice. I use these unfortunate opportunities to model my approach to trainees. Before we enter the patient’s room, I prime the trainee(s) that I will model how I break bad news. I ensure the patient is comfortable having trainees in the room and generally limit the number, given the sensitive nature of the situation. After I have finished and answered the patient’s or family’s questions and left the room, I then debrief with the trainee(s) about how they felt it went, and how what they saw relates to what they were taught, with respect to breaking bad news. In my experience, most of my colleagues view this role modelling as one of the most important aspects of bedside teaching, but bookending it with priming the trainee(s) before entering the room and debriefing them afterwards really drives it home.

The last approach is observation of a trainee and the two competencies that lend themselves best are history taking and physical examination. This instructional activity can also be an assessment activity if scored and documented—which is the which is the basis of the Mini-Clinical Evaluation Exercise (Mini-
CEX). The Mini-CEX involves approximately 15 minutes of observation and 5 minutes of feedback; however, the length of observation used as an instructional activity can be tailored to the task. To incorporate the Mini-CEX into daily workflow, one can make it a part of the case review.

Instead of listening to a trainee present the history and physical exam data on a newly admitted patient, the preceptor asks another learner to demonstrate one of these skills. To observe a focused physical exam, the trainee who admitted the patient shares the history. Then the preceptor asks a second trainee to state the most likely diagnosis and differential and then perform a focused physical exam based on what they suspect. The entire team observes the physical, after which the trainee who admitted the patient shares their findings, and the team compares the two.

To use this approach for history taking, a learner who is unaware of the patient’s diagnosis is given only the presenting complaint (e.g., shortness of breath) and then asked to take a focused history. Once the history is completed, the team compares notes between this and the admitting trainee’s history and resolves any discrepancies by clarifying with the patient.

Immediately after any teaching session, learners are asked if they have any questions (debriefing) and are then given specific, behaviour-based, constructive feedback. The approach to giving feedback is beyond the scope of this paper, but there are excellent reviews of this, such as the one by Ramani and Krackov. As the teacher, a second critical step is to reflect on what went well and what could have been done better and to use these reflections to improve future sessions. One powerful way to do this is to have a colleague observe you. Beckman reported on experiences of a peer-review bedside teaching project at the Mayo Clinic, and one of the key findings was how valuable peer review was to both the observed and the observer. Colleagues of mine at the University of Alberta have developed a tool for highlighting the domains of feedback when observing bedside teaching, which has greatly helped the observation and feedback process. This is available upon request.

Summary
To summarize, being explicit about bedside teaching can prime learners and allow teachers to reflect on their teaching. Incorporating bedside teaching into daily workflow can increase its frequency and enhance its value to learners. And, finally, using the aforementioned framework (summarized in Figure 2) can be helpful for improving bedside teaching.

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References
Scholarly Success Among Internal Medicine Residents in Canada

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Abstract
Scholar activity is an integral component of postgraduate medical education in Canada. We describe the opportunities in research training among Canadian internal medicine (IM) programs, including program requirements and supportive infrastructure, as well as barriers and enablers of research success.

Methods: An email survey was sent to all program directors (PDs) \( (n = 14) \) and core IM residents \( (n = 1119) \) from English-speaking IM Residency Training Programs in Canada to describe research support and productivity. We evaluated factors associated with achieving an abstract presentation at a scientific meeting or publication of a manuscript in a peer-reviewed journal.

Results: A total of 10 of 14 PDs (71%) and 308 of 1119 residents (28%) responded to the survey. Of 10 evaluable programs, 6 had a formal research curriculum and 8 had a mechanism of pairing residents with research mentors. A total of 236 (76%) residents completed a research project during core IM training; of those, 171 (55%) published \( (n = 84) \) or presented \( (n = 150) \) their research. A mechanism for linking residents with suitable research mentors, instruction on medical writing, and instruction on data analysis were associated with residents’ achieving publication in a peer-reviewed journal.

Conclusion: Requirements for resident research are variable across Canadian IM programs. Instruction on medical writing and statistics, as well as a mechanism to pair residents with suitable research mentors, contribute to resident research success.

Résumé
Les activités de recherche font partie intégrante des études de doctorat en médecine au Canada. Nous décrivons ici les différentes possibilités de formation en recherche offertes par les programmes de médecine interne (MI) au Canada, notamment les exigences et l’infrastructure de soutien des programmes, ainsi que les obstacles et les outils inhérents à la réussite en matière de recherche.

Méthode : Un sondage a été envoyé par courriel à tous les directeurs de programmes (DP) \( (n = 14) \) et aux résidents inscrits dans les programmes de formation de base en résidence en MI \( (n = 1119) \) offerts en anglais au Canada pour mieux cerner les mesures de soutien aux activités de recherche et leur efficacité. Nous avons évalué les facteurs qui mènent à la présentation d’un résumé de recherche dans un congrès scientifique ou à la publication d’un article dans une revue à comité de lecture.

Résultats : Un total de 10 DP sur 14 (71 %) et de 308 résidents sur 1119 (28 %) ont répondu au sondage. Sur les 10 programmes pouvant être évalués, 6 ont un curriculum officiel en matière de recherche et 8 ont un mécanisme de jumelage entre résidents et mentors de recherche. Un total de 236 résidents (76 %) ont complété un projet de recherche durant leur formation de base en MI; de ceux-ci, 171 (55 %) ont publié...
Scholarly Success Among Internal Medicine Residents in Canada

(\(n = 84\)) or présenté \((n = 150)\) leurs travaux de recherche. La présence d’un mécanisme de jumelage entre résidents et mentors de recherche appropriés, de même que l’apport de directives portant sur la rédaction médicale et sur l’analyse des données ont été associés à ce qui permet à un résident de publier dans une revue à comité de lecture.

Conclusion : Les exigences relatives aux activités de recherche poursuivies par les résidents varient selon les programmes canadiens de MI. L’apport de directives portant sur la rédaction médicale et les statistiques, de même que la présence d’un mécanisme de jumelage entre résidents et mentors de recherche appropriés contribuent à la réussite des activités de recherche des résidents.

Summary

Scholar activity is an integral component of postgraduate medical education in Canada, but with variable expectations across training programs. In light of a growing interest in competency-based curricula, we describe Canadian Internal Medicine (IM) program requirements and supportive infrastructure, as well as barriers and enablers of resident research success.

We surveyed program directors \((n = 10/14)\) and residents \((n = 308/1119)\) from all English-speaking IM training programs across Canada. Descriptive statistics were compiled from both resident and program director responses. Logistic regression was used to determine the association between resident characteristics and i) publication in a peer-reviewed journal, or ii) presentation at a regional, national, or international scientific meeting. Using categorical responses obtained from program directors, we used the chi-square test to evaluate programmatic factors that contribute to the achievement of abstract presentation or manuscript publication by residents.

Based on our findings, we recommend that IM programs include a scholar curriculum with instruction on medical writing and statistics and establish a mechanism for linking residents with suitable research mentors.

Introduction

Scholar activity is defined as one of seven core competencies in Canadian postgraduate medical education programs, as outlined in the CanMEDS framework, but there are variable expectations for achieving competency in this area. With a growing concern that fewer physician–scientists are being trained, it is important that residents receive exposure to research training and opportunities for research experience, as this may guide their future decisions regarding a research career. Furthermore, with reduced resident duty hours and increasing implementation of competency-based curricula, it is critical that requirements for scholar activity are defined and that the importance of research training is not diminished.

This study describes current program requirements and research activities among trainees in Canadian Internal Medicine (IM) residency training programs. Enablers of research output, infrastructure to support resident research, and barriers to research success are described. The ultimate aim of this study is to provide practical suggestions for postgraduate programs for the development of focused research curricula and methods to maximize resident research success.

Methods

We designed an electronic email survey for program directors and residents to assess the resources available for research in IM training programs and individual experiences among residents in research. We surveyed program directors \((n = 14)\) and residents \((n = 1119)\) from all 14 English-speaking IM training programs across Canada. A reminder email was sent to program directors and residents, 4 weeks and 8 weeks after the initial invitation. A reasonable gift incentive was offered to encourage participation. Chief medical residents and program assistants were contacted to help disseminate the surveys and ensure compliance locally among IM residents.

The survey for program directors was adapted from an existing tool. Program directors were asked to indicate the requirements for scholar activity in their program, the type of research projects actually completed by residents, and the proportion that are published or presented at a conference. Presence of infrastructure to support resident research activity (research committee, research director, statistician, funding, etc.) and barriers to resident research were also probed. In addition, if a structured scholar curriculum existed, details regarding its composition were obtained. Categorical (yes/no) and nominal responses (Likert scale) were collected.

Demographic data of residents, including undergraduate medical school, current institution, and year of residency training, are illustrated in Table 1. Information regarding career aspirations (community versus academic career), sub-specialty training, and motivation to complete a research project were also captured. The surveys were piloted by residents \((n = 5)\) at McMaster and edited, based on their feedback.

Statistical Analysis

Descriptive statistics were compiled from resident and program director responses. Logistic regression was used to determine the association between resident characteristics and i) publication in a peer-reviewed journal, or ii) presentation at a regional, national, or international scientific meeting. Using categorical
responses obtained from program directors, we used the chi-square test to evaluate programmatic factors that contribute to the achievement of abstract presentation or manuscript publication by residents.

Research ethics approval for this study was obtained from the Hamilton Integrated Research Ethics Board.

Results
Ten of 14 program directors (71%) and 308 of 1119 residents (28%) participated in the study. Fifty one percent of residents were interested in an academic career, and all training levels (years 1–3) were represented. Demographic information regarding IM training programs and participating residents is indicated in Table 1.

Resident Research Output and Program Requirements
There was significant variability in the type of scholar activity required by Canadian IM training programs for graduation. For example, a topic review with an oral presentation fulfilled graduation requirements for half of the training programs, but did not fulfill requirements for the remaining programs. Discussion of an article at journal club, a case presentation at morning report, and a written case report fulfilled requirements in 30, 10, and 90 percent of surveyed programs, respectively.

The majority of programs did not require a research project for graduation. Two programs mandated a quality improvement project and two different programs required a hypothesis-generating study. The scholar activities performed by residents are illustrated in Figure 1.

Program Infrastructure and Curriculum
A dedicated research rotation, additional research elective time, and a forum for presentation were available in all surveyed

<table>
<thead>
<tr>
<th>Internal Medicine Program Factor</th>
<th>Percentage of Participating IM Programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of funding</td>
<td>50</td>
</tr>
<tr>
<td>Mandatory research project</td>
<td>40</td>
</tr>
<tr>
<td>Mandatory CQI</td>
<td>20</td>
</tr>
<tr>
<td>Hypothesis driven project</td>
<td>20</td>
</tr>
<tr>
<td>Training in faculty research mentorship</td>
<td>60</td>
</tr>
<tr>
<td>Mechanism to help residents identify mentors</td>
<td>80</td>
</tr>
<tr>
<td>Resident research committee</td>
<td>50</td>
</tr>
<tr>
<td>Resident research director</td>
<td>80</td>
</tr>
<tr>
<td>Forum (on-site) for resident presentation</td>
<td>100</td>
</tr>
<tr>
<td>Research rotation available</td>
<td>100</td>
</tr>
<tr>
<td>Additional research elective time</td>
<td>100</td>
</tr>
<tr>
<td>Research curriculum</td>
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</table>

<table>
<thead>
<tr>
<th>Resident Characteristic</th>
<th>Percentage of Participating IM Residents</th>
</tr>
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<tr>
<td>Level of training</td>
<td></td>
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<tr>
<td>PGY1</td>
<td>41</td>
</tr>
<tr>
<td>PGY2</td>
<td>33</td>
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<tr>
<td>PGY3</td>
<td>26</td>
</tr>
<tr>
<td>Future career goal</td>
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<tr>
<td>Academic position</td>
<td>51</td>
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<tr>
<td>Community job</td>
<td>19</td>
</tr>
<tr>
<td>Unsure</td>
<td>28</td>
</tr>
</tbody>
</table>

IM = internal medicine.

Figure 1. Scholar activity completed by Canadian Internal Medicine residents, as self-reported by residents
programs. Sixty percent of programs did not have a formal research curriculum.

Regardless of the presence of a structured curriculum, residents reported the thoroughness of teaching of key concepts (thoroughly taught, somewhat taught, or not taught). Critical appraisal and literature searching were felt to be thoroughly taught by 80 percent and 40 percent of residents, respectively. Twenty percent or fewer residents reported thorough teaching of other curricular components, including medical writing and biostatistics/data analysis.

Barriers to Research
Residents and program directors most commonly cited lack of resident and faculty time as the biggest barriers to resident research. Lack of support with statistical analysis was the third most common barrier identified by residents (44%), while lack of administrative support was third ranked among program directors (50%). Lack of a structured research curriculum was the fourth most common barrier, indicated by 43% of residents and 40% of program directors. Lack of funding was identified by 30% of program directors and 46% of residents.

Factors Influencing Resident Research Success
Residents' self-motivation, natural interest in research, motivation for fellowship acceptance, and pursuit of a competitive specialty were associated with their success in publishing their research in a peer-reviewed journal (Table 2). Age, undergraduate medical school, and current institution were not associated with research success.

Programs that had a formal mechanism to link residents with research mentors were more likely to have their residents publish their work. Residents who reported thorough teaching of statistics and medical writing as part of their IM training were more likely to publish their work. Thorough teaching of research design, research ethics, and presentation skills were also associated with resident research success (Table 2). The number of residents in the program and presence of a mandatory research project were not significant in predicting publication or presentation.

### Table 2. Factors Associated With Resident Research Success in Publication and Presentation

<table>
<thead>
<tr>
<th>Curricular Components</th>
<th>Peer-Reviewed Publication</th>
<th>Presentation at a Meeting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Critical appraisal</td>
<td>1.4 (0.8–2.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Research design</td>
<td>2.1 (1.0–4.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Research ethics</td>
<td>2.9 (1.3–6.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Statistics</td>
<td>3.8 (1.4–10.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Literature searching</td>
<td>1.2 (0.6–2.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>Medical writing</td>
<td>4.9 (1.2–15.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Presentation skills</td>
<td>2.4 (1.2–4.8)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resident Qualities</th>
<th>Peer-Reviewed Publication</th>
<th>Presentation at a Meeting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Self-motivation</td>
<td>1.9 (1.1–3.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Natural interest in research</td>
<td>2.0 (1.2–3.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Desire for fellowship acceptance</td>
<td>2.9 (1.7–5.1)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Pursuit of competitive specialty*</td>
<td>1.8 (1.0–3.1)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio

*Cardiology, gastroenterology, critical care fellowships constituted competitive specialties.
Discussion

Lack of resident and faculty time were the most significant barriers for resident research success in Canadian IM programs, while a research curriculum was identified to be a critical enabler. Thorough teaching of statistics and medical writing were most strongly associated with residents' success in achieving a publication, which is arguably the most meaningful measure of research success. Other program-related factors, including the size of the program and presence of a mandatory research project, were not significant. Self-motivation and natural interest among residents was beneficial.

Levine et al. surveyed American university and non-university IM program directors to determine how the Accreditation Council for Graduate Medical Education (ACGME) requirements for scholarly activity are fulfilled and to identify barriers to resident research. This is the first comparable Canadian study that defines scholar activity among IM programs and barriers to resident research, but also identifies factors that are predictive of resident research success.

The results of this study indicate that a bigger program does not equate to a better program when it comes to resident research success. Furthermore, mandating a resident research project does not impact the success of trainees; in other words, quantity doesn’t mean quality. Residents who are self-motivated and naturally interested in research are likely to complete a project and publish/present their results, regardless of program requirements. The only program-related factor associated with residents' success in publication is the presence of a formal mechanism to link residents with suitable research mentors.

Residents' natural interest in research and drive to be accepted into a fellowship program are associated with their success in presenting and publishing their research projects. Although a natural interest in research cannot be contrived, selecting a project of genuine interest to the resident may be of benefit. A topic that is relevant to a resident’s desired specialty should be considered, given that motivation for acceptance into a fellowship program was associated with research success.

Although it may be intuitive, this is the first study to our knowledge proving that research curricula enhance resident research success. Given that only 40% of surveyed programs have a formal scholar curriculum and 20% or fewer programs report thorough instruction on most relevant topics, this study heralds the need for a formal and enhanced scholar curricula across Canadian IM programs.

The major methodological limitation in our project is the incomplete response rate in the group of survey responders. Because a database for resident research does not exist, response bias by program directors needs to be considered.

Conclusions

This is the first study to comprehensively document research output and program requirements for scholar activity in Canadian IM programs. Based on our findings, we recommend that IM programs include a scholar curriculum with instruction on medical writing and statistics, and establish a mechanism for linking residents with suitable research mentors. Given a significant degree of variability among programs, the possibility of setting minimum requirement for scholar activity to ensure consistency in residency training across Canada should be considered.

Acknowledgment

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Prior presentations: The final results of this study were presented at the International Conference on Residency Education on September 27, 2013.

Conflict of interest: None declared.

References

Löffler’s Endocarditis: First Report of Successful Mitral and Tricuspid Valve Replacements in a Patient with Long-Standing Hypereosinophilia

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Sahar Iqbal, MBBS, MSc, FRCPC, FACP

Summary
Löffler’s endocarditis is a condition that occurs in patients with hypereosinophilic syndrome (HES). First described in 1975, HES is a relatively new syndrome that is characterized by elevated eosinophils with end organ damage. Hypereosinophilia is defined as elevated eosinophils of 1.5 x 10^9/L for at least one month, or tissue involvement as evidenced by bone marrow section with 20% eosinophils, tissue infiltration, and/or deposition of eosinophil granule proteins in tissue. Prevalence of HES in the United States is estimated to be 0.36–6.3/100,000 people, of which Löffler’s endocarditis represents only a fraction of cases. We present a case where a patient presented with palpitations and shortness of breath, with a background of chronically elevated eosinophils. HES was previously diagnosed in this patient due to persistently elevated eosinophils with lung damage (Löffler’s syndrome). On biopsy, she was found to have endomyocardial fibrosis with a thickened endocardium secondary to eosinophils. Echocardiogram showed moderate to severe regurgitation in both mitral and tricuspid valves due to regurgitation secondary to fibrosis. She subsequently underwent a successful dual valve replacement. This is the first case, to our knowledge, where a dual valve replacement was performed successfully in a patient with Löffler’s endocarditis.

Résumé
L’endocardite fibroblastique de Löffler survient au cours du syndrome hyperéosinophilique (SHE). Défini en 1975, le SHE, relativement nouveau, se caractérise par une élévation des éosinophiles et des lésions viscérales. L’hyperéosinophilie se dit d’un taux d’éosinophiles de 1,5 x 10^9/L pendant un mois à tout le moins ou de l’infiltration tissulaire comme en témoigne la présence de 20 % d’éosinophiles dans la moelle osseuse, l’infiltration de tissus par les éosinophiles ou l’accumulation de granulations d’éosinophiles dans des tissus. L’on estime que la prévalence du SHE aux États-Unis est de 0,36 à 6,3 par 100 000 personnes; l’endocardite de Löffler ne se produit que dans une fraction de ces cas. Le cas que nous décrivons ici est celui d’une femme présentant des palpitations et de l’essoufflement sur fond d’élévation chronique des éosinophiles. On lui a déjà diagnostiqué un SHE sur le motif de la persistance de l’hyperéosinophilie et de la présence de lésions pulmonaires (syndrome de Löffler). À la biopsie, on découvre une fibrose endomyocardique accompagnée d’un épaississement de l’endocarde due aux éosinophiles. L’échocardiogramme révèle une régurgitation mitrale et tricuspide modérée à grande secondaire à la fibrose. La patiente a subi une chirurgie de remplacement valvulaire, intervention réussie. Pour autant que nous sachions, il s’agit du premier cas de remplacement valvulaire double réussi chez un patient présentant une endocardite de Löffler.
Introduction
Löffler’s endocarditis, first described in 1936, is a syndrome within the umbrella of hypereosinophilic syndromes (HES). It is characterized by elevated eosinophils, which penetrate cardiac myocytes, leading to fibrotic thickening of portions of the heart. HES was originally presented in 1975 and was initially proposed to have three defining features: serum eosinophilia greater than 1500 cells per microliter over a six-month period, no apparent cause to explain the rise in eosinophil count, and signs/symptoms of end organ damage secondary to the hypereosinophilia. However, the definition has since changed to include patients receiving treatment before the full six-month period of hypereosinophilia (HE) has lapsed and has further included patients with known causes of HE. We present a patient who, for all intents and purposes, had idiopathic Löffler’s endocarditis according to the originally proposed definition.

Case
A 44-year-old woman presented with a two-week history of palpitations, shortness of breath on exertion, and ST depression and T-wave inversion across multiple leads on ECG, on a background family history of Lynch syndrome. Her medical history was significant for 10-year history of pulmonary eosinophilia with asthma-like symptoms, osteoporosis, and environmental allergies. She denied any smoking or alcohol use. On examination, the patient appeared flushed, but not in distress. Her heart rate was 130 beats per minute, with normal heart sounds, an elevated jugular venous pressure, and bilateral lower limb pitting edema. Decreased breath sounds were auscultated in the lower lung lobes, with bilateral crackles on deep inspiration. Palpation of her abdomen produced mild right upper quadrant tenderness.

Investigations were extensive, but her leukocyte count was 11.8 x 10⁹/L, with an elevated absolute eosinophil count of 2.9 x 10⁹/L. Her hemoglobin level, lactate dehydrogenase, tryptase, and creatinine kinase were 123 grams/L, 426 units/L, 2.4 mcg/L, and 253 units/L, respectively. Her troponin was positive at 0.34 mcg/L. Her erythrocyte sedimentation rate was 2 mm/hour; however, her rheumatoid factor and C-reactive protein were both positive at 36.3K UI/L and 9.93 mg/L, respectively. Initial gamma-glutamyl transpeptidase was elevated at 159 mcg/L. Connective tissue disease and vasculitis screen was found to be negative for antinuclear antibody, perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibody.

Transthoracic echocardiogram (TTE) on post-admission Day 1 showed significant dilatation of the left and right atria, at approximately 4.5–5 cm each, and thickening of the ventricles bilaterally at the apex, measuring 2.1 cm. The interventricular septum and posterior walls were within normal limits. Contractility was 55%, with decreased movement at the ventricular apex. There was limited atrial annulus motion consistent with a restrictive pattern. The mitral and tricuspid valves had a normal echogenicity; however, there was moderate to severe 3+ mitral insufficiency and moderate 3+ tricuspid insufficiency. Interventricular thrombus was ruled out on magnetic resonance imaging (MRI), and endocardial hypertrophy was confirmed on a follow-up TTE (Figure 1). Computed tomography (CT) scan 11 days post-admission showed a small pericardial effusion with contrast accumulation in the left ventricular apex, demonstrating an isodense mass surrounding a central hypoattenuated area inconsistent with an aneurysm or a thrombus.

Cardiac catheterization showed infiltrative processes in both ventricles. The left ventricle was normal, with mild “sluggishness” in the inferior wall, and the right ventricle was nearly obliterated. Biopsies revealed endomyocardial fibrosis (Figure 2) with diffuse eosinophilic infiltrate (Figure 3).

Prednisone 40 mg daily was prescribed and subsequent blood work demonstrated a decreasing eosinophil count. A bone marrow biopsy two months later demonstrated no dyserythropoiesis, with normal distribution of leukocyte subsets. There was no evidence of eosinophils in the peripheral blood. Immunologic, cytogenetic, and molecular studies demonstrated no underlying myeloproliferative disorders. The myeloproliferative cancer gene mutation, JAK2-v617F, was negative.

A mechanical mitral and bioprosthetic tricuspid valve replacement were performed with removal of endomyocardial fibrosis from both ventricles four months after initial presentation. Subsequent echocardiograms showed normal functioning valves and no residual interventricular fibroses. She is currently on a tapering dose of prednisone, with the goal of maintaining remission, while minimizing the risk of glucocorticoid-induced osteoporosis.

Figure 1. Transthoracic echocardiogram demonstrating endocardial thickening of the ventricles.
Discussion
This patient was diagnosed with idiopathic Löffler’s endocarditis as a result of having long-standing eosinophilia without an identified etiology associated with objective end organ damage.

The new definition of HES is more encompassing than the original definition proposed by Chusid and colleagues in 1975. A panel of experts in the 2011 Working Conference on Eosinophil Disorders and Syndromes defined HE by the presence of eosinophilia greater than $1.5 \times 10^9/L$ for at least one month or tissue involvement as evidenced by bone marrow section with 20% eosinophils, tissue infiltration, and/or deposition of eosinophil granule proteins in tissue. A principal reason for this revision was to expedite timely treatment rather than having to wait six months to confirm a diagnosis. HES, accordingly, is defined as HE with eosinophil-mediated organ damage or dysfunction. It may include situations where the etiology for the eosinophilia is known.

HES can be further sub-classified as primary, secondary, or complex. Primary HES results from underlying stem cell, myeloid, or eosinophilic neoplasm causing clonal expansion. Secondary HES is a reactive type of HE caused by parasites or lymphomas, etc., causing an overproduction of eosinophilopoietic cytokines. Complex HES is used to describe patients who cannot be classified under primary or secondary HES but who present with clinical stigmata of HES. Eosinophils tend to be polyclonal in these cases. Some experts have called for the elimination of the classification of idiopathic types of HES altogether, because causes can usually be found with extensive investigation; however, determining the underlying cause might only be of academic value and can be expensive.

The true prevalence of HES is unknown but believed to be quite rare. As a result, Löffler’s endocarditis is rare as well. One study estimated the prevalence of HES to be about 0.36–6.3/100,000 in the US; however, this number was determined by extrapolating from the Surveillance, Epidemiology, and End Results (SEER) program using estimates from literature. Furthermore, the lack of a specific International Classification of Diseases, Ninth Edition (ICD-9) code for HES makes determining the prevalence even more difficult. Estimated 10-year survival is less than 50% in patients with HES and less than 30% in those with endomyocardial fibrosis. Some 60% of patients with HES tend to have cardiac involvement, with endomyocardial fibrosis being the main finding, sometimes with valve leaflet vegetations leading to progressive scarring and restricted valve movement. Classic history and physical signs are highlighted in Table 1.

Table 1. Key Points Learned From This Case

<table>
<thead>
<tr>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Do not wait 6 months to confirm hypereosinophilia to begin treatment for Löffler’s endocarditis.</td>
</tr>
<tr>
<td>- The nidus can typically be identified; however, if the common reversible causes are ruled out, further specific testing may not necessarily be clinically useful.</td>
</tr>
<tr>
<td>- Hypereosinophilic syndrome is a rare syndrome, with Löffler’s syndrome representing a smaller subgroup.</td>
</tr>
<tr>
<td>- It is imperative to reduce long-term cardiac sequelae with the use of angiotensin converting enzyme (ACE)-inhibitors and β-blockers. Anticoagulation should be considered if a thrombus is identified or if valve replacements are performed.</td>
</tr>
</tbody>
</table>
Treatment is a multi-step process that involves treating the underlying disease, if one exists, and then tackling the elevation in eosinophils. Eosinophils have been postulated to cause damage via degranulation. Thus, normalizing the eosinophil level has been the current mainstay of treatment through corticosteroid treatment, as in our case. In the case of corticosteroid-resistance, trials of myelosuppresive agents (i.e. hydroxyurea), interferon-gamma, and tyrosine kinase inhibitor imatinib have been shown to work. Imatinib has been shown to cause rapid regression of eosinophilic proliferation and resolution of hypereosinophilia. It is even proposed as first-line treatment due to its effectiveness, especially if the FIP1L1/PDGFA fusion gene is detected.

Guidelines for the Prevention of Chronic Heart Failure have recommended that prevention of ventricular re-modelling secondary to HE should be considered to reduce long-term sequelae, using angiotensin converting enzyme (ACE) inhibitors and beta blockers. Anticoagulation may be started if evidence of thrombus is seen, in order to reduce embolic events. The use of a bioprosthetic valve in lieu of a prosthetic mechanical valve in the tricuspid replacement is due to previous literature describing exaggerated platelet aggregation causing thrombotic complications.

Several case reports have been published, detailing various presentations Löeffler’s endocarditis. Many have similar presentations to our case, with right-sided heart failure and possible thrombi in the ventricles. However, to the best of our knowledge, this case is the first in reporting both a mitral and tricuspid valve presentation with successful treatment involving atrio-ventricular valve replacements.

### References


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**Table 2. History and Physical Examination Findings in Patients with Löffler’s Endocarditis**

<table>
<thead>
<tr>
<th>Findings on History (generally non-specific)</th>
<th>Findings on Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Weight loss</td>
<td>- Peripheral edema</td>
</tr>
<tr>
<td>- Fever</td>
<td>- Arrhythmias</td>
</tr>
<tr>
<td>- Rash</td>
<td>- Tachycardia</td>
</tr>
<tr>
<td>- Symptoms suggestive of congestive heart failure</td>
<td>- Cardiomegaly</td>
</tr>
<tr>
<td>o Shortness of breath</td>
<td>o Displaced apex beat</td>
</tr>
<tr>
<td>o Cough</td>
<td>o Heaves</td>
</tr>
<tr>
<td>o Dizziness</td>
<td>- Murmurs</td>
</tr>
<tr>
<td>o Fatigue</td>
<td>o Dependent on valve affected by fibrosis</td>
</tr>
<tr>
<td></td>
<td>o Difficult to ascertain on physical examination specific murmurs due to multi-valve fibrosis</td>
</tr>
<tr>
<td></td>
<td>- Findings suggestive of thromboembolic event</td>
</tr>
<tr>
<td></td>
<td>o Stroke</td>
</tr>
<tr>
<td></td>
<td>o Finger/toe tip ulcers</td>
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</tbody>
</table>
Severe Hypomagnesemia with Long-Term Use of a Proton Pump Inhibitor: A Case Report

Amy M Trottier MSc MD, Paul S Gibson MD FRCPC

Summary
Hypomagnesemia is a rare, though likely under-recognized, adverse effect of long-term use of proton pump inhibitors (PPIs), one of the most commonly prescribed classes of medications in North America. Hypomagnesemia can cause potentially life-threatening neurologic abnormalities, cardiac arrhythmias, and secondary electrolyte disorders. In this manuscript we present the case of a long-term PPI user who presented with an episode of decreased level of consciousness. He was found to have severe hypomagnesemia with avid renal retention of magnesium, secondary hypocalcemia with an inappropriately normal parathyroid hormone level, and hypokalemia. His serum magnesium and other electrolyte abnormalities rapidly corrected with cessation of PPI use and electrolyte supplementation. Given the propensity for patients with hypomagnesemia associated with PPI use to go unrecognized until they present with severe symptomatic hypomagnesemia, we recommend that patients being started on a PPI for an intended long-term course have baseline testing of serum magnesium and monitoring of magnesium on an annual basis, or sooner, if they develop symptoms.

Résumé
L’hypomagnésémie est un effet indésirable rare, quoique probablement sous-décelé, qui découle de l’usage prolongé d’inhibiteurs de la pompe à protons (IPP), l’une des classes de médicaments les plus fréquemment prescrits en Amérique du Nord. L’hypomagnésémie peut causer des anomalies neurologiques, de l’arythmie cardiaque et des troubles secondaires de l’équilibre électrolytique pouvant entraîner la mort. Le présent document porte sur le cas d’un utilisateur à long terme d’IPP présentant une diminution du niveau de conscience. On a diagnostiqué chez celui-ci une sévère hypomagnésémie, accompagnée d’une très forte rétention rénale pour le magnésium, d’une hypocalcémie secondaire montrant un niveau contre toute attente normal de l’hormone parathyroïde, en plus d’une hypokaliémie. Le taux de magnésium sérique et les autres anomalies électrolytiques sont rapidement revenus à la normale avec la suppression de l’IPP et un apport complémentaire d’électrolytes. Compte tenu de la propension à ne pas déceler l’hypomagnésémie chez les patients faisant un usage prolongé d’IPP tant que ceux-ci ne présentent pas une hypomagnésémie symptomatique sévère, nous recommandons que les patients qui commencent à prendre un IPP dans une optique de long terme soient soumis à un contrôle du niveau de base de leur magnésium sérique, puis que leur taux de magnésium soit vérifié sur une base annuelle ou plus rapidement advenant l’apparition de symptômes.
Case Report
A 70-year-old man presented to the emergency department following a 10-minute episode of decreased level of consciousness. During this period, the patient gasped for air, stared blankly, and was unresponsive to verbal commands. There was no incontinence, tongue biting, focal neurologic signs, or tonic-clonic activity. Prior to this episode the patient was well. His medical history included a myocardial infarction with angioplasty, hypertension, gastroesophageal reflux disease (GERD), and a remote cholecystectomy. His home medications included atorvastatin, ramipril, metoprolol, nitroglycerin spray, and omeprazole 20 mg daily, the latter of which he had been taking for the past 8 years. He did not drink alcohol.

Initial examination, including a cardiovascular, respiratory, abdominal, and neurologic exam, did not reveal any abnormalities. The patient was afebrile and had no history of recent illness, vomiting, or diarrhea. Initial blood work showed marked electrolyte disturbances, with severe hypomagnesemia, hypocalcemia, and hypokalemia, as shown in Table 1. Serum parathyroid hormone (PTH) was within the normal range, representing a state of relative hypoparathyroidism given the patient’s degree of hypocalcemia. Urinary electrolytes showed high renal retention of magnesium with a fractional excretion of 0.11%.

Table 1. Initial Laboratory Results of a Patient Presenting with an Episode of Decreased Level of Consciousness.

<table>
<thead>
<tr>
<th>Measured Value</th>
<th>Normal Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>137–180 g/L</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>4.0–11.0 x10⁹/L</td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>150–400 x10⁹/L</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>133–145 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>3.3–5.1 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>50–120 μmol/L</td>
<td></td>
</tr>
<tr>
<td>Random blood glucose</td>
<td>3.3–11.0 mmol/L</td>
<td></td>
</tr>
<tr>
<td>hsTroponin-T*</td>
<td>1–14 ng/L</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>2.10–2.55 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>33–48 g/L</td>
<td></td>
</tr>
<tr>
<td>Ionized calcium</td>
<td>1.15–1.35 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>13–54 ng/L</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.65–1.05 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.80–1.50 mmol/L</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>0.20–6.00 mIU/L</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>80–200 nmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Major electrolyte abnormalities found on initial laboratory investigations included severe hypomagnesemia, hypocalcemia, and hypokalemia. Parathyroid hormone was inappropriately normal.

The patient’s omeprazole was discontinued upon hospital admission and substituted with ranitidine, an H2 receptor antagonist (H2RA). He initially received IV MgSO₄, which rapidly corrected the serum magnesium. This was followed by oral supplementation with 10.4 mmol of elemental magnesium, three times daily, starting on the second day of admission. On the third day of admission, the patient’s serum magnesium dropped slightly and he was given another dose of IV MgSO₄. By the fourth day, his magnesium remained within the normal range. His calcium was supplemented orally with 500 mg of elemental calcium, four times daily. His serum calcium gradually increased and was normal at the time of discharge on Day 4. See Figure 1 for a graphic trend of the patient’s serum electrolytes and the course of electrolyte supplementation.

A work-up for other potential causes of episodic decreased level of consciousness, such as acute coronary syndrome, pulmonary embolism, cardiac arrhythmia, seizure disorder, and cerebral vascular accident, were pursued and were negative. Troponin-T was within the normal range. An electrocardiogram (EKG) showed no sign of ischemia or infraction, and a 24-hour holter monitor showed no significant arrhythmias. Computed tomography (CT) scan of the head was normal, as was an electroencephalogram (EEG). CT scan of the chest with pulmonary embolism (PE) protocol showed no sign of pulmonary embolism or any other significant abnormality. The patient had no further episodes of decreased level of consciousness during his admission.

By the time of discharge on Day 4, the patient’s serum magnesium, calcium, and potassium were all within normal limits. He was discharged home on oral calcium supplementation once daily and vitamin D 2000 IU daily, as his vitamin D was found to be slightly low (see Table 1). Magnesium supplementation was stopped and he continued to take an H2RA. Twelve days post-discharge the patient’s serum magnesium and calcium remained normal. He was advised to avoid use of any proton pump inhibitors (PPIs) in the future.

Discussion
This case illustrates a long-term PPI user presenting with decreased level of consciousness in the setting of severe hypomagnesemia and secondary hypocalcemia. His hypomagnesemia quickly improved with PPI cessation and concurrent electrolyte supplementation. The serum calcium improved, with the aid of oral supplementation, as the hypomagnesemia resolved. Application of the Naranjo Scale, a validated method for estimating the probability of adverse drug reactions, to our case gives a score of 6, within the probable adverse drug reaction category (definite ≥ 9, probable 5–8, possible 1–4, doubtful ≤ 0). Of note, four of the ten questions
Hypomagnesemia with Proton Pump Inhibitor

Trottier and Gibson

on the Narajo Scale were inapplicable to this case and were assigned a score of 0.

This case highlights a serious adverse effect of PPIs that may be under-recognized due to a lack of awareness of the association between PPIs and hypomagnesemia. The case also illustrates how prompt cessation of PPI use can lead to rapid improvement in a patient’s electrolyte abnormalities and clinical condition. The remainder of this document summarizes our review of the literature for other reported cases of hypomagnesemia in association with PPI use and describes the purported mechanism of this adverse medication effect.

PPIs achieve their therapeutic effect through potent inhibition of gastric acid release from gastric parietal cells by irreversibly blocking the hydrogen potassium adenosine triphosphatase enzyme system (H+/K+ ATPase). PPIs are commonly prescribed to treat conditions such as GERD, peptic ulcer disease, dyspepsia, and esophagitis. There are currently six PPIs available by prescription in the US and Canada, including omeprazole, lansoprazole, dexlansoprazole, esomeprazole, pantoprazole, and rabeprazole.

PPIs are some of the most commonly prescribed medications. There were 65.7 million prescriptions for omeprazole alone in the US in 2012. In Canada, Nexium (esomeprazole) was the sixth most prescribed drug in 2010, with over 3.9 million prescriptions. PPIs have long been thought by physicians to be safe, with few adverse effects; however, the longer that PPIs have been on the market, the more evidence that has come to light suggesting they may be associated with significant side effects. Adverse effects, including respiratory infections, Clostridium difficile colitis, bone fractures, and acute interstitial nephritis, have all been described. In addition, a recent association has been found between long-term PPI use and hypomagnesemia. The concern over this association and the serious consequences it may pose prompted Health Canada to release an adverse drug reaction notification in 2011, warning that prescription PPIs may cause hypomagnesemia if taken for periods of time longer than one year.

In 2006 Epstein et al. described two cases of hypomagnesemia associated with long-term PPI use, which resolved following PPI cessation. Since this publication, there have been over 30...
cases reported in the literature of severe hypomagnesemia in PPI users. Severe hypomagnesemia can lead to such nonspecific symptoms as weakness, tremors, tetany, and nausea, as well as potentially life-threatening complications including seizures, cardiac arrhythmias, and secondary electrolyte disturbances, such as hypocalcemia and hypokalemia. The risk of these adverse effects may be greater in patients with a history of seizure disorder, with cardiac conduction abnormalities, or who are on medications such as digoxin or diuretics. The magnitude of increased risk in these situations, however, is unclear.

A 2013 cross-sectional study of patients admitted to an intensive care unit showed a statistically significant association between PPI use and hypomagnesemia among those who were concurrently taking diuretics. This is in contrast to the results from a 2012 systematic review, in which no specific risk factors, beyond PPI use itself, were found to be correlated with hypomagnesemia in PPI users. In the cross-sectional study, the duration of outpatient PPI use was unknown, and patients were acutely ill with various conditions. This study is therefore not generalizable to a broader ambulatory population. Given the high prevalence of PPI users and the potential severity of hypomagnesemia, there is a need for large prospective studies to better delineate the potential causative role of PPIs on hypomagnesemia and to determine the incidence of this adverse effect.

The exact mechanism by which PPIs induce hypomagnesemia is unknown, but evidence from case reports and recent modelling studies have elucidated probable hypotheses. As highlighted in the systematic review by Hess and colleagues, case reports of hypomagnesemia with PPI use consistently show low renal magnesium excretion. These findings suggest reduced intestinal absorption as the source of magnesium loss. This is in contrast to other medications such as gentamycin, calcineurin inhibitors, cisplatin, and diuretics that cause reduced proton secretion into the interstitium, resulting in PTH resistance and impaired PTH-induced release of calcium from bone. Magnesium deficiency is also frequently associated with hypokalemia that is unresponsive to potassium supplementation alone. The mechanism for this involves hypomagnesemia-induced reduced inhibition of renal outer medullary potassium channels (ROMK), causing increased ROMK activity and thus increased renal potassium excretion.

We recommend that patients being started on a PPI for an intended long-term course have a baseline serum magnesium level drawn and have periodic monitoring of serum magnesium levels. The optimal timing for monitoring magnesium levels...
is unknown, but annual monitoring (sooner if the patient develops symptoms) may be reasonable. Clinical judgement should always be applied to individual cases. Presently there are no large prospective trials to better define the necessity of or timing for magnesium monitoring. Such a study would be valuable in defining the true incidence and timing of PPI-associated hypomagnesemia. Long-term use of PPIs should be considered in the differential diagnosis for hypomagnesemia.

Prior Presentations: 2013 Rocky Mountain/ACP Internal Medicine Conference in Banff, AB. November 14th, 2013.

Conflict of interest: none declared

References

CSIM EDUCATION AND RESEARCH FUND (Deadline: November 2, 2015)

- Encourage residents to pursue careers in both community and university-based General Internal Medicine (GIM) to do an elective at another Canadian site to pursue a scholarly activity in medical education, clinical research project or QI project.
- Encourage the development of GIM (community and university-based) as a specialty by facilitating scholarly activity, knowledge exchange and pursuit of new knowledge.
An Unusual Cause of Severe Immunosuppression

Karan Bami MD, Winnie Chan MD, Oren Steen MD, Ally PH Prebtani MD, Nishma Singhal MD

About the Authors
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Abstract
Ectopic adrenocorticotropic hormone secretion (EAS) is a rare cause of endogenous Cushing’s syndrome and is associated with immunosuppression and opportunistic infections. We report the case of a person who presented with rapid onset of hypertension, diabetes mellitus, and severe hypokalemia in the context of significantly elevated adrenocorticotropic hormone (ACTH) levels and marked hypercortisolism. Subsequent investigations led to a diagnosis of EAS without an identifiable source. Her clinical status continued to deteriorate despite medical management of her hypercortisolism, thus an urgent bilateral adrenalectomy was performed. This patient’s course was complicated by multiple opportunistic infections with cytomegalovirus, Pneumocystis jirovecii (PJP), Mycobacterium tuberculosis and possibly BK virus. To the best of our knowledge, this is the first description of this specific constellation of opportunistic infections in the setting of EAS. Our case highlights the need to consider multiple and rare opportunistic infections while managing EAS and supports early bilateral adrenalectomy in critically ill patients with EAS of unknown origin.

Résumé
La sécrétion ectopique de l’hormone adrénocorticotrope (SEA) est une cause rare du syndrome de Cushing endogène et est associée à un déficit immunitaire et à des infections opportunistes. Nous rapportons ici le cas d’une femme qui a présenté un début rapide d’hypertension, de diabète sucré et d’une sévère hypokaliémie dans un contexte de niveaux considérablement élevés de l’hormone adrénocorticotrope (ACTH) et un hypercortisolisme prononcé. Des investigations complémentaires ont mené à un diagnostic de SEA sans détermination de l’origine de celle-ci. Puisque la condition clinique de la patiente continuait de se détériorer malgré la prise en charge médicale de l’hypercortisolémie, une surrénalectomie bilatérale a été réalisée en urgence. Le traitement de cette patiente a été compliqué par de nombreuses infections opportunistes dues au cytomégalovirus, au Pneumocystis jirovecii, au Mycobacterium tuberculosis et peut-être également au virus BK. À notre connaissance, ce cas constitue la première description de cette constellation particulière d’infections opportunistes dans un contexte de SEA. Le cas rapporté souligne la nécessité d’envisager la présence d’infections opportunistes multiples et rares lors de la prise en charge d’une SEA et vient à l’appui de la réalisation d’une surrénalectomie bilatérale rapide chez les patients gravement malades en raison d’une SEA d’origine inconnue.
Case
A 74-year-old female woman presented to a community hospital with a one-month history of progressive fatigue, weight loss, and muscle weakness. She was diagnosed with hypertension, diabetes mellitus, and severe hypokalemia. Physical examination demonstrated severe proximal muscle weakness and cachexia. Classic cushingoid features were absent, but investigations revealed markedly elevated levels of adrenocorticotropic hormone (ACTH) and 24-hour urinary free cortisol (Table 1). Cortisol levels did not suppress with high dose dexamethasone (8 mg). A magnetic resonance imaging (MRI) head with gadolinium did not exhibit any sellar lesions. Given a negative dexamethasone suppression test, no pituitary lesion on MRI, and the rapidity of disease progression, a diagnosis of ectopic ACTH syndrome was made. Corticotropin-releasing hormone (CRH) testing was unavailable and thus could not performed. Given the evidence pointing towards EAS over a pituitary source of ACTH, the risk of inferior petrosal vein sampling was felt to outweigh the benefits.

Computerized tomography (CT) of the chest, abdomen, and pelvis demonstrated bilateral adrenal enlargement. An octreotide scintigraphy with single-photon emission (SPE)-CT (with imaging at 24 and 48 hours) showed increased uptake in the left adrenal gland without evidence of lesions elsewhere, suggesting a possible adrenal source of ectopic ACTH production. The patient was started on insulin for diabetes and spironolactone, as well as potassium replacement for hypertension and hypokalemia. She was discharged home from the community hospital with a referral to an endocrinologist at our centre.

Within days following discharge, the patient presented to our tertiary care hospital with confusion, productive cough, and dyspnea. She was treated for pneumonia with levofloxacin. On the fourth day of admission, she was intubated for decreased level of consciousness. Her clinical status continued to deteriorate despite management with ketoconazole and octreotide for hypercortisolemia. She also developed a gastrointestinal (GI) bleed with a hemoglobin nadir of 56 g/L. Endoscopy revealed diffuse gastritis with duodenal ulceration and biopsy showed cytomegalovirus (CMV) duodenitis (Figure 1). Her plasma CMV PCR was 1,705,000 IU/mL (Figure 1) and HIV serology was negative. Ganciclovir was initiated, along with trimethoprim-sulfamethoxazole (TMP-SMX) for PJP prophylaxis.

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Value (normal range) references: g</th>
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<tr>
<td>24-hr urinary-free cortisol</td>
<td>5871 nmol/d (30–300 nmol/d)</td>
</tr>
<tr>
<td>Random ACTH</td>
<td>52.4 pmol/L (&lt;10.3 pmol/L)</td>
</tr>
<tr>
<td>High dose (8 mg) overnight dexamethasone suppression test</td>
<td>2279 nmol/L → 2549 nmol/L No suppression</td>
</tr>
</tbody>
</table>

Panel A: Numerous CMV inclusions were evident in epithelial (arrows) and endothelial cells of the inflamed edematous and hemorrhagic duodenal mucosa. Panel B: Crypt epithelial cell with CMV nuclear inclusion (arrow). Panel C: CMV immunohistochemistry highlights nuclear inclusions.

Figure 1. Duodenal Biopsy Specimen

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Adrenal vein sampling was performed, given the increased uptake demonstrated on the octreotide scan. This failed to demonstrate an ACTH gradient, ruling out the left adrenal gland as the ACTH source. Catheter position during the sampling was verified with corresponding adrenal vs. peripheral cortisol levels (approximately six-fold higher in the adrenal veins). Given the patient’s rapid life-threatening deterioration and no identifiable source of ACTH production, urgent bilateral adrenalectomy was performed. Pathology revealed bilateral adrenal hyperplasia.

Post-operatively, the patient’s hypokalemia resolved, antihypertensives were discontinued, and insulin was weaned. The patient was started on a steroid replacement regimen of hydrocortisone 50 mg IV every 8 hours, eventually weaning to 20 mg IV every 12 hours.

Unfortunately, her respiratory status and chest radiography worsened. Bronchial alveolar lavage (BAL) demonstrated PJP despite TMP-SMX prophylaxis. Accordingly, the patient was switched to treatment doses of trimethoprim-sulfamethoxazole (TMP-SMX). Three weeks later, her bronchoalveolar lavage (BAL) cultures grew *Mycobacterium tuberculosis*. Quadruple anti-tuberculosis therapy was initiated. She also developed hemorrhagic cystitis, possibly secondary to BK virus, as urine cytology revealed atypical urothelial cells with viral cytopathic changes.

The patient was extubated after two months of mechanical ventilation. Her steroid regimen at the time of discharge was prednisone 10 mg daily and fludrocortisone 0.1 mg daily. After extensive rehabilitation for critical illness polyneuropathy and myopathy resulting from the extended ICU stay, she returned home.

Post-discharge, she was followed for ongoing outpatient surveillance and work up for a possible ACTH source. Calcitonin was 7 ng/L (normal < 7 ng/L) and no discrete thyroid nodule was seen on ultrasound. Repeat imaging was done approximately nine months after her initial scans. A CT thorax showed new pulmonary nodules and necrotic right cervical and supraclavicular lymph nodes. The Octreoscan showed uptake in the right supraclavicular lymph nodes. Biopsy of the supraclavicular lymph nodes was nondiagnostic. Subsequent biopsy of a pulmonary nodule showed necrotizing granulomatous inflammation, but was negative for neoplasia, mycobacteria, and fungal organisms. Bronchoscopy was negative for malignant cells, Mycobacteria, PJP, HSV, CMV, respiratory virus PCR, or pathogenic bacteria. Her steroid regimen has been titrated to prednisone 5 mg daily by mouth and fludrocortisone 0.2 mg daily by mouth.

Discussion

EAS is a relatively uncommon condition accounting for approximately 10% of endogenous Cushing’s syndrome cases. Compared with other causes of Cushing’s syndrome, EAS is associated with a higher magnitude of hypercortisolemia and, therefore, potentially life-threatening complications. Additionally, in our case, the patient’s lack of classic cushingoid features at initial presentation, despite extremely high cortisol levels, suggests a rapid onset of disease. As such, prompt recognition and investigation of EAS is vital and should be considered in patients presenting with muscle weakness, new onset hypertension, diabetes, or hypokalemia. A diagnosis of EAS warrants investigation into the source of ACTH. Yet, despite an exhaustive search, the source may not be found in up to 12% of cases.

Individuals with EAS are at risk for more severe immunosuppression than other causes of Cushing’s syndrome, likely related to the higher degree of hypercortisolemia. Among patients presenting with manifestations of such severe immunosuppression as opportunistic infections, in the absence of known malignancy, immunosuppressive medications, inflammatory disorders, or HIV, endogenous hypercortisolemia is important to consider in the differential diagnosis. Timely identification and control of hypercortisolemia are

<table>
<thead>
<tr>
<th>Complications</th>
<th>Investigations</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Upper GI bleed</td>
<td>OGD: diffuse gastritis and duodenal ulceration Pathology: CMV duodenitis CMV PCR: 1,705,000 IU/ml</td>
<td>Blood transfusions PRN Gancyclovir → Valgancyclovir</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>BAL: PJP pneumonia HIV testing negative</td>
<td>TMP-SMX treatment doses initiated</td>
</tr>
<tr>
<td>Difficulty weaning off ventilator</td>
<td>BAL (3 weeks incubation): Mycobacterium tuberculosis</td>
<td>Quadruple therapy initiated (rifampicin, isoniazid, pyrazinamide and ethambutol)</td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>Urine cytology: atypical urothelial cells with viral cytopathic changes: ? BK virus</td>
<td>No treatment</td>
</tr>
</tbody>
</table>
central to the successful prevention and management of EAS complications. As our case demonstrates, when the source of ACTH cannot be localized, bilateral adrenalectomy may be necessary and life-saving in critically ill patients.

In several small case series, the most common opportunistic pathogens identified in patients with endogenous Cushing’s were Aspergillus fumigatus, Pneumocystis jirovecii, Cryptococcus neoformans, and Nocardia sp. CMV infection is rarely a complication of endogenous Cushing’s syndrome, with only three previously published cases. In most instances, patients developed a single or perhaps two simultaneous opportunistic infections.

Two previously published cases describe multiple opportunistic infections in conjunction with EAS. Sieber and colleagues described a man who developed CMV pneumonia, Pneumocystis jirovecii pneumonia and disseminated aspergillosis due to an ectopic ACTH-producing oat cell lung carcinoma. An additional case of EAS was complicated by simultaneous infections with Pneumocystis jirovecii, Staphylococcus aureus, Candida albicans, Aspergillus fumigatus, and herpes simplex.

Our case uniquely demonstrates simultaneous infections with CMV, Pneumocystis jirovecii, Mycobacterium tuberculosis, and possibly BK virus. This specific constellation of opportunistic infections in the setting of EAS has not, to the best of our knowledge, been previously reported. Additionally, it is the first report of EAS resulting in CMV gastritis and duodenal ulceration manifesting as an upper gastrointestinal bleed. It is also the first report of possible BK virus hemorrhagic cystitis as a complication of EAS in the literature. It therefore highlights the extent of immunosuppression that may result from EAS and the need to maintain a high index of suspicion for multiple, uncommon, opportunistic co-infections in such cases. Furthermore, our case supports early bilateral adrenalectomy as a potentially life-saving treatment in severely ill patients with EAS of unknown origin.

Financial disclosures: none to declare.

References
A 44-Year-Old Man with Fever, Mucocutaneous Ulcers, and a Rash

Meghan J Ho MD, Ines Sherifi MSc MD, Rodrigo Cavalcanti MSc MD

Summary
We report the case of a 44-year-old man who presented with mucocutaneous ulcers, purpuric rash, fever, pharyngitis, cervical lymphadenopathy, and arthralgias. The patient’s symptoms resolved with prednisone treatment. He later experienced recurrence of oral ulcers that responded to colchicine treatment. Behcet’s disease is a systemic vasculitis characterized by recurring oral and genital mucocutaneous lesions and accompanying ocular, gastrointestinal, articular, pulmonary, neurologic, or peripheral vascular manifestations. Sweet’s syndrome typically presents with flu-like symptoms, fever, neutrophilia, and painful erythematous skin lesions. Along with skin biopsy, classification criteria exist for both conditions, which may help differentiate the two diagnoses on initial presentation.

Résumé
Il s’agit du cas d’un homme de 44 ans qui présente des ulcères cutanéo-muqueux, une éruption cutanée purpurique, de la fièvre, une pharyngite, une adénopathie cervicale et des arthralgies. Les symptômes du patient disparurent à la suite de l’administration de prednisone. Plus tard, une récurrence d’aphtes buccaux réagit à l’administration de colchicine. La maladie de Behcet est une vascularite systémique caractérisée par des lésions cutanéo-muqueuses buccales et génitales récurrentes accompagnées de manifestations oculaires, gastro-intestinales, articulaires, pulmonaires, neurologiques ou vasculaires périphériques. En comparaison, le syndrome de Sweet se caractérise habituellement par des symptômes pseudo-grippaux, de la fièvre, une neutrophilie et des lésions cutanées érythémateuses douloureuses. La distinction entre les deux diagnostics est facilitée par la réalisation d’une biopsie cutanée et la référence à des critères de classification des deux pathologies dès la présentation.
Case

A 44 year-old man of Chinese descent presented with a one-week history of pharyngitis and fever, followed by oral and genital ulcers, myalgias, and a palpable purpuric rash. He was previously healthy and denied sick contacts, animal or insect exposures, or recent travel. He reported recent unprotected heterosexual contact but denied dysuria, genital discharge, or pruritus. After symptom onset, he had taken Chinese herbal remedies but denied use of any other medications or drugs. Family history was unremarkable.

On examination, the patient looked unwell, was febrile (38.8°C orally), and was diaphoretic. He was initially tachycardic (heart rate [HR] = 120) but responded to intravenous fluids. Examination of the oral cavity revealed painful oral ulcers (Figure 1b) and tonsillar and pharyngeal exudates. He had tender cervical lymphadenopathy and non-tender scrotal and penile ulcers. A palpable, purpuric, non-blanchable, non-pruritic and painless rash (Figure 1c) was present on his lower legs bilaterally, with some lesions displaying central papules. Larger discrete lesions at each wrist had a more nodular appearance with central discolouration (Figure 1a). Lesions were also present on his upper abdomen and buttock. There were no other skin or nail findings. He had mild peri-articular ankle swelling and right knee stress tenderness with flexion, but no joint effusions. Cardiac, respiratory, abdominal, and neurological exams were unremarkable.

Laboratory investigations revealed a normal white blood cell (WBC) count with neutrophilia, mild anemia (Hb 126), transaminitis, and an elevated erythrocyte sedimentation rate (ESR; 110). The patient was admitted to hospital and given 1 g ceftriaxone and azithromycin 1 g daily for empiric treatment of suspected gonococcal infection and possible chlamydia co-infection. The antibiotics were discontinued after additional investigation results became available and the patient remained febrile despite antibiotics. Bacterial blood and urine cultures were negative, a throat swab was negative for Group A Streptococcus, and the oral lesion swab was negative for herpes simplex virus. The patient was hepatitis B immune. Hepatitis C and HIV 1/2 antibody and p24 antigen tests were negative. Cytomegalovirus, syphilis, parvovirus B12 IgM, EBV monospot and brucella serology testing were negative. Urine testing for Mycoplasma showed no isolates.

Figure 1. a–c) Skin and oral manifestations at presentation; e) neutrophilic dermatoses on skin biopsy; d,f) skin manifestations after 13 days of prednisone therapy.
Autoimmune work up (ANA, RF, ANCA, anti-ds DNA, complements) was negative. Skin lesion biopsy demonstrated a neutrophilic dermatosis, with fibrin deposition and small vessel vasculitis in the deep dermis and no eosinophils (Figure 1e). A sub-corneal follicular pustule was present in the biopsy fragment. Skin pathergy test was negative. The patient was started on prednisone 40 mg daily for a presumptive diagnosis of Behcet’s disease (BD) and was discharged afebrile after clinical improvement. Follow-up appointments with rheumatology and ophthalmology were arranged for the patient; there was no evidence of uveitis during the admission. Chest x-ray, electrocardiogram, and echocardiogram performed in hospital were within normal limits.

The patient was seen in clinic 11 days after discharge and exhibited almost complete resolution of his oral ulcers, as well as improvement in the rash (Figure 1d, f) and genital ulcers. Five months after his initial presentation, he presented with recurrent oral ulcers that responded to colchicine treatment.

**Discussion**

**Neutrophilic Dermatosis**

Sweet’s syndrome is classically characterized by fever, neutrophilia, painful erythematous skin lesions with neutrophilic infiltrate in the upper dermis, and immediate response to systemic corticosteroids. It typically presents in middle-aged women and may be associated with upper respiratory tract and gastrointestinal (GI) infections, pregnancy, inflammatory bowel disease, and malignancy (often hematologic), or it can be drug-induced. Generalized flu-like symptoms are common in Sweet’s syndrome, as are joint manifestations. Involvement of mucous membranes, with oral ulcers and ocular lesions, as well as ears, bone, central nervous system (CNS), and intra-abdominal and intrathoracic organs has been reported. In most cases, there is a leukocytosis with elevated neutrophils.

In Sweet’s syndrome, the typical skin lesions are tender erythematous papules and nodules that may coalesce into irregular plaques. Most frequently they occur on the face, neck, and arms. Pathergy may be present. Pustular lesions are rarely observed and, when present, primarily occur on the extensor surfaces of the distal arms (neutrophilic dermatosis of the dorsal hands) in patients with ulcerative colitis.

Histopathological findings typical of Sweet’s syndrome are a major diagnostic criteria (Table 1). On histopathology, the neutrophilic infiltrate in the dermal layer is separated from the epidermis by edema. Although vascular lesions may be present, there is no true vasculitis in Sweet’s syndrome, with fibrin deposition and neutrophilic vasculitis typically being absent. Drug-induced Sweet’s syndrome may show an inflammatory infiltrate with eosinophils. In contrast, “pustular lesions on purpuric bases” or “pustular vasculitis” have been used to describe BD, which is characterized by a neutrophilic vascular reaction. Thus, male sex, presentation, and distribution of non-tender cutaneous lesions, absence of leukocytosis, morphology of the neutrophilic dermatosis, and recurrence of oral ulcers favours a diagnosis of BD over Sweet’s syndrome (with neither major diagnostic criteria being met).

**Behcet’s Disease**

**Epidemiology**

BD is a systemic vasculitis characterized by chronic recurrent clinical symptoms of oral and genital mucocutaneous lesions and ocular, GI, articular, pulmonary, neurologic, and peripheral vascular manifestations (Table 1). BD has roughly equal distribution among men and women, and typical age of onset is 20–40 years. Younger age at diagnosis and male sex are worse prognostic features, with higher mortality and increased ocular morbidity. The disease has the highest incidence in ethnicities found along the Silk Road, including regions in the Middle East, the Mediterranean basin, and Asia (between 30 and 45 degrees northern latitude) and is uncommon in developed countries; reasons for these geographic differences are unknown.

**Pathogenesis**

The etiology of BD is unknown. Although believed to be an autoimmune process, it has not been associated with any autoantibodies. An association of HLA-B51 and BD has been established; however, the specific role of HLA-B51 in the pathogenesis of BD has not been elucidated, as it only explains 20% of disease heritability.

<table>
<thead>
<tr>
<th>Table 1. Proposed Diagnostic Criteria for Sweet’s Syndrome.</th>
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<tr>
<td><strong>Major Criteria</strong></td>
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<tr>
<td>- Abrupt onset of tender or painful erythematous or violaceous plaques or nodules</td>
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<td>- Predominantly dermal neutrophilic infiltration without leukocytoclastic vasculitis</td>
</tr>
<tr>
<td><strong>Minor Criteria</strong></td>
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<tr>
<td>- Preceding fever or infection</td>
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<tr>
<td>- Accompanying fever, arthralgia, conjunctivitis or underlying malignancy</td>
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<tr>
<td>- Leukocytosis</td>
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<tr>
<td>- Good response to systemically administered corticosteroids and not to antibiotics</td>
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<tr>
<td>- Increased erythrocyte sedimentation rate</td>
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Definitive diagnosis requires 2 major and 2 minor criteria. Modified from (3)
Clinical Features
The original descriptive triad of BD included recurrent oral ulcers, genital ulcers, and uveitis as hallmark features of the disease. Aphthous ulcers less than 1 cm in diameter are the most common type of oral ulcer in BD, with 85% prevalence. They may be present anywhere on the oral mucosa, with the lips being the most frequent site. Genital ulcers are also common (found in 85% of cases), and distribution usually involves the scrotum. GI tract involvement includes mucosal ulceration, mainly in the ileum and colon, and symptoms of colicky abdominal pain and diarrhea. Skin involvement includes nodular lesions resembling erythema nodosum, papulopustular lesions similar to acne vulgaris, superficial thrombophlebitis, and positive pathergy test. Pustulosis, a vasculitis consisting of a sterile pustule on a rounded erythematous-edematous or purpuric base, is the most frequent skin lesion in BD.

Ocular involvement is usually in the form of bilateral relapsing uveitis. Musculoskeletal symptoms include myositis, non-erosive peripheral arthritis, and arthralgias. The most serious symptoms of BD and major causes of mortality include vasculitides of major vessels and neurologic manifestations. In nationwide Iranian surveys of patients with BD, Davatchi and colleagues found that oral and genital aphthosis and skin manifestations were the most common symptoms among 1,996 patients (93%, 76%, and 69%, respectively), with ocular manifestations found in only 35%, joint involvement in 30%, and phlebitis, CNS, and GI involvement being relatively uncommon (6.5%, 8.8%, and 5.3%).

Diagnosis
Fifteen different classification systems or diagnostic criteria have been proposed for BD, with the latest one being the International Criteria for Behcet’s Disease (ICBD). In Davatchi and others’ review of all 15 BD criteria using a disease registry in Iran (where BD prevalence is high), the ICBD (Table 2) was found to be the most accurate, with an accuracy of 93.8%, sensitivity of 96.1%, and specificity of 88.7%. The patient in this case meets BD diagnosis by having 4 points on the ICBD system.

Treatment
Various double-blind, randomized controlled trials have been performed with patients with BD, using agents such as methylprednisolone, azathioprine, thalidomide, colchicine, dapsone, cyclosporine, and azapropazone. There is no clear first-line agent considered the overall standard of care for BD, and despite the common use of oral steroids, no clear evidence on their efficacy for BD has been published. In 2008, the European League Against Rheumatism developed nine recommendations for managing BD based on expert opinion and uncontrolled evidence, further highlighting the need for controlled trials.

Key Points
• Sweet’s syndrome and Behcet’s disease should be considered in the differential for patients presenting with fever, rash, and mucocutaneous ulcers.
• Behcet’s disease typically presents in younger patients and is more common in ethnicities found along the Silk Road.
• Oral and genital ulcers and skin manifestations are common features of Behcet’s disease, while Sweet’s syndrome may be preceded by infection and/or associated with malignancy.
• Skin biopsy is helpful in narrowing the diagnostic differential and guiding treatment.

References

Table 2. Revised International Criteria for Behcet’s Disease (traditional format).

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>Oral aphthosis</td>
<td>1</td>
</tr>
<tr>
<td>Skin manifestations</td>
<td>1</td>
</tr>
<tr>
<td>Vascular lesions (thrombosis, aneurysm)</td>
<td>1</td>
</tr>
<tr>
<td>Pathergy phenomenon</td>
<td>1</td>
</tr>
<tr>
<td>Genital aphthosis</td>
<td>2</td>
</tr>
<tr>
<td>Ocular lesions</td>
<td>2</td>
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<tr>
<td>Diagnosis requires 3 or more points.</td>
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Modified from 9
Cavitating Mesenteric Lymph Node Syndrome and Enteropathy-Associated T Cell Lymphoma as First Manifestation of Celiac Disease

Rouslan Kotchetkov MD, and Vishal Kukreti MD

Summary
Celiac disease (CD) is a common systemic disease, affecting about 1.0% of the population. Classical presentation includes malabsorption syndrome and deficiencies of macro-/micronutrients. Patients with undiagnosed CD may be referred to hematologists with different hematologic issues, including anemia, thrombocytosis, thrombocytopenia, leukopenia, venous thromboembolism, hyposplenism, and IgA deficiency. CD imposes an increased risk of various lymphomas, especially intestinal T- and B-cell lymphomas. Enteropathy-associated T-cell lymphoma (EATL) is a rare and aggressive disease with poor prognosis and often fatal complications. Here we present a case of EATL associated with cavitating mesenteric lymph node syndrome as a first manifestation of undiagnosed CD.

Résumé
La maladie coeliaque (MC) est une maladie systémique que l’on rencontre fréquemment et qui touche 1,0 % de la population. Ses manifestations classiques comprennent le syndrome de malabsorption et certaines carences en micro/macronutriments. Les patients chez qui la maladie n’a pas été diagnostiquée sont parfois adressés à un hématologue pour divers problèmes hématologiques, comme de l’anémie, une thrombocytose, une thrombocytopenie, une leucopénie, une thromboembolie veineuse, un hyposplénisme et une carence en IgA. La MC entraîne un risque accru de divers lymphomes, en particulier des lymphomes T et des lymphomes malins à cellules B de l’intestin. L’entéropathie associée au lymphome T (EALT) est une maladie rare et agressive, à pronostic sombre et dont les complications sont souvent fatales. Nous présentons ici un cas d’EALT associé à un syndrome de ganglions mésentériques avec formation de cavernes en tant que première manifestation d’une MC non diagnostiquée.
Case

A 71-year old South American woman was referred for a suspected diagnosis of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). She had an over 20-year history of intermittent abdominal discomfort and noticed progressive symptoms over the last 3 years. Three months prior to the visit, the patient developed fatigue, night sweats, anorexia, increasing abdominal girth, heartburn, abdominal pain with intermittent diarrhea, and weight loss. She denied lymphadenopathy, skin rash, fever, or cough. There was no history of travel and consumption of unusual or uncooked food. Her medical history was significant for osteoarthritis, hypertension (currently controlled on Propranolol, 40 mg daily). She was a lifelong non-smoker and occasional ethanol consumer with an unremarkable family history. She denied any hepatitis or human immunodeficiency virus (HIV) risk factors. Physical exam was unremarkable, except for soft and distended abdomen with tenderness on palpation.

Investigations showed mild macrocytic anemia (hemoglobin = 114 g/L, mean corpuscular volume = 100.2) and leukopenia (white blood cells [WBCs] = 3.9 x 10^9/L). Platelet count was normal (237 x 10^9/L) and chemistry was normal except for an elevated lactate dehydrogenase [LDH] (259 U/L, N ≤ 220). Computed tomography (CT) of the thorax was clear, but abdomen/pelvis CT revealed numerous multiple rim-enhancing hypoattenuating cystic-like round lesions within the jejunal mesentery and left paraaortic areas, suspicious for multiple necrotic lymphadenopathy (Figure 1). The largest of them was 4.6 x 3.8 cm. Repeated CT noticed overall interval increase in size of most of these lesions and reported them as possible cavitary mesenteric lymph node syndrome. Mesenteric fine needle biopsy aspiration yielded chylous milky fluid, associated with collapse of the cyst (Figure 2A). There was no solid component suitable for the core biopsy, and clinically the lymph nodes were not amenable to surgical excisional biopsy. Available material yielded malignant-looking lymphocytes, with atypical enlarged convoluted nuclei and deeply basophilic cytoplasm.

Flow cytometry identified population of T-cells positive for markers CD2 and CD7, negative for CD3, CD4, CD5, and CD8. Further work up for cystic findings in the mesentery was negative for HIV 1 and 2, Epstein-Barr virus (EBV), hepatitis B, Echinococcus, and Schistosoma. Bone marrow aspiration showed mild T-cell lymphocytosis, with a subpopulation of small- to medium-sized T-cells, with the same immunophenotype, consistent with T-cell lymphoproliferative
disorder. Based on clinical and laboratory data, we diagnosed her with enteropathy-associated T-cell lymphoma (EATL) type I in association with cavitating mesenteric lymph node syndrome.

At that time we raised the possibility of celiac disease (CD). Her gliadin antibody IgG was 110 units, Ig A was 390 units, tissue transglutaminase IgG was less than 4 units, and tissue transglutaminase IgA was 290 units (our laboratory ranges are negative as < 20, weakly positive as 20–30, and positive as > 30 units). To confirm the diagnosis of celiac disease, an esophagogastroduodenoscopy was performed. Duodenal biopsy showed severe mucosal flattening, villous atrophy with loss of architecture, and intraepithelial infiltrate with atypical T-cells, consistent with EATL on a background of CD (Figure 2B). Within one week of starting a gluten-free diet, the patient noticed improvement in gastrointestinal symptoms. She has since started CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) chemotherapy for the management of her Stage 4B EATL. Initially she responded to chemotherapy and achieved partial response, however tumor progressed and the patient was taken off active treatment.

Discussion
The natural history of CD varies widely among patients. The usual sequence of events is the following: 1) serological appearance of celiac-specific antibodies, 2) development of intestinal enteropathy, 3) onset of symptoms, 4) progression to complications. However, not all the events may occur. The duration of each phase can range from weeks to decades. Frequent manifestations, presenting in 40–50% of patients with CD, are chronic diarrhea, weight loss, and abdominal distention. Other presentations include isolated iron deficiency with or without anemia, recurrent abdominal pain, aphthous stomatitis, high level of aminotransferases, chronic fatigue, and reduced bone mineral density. CD is a common cause of various hematologic disorders. Anemia is the most common presentation of CD and is most frequently found in patients with undiagnosed or untreated CD. Anemia in CD is usually hypoproliferative, secondary to impaired absorption of essential nutrients, as follows: iron, folate, B12, and less frequently copper, B6, pantothenic acid, and riboflavin. Thrombocytosis occurs in up to 60% with CD.

On the other side, patients with CD may develop thrombocytopenia. CD is also associated with both increased venous thromboembolism, which may be the presenting feature, and abnormalities in coagulation factors (e.g., vitamin K), resulting in an abnormal bleeding tendency. Other manifestations include hyposplenism with Howell-Jolly bodies in peripheral blood film and IgA deficiency.

Development of intestinal lymphoma is well described and is possibly a major contributor to mortality in patients with CD. The risk is highest for intestinal EATL, which is a rare primary extranodal and aggressive malignancy with an incidence of less than 1% of all non-Hodgkin’s lymphomas. EATL is usually associated with refractory CD, EATL type I. This type frequently has large-cell or pleomorphic cytology with various, abnormal, multinucleated forms and is usually CD56 negative. It has a poor prognosis, whether it occurs de novo or results from long-term untreated refractory CD. The largest reported series in the literature showed a 1-year survival of only 31% and 5-year survival of 11%.

Cavitating mesenteric lymph node syndrome (CMLNS) is a rare complication of CD. A paper by McBride and colleagues summarized 38 case reports of CMLNS and celiac disease worldwide. CMLNS is typically presented as multiple cystic masses containing milky creamy fluid. On CT, these cystic masses have central low attenuation with a thin enhancing rim, often with fat-fluid levels. CMLNS is associated with a very poor prognosis and up to 50% mortality, mainly due to severe malnutrition, intestinal hemorrhage secondary to ulceration, and overwhelming sepsis, as a combination of hyposplenism plus malnutrition.

Association between CMLNS and EATL is seen much less frequently and, to our knowledge, is described in only two literature cases. In the first case, the CMLNS and EATL developed in a CD patient with persisting symptoms, despite adherence to the gluten-free diet. The second patient...
developed CMLNS and EATL at the terminal ileum and subsequently was diagnosed with CD. In our patient, EATL with CMLNS was the first presentation of undiagnosed CD. It is not feasible to assess the proper status of CD at that stage, but clinical improvement with a gluten-free diet may indicate that this patient did not have a true refractory disease. We may suggest that, in this case, an absence of a proper diagnosis of CD and continuous load with gluten mimicked refractoriness of the disease.

A validated standard treatment of EATL in patients with CD is lacking. The surgical role is in local debulking and in resection of tumour masses with a high risk of obstruction or perforation. Therapy for CD-associated lymphoma is not different from that used in similar lymphomas in patients without CD. Chemotherapy with anthracycline-containing regimen, like CHOP is the most widely used and is generally responsible for an overall 5-year survival rate of 9–22%. However, in routine practice, chemotherapy cannot be administered in more than one-half of cases due to low performance status, malnourishment from preexisting unresponsive CD, lymphoma dissemination, recurrent infections, and frequently advanced age. In addition, a further 50% of those patients who begin chemotherapy are not able to complete it due to complications, disease relapse, or iatrogenic toxicity.

The Scotland and Newcastle Lymphoma Group published treatment results with chemotherapy regimen IVE/MTX (ifosfamide, vincristine, etoposide /methotrexate), followed by ASCT on newly diagnosed patients with EATL eligible for intensive treatment, followed by auto-stem cell transplantation. Five-year, progression-free survival and overall survival were 52% and 60%, respectively; both are significantly better, compared with the historical group treated with anthracycline-based chemotherapy. A current trial evaluates pirarubicin in combination with CTOP/ITE/MTX (cyclophosphamide, vincristine, prednisone, ifosfamide, etoposide, and methotrexate) for the de novo young patients with T-cell lymphoma, including EATL. Administration of radiotherapy is seldom adopted in the treatment of patients with EATL. Novel therapies, including combination of proteosome inhibitor Bortezomib with histone deacetylase inhibitor Panobinostat or Vorinostat, MLN8237 (a Novel Aurora A Kinase Inhibitor) are being evaluated in clinical trials for patients with T-cell lymphomas, including EATL.

Consolidation of chemotherapy with autologous stem cell transplantation is a potential option for patients who can tolerate more intensive treatment. The administration of radiotherapy is seldom adopted in the treatment of patients with EATL.

**Conclusion**

In conclusion, EATL accompanied by CMLNS is an unusual combination of CD complication with a very poor prognosis. It may be diagnosed in patients without a known history of CD and is a potentially reversible condition that requires early diagnosis. Thus, a high level of clinical suspicion for an overt lymphoma should lead to an extensive work up, including abdominal imaging, endoscopy, and histological examination of gut biopsies. For patients with known history of CD, the strict adherence to a gluten-free diet remains the best option to prevent EATL.

**Acknowledgment**

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**References**

Case Report:
A 21-Year-Old Woman with Hepatomegaly

Caroline R. Barry MD, Amr M. Zaki MD MSc; Vicki Munro MD; Glenn Patriquin MD MSc, Weei-Yuarn Huang MD, Karthik Tennankore MD

Summary
We report the case of a 21-year old woman with uncontrolled diabetes mellitus type 1 presenting with tender hepatomegaly and mildly elevated liver enzymes, with negative investigations for common causes. She was diagnosed by liver biopsy with glycogenic hepatopathy, an uncommon and likely under-recognized complication of poor glycemic control. The disease is typically reversible after weeks to months of appropriate insulin therapy and is unlikely to lead to permanent liver disease. Our patient was treated with a new insulin regimen and analgesics and discharged home. Unfortunately, on follow-up imaging in our patient 10 months later, her hepatomegaly persists. Her glycemic control remains unchanged and she has since been admitted to hospital twice for episodes of diabetic ketoacidosis.

Résumé
Il s'agit du cas d'une femme de 21 ans présentant un diabète de type 1 non équilibré accompagné d'une hépatomégalie douloureuse et d'une légère augmentation du taux des enzymes du foie, et pour qui les investigations du côté des causes courantes s'avèrent négatives. Une biopsie du foie mena à un diagnostic d'hépathopathie glycogénique, une complication peu courante et souvent mal identifiée qui résulte d'un mauvais contrôle de la glycémie. La maladie est habituellement réversible en quelques semaines ou mois d'insulinothérapie et même rarement à des atteintes hépatiques permanentes. La patiente a été traitée à l'aide d'une nouvelle insulinothérapie et des analgésiques et a pu retourner à la maison. Malheureusement, lors de l'imagerie médicale de suivi effectuée sur la patiente dix mois plus tard, l'hépatomégalie est toujours présente. La glycémie s'avère inchangée et depuis ce suivi la patiente a dû être hospitalisée deux fois pour des épisodes d'acidocétose diabétique.
Case Presentation

A 21 year-old woman with type 1 diabetes, diagnosed at seven years of age, initially presented to the emergency department (ED) with a two-week history of nausea, vomiting, right upper quadrant (RUQ) abdominal pain and distension, but no documented history of hepatomegaly on physical examination. The patient’s medical history was significant for two episodes of diabetic ketoacidosis (DKA) (at age 16 years and three months prior to presentation), suboptimal control of her diabetes (A1C ranging from 12.0–14.3% [normal is 4.6–6.3%] over the preceding two years), and gastro-esophageal reflux. Her only medications were a proton pump inhibitor and rapid-acting insulin (30–40 units), which she administered daily in 4–5 divided doses. She had discontinued her insulin pump months prior and did not use basal insulin. Her vitals were stable and her physical examination was remarkable for RUQ tenderness on palpation. Laboratory investigations showed a glucose level of 9.4 mmol/L, a leukocyte count of 12.4 × 10^9 (normal being 4.5–11.0 × 10^9) cells/L, a platelet count of 390 × 10^9 (normal being 150–350 × 10^9). The patient’s alanine aminotransferase (ALT) concentration was 113 (normal 14–54) U/L, aspartate aminotransferase (AST) was 98 (normal 15–41) U/L, alkaline phosphatase (ALP) was 103 (normal 32–92) U/L and gamma-glutamyl transpeptidase (GGT) was 70 (normal 5–50) U/L. Her hemoglobin, electrolytes, creatinine, direct and total bilirubin, lipase, international normalized ratio, partial thromboplastin time, and albumin were normal. An abdominal ultrasound revealed an enlarged liver measuring 23 cm in its maximum cranio-caudal dimension. Initial work up for hepatitis was negative, including serum testing for Hepatitis A, B, C and Epstein Barr Virus. She was tentatively diagnosed with hepatitis not yet diagnosed and discharged home to follow up with her family physician.

She returned to the ED four weeks later with worsening RUQ pain, nausea, vomiting, and anorexia. Additional signs and symptoms included hot flashes, pale stools, early satiety, weight loss (approximately 4.5 kg over 4 weeks), and irregular menstrual periods. She denied infectious symptoms or overt signs of bleeding. She had no risk factors for liver disease, such as intravenous drug use, unprotected sex, or alcohol misuse.

On examination, the patient was 167.6 cm tall and weighed 66 kg (body mass index 23.5 kg/m^2). She had abdominal distension, with some voluntary guarding in the RUQ, and hepatomegaly, with the liver edge palpable 7–10 cm below the right costal margin. There were no stigmata of chronic liver disease. Repeat laboratory investigations showed increase in her liver enzymes (AST 177 U/L, ALT 299 U/L, ALP 121 U/L, and GGT 169). She was admitted to the internal medicine service for pain control and further work up. A computed tomography (CT) scan of her abdomen showed further enlargement of the liver to 28 cm in length, extending inferiorly to the right iliac fossa (Figure 1).
Case Report: A 21-Year-Old Woman with Hepatomegaly

Barry et al.

Additional laboratory testing ruled out Wilson’s disease, alpha-1 antitrypsin deficiency, and hemochromatosis. She had poor glycemic control due to a limited ability to afford insulin therapy. She had been admitted for DKA 3 months’ prior, and there had been no mention of hepatomegaly. As other causes of hepatitis were ruled out, the clinical presentation in the context of poorly controlled Type 1 diabetes suggested glycogenic hepatopathy. The gastroenterology service was consulted and performed a percutaneous liver biopsy. Pathology (Figure 2) revealed extensive swollen hepatocytes with accentuated cell borders, clear cytoplasm, glycogenic nuclei, and occasional megamitochondria consistent with glycogenic hepatopathy. In addition, mild to moderate macrovesicular steatosis (less than 40%) was also present, suggestive of co-existing non-alcoholic fatty liver disease (NAFLD). However, features of steatohepatitis such as ballooning degeneration, mallory hyaline, or sinusoidal fibrosis were not seen.

In hospital, the patient was seen by the diabetic case manager and with improved blood glucose control, her RUQ pain improved significantly over the course of a week. She was discharged home with follow-up arranged with endocrinology and hepatology services. Under the management of an endocrinologist, she was prescribed twice daily insulin glargine in addition to mealtime insulin glulisine based on carbohydrate intake; however, her hemoglobin A1C did not improve under this regimen. Upon reassessment by the hepatology service eight months post-discharge, she was found to have no palpable hepatomegaly, with slight improvement in her hepatomegaly by CT scan ten months post-discharge. Unfortunately, she was admitted for DKA on two further occasions after her diagnosis of glycogenic hepatopathy.

Discussion

Glycogenic hepatopathy is a rare but important differential diagnosis for hepatomegaly and transaminitis in patients with diabetes mellitus. It was initially described by Mauriac in 1930 as part of Mauriac’s syndrome, which was characterized by uncontrolled diabetes, dwarfism, hypercholesterolemia, cushinoid features, delayed sexual maturity, and hepatomegaly; however, it can occur without any associated findings. In most types of cells, glucose entry is insulin dependent. But in the liver, glucose can enter through facilitated diffusion independent of insulin. Once it enters and converts into glucose-6-phosphate by glucokinase, it is trapped inside the cell. Glucose-6-phosphate is then used to form glycogen by the enzyme phosphatase, which is dependent on glucose and insulin. Thus, patients who have poorly controlled diabetes with hyperglycemia and intermittent insulin usage promote entry of glucose into cells and subsequent polymerization into glycogen. Even after insulin levels decline, glycogen production persists, leading to glycogen accumulation in the liver.

Clinical Manifestations

As there are only a few case reports and case series on glycogenic hepatopathy, the prevalence is unknown. Clinical manifestations are variable. One review of 42 patients with glycogenic hepatopathy identified that 92% of patients had hepatomegaly, 95% had either mild or strong transaminitis, and 72% had an increase in alkaline phosphatase. Other clinical manifestations include abdominal pain and obstructive symptoms, such as early satiety, nausea, and vomiting. Occasionally there have been reports of ascites, but synthetic liver function is usually normal. Glycogenic hepatopathy usually occurs in type I diabetes, but can sometimes occur in type II diabetes. It has also been reported in association with short-term high-dose steroid therapy.
Diagnosis

The most common cause of hepatomegaly in patients with diabetes mellitus is NAFLD, which can occur in over 80% of patients with diabetes and hepatomegaly. NAFLD is more commonly associated with type 2 diabetes than type 1, and as previously mentioned, glycogenic hepatopathy is more common in type 1 diabetes. Other causes of liver disease, such as viral, autoimmune, and infiltrative diseases should be ruled out before assuming the diagnosis is due to glycogenic hepatopathy.1,2,7

Unfortunately, glycogenic hepatopathy cannot be distinguished from NAFLD on ultrasound or clinical presentation,7 as NAFLD can also present with right upper quadrant pain and dullness, as well as mild to moderate hepatomegaly. Typically patients with NAFLD also have other parts of the metabolic syndrome, including obesity, type 2 diabetes, and hyperlipidemia, and are often asymptomatic.8 The only way to differentiate between NAFLD and glycogenic hepatopathy is through a liver biopsy. The usual histological appearance of glycogenic hepatopathy is of pale hepatocytes with compression of sinusoids, glycogenated nuclei, and giant mitochondria.2,7 Interestingly, our patient had evidence of glycogenic hepatopathy with pancreas transplant resulted in resolution of hepatomegaly and eventual resolution of elevated liver enzymes upon adequate insulin therapy.4,5,11,12 The disappearance of clinical hepatomegaly and resolution of symptoms after initiation of insulin can range from weeks to months.2,9,10 Improvement or normalization of serum markers may occur several months later.11

In two cases of recurrent glycogenic hepatopathy, or in which achieving optimal glucose targets posed substantial risk of hypoglycemia, pancreatic transplant resulted in resolution of hepatomegaly and of glycogenic hepatopathy.12 Published case reports lack prolonged follow-up, yet the reported resolution would suggest there are no long-term complications associated with the diagnosis. Since our patient has not been able to achieve glycemic control, her glycogenic hepatopathy persists. Long-term data and prognosis of untreated glycogenic hepatopathy are not available in the current literature. NAFLD without evidence of non-alcoholic steatohepatitis (as in her case) is usually a relatively benign condition but can progress to fibrosis and cirrhosis.8

Conclusion

Glycogenic hepatopathy is an under-recognized clinical entity that should be suspected in patients with tender hepatomegaly in the setting of diabetes mellitus. It is radiographically indistinguishable from NAFLD, and liver biopsy is required for definitive diagnosis. Some authors suggest a trial of four weeks of optimal glycemic control and assessment for resolution of hepatomegaly is a reasonable approach in pediatric diabetic patients once other serum-based etiologies of acute hepatitis and hepatomegaly are ruled out.9 The diagnosis should prompt exploration of barriers to poor glucose control, improved diabetes education, and close monitoring of glucose indices and diabetic complications.

Competing Interests: none declared.

References

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Reference:

*Clinical significance has not been established.

† A multicentre, randomized, double-blind, placebo-controlled trial evaluating once-daily Saxenda® (n=2437) compared to placebo (n=1213), in conjunction with a reduced food intake and increased physical activity, in patients without diabetes and with a BMI ≥30 kg/m², or 27–29.9 kg/m² with at least one weight-related comorbidity condition. Saxenda® was titrated to 3 mg daily during a 4-week period. The primary endpoints were mean percent change in body weight and the proportion of patients achieving ≥5% and ≥10% weight loss from baseline to week 56. Mean baseline weight: 106.3 kg for both groups.

‡ Treatment with Saxenda® should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight.

Fictitious case. May not be representative of all patients.