Self Learning

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Volume 40.21 2025
SAMPs Special Edition

This volume features the following topics:

- Epilepsy
- Depression in Older Adults
- Anorexia
- Food Allergy
- Ulcerative Colitis
- Essential Tremor
- Obesity Management

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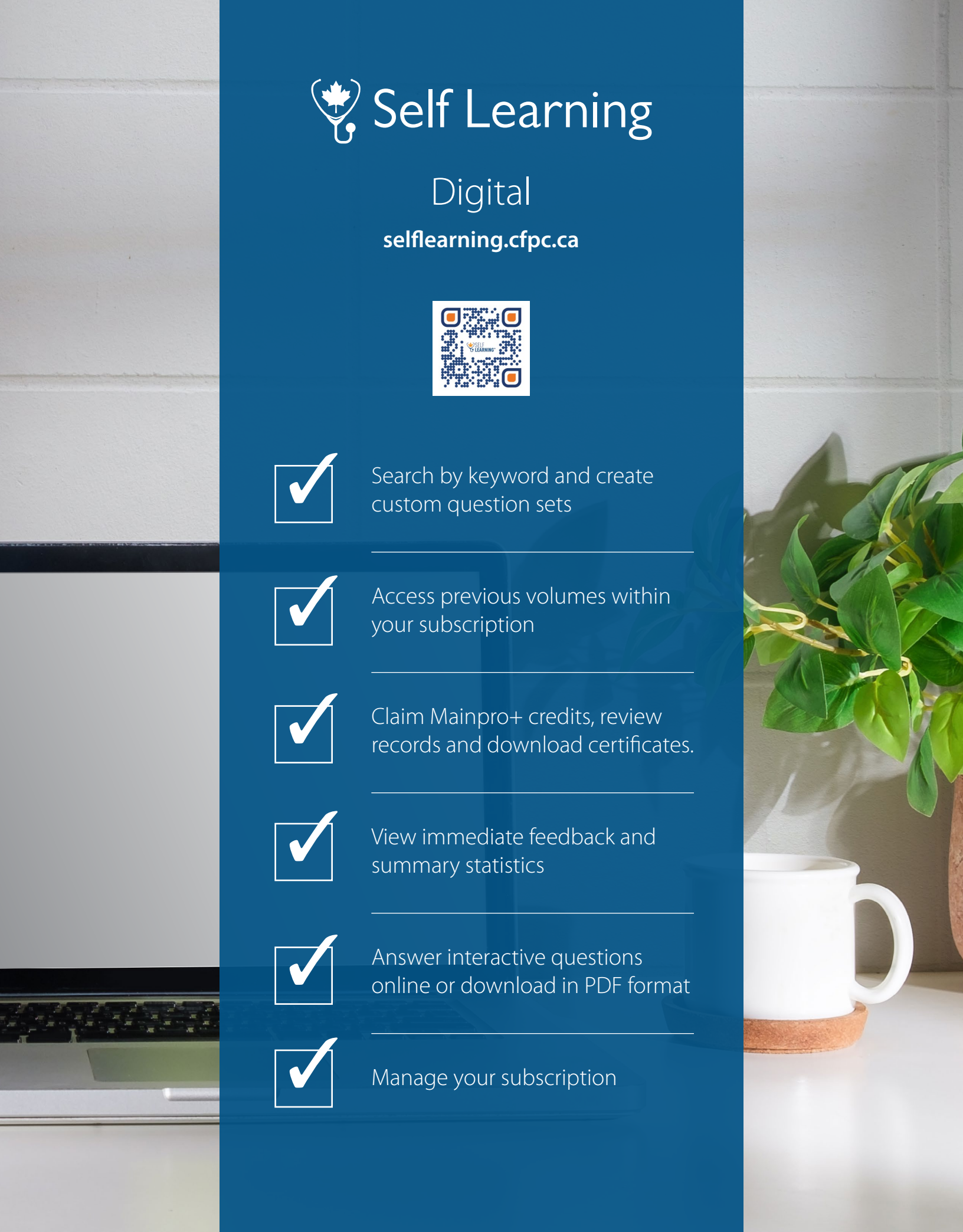

Self Learning

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Self Learning

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Welcome to Self Learning™

The Self Learning Committee is excited to share the 2025 Special Edition of Self Learning, dedicated entirely to Short Answer Management Problems (SAMPs). Following the success of our 2023 edition, which featured a curated selection of Gold Star questions, this year's edition dives deeper with an exclusive set of SAMP-style questions crafted to sharpen your clinical reasoning and decision-making. Get ready for a dynamic, case-based learning experience designed by family physicians, for family physicians.

We are offering this special edition of the Self Learning Program as an educational resource available at no cost to CFPC members. Our goal is to keep you updated of the latest medical evidence, while giving you a deeper dive into the value and flexibility that the Self Learning Program offers. Self Learning is an innovative educational program from the College of Family Physicians of Canada (CFPC) designed to provide subscribers the opportunity to learn anytime, anywhere, with a focus on information that is timely and relevant to family medicine. Each regular Self Learning issue contains 40 clinical questions based on recent articles from a wide variety of peer-reviewed journals. The questions are developed by over 50 experienced family physician volunteers across Canada. We encourage you to apply the same critical appraisal to articles featured in the program as you would when reading articles in any medical journal.

You may find some content controversial. This is a deliberate aspect of introducing new information, research results, and therapeutic techniques. The purpose is to challenge your knowledge with the latest material available in the literature. Of course, new findings sometimes cannot be duplicated or are discredited over time. The educational points are not consensus statements about how best to conduct your practice; rather, they are items selected by your peers in family practice as being relevant and challenging.

We hope you enjoy this complimentary edition of Self Learning!

We'd love to hear your thoughts and stay connected. Please take a moment to complete our quick 2-minute survey by clicking the link below or scanning the QR code.

Thank you for your time and support!

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Evidence-Based Medicine Glossary

Absolute risk reduction (ARR): (also called RD or risk difference) The absolute difference between control/relative event rates often looks less impressive if the baseline risk is a small reduction. Used to calculate number needed to treat. ARR = CER – EER (e.g., 10% – 14% = -4%).
The lower the event rate in the control group, the larger the difference between the RRR and RD.

Case control studies: This type of study compares groups of people who are as similar as possible aside from the difference of interest (e.g., having a certain medical condition). They then attempt to work backward to determine whether risk factors in the past may have contributed to the present difference. This can be challenging and is prone to problems with recall and lack of records.

Case report: This is a study attempting to describe a patient, event, or case. It can be used to provide specific details in a specific case; however, it may describe a rare occurrence and is not very generalizable.

Clinical practice guidelines: These are guidelines based on the body of literature from expert bodies that attempt to give the best possible advice on optimal clinical practice.

Confidence intervals: Data are usually presented as a 95% confidence interval, meaning that if the study is repeated multiple times, 95% of the studies will have result within that range. A narrow or tight confidence interval represents a precise estimate. These are usually found in studies with a large number of participants.

Control event rate (CER)/Experimental event rate (EER): The rate at which events occur in the control group or experimental group, respectively. It may be represented by a percentage (10%) or as a proportion (0.1).

Cross sectional study: This is a one-time survey of a random group of people. For example, this could be useful for determining what proportion of a population has had cancer screening.

Event rate: The number who experience an event (e.g., stroke as a proportion of the number of people in the population or clinical cure).

GRADE (Grading of Recommendations, Assessment, Development, and Evaluation): A common way to evaluate studies. Essentially, RCTs start as high quality evidence, and observational studies start as lower quality of evidence. The study quality can be adjusted based on a variety of factors.

Study Design	Quality of Evidence	Lower if	Higher if
RCT	High	**Risk of bias** -1 Serious -2 Very serious **Inconsistency** -1 Serious -2 Very serious **Indirectness** -1 Serious -2 Very serious **Imprecision** -1 Serious -2 Very serious **Publication bias** -1 Likely -2 Very likely	**Large effect** + Large +2 Very large **Dose response** +1 Evidence of a gradient **All plausible Confounding** +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Moderate		
Observational study	Low		
	Very low		

Hazard ratio: This is similar to odds ratio but is a snapshot at a point in time looking at the difference between two groups (e.g., a certain point on a survivorship curve). It will only look at a single point in time so it may not be that useful if the wrong time point is picked. This may make a treatment seem falsely ineffective.

Incidence: The percentage of the population that will develop a disease during an interval (e.g., the incidence of diabetes is 0.2% per year, referring only to new cases).

I^2: This is a measure of heterogeneity. Usually it is used in the setting of a meta analysis to explore heterogeneity between studies. It is expressed as a percentage with 0% meaning no heterogeneity and 100% meaning extreme heterogeneity.

Evidence-Based Medicine Glossary

Incidence rate (IR): The rate at which an outcome will occur over a period of time in a specific group. (e.g., two people from the study group will develop diabetes per 1,000 person years).

Incidence rate ratio (IRR): This compares the IR between different groups. For example, the IR of diabetes for BMI > 30 is three per 1,000 person years and the IR for BMI < 30 is one per 1,000 person years. Therefore, the IRR is three.

Intention to treat: Participants are analyzed in the group to which they were randomized, whether or not they completed the intervention of that group. The advantage of this approach is that it makes it more difficult for study runners to bias the results by selecting for patients who are likely to do the best.

Interquartile range (IQR): This is a measure of the variation in data. It is the difference between the 3rd quartile (75th percentile) and the 1st quartile (25th percentile).

It can be calculated as:
IQR = Q3 (median of the 3rd quartile) – Q1 (median of the 1st quartile)

Likelihood ratio (LR): Positive likelihood ratio (LR of a positive test)
= Sensitivity ÷ 1 – Specificity
= a/(a + c) ÷ b/(b + d)

Negative likelihood ratio (LR of a negative test)
= 1 – Sensitivity / Specificity
= c/(a + c) ÷ d/(b + d)

The larger the positive likelihood ratio, the greater likelihood of disease. The smaller the negative likelihood ratio, the less likelihood of disease. This is useful for clinicians. It can be applied to a nomogram to calculate probability of disease.

+ LR (likelihood ratio of a positive)		- LR (likelihood ratio of a negative)	
2–1 (or less)	Poor	0.5 – 1 (or >)	Poor
5–2	Small/moderate	0.5 – 0.2	Small/moderate
10–5	Good	0.2 – 0.1	Good
> 10	Excellent (rule in)	< 0.1	Excellent (rule out)

Meta-analysis: This is a type of study that incorporates multiple similar RCTs to attempt to unify their data to function as one large RCT, to have the greatest possible statistical power.

Number needed to treat (NNT)/Number needed to harm (NNH): The number of patients who would have to receive the treatment in order for one of them to benefit or be harmed.
NNT = 1 ÷ ARR
NNH = 1 ÷ (EER – CER)

		Disease		
		Positive	**Negative**	
Test	**Positive**	True Positive **a**	False Positive **b**	All Positive tests **a + b**
	Negative	False Negative **c**	True Negative **d**	All Negative tests **c + d**
		All with Disease a + c	**All without Disease b + d**	

Odds ratio (OR): Measure of association between exposure and outcome. Odds the outcome will occur with exposure, compared to odds it will occur without the exposure. Often used in case-control studies. This is odds in exposed group/odds in non-exposed group.
OR = (exposed cases ÷ unexposed cases)
(exposed non-cases ÷ unexposed non-cases)

OR = 1 means no effect; OR >1 exposure increases odds of outcome; OR <1 exposure decreases odds of outcome.
In some cases this can be weighted with each value multiplied by its weight.

Other diagnosis calculations:
Positive predictive value = a ÷ (a + b)
If a test is positive, what is the chance the person has disease.
Negative predictive value = d ÷ (d + c)
If a test is negative, what is the chance the person does not have disease.

Evidence-Based Medicine Glossary

***P* value:** A measure of probability that a difference between groups during an experiment would happen by chance if there was not a true difference between groups. For example, a *P* value of 0.05 means if there was no true difference between groups (the null hypothesis was true) then you would see the amount of difference between groups in your experiment one of every 20 times. By convention, a *P* value of 0.05 or less is considered to be statistically significant.

Per protocol analysis: Patients are analyzed based on which treatment they receive. May be vulnerable to manipulation if non-random patients are excluded.

Power: This means the likelihood that your study will be able to detect an actual effect between groups based on your study size. If power is too low then a real difference may be missed. If it is too high then statistically significant but clinically meaningless differences may be found.

Prevalence: The probability of disease in the entire population at any point in time (e.g., 2% of the United States' population has diabetes).

Prospective cohort study: This type of study follows groups forward in time to see what happens based on a difference of interest. For example, exercisers versus sedentary people could be followed to determine differences in cardiovascular disease.

Qualitative study/Quantitative study: A qualitative study looks at what a narrative experience has been like. For example, someone's experience with a specific disease or a specific procedure.
A quantitative study attempts to compare with actual numbers.

Randomized control trial (RCT): This is a study where randomly divided but similar groups have an intervention or control applied to the groups. This lets us see what the difference in outcome is based on the intervention. An example is a medication compared to a placebo (which is an inactive dummy drug). This can be blinded where the group members don't know which group they are in or double blinded where neither the study runners nor group members know which group they are in. If everyone knows what group they are in it is called an open label trial.

Relative risk (RR): Risk in the experimental group compared to the control group.
RR = EER ÷ CER.

Relative risk reduction (RRR): Change in risk relative to the overall population (often looks more impressive as it will be a percentage of the population).
RRR = (EER – CER) ÷ CER
For example: (10% – 14%) ÷ 10% = -0.4

Risk ratio: This is similar to odds ratio but instead is the ratio of event to total outcomes. For example, treatment success/(treatment success + treatment failure).

Sensitivity = a ÷ (a + c): The probability of a positive test among patients with disease.

SNOut: Sensitive tests when **N**egative help rule **Out** disease

Specificity = d ÷ (d + b): The probability of a negative test among patients without disease.

SPIn: Specific tests, when **P**ositive, rules **In** disease

Statistical dependency: This is a statistical measure that means the odds of one event will influence the odds of another event.

Survivorship curve: This is a graph showing the proportion of a given population that continues to survive over time. This could mean actual survival over death, but it could also mean time without being diagnosed with a given disease or complication. Curves for different populations (e.g., treatment vs control) can be compared easily.

Systematic review: This is a type of study that starts with a clear question and uses systematic methods to attempt to identify and critically appraise all relevant research.

Frequently Used Abbreviations

ACE	=	angiotensin-converting enzyme
AF	=	atrial fibrillation
AIDS	=	acquired immune deficiency syndrome
ARB	=	angiotensin II receptor blocker
BMI	=	body mass index
BPH	=	benign prostatic hyperplasia
COVID-19	=	coronavirus disease 2019
COPD	=	chronic obstructive pulmonary disease
CI	=	confidence interval
CT	=	computed tomography
FDA	=	Food and Drug Administration
GCS	=	glasgow coma scale
GLP-1	=	glucagon-like peptide-1
HIV	=	human immunodeficiency virus
HPV	=	human papilloma virus
HR	=	hazard ratio
ICU	=	intensive care unit
IM	=	intramuscular
IQR	=	interquartile range
LFTs	=	liver function tests
MI	=	myocardial infarction
MRI	=	magnetic resonance imaging
NNH	=	number needed to harm
NNT	=	number needed to treat
NPV	=	negative predictive value
NSAID	=	non-steroidal anti-inflammatory drugs
OR	=	odds ratio
PE	=	pulmonary embolism
PPI	=	proton pump inhibitors
PPV	=	positive predictive value
RBC	=	red blood cell
RCT	=	randomized, controlled trial
RD	=	risk difference
RRR	=	relative risk reduction
SARS-CoV-2	=	severe acute respiratory syndrome coronavirus-2
SD	=	standard deviation
SGLT-2	=	sodium/glucose cotransporter 2
SNRI	=	serotonin-norepinephrine reuptake inhibitor
SSRI	=	selective serotonin reuptake inhibitor
STI	=	sexually transmitted infection
UTI	=	urinary tract infection
VTE	=	venous thromboembolism
WHO	=	World Health Organization

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*see page ix for Conflict of Interest Disclosures respectively.
All others have no conflicts of interests to declare.

Conflict of Interest Disclosures

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Dr. Manal Badi	Dr. Badi was a representative in the Newfoundland Lung Cancer Screening Pilot Project for the Endeavor Family Practice Network and received honoraria for this work. She has a membership on the advisory boards for the Clinical Prevention Leaders Network of the Canadian Task Force on Preventive Health Care (CTFPHC). She is a volunteer Clinical Prevention Leader acting as an ambassador to encourage the implementation of CTFPHC guidelines..
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Dr. Sarah Lespérance	Dr. Lespérance is a Board Member of the CFPC. She was also the President of the Society of Rural Physicians of Canada. Her term ended in April 2024 and she received honoraria.
Dr. Dennis Paige	Dr. Paige is a Quality Improvement Lead at the University of Manitoba and receives honoraria.
Dr. Molly Whalen-Browne	Dr. Whalen-Browne is the medical director for the New Canadians Health Centre in Alberta and receives honoraria.

Short Answer Management Problems

Q1 Chlamydia and Gonorrhea

You are starting a new position at a student health centre. In preparation for your first shift, you decide to review the current recommendations for the diagnosis and management of chlamydia and gonorrhea.

1. For asymptomatic patients with a penile urethra, what screening test is recommended?

2. For asymptomatic patients with a cervix or vagina what screening test is preferred?

3. For symptomatic patients with a penile urethra what test is recommended?

4. For symptomatic patients with a cervix or vagina what test is recommended?

5. In symptomatic patients, patient collected swabs are considered acceptable.
   - ❍ True
   - ❍ False

6. According to Canadian guidelines, what are the preferred treatments for chlamydia? List two.

7. According to Canadian guidelines, what are the preferred treatments for gonorrhea? List two.

8. List three indications for a test of cure in patients treated for chlamydia.

9. List three indications for a test of cure in patients treated for gonorrhea.

Educational Point: The 2 most frequent reportable bacterial sexually transmitted infections (STIs) worldwide and in Canada are those caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Rates of both infections have been increasing over the last decade despite public health efforts aimed at prevention, testing and treatment. In 2019, 139389 cases of chlamydia and 35443 cases of gonorrhea were reported in Canada, an increase of 33.1% and 181.7%, respectively, since 2010. These increases may reflect improved diagnostics, increased screening and contact tracing or a true increase in incidence.

Sexually transmitted infections have a substantial impact on affected individuals and communities. *Chlamydia trachomatis* and *N. gonorrhoeae* are commonly implicated pathogens in pelvic inflammatory disease and, if untreated, can lead to infertility. Infection with a bacterial STI is associated with increased risk of HIV acquisition or transmission. Perinatal transmission of *C. trachomatis* and *N. gonorrhoeae* can lead to ophthalmia neonatorum in infants, among other pathologies. Treatment has become more challenging, given the increase in antimicrobial resistance in gonorrhea.

Opportunistic screening is critical in identifying asymptomatic chlamydia and gonorrhea infections. The Canadian Task Force on Preventive Health Care recommends annual opportunistic screening for chlamydia and gonorrhea in all sexually active people younger than 30 years. Although based on low-quality evidence, an opportunistic approach to screening is likely to increase the number of STIs diagnosed and destigmatize sexual health conversations.

More frequent screening should be offered to people at higher risk of acquiring STIs, although little evidence exists to guide the optimal frequency of screening. Among men who have sex with men, current guidance suggests, at minimum, anatomic site-based screening for chlamydia and gonorrhea annually. More frequent screening (i.e., every 3–6 months) is recommended for at-risk people of any gender within groups who may be disproportionately affected by STIs, including those taking HIV pre-exposure prophylaxis (PrEP), those who have recently had an STI, those living with HIV or those with multiple sexual partners. Pregnant patients should be screened at their first prenatal visit, with rescreening in the third trimester if they initially test positive for or are at ongoing risk of STIs.

In asymptomatic patients, approaches to sample collection for nucleic acid amplication testing (NAAT) for chlamydia and gonorrhea include a first-void urine (first 10–20 mL, any time of day, at least 1 hour since previous void) or vaginal swab; other options include a urethral or cervical swab (Table 2). In patients with a vagina, a vaginal swab is preferred over first-void urine, as urine testing may detect 10% fewer infections. Those with a neovagina or gender-affirming penile reconstruction should provide a urine sample for NAAT. Extragenital testing options include a pharyngeal or rectal swab for chlamydia and gonorrhea NAAT. **In symptomatic patients, first-void urine and swabs of sites of reported symptoms should be collected for chlamydia and gonorrhea NAAT, and for gonorrhea culture and sensitivity testing. Patient-collected swabs are acceptable, as studies have shown equivalence between self- and clinician-collected oral, vaginal and rectal swabs for chlamydia and gonorrhea testing.** Self-collection may also improve uptake of STI screening.

Treatment of gonorrhea is challenging, as it readily develops antimicrobial resistance, and guidelines are not congruent in their recommendations. The Canadian STI guideline recommends dual therapy with ceftriaxone or cefixime, plus azithromycin or doxycycline (Table 3). The STI treatment guideline from the United States Centers for Disease Control and Prevention (CDC) increased the previously recommended ceftriaxone dose (Table 3). The CDC also recommended against dual therapy based on increasing antimicrobial resistance, and concern for impacts on the microbiome and selective pressure on other pathogens. It is likely that this approach will be adopted by guidelines from other jurisdictions in the future. If monotherapy with ceftriaxone is used, an increased dose of ceftriaxone is recommended, compared with that used in dual therapy (Table 3). Currently, given varying recommendations, clinicians should follow local guidance, which will be based on resistance patterns in their area.

The Canadian STI guideline recommends doxycycline or azithromycin as the first-line (preferred) treatment for chlamydia, whereas the CDC recommends doxycycline as first-line treatment, with azithromycin as a second-line (alternate) regimen (Table 3). The preference for doxycycline is based on a systematic review and meta-analysis comparing treatment with azithromycin and doxycycline for chlamydia,

which found that treatment failed more often with azithromycin, particularly among men with rectal chlamydia. Thus, doxycycline is the preferred agent for treating rectal chlamydia. If adherence to therapy is a concern, single-dose azithromycin may be preferred. For pregnant patients, azithromycin is the first-line treatment. For patients with suspected or confirmed lymphogranuloma venereum, treatment with doxycycline should be continued for 21 days.

Given the potential complexity of cases and the evolving treatment landscape, providers should consult with an expert in STI management when necessary. All patients being treated for chlamydia or gonorrhea should be strongly advised to abstain from sexual activity for 7 days after treatment and until all partners have been treated. Sexual partners from the previous 60 days should be tested and treated, or offered expedited partner treatment (i.e., clinicians can provide empiric treatment for the patient to give to their partner), which has been found to reduce the rates of recurrent or persistent infection. **Details around indications and timing of tests of cure are discussed in Table 3.** Tests of cure and repeat screening recommendations are often not followed, although they remain important for the appropriate care of the patient and to decrease transmission.

Table 2. Testing for chlamydia and gonorrhea

Site	Approach for asymptomatic patients or screening	Approach for symptomatic patients
Penile urethra	• **First-void urine for NAAT for chlamydia and gonorrhea.**	• **Urethral swab for gonorrhea culture and sensitivity testing, and first-void urine for NAAT for chlamydia and gonorrhea.**
Cervix or vagina*	• **Vaginal swab (preferred), cervical swab or first-void urine for NAAT for chlamydia and gonorrhea.**	• **Cervical swab for gonorrhea culture and sensitivity testing, and for NAAT for chlamydia and gonorrhea, or** • **Vaginal swab for gonorrhea culture and sensitivity testing, and for NAAT for chlamydia and gonorrhea, or** • **First-void urine for NAAT for chlamydia and gonorrhea.**
Throat	• Throat swab for NAAT for chlamydia and gonorrhea.	• Throat swab for gonorrhea culture and sensitivity testing, and for NAAT for chlamydia and gonorrhea.
Rectum	• Rectal swab for NAAT for chlamydia and gonorrhea.	• Rectal swab for gonorrhea culture and sensitivity testing, and for NAAT for chlamydia and gonorrhea.

Note: NAAT = nucleic acid amplification test.
*For patients with a neovagina, a first-void urine is the preferred screening test. In symptomatic patients, efforts should be made to conduct gonorrhea culture and sensitivity testing, as well as NAAT for chlamydia and gonorrhea. When culture and sensitivity testing is not possible, either a cervical or vaginal swab for NAAT or a first-void urine is appropriate.

Table 3. Treatment of chlamydia and gonorrhea

Pathogen	Canadian guideline(13)	CDC guideline(24)	Test of cure	Follow-up
Chlamydia trachomatis	**Preferred treatment** • **Doxycycline (100 mg orally, twice daily for 7 d) or azithromycin (1 g orally, once)** • LGV: doxycycline (100 mg orally, twice daily for 21 d) **Alternative treatment** • Levofloxacin (500 mg orally, daily for 7 d) **Treatment for pregnant patients*** • Azithromycin (1 g orally, once)	**First-line treatment** • Doxycycline (100 mg orally, twice daily for 7 d) • LGV: doxycycline (100 mg orally, twice daily for 21 d) **Second-line treatment** • Azithromycin (1 g orally, once) or levofloxacin (500 mg orally, daily for 7 d) **Treatment for pregnant patients*** • Azithromycin (1 g orally, once) (preferred), or amoxicillin (500 mg orally, 3 times daily for 7 d)	**Indications** • **Suspected treatment failure** • **Suspected poor adherence** • **Nonpreferred regimen used** • **Pregnancy** **Approach** • Swab for NAAT for chlamydia and gonorrhea 4 wk after therapy completed	• Re-screen 3 mo after treatment completed
Neisseria gonorrhoeae	**Preferred treatment** • **Ceftriaxone (250 mg IM, once) and azithromycin (1 g orally, once), or** • **Cefixime (800 mg orally, once) and azithromycin (1 g orally, once); this is considered an alternative regimen for pharyngeal infections and treatment of MSM** **Alternative treatment** • Ceftriaxone (250 mg IM, once) or cefixime (800 mg orally, once), and doxycycline (100 mg orally, twice daily for 7 d), or • Azithromycin (2 g orally, once) and gentamicin (240 mg IM, once); this regimen should be considered only if severe allergy or documented resistance to cephalosporins **Treatment for pregnant patients*** • Ceftriaxone (250 mg IM, once) or cefixime (800 mg orally, once), and azithromycin (1 g orally, once)	**First-line treatment** • Ceftriaxone (500 mg IM, once, if patient weighs < 150 kg; 1 g IM, once, if patient weighs > 150 kg) **Second-line treatment** • Cefixime (800 mg orally, once or gentamicin (240 mg IM, once), and azithromycin (2 g orally, once) **Treatment for pregnant patients*** Same as above	Consider for all positive sites **Indications** • **Suspected treatment failure** • **Suspected poor adherence** • **Nonpreferred regimen used** • **Pregnancy** • **Pharyngeal infection** • **Documented antimicrobial resistance** **Approach** • Swab for gonorrhea culture and sensitivity test 3–7 d after treatment (preferred) or swab for NAAT for chlamydia and gonorrhea 4 wk after treatment	Re-screen 3 mo after treatment completed

Note: CDC = Centers for Disease Control and Prevention, IM = intramuscularly, MSM = men who have sex with men, NAAT = nucleic acid amplification test.
*Doxycycline is contraindicated in pregnancy.

Reproduced from Van Ommen CE, et al. with permission from the Medical Association Journal © A practical approach to the diagnosis and management of chlamydia and gonorrhea. *CMAJ*. 2023 Jun 19;195(24):E844-E849. https://pubmed.ncbi.nlm.nih.gov/37336564/

Acceptable answers:

1. First-void urine for NAAT for chlamydia and gonorrhea.
2. Vaginal swab for NAAT for chlamydia and gonorrhea.
3. Urethral swab for gonorrhea culture and sensitivity testing, and first-void urine for NAAT for chlamydia and gonorrhea.
4. Cervical swab for gonorrhea culture and sensitivity testing, and for NAAT for chlamydia and gonorrhea; or vaginal swab for gonorrhea culture and sensitivity testing, and for NAAT for chlamydia and gonorrhea; or first-void urine for NAAT for chlamydia and gonorrhea.
5. True. Patient-collected swabs are acceptable, as studies have shown equivalence between self- and clinician-collected oral, vaginal and rectal swabs for chlamydia and gonorrhea testing.
6. Doxycycline (100 mg orally, twice daily for 7 days) or azithromycin (1g orally once).
7. Ceftriaxone (250 mg IM, once) and azithromycin (1g orally once) or Cefixime (800 mg orally, once) and azithromycin (1g orally once); this is considered an alternative regimen for pharyngeal infections and treatment of MSM.
8. Suspected treatment failure, suspected poor adherence, nonpreferred regimen used, pregnancy.
9. Suspected treatment failure, suspected poor adherence, nonpreferred regimen used, pregnancy, pharyngeal infection, documented antimicrobial resistance.

Reference: Van Ommen CE, Malleson S, Grennan T. A practical approach to the diagnosis and management of chlamydia and gonorrhea. *CMAJ*. 2023 Jun 19;195(24):E844-E849.
Link: https://pubmed.ncbi.nlm.nih.gov/37336564/
PMID: 37336564

Q2 Epilepsy

Your next patient is a 19-year-old female. While cooking supper, her girlfriend witnessed the patient lose consciousness and experience a tonic-clonic generalized seizure. The ambulance brought the patient to the emergency room.

1. Is this seizure considered provoked or unprovoked?

2. What is the differential diagnosis for seizure-like episodes? List four.

You question the patient. She is healthy, with no medical comorbidities. She does not take any medication. Her family history is negative. As a precaution, an EEG and an MRI are ordered, which come back normal.

3. What risk factors would make you more likely to start an anti-seizure medication after a first unprovoked seizure? List three.

You decide not to treat the patient with anti-seizure medication. You order a long-term video-EEG monitoring, which is scheduled in 2 weeks.

1 week later, she comes back to the emergency room. She had another unprovoked tonic-clonic seizure while at school.

4. What is the definition of epilepsy?

You decide to initiate anti-seizure medication.

5. Which medications are considered appropriate first-line agents for generalized seizures?

Your patient wants to know if there is anything she should do or avoid in order to prevent another seizure.

6. What seizure triggers should be discussed with the patient? List three.

Educational Point: Managing first-time seizures and epilepsy often requires consultation with a neurologist or epileptologist for diagnosis and subsequent management, including when medical treatment fails or in determining whether patients may benefit from surgery. However, given the high prevalence of epilepsy and even higher incidence of a single seizure, family physicians contribute significantly to the management of these patients. The main issues are managing a first-time seizure, making the diagnosis, establishing a treatment plan, and exploring triggers and mitigating factors.

Provoked seizures are due to an acute brain insult such as toxic-metabolic disorders, concussion, alcohol withdrawal, an adverse effect of a medication or its withdrawal, or photic stimulation presumably by disrupting the brain's metabolic homeostasis or integrity. The key factor is that provoked seizures always happen in close temporal association with an acute insult. A single provoked seizure happens each year in 29 to 39 individuals per 100,000. While these seizures typically occur singly, there is a small risk they may recur if the triggering insult persists or repeats. Therefore, more than 1 seizure per se may not indicate epilepsy.

Unprovoked seizures reflect an underlying brain dysfunction. A single unprovoked seizure happens in 23 to 61 individuals per 100,000 per year, often in men in either younger or older age groups. Unprovoked seizures may occur only once or may recur (ie, evolve into epilepsy). The latter scenario happens in only about half of cases; the overall risk for a recurrent seizure within 2 years of a first seizure is estimated at 42% (24% to 65%, depending on the etiology and electroencephalogram [EEG] findings). More specifically, without treatment the relapse rate will be 36% at 1 year and 47% at 2 years. Further, a second unprovoked seizure, if untreated, would increase the risk for third and fourth seizures to 73% and 76%, respectively, within 4 years.

Evaluating the first-time seizure: Ask the patient or observers about the circumstances of the event to differentiate provoked from unprovoked onset. For one thing, not all "spells" are seizures. **The differential diagnoses may include syncope, psychogenic nonepileptic events, drug intoxication or withdrawal, migraine, panic attacks, sleep disorders (parasomnia), transient global amnesia, concussion, and transient ischemic attack.**

EEG, neuroimaging, and other relevant diagnostic tests often are needed (eg, electrocardiogram/echocardiogram/Holter monitoring to evaluate for syncope/cardiac arrhythmia). Clinically, syncopal episodes tend to be brief with rapid recovery and no confusion, speech problems, aura, or lateralizing signs such as hand posturing or lip smacking that are typical with focal seizures. However, cases of convulsive syncope can be challenging to assess without diagnostic tests.

True convulsive seizures do not have the variability in clinical signs seen with psychogenic nonepileptic events (eg, alternating body parts involved or direction of movements). Transient global amnesia is a rare condition with no established diagnostic test and is considered a diagnosis of exclusion, although bitemporal hyperintensities on magnetic resonance imaging (MRI) may appear 12 to 48 hours after the clinical episode. Blood work is needed in patients with medical issues treated with multiple medications to evaluate for metabolic derangements; otherwise, routine blood work provides minimal information in stable patients.

A routine EEG to record epileptiform discharges and a high-resolution brain MRI to rule out any intracranial pathology are indicated. However, if the EEG indicates a primary generalized (as opposed to focal-onset) epilepsy, a brain MRI may not be needed. If a routine EEG is unrevealing, long-term video-EEG monitoring may be needed to detect an abnormality.

Available data and prediction models identify risk factors that would help determine whether to start an antiseizure medication after a first unprovoked seizure: abnormal EEG with particular epileptiform activity, abnormal neurologic exam, abnormal computerized tomography or MRI results, nocturnal seizure, focal seizure, or family history

of seizures. In the absence of such risk factors, chances of further unprovoked seizures are not high enough to justify treatment with antiseizure medications. **However, if a second unprovoked seizure were to occur, that would meet the definition of epilepsy, and treatment is indicated due to the high risk for further seizures.**

The International League Against Epilepsy (ILAE) previously defined epilepsy as 2 unprovoked seizures more than 24 hours apart. However, a more recent ILAE task force modified this definition: even a single unprovoked seizure would be enough to diagnose epilepsy if there is high probability of further seizures—eg, in the presence of definitive epileptiform discharges on EEG or presence of a brain tumor or a remote brain insult on imaging, since such conditions induce an enduring predisposition to generate epileptic seizures. Also, a single unprovoked seizure is enough to diagnose epilepsy if it is part of an epileptic syndrome such as juvenile myoclonic epilepsy. Further, a time limit was added to the definition—ie, epilepsy is considered resolved if a patient remains seizure free for 10 years without use of antiseizure medications during the past 5 years. However, given the multitude of variables and evidence, the task force acknowledged the need for individualized considerations.

Treatment with antiseizure medications (ASMs; formerly known as antiepileptic drugs) is the mainstay of epilepsy management. Achieving efficacy (seizure freedom) and tolerability (minimal adverse effects) are the primary goals of treatment. Factors that should govern the selection of an ASM include the seizure type/epilepsy syndrome, adverse effect profile of the ASM, pharmacodynamic/pharmacokinetic considerations, and patient comorbidities. **In summary, levetiracetam and valproate (not to be used in women of childbearing potential) are considered appropriate first-line agents for generalized and unclassified epilepsies while lamotrigine is deemed an appropriate first-line agent for focal epilepsies.**

Epilepsy mostly affects patients during seizure episodes; however, the unpredictability of these events adds significantly to the burden of disease. There are no reliable methods for predicting seizure other than knowing of the several potential risks and recognizing and avoiding these triggers.

Noncompliance with antiseizure medications is a common seizure trigger affecting up to one-half of patients with epilepsy. Medications may provoke seizures in susceptible individuals. Sleep deprivation is a potential seizure trigger in people with epilepsy based on observational studies, case reports, patient surveys, and EEG-based studies, although data from randomized controlled studies are limited. The standard best practice is to encourage appropriate sleep hygiene, which involves getting at least 7 hours of sleep per night. Alcohol is a GABAergic substance like benzodiazepines with antiseizure effects. However, it acts as a potential precipitant of seizures in cases of withdrawal or acute intoxication, or when it leads to sleep disruption or nonadherence to antiseizure medications. Therefore, advise patients with alcohol use disorder to slowly taper consumption (best done through a support program) and avoid sudden withdrawal. The 2 main biologically active components of marijuana are delta-9-tetrahydrocannibinol (THC), the main psychoactive constituent, and cannabidiol (CBD). Animal and human studies have demonstrated anticonvulsant properties of THC and CBD. **But THC, in high amounts, can result in adverse cognitive effects and worsening seizures.** A purified 98% oil-based CBD extract (Epidiolex) has been approved as an adjunctive treatment for certain medically refractory epilepsy syndromes in children and young adults—ie, Dravet syndrome, Lennox-Gastaut syndrome, and tuberous sclerosis complex syndrome. There are no reliable data on the effect of recreational use of marijuana on seizure control. **Other illicit substances such as cocaine may lower seizure threshold by their stimulatory and disruptive effects on sleep, diet, and healthy routines.**

Acceptable answers:

1. Unprovoked
2. Syncope
   Psychogenic nonepileptic events
   Drug intoxication or withdrawal
   Migraine
   Panic attacks
   Sleep disorders (parasomnia)
   Transient global amnesia
   Concussion
   Transient ischemic attack.
3. Abnormal EEG with particular epileptiform activity
   Abnormal neurologic exam
   Abnormal computerized tomography or MRI results
   Nocturnal seizure
   Focal seizure
   Family history of seizures
4. The International League Against Epilepsy (ILAE) previously defined epilepsy as 2 unprovoked seizures more than 24 hours apart. However, a more recent ILAE task force modified this definition: even a single unprovoked seizure would be enough to diagnose epilepsy if there is high probability of further seizures—eg, in the presence of definitive epileptiform discharges on EEG or presence of a brain tumor or a remote brain insult on imaging, since such conditions induce an enduring predisposition to generate epileptic seizures.
5. Levetiracetam and valproate are considered appropriate first-line agents for generalized seizures.
6. Noncompliance with antiseizure medications
   Sleep deprivation
   Alcohol can precipitate seizures in cases of withdrawal or acute intoxication.
   Delta-9-tetrahydrocannibinol (THC), in high amounts
   Cocaine

Reference: Tirol FG, Levine MR, Wang T, Cho YW, Motamedi GK. An FP's guide to caring for patients with seizure and epilepsy. *J Fam Pract*. 2023 Nov;72(9):366-385.
Link: https://www.mdedge.com/familymedicine/article/266465/neurology/fps-guide-caring-patients-seizure-and-epilepsy
PMID: 37976335

Q3 Hirsutism

A 20-year-old nulliparous, nulligravid female presents to your outpatient clinic concerned about unwanted facial and body hair growth. The hair growth began at 13 years of age - at the time of menarche. Her mother suffers from a similar pattern of hair growth. Further history-taking reveals that the patient does not have any significant associated symptoms. In particular, she describes regular menses and denies dysmenorrhea. She has not used any prescription medications over the last ten years. You examine her further to help determine the etiology of the hair growth.

1. Which is the most widely-used physical exam scoring system for hirsutism?

2. Which clinical findings would give evidence for virilization? List two.

According to her score, she meets criteria for hirsutism. She does not have signs of masculinization nor virilization. Based on her clinical presentation, laboratory testing is indicated.

3. Which test(s) should you consider?

The laboratory test results are normal. Based on your assessment, you diagnose your patient with idiopathic hirsutism. You discuss treatment options. She states that she would be content with a treatment option which could address her facial hair growth as the other hair is less bothersome.

4. Which topical pharmaceutical could be considered?

At the six-month follow-up visit, she is displeased with the results of the topical pharmaceutical. She is open to trying an oral therapy.

5. Which medications aside from oral contraceptives would you consider? List two.

Educational Point: Hirsutism is defined as excessive terminal hair growth in androgen-dependent areas of the female body (i.e., face, chest, abdomen, lower back, upper arms, and thighs). This common condition affects 5%-15% of reproductive-aged females and is commonly associated with acne and oily skin. **The modified Ferriman-Gallwey (mFG) score is the preferred and most widely used method for scoring excess terminal hair in the assessment of hirsutism. Scores range from 0 to 4 for each body area, with a total score range of 0-36.** Typically, scores above the 95th percentile for a population are used to confirm hirsutism; however, because of racial differences in normal hair distribution, cut-off mFG scores for hirsutism vary as follows: >8 (for Black or White patients), >9-10 (for Mexican, Mediterranean, South Asian and Middle Eastern patients), >6 (for Latin American patients), >2-3 (for Chinese, Japanese, Korean, North American Indigenous, and Inuit patients), and >7 (for Southern Chinese patients). Nevertheless, patients with mFG scores >3 had similar complaints of hirsutism and use of hair removal treatments as those with scores >8, suggesting targets for initiation of investigations and management may be lower than traditional mFG scores.

It is important to distinguish between hirsutism, masculinization, and virilization. Masculinization is the development of male secondary sexual characteristics (facial hair, voice depth, body fat distribution, increased pectoral musculature) in a female. **Virilization is an extreme degree of hirsutism and masculinization with male pattern balding, voice deepening, increased muscle bulk, changes in libido, and clitoromegaly (clitoral diameter greater than 4 mm).** Virilization is a sign of high and often rapid androgen production, suggesting an androgen-secreting tumour.

Hyperandrogenic hirsutism is the most common category (>80% of cases) and is usually due to increased androgen production from the ovaries or adrenal glands. Elevated levels of dehydroepiandrosterone sulfate (DHEA-S) are almost always of adrenal origin, while high testosterone levels may be of ovarian or adrenal origin. Patients with hyperandrogenism often have irregular menses, anovulation, infertility, hyperinsulinemia, and a risk of endometrial hyperplasia or neoplasia because of unopposed estrogen. The conditions primarily accounting for hyperandrogenic hirsutism are PCOS, nonclassical congenital adrenal hyperplasia (NC-CAH) and androgen-secreting tumours.

Polycystic ovary syndrome (PCOS) is the most common cause of hirsutism. 74% of patients with hirsutism have PCOS, and 76% of patients diagnosed with PCOS have hirsutism. This finding is independent of ethnicity. Hyperandrogenism in PCOS is primarily the result of gonadotropin-dependent functional ovarian androgen excess, due to increased theca cell androgen production related to chronic elevations in luteinizing hormone. Adrenocorticotropic hormone (ACTH)-dependent adrenal androgen production also contributes to the hyperandrogenism. Furthermore, hyperinsulinemia also inhibits hepatic synthesis of sex hormone-binding globulin, increasing circulating levels of serum free testosterone. The rare hyperandrogenism, insulin resistance, and acanthosis nigricans syndrome is a severe variant of PCOS, caused by abnormal number or function of the insulin receptor, or antibodies against the insulin receptor.

Androgen-secreting ovarian and adrenal tumours are rare (0.2% of hirsutism cases). Half of all androgen-secreting tumours are malignant. Androgen-secreting tumours present with rapid onset hirsutism, virilization, or an abdominal or pelvic mass.

NC-CAH has an overall prevalence of 0.1% in the White population and 4.2% worldwide. It is rarely reported in African Americans. Ashkenazi Jewish patients are at higher risk, with a 37-fold greater prevalence than the general White population. Patients with NC-CAH remain asymptomatic until after puberty. NC-CAH is the most common adrenal cause of hyperandrogenism and results from a partial deficiency of enzymes leading to cortisol production, most commonly 21-hydroxylase. It is inherited in an autosomal recessive pattern. The clinical picture of NC-CAH is similar to that of PCOS, although there are different manifestations of this disorder depending on the severity of the hormone biosynthesis defect. NC-CAH is suspected when an elevated 17-hydroxyprogesterone (17- OHP) level is identified, with confirmation of the diagnosis using an ACTH stimulation test. The diagnosis of NC-CAH does not generally alter the treatment plan for hirsutism, but there may be genetic implications for future pregnancies and a risk of classical congenital adrenal hyperplasia in the offspring of affected individuals.

Hirsutism may develop following the use of medications such as danazol, performance-enhancing anabolic steroids, cyclosporine, diazoxide, penicillamine, interferon, phenytoin, cetuximab, glucocorticosteroids, androgen creams or patches, progestins, and estrogen antagonists (e.g., clomiphene, tamoxifen). Endocrinopathies (such as hypo- or hyperthyroidism, hyperprolactinaemia, Cushing syndrome, and acromegaly) are uncommon causes of hirsutism with the diagnosis usually made by recognizing the other signs and symptoms of these disorders.

Idiopathic hirsutism is the term used to describe hirsutism that occurs in association with normal ovulatory menstrual cycles and normal androgen concentrations. It is diagnosed by the exclusion of other etiologies, and, when strictly defined, accounts for 5%-15% of all cases of hirsutism. Idiopathic hirsutism may be due to increased sensitivity to androgens in

the pilosebaceous unit, a genetic increase in the peripheral conversion of testosterone to dihydrotestosterone by 5a-reductase, or a change in the androgen receptor function. A typical example of idiopathic hirsutism is the familial hirsutism that often affects individuals of Mediterranean or South Asian (Indian) descent.

Since hirsutism is a symptom or sign, an underlying etiology should be considered, including systematic evaluation for hyperandrogenism. Diagnostic evaluation is influenced by the severity of hirsutism (mFG score), patient concerns, which may not meet the criteria for hirsutism using the mFG score, and the potential of underlying hyperandrogenism. A thorough and detailed history should be obtained and a physical examination including anthropometric characteristics (i.e., BMI, waist circumference, and blood pressure) will aid in the diagnosis of hyperandrogenism. **Recent guidelines support measuring total testosterone, DHEA-S, and sex hormone-binding globulin (SHBG) in all patients with an abnormal mFG score, but not in eumenorrheic patients with local hair growth and a normal mFG score <8.** There are, however, arguments against testing of testosterone for all patients with hirsutism and irregular cycles. Although some patients have elevated levels of androgens, the majority have normal levels, with research confirming that severity of hirsutism does not correlate with the level of androgen excess. Laboratory investigations differentiate hyperandrogenic from idiopathic hirsutism and assist in ruling out other etiologies. **Thus, a high-quality total testosterone level should be drawn on menstrual cycle days 4-10 when levels are the highest, with a concomitant SHBG measurement.** A low SHBG level is associated with insulin resistance and an increased risk of developing type 2 diabetes mellitus in the future. **To screen for adrenal hyperandrogenism, serum DHEA-S levels should be measured. In severe DHEA-S elevation, an adrenal or ovarian neoplasm should be suspected.** Importantly, treatment response to hirsutism is based on clinical signs, not laboratory values, so repeat testosterone or DHEA-S measurements to monitor treatment "success" are both unnecessary and wasteful.

A serum assessment of 17-Hydroxyprogesterone (17-OHP) should be routinely performed for all patients with hyperandrogenic hirsutism to screen for NC-CAH. 17-OHP should be measured between 7 and 9 AM in the early follicular phase of the menstrual cycle or at any time if the patient is anovulatory. In patients with hyperandrogenic hirsutism who also have oligomenorrhea (and in whom determining the early follicular phase may be challenging), a serum progesterone level should also be measured simultaneously as elevated progesterone can lead to a compensatory rise in 17-OHP, leading to misdiagnosis.

Medical therapy involves androgen suppression or antiandrogens and is most beneficial in hyperandrogenic hirsutism but may also be useful in idiopathic hirsutism. Given the lifespan of terminal hair, at least 6 months of medical therapy is required before slower and finer regrowth of hair is noted. Hair growth tends to recur after cessation of medical therapy. Concomitant physical hair removal may be used for temporary results and may hasten the effects of medical therapy.

Eflornithine hydrochloride cream, an ornithine decarboxylase inhibitor, has been shown to reduce facial hirsutism over placebo after 8 weeks of use. In Canada, eflornithine is only indicated for the management of unwanted facial hair and should not be used for larger areas.

Combined hormonal contraceptives (CHCs) contain both estrogen and progestin components, and include oral, transdermal, and vaginal ring options. In the absence of contraindications to CHCs, first-line suppressive therapy involves the use of a CHC to suppress gonadotropins, decrease ovarian androgen production, and augment hepatic production of SHBG, effectively decreasing free testosterone levels. Oral CHCs with nonandrogenic (i.e., desogestrel, norgestimate) or antiandrogenic progestins (i.e., cyproterone acetate, drospirenone) may be more effective in treating hirsutism compared to CHC with more androgenic progestins. However, there is conflicting evidence as to whether these newer generation CHCs carry an increased risk of venous thromboembolism.

Antiandrogens are especially useful for idiopathic hirsutism or as adjuncts to androgen suppressive therapies. Patients who may become pregnant require a reliable form of contraception if using an antiandrogen because of the risk of feminization of a male fetus. For moderate and severe hirsutism, the addition of antiandrogens can enhance the effect of a CHC and should be considered if there is no improvement after 6 months of therapy. **Spironolactone** competes for the androgen receptor in skin fibroblasts and produces limited suppression of gonadal and adrenal androgen biosynthesis. **Cyproterone acetate** is a progestational agent which inhibits gonadotropin release (thereby decreasing androgen production) and binds competitively to androgen receptors. For mild hirsutism, cyproterone acetate is most conveniently administered as a combined pill with ethinyl estradiol (35 mg ethinyl estradiol and 2 mg cyproterone acetate), which is effective in controlling acne and hirsutism alone or in combination with spironolactone. **Finasteride** 5 mg daily blocks the 5a-reductase enzyme responsible for converting testosterone to dihydrotestosterone and is useful in the treatment of idiopathic hirsutism. Finasteride has a significant teratogenic potential. **Flutamide** is the first

nonsteroidal antiandrogen available that is devoid of any other hormonal activity. Flutamide alone or in combination with a CHC appears as or more effective than other antiandrogens. However, flutamide is associated with hepatotoxicity and risk of liver failure. Flutamide should not be used as a first-line therapy.

Glucocorticoids can be used to suppress adrenal androgen production and may be used in NC-CAH; however, its use for other causes of hirsutism is not proven and can be associated with significant adverse effects. Gonadotropin-releasing hormone analog can induce a medical oophorectomy effect to treat refractory hirsutism due to ovarian hyperandrogenism. Insulin sensitizers such as metformin or thiazolidinediones may improve several clinical parameters in PCOS, but to date there is insufficient evidence to determine the effectiveness of this approach for hirsutism. Although short courses of oral medroxyprogesterone acetate (to induce a withdrawal bleed in individuals with PCOS) have been shown to reduce androgen levels, there are no studies assessing efficacy of long-term therapy. Lifestyle interventions and weight loss through dietary, exercise, or behavioural interventions have been shown to lower total testosterone, increase SHBG, and improve hirsutism scores.

Acceptable answers:

1. The modified Ferriman-Gallwey score
2. Extreme hirsutism
   Male pattern balding
   Voice deepening
   Increased muscle bulk
   Clitoromegaly
3. Total serum testosterone level
   Serum dehydroepiandrosterone sulfate level
   Serum sex hormone-binding globulin level
4. Eflornithine hydrochloride cream
5. Spironolactone
   Cyproterone acetate
   Finasteride
   Flutamide

Reference: Elliott J, Liu K, Motan T. Guideline No. 444: Hirsutism: Evaluation and Treatment. *J Obstet Gynaecol Can*. 2023 Dec;45(12):102272.
Link: https://www.jogc.com/article/S1701-2163(23)00635-7/fulltext
PMID: 38049282

Q4 Osteoporosis Guidelines

One of your patients comes to see you in the office for a renewal of her hypertension medications. While there, she asks if she should have a bone mineral density test as many of her friends have started getting them.

1. According to the new Canadian Osteoporosis guidelines, which populations of patients should be offered a bone mineral density test? List two.

2. What risk factors should be considered when deciding age of bone mineral density screening onset? List three.

3. Both CAROC (Canadian Association of Radiologists and Osteoporosis Canada) and FRAX (fracture risk assessment tool) calculators are validated for calculating fracture risk. Which is preferred?

4. Which groups of patients should be offered pharmacotherapy for fracture prevention? List two.

5. What initial pharmacotherapy treatments should be considered? List two.

6. When should a follow up bone mineral density be ordered?

7. When should a drug holiday from bisphosphonates be considered?

Educational Point: In Canada, more than 2 million people live with osteoporosis, a disease that increases the risk for fractures, which result in excess mortality and morbidity, decreased quality of life and loss of autonomy. This guideline is an update of the 2010 Osteoporosis Canada clinical practice guideline on the diagnosis and management of osteoporosis in Canada. **They suggest an approach based on the assessment of age and the presence of clinical risk factors (i.e., a "targeted" approach) for identifying people who should undergo BMD measurement (low-certainty evidence in postmenopausal females aged 50–64 years; moderate-certainty evidence in females aged ≥ 65 years; very low-certainty evidence in males).** This strategy delays BMD testing in most people until age 70 years and allows for appropriate categorization of those at high fracture risk with the fracture risk assessment tools available in Canada.

In Canada, validated 10-year major osteoporotic fracture assessment tools include FRAX and CAROC. FRAX's performance is as good as or slightly better than that of other tools, and results in better fracture risk classification than CAROC. **They suggest the use of the Canada-specific FRAX tool as the preferred tool for fracture risk estimation.**

Previous fracture of the vertebra (clinical or documented on imaging) or the hip, and more than 1 fracture, indicate high risk for future fractures. In addition, given observational data from a large clinical registry, **an intervention threshold of 20% for 10-year major fracture risk (as measured by FRAX or CAROC) was also selected** (as a conditional recommendation), as this strategy was highly ranked in terms of number of fractures prevented among females aged 50 years and older and the number of females treated (to limit overtreatment).

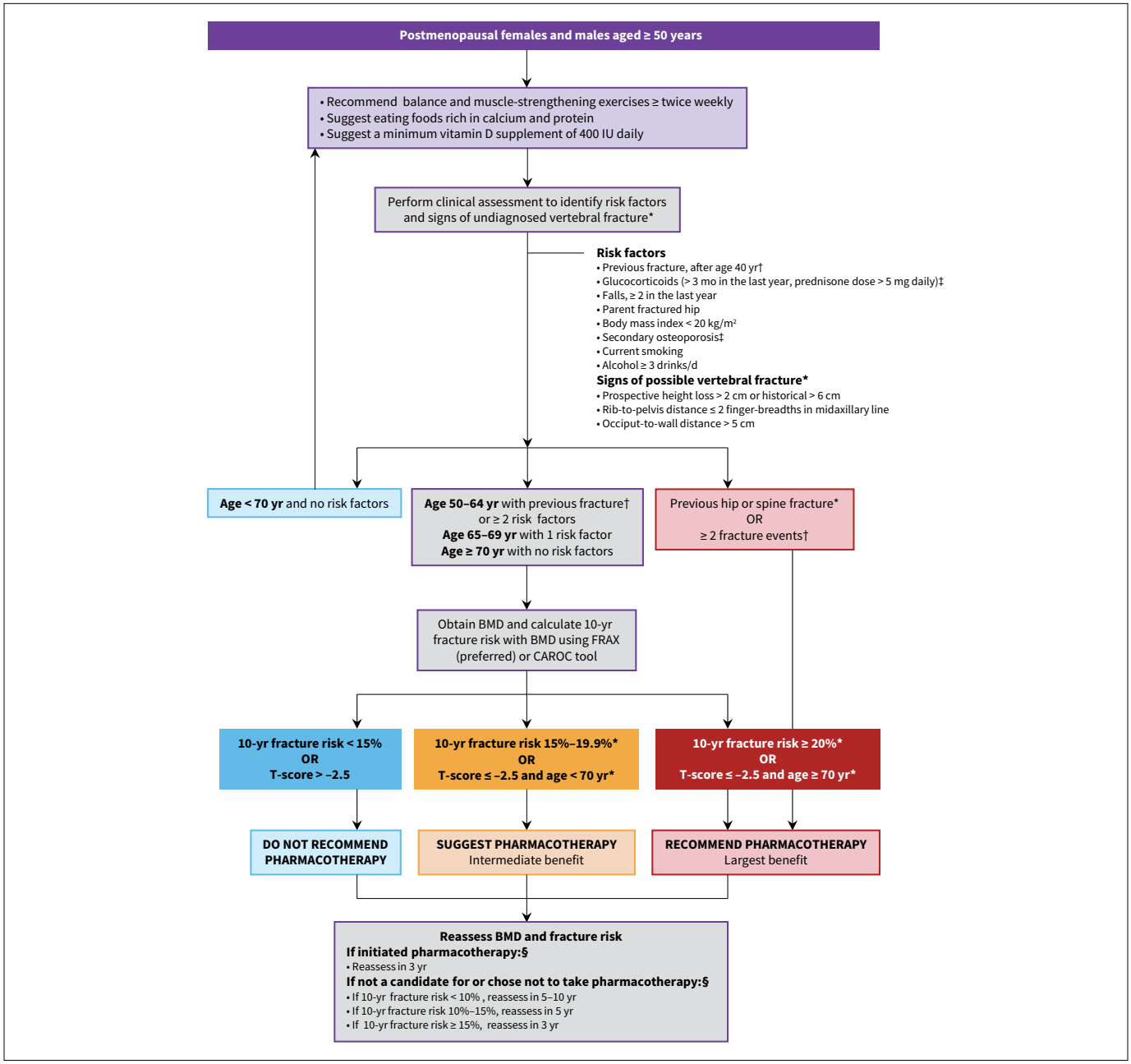
Bisphosphonate therapy for 3 years results in 20–30 fewer vertebral, 10 fewer nonvertebral, and 3 fewer hip fractures per 1000 people than no treatment. Compared with placebo, there may be very few harms with short-term (≤ 3 yr) use of oral bisphosphonate therapy, including gastrointestinal events such as esophagitis and ulcers (< 1% difference), and transient flu-like symptoms with zoledronic acid infusions, as well as very uncertain evidence for an increased risk of atrial fibrillation. **The benefits of denosumab are similar to those of zoledronic acid,** but there may be greater harms with denosumab: 7% more serious adverse events (such as infections requiring hospital admission) than with placebo and 14% and 7% more when compared with alendronate and zoledronic acid, respectively. Delayed dosing or discontinuation of denosumab is associated with rapid bone loss and may lead to vertebral fractures.

In females with higher risk of fractures (e.g., recent severe vertebral fracture, or > 1 vertebral fracture and T-score ≤ –2.5), there is high-certainty evidence that anabolic therapy (teriparatide or romosozumab) results in greater reductions in vertebral, nonvertebral and hip fractures than bisphosphonates (35, 18 and 5 fewer, respectively, per 1000 people). This evidence is indirect in males and therefore of moderate certainty. Stopping anabolic treatment without subsequent antiresorptive therapy risks the loss of bone density gains. For most people, the downsides of teriparatide, romosozumab or denosumab (such as injection schedules, the risks associated with and need for transition therapy when stopping the medication, and costs) probably outweigh the benefits compared with bisphosphonates. However, for people at higher risk of fractures, the benefits may outweigh these downsides.

Taking oral bisphosphonates for 5 years or more (e.g., for as long as 10 yr in the oral alendronate extension study), compared with shorter durations, likely results in no difference in hip or overall number of fractures, but a moderate-to-small reduction in clinically (22 fewer per 1000) and radiologically (17 fewer per 1000) identified vertebral fractures. Taking zoledronic acid annually for 6 years, compared with 3 years annually, likely results in no difference in hip and nonvertebral fractures, but radiologically confirmed vertebral fractures may be substantially reduced, although the evidence is uncertain.

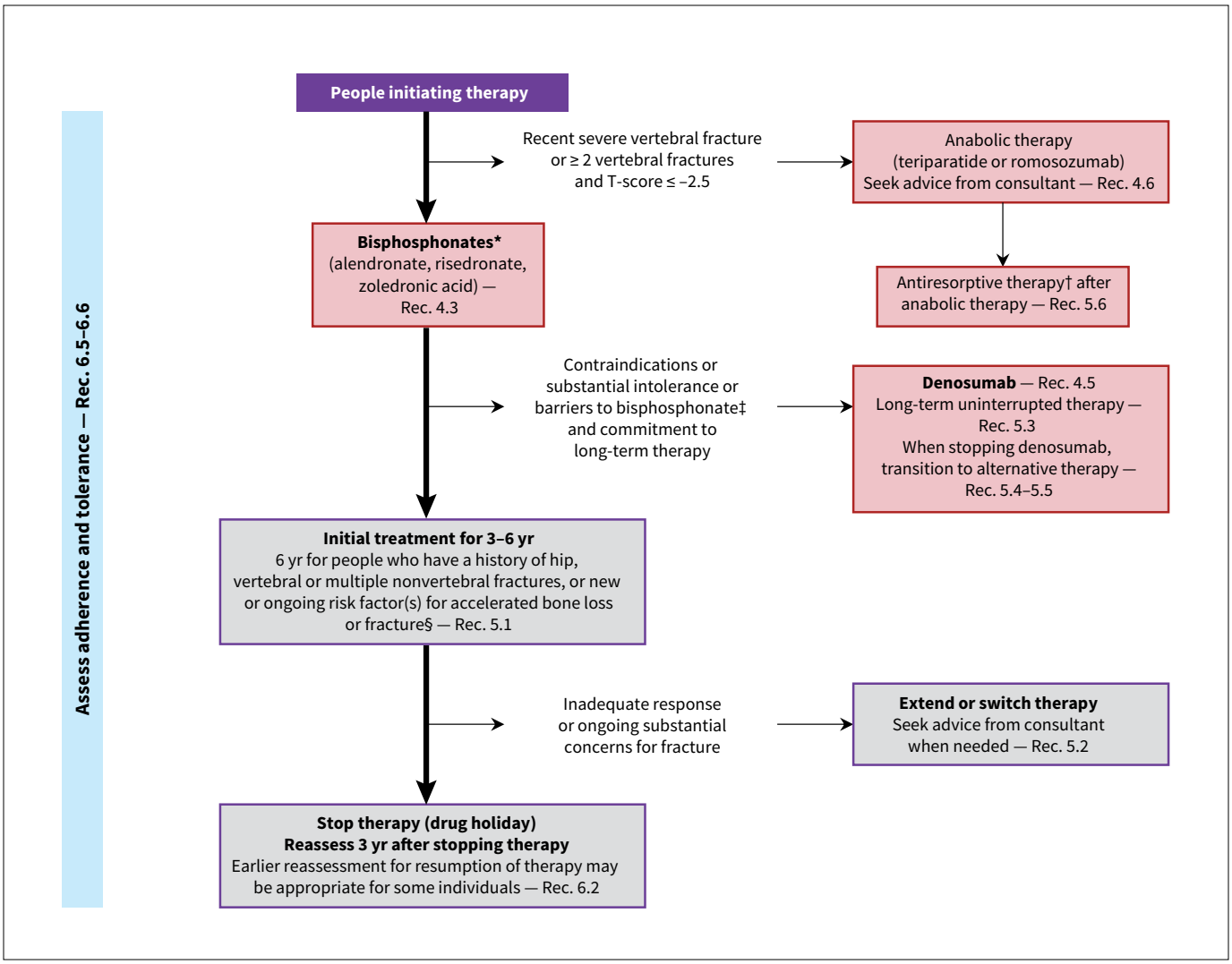
Harms may be increased with longer durations of bisphosphonates: after 6 years, there are 39–131 atypical femur fractures (a stress or insufficiency fracture occurring in the femoral shaft) per 100 000 person-years, compared with 25 at 3–5 years, and higher risk in females who self-report Asian race or ethnicity; and the risk of osteonecrosis of the jaw (a condition in which ≥ 1 parts of the jaw bone becomes necrotic and exposed to the oral cavity) is 25 per 100 000 person-years, and approximately doubles with use longer than 5 years. At 6 years, these harms likely outweigh the benefits of continued therapy, except in people at higher risk of fractures (e.g., previous hip or vertebral fractures, recent fracture, multiple fractures).

Figure 1: Integrated approach to the management of bone health and fracture prevention in postmenopausal females and males aged 50 years and older. See Appendix 1, Supplementary Tables 1–6 (available at www.cmaj.ca/lookup/doi/10.1503/cmaj.221647/tab-related-content) for more information on exercise and nutrition, secondary causes of osteoporosis and vertebral fracture assessment. Note: BMD = bone mineral density. *Consider lateral spine imaging to identify vertebral fracture(s). Finding of undiagnosed vertebral fracture(s) can guide appropriate choice and duration of therapy (Appendix 1, Supplementary Table 6). †Fractures that occur after the age of 40 years, in the setting of low trauma. Fractures of the hands, feet and craniofacial bones are not considered osteoporotic fractures.



‡Conditions known to cause secondary osteoporosis (Appendix 1, Supplementary Table 5); consider referral to specialists with expertise for co-management. Should be reassessed earlier if patient develops secondary causes (Appendix 1, Supplementary Table 5), new fracture or other risk factor for rapid bone loss.

Figure 2: Approach to pharmacotherapy to prevent fractures. Note: Rec. = recommendation (see Tables 4, 6 and 7 for full recommendations). * Menopausal hormone therapy is a suggested alternative for females younger than 60 years or within 10 years after menopause who prioritize alleviation of substantial menopausal symptoms (Rec. 4.4). †Antiresorptive therapy includes bisphosphonates (alendronate, risedronate and zoledronic acid), denosumab, raloxifene and menopausal hormone therapy. ‡Raloxifene is suggested rather than no treatment for females who have contraindications or substantial intolerance to, or who choose not to take, other suggested therapies) (Rec. 4.7). §See Figure 1 for list of risk factors and Appendix 1, Supplementary Table 5, for causes of secondary osteoporosis.



Acceptable answers:

1. a. All males and post-menopausal females age 70 and over.
   b. All males and post-menopausal females age 65 and over with 1 clinical risk factor for fracture.
   c. All males and post-menopausal females age 50 and over with previous osteoporosis related fracture or at least 2 risk factors for fracture. (see Figure 1)

2. Previous fracture after age 40
   2 or more falls in the last year
   BMI under 20
   Current smoking
   Glucocorticoid use
   Parent fractured hip
   Secondary osteoporosis
   3 or more alcoholic drinks a day (see Figure 2)

3. FRAX

4. Recommend therapy:
   10-year fracture risk of 20% risk based on FRAX
   Previous fracture of the spine or hip
   2 or more previous fractures after the age of 40 after low trauma
   T score under -2.5 and age 70 or over
   Suggest therapy:
   10-year fracture risk of 15-19.9% based on FRAX
   T score <-2.5 and age <70
   (see Figure 2)

5. If recent severe vertebral fracture or 2 or more vertebral fractures with t-score under -2.5 should be referred and offered anabolic therapy.
   Otherwise bisphosphonates: alendronate, risedronate, zoledronic acid.
   Start denosumab if contraindications to bisphosphonates, intolerance to bisphosphonates, barriers to bisphosphonates, commitment to long term therapy.
   (see Figure 2)

6. If start medication then in 3 years.
   If don't start medication:
   I. Risk under 10% then in 5-10 years
   II. Risk 10-15% then in 5 years
   III. Risk 15% or over then 3yrs
   (see Figure 1)

7. After starting bisphosphonates, after 3 years unless inadequate response.
   Only consider after 6 years if there is a history of hip, vertebral or multiple non-vertebral fractures.
   Re-assess the drug holiday after 3 years.
   (see Figure 2)

Overuse Alert!
This practice questions aligns with Choosing Wisely Canada's patient pamphlet on **Bone Density Tests** and the College of Family Physicians of Canada's recommendation: **Don't order Dual-Energy X-ray Absorptiometry (DEXA) screening for osteoporosis on low-risk patients. Use "risk-assessment first" screening before ordering DEXA.**

Reference: Morin SN, Feldman S, Funnell L, Giangregorio L, Kim S, McDonald-Blumer H, et al. Clinical practice guideline for management of osteoporosis and fracture prevention in Canada: 2023 update. *CMAJ*. 2023 Oct 10;195(39):E1333-E1348.
Link: https://www.cmaj.ca/content/cmaj/195/39/E1333.full.pdf
PMID: 37816527

Q5 Treatment Resistant Depression in Older Adults

A 72 year old retired immigrant engineer returns to your clinic with his wife to follow up on the efficacy of the second antidepressant prescribed for his depression.

Symptoms first started about nine months ago. He started to see you seven months ago. He tried an SSRI at a therapeutic dose daily for three months and, when asked to rate his progress at that time, indicated an improvement in his symptoms of about 25%. After taking another SSRI at therapeutic dose daily for a little more than another three months, the couple reported that the second drug improved symptoms about 25%. You feel the patient meets the criteria for treatment resistant late life depression given his age.

You inform them that the diagnosis is referred to as treatment-resistant late-life depression. The couple is not familiar with the diagnosis and risk factors.

1. What is the most commonly accepted definition for treatment-resistant depression?

2. One-third of older adults with depression meet criteria for treatment-resistant depression.
   - ❍ True
   - ❍ False

3. a. Name two risk factors for the development of treatment resistant depression.

   b. What is an additional risk factor for treatment resistant late-life depression?

4. What is the prognosis and response for older adults with depression compared to younger adults?

5. Name three possible concerning outcomes for those with treatment resistant late-life depression.

Your patient's wife is wondering about psychotherapy for management. Your patient is not interested in psychotherapy. He is curious about diet and exercise.

6. How beneficial is non-pharmacologic therapy (e.g. diet, psychotherapy) in treatment resistant late-life depression?

The couple are wondering about the next pharmacological options.

7. a. Name three pharmacological therapies that have the most evidence of benefit as add-on therapy in treatment resistant late-life depression?

b. What pharmacological therapy has the most evidence of benefit to potentially be used as monotherapy in treatment resistant late-life depression?

8. a. Name four extra considerations regarding adverse drug effects that should be taken into account with antidepressant use in older adults.

b. What drugs should be avoided in this age group?

You prescribe a pharmacological add-on therapy. The couple ask what is offered if add-on therapy is ineffective.

9. Electroconvulsive therapy is a safe, efficacious, and well-tolerated treatment when conventional therapies have been unsuccessful in the older adult.
   - ❍ True
   - ❍ False

10. Repetitive transcranial magnetic stimulation is an emerging therapy with promising results in those with treatment resistant late-life depression.
   - ❍ True
   - ❍ False

Educational Point: Major depressive disorder is the second most common psychiatric disorder diagnosed in older adults and is most often referred to as late-life depression (LLD). **Among the depressed older adult population, one third meet criteria for treatment-resistant depression (TRD), most often called treatment-resistant late-life depression (TRLLD). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition does not offer criteria for TRD; however, the most accepted definition is a lack of response to two or more adequate trials of antidepressant medications.**

Risk factors for the development of TRD include a history of childhood abuse, earlier age of depression onset, lower education level, previous episodes of depression, comorbid anxiety or personality disorder, and an increased medical burden. An additional risk factor for TRLLD, specifically, is vascular depression with impaired executive function.

Evidence suggests older adults with depression often have a poorer prognosis and response to antidepressant treatment when compared to younger adults. They are also

at risk for worse medical outcomes, increased disability, faster cognitive decline, and dementia. Additionally, TRLLD is correlated with higher health resource utilization and healthcare costs compared with those with non-TRD or no diagnosis of depression.

Despite the increased morbidity associated with TRLLD, evidence to guide therapeutic intervention in this patient population is sparse. **Non-pharmacologic therapy (e.g., diet, psychotherapy) has little data to support its benefit in this population but can be utilized as adjunctive therapy.**

Meta-analyses and systematic reviews have found exercise to have a modest effect as adjunctive treatment for TRD in those receiving pharmacotherapy, although not in older adults specifically.

Extra consideration should be taken into account with antidepressant use in older adults, including the risk of falls, hyponatremia, bone loss, extrapyramidal side effects, and drug–drug interactions. In addition, age-related pharmacokinetic changes and comorbidities such as cognitive impairment, medical illness, and frailty place older adults at an increased risk for adverse effects when prescribed antidepressants. The Beers Criteria specifically recommends avoidance of paroxetine and tricyclic antidepressants (TCAs) because of their higher risk of adverse effects.

For older patients who respond well to antidepressants, evidence suggests treatment should be continued beyond the point of achieving remission in order to prevent recurrence and relapse.

The majority of pharmacotherapy trials in the TRLLD population lack strong methods and external validity. **However, the use of venlafaxine as monotherapy and add-on, as well as lithium, bupropion, and aripiprazole as add-on therapy to standard antidepressant therapy have enough evidence that a trial with appropriate monitoring is a prudent strategy.**

Electroconvulsive therapy is a safe, efficacious, and well tolerated treatment when conventional therapies have been unsuccessful in the older adult and is strongly supported by recent treatment guidelines. One multicenter RCT in 47 older adult patients with moderate depression in a 6-week trial of ECT was compared to 81 patients who participated in a 12-week trial of either venlafaxine (n = 40) or nortriptyline (n = 41). The ECT cohort remitted faster than the pharmacotherapy cohort had a remission rate of 63.8% versus 33.3%, respectively. The ECT group used more antidepressants versus the medication group prior to the trial, implying this may be a good option for those with TRLLD.

Repetitive transcranial magnetic stimulation (rTMS) is a therapy that uses magnetic field pulses that can be given on the left side of the head only or bilaterally. Treatments are usually given for 5 days per week for 4–6 weeks. Based on described studies, **rTMS can be an effective and well-tolerated augmentation option for patients with TRLLD.** Recently published guidelines recommended the use of left-sided or bilateral rTMS for older adults who have not responded to more than one or more antidepressant trials.

The authors conclude ensuring non-pharmacologic and pharmacologic strategies are optimized and given a sufficient trial in those with TRLLD is the best we can do for this vulnerable population.

Acceptable answers:

1. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition does not offer criteria for Treatment Resistant Depression; however, the most accepted definition is a lack of response to two or more adequate trials of antidepressant medications.
2. True
3. a. Risk factors for the development of treatment resistant depression include a history of childhood abuse, earlier age of depression onset, lower education level, previous episodes of depression, comorbid anxiety or personality disorder, and an increased medical burden.
   b. An additional risk factor for treatment-resistant late-life depression is vascular depression with impaired executive function.
4. Evidence suggests older adults with depression often have a poorer prognosis and response to antidepressant treatment compared with younger adults.
5. Those with treatment resistant late-life depression are also at risk for worse medical outcomes, increased disability, faster cognitive decline, and dementia. Additionally, treatment resistant late-life depression is correlated with higher health resource utilization and healthcare costs compared with those with non-treatment resistant depression or no diagnosis of depression.
6. Non-pharmacologic therapy has little evidence of benefit in treatment-resistant late-life depression; however, a trial in conjunction with other modalities can be a low-risk option.
7. a. Pharmacotherapy trials in the treatment-resistant late-life depression population lack strong methods and external validity; however, venlafaxine, bupropion, lithium, and aripiprazole have the most evidence of benefit as add-on therapy in the treatment-resistant late-life depression population.
   b. Venlafaxine has the most evidence of benefit to potentially be used as monotherapy in treatment resistant late-life depression.
8. a. Extra consideration that should be taken into account with antidepressant use in older adults include: the risk of falls, hyponatremia, bone loss, extrapyramidal side effects, and drug–drug interactions. In addition, age-related pharmacokinetic changes and comorbidities such as cognitive impairment, medical illness, and frailty place older adults at an increased risk for adverse effects when prescribed antidepressants.
   b. The Beers Criteria specifically recommends avoidance of paroxetine and tricyclic antidepressants.
9. True
10. True

Reference: Blaszczyk AT, Mathys M, Le J. A Review of Therapeutics for Treatment-Resistant Depression in the Older Adult. *Drugs Aging*. 2023 Sep;40(9):785-813.
Link: https://link.springer.com/article/10.1007/s40266-023-01051-3
PMID: 37596380

Q6 Anorexia

A 16-year-old female patient presents to your clinic for assessment of amenorrhea for the past 5 months. The patient reports previously regular cycles since menarche at age 11. She discloses feeling increasingly preoccupied with weight, expressing a strong desire to "become healthier" through exercising and monitoring her food intake.

After questioning the patient, you suspect that she is suffering from an eating disorder.

1. What are common physical symptoms and signs of eating disorders? List five.

You measure her vital signs, height, and weight. A urine pregnancy test is negative. Considering your findings during your physical examination and her BMI, you suspect atypical anorexia nervosa.

2. What is the definition of atypical anorexia nervosa?

3. What initial bloodwork would you consider? List five.

You consider setting a treatment goal weight with the patient.

4. Using a patient's prior growth curve to project treatment goal weight is recommended.
   - ❍ True
   - ❍ False

After your initial evaluation, you decide that outpatient management is the treatment of choice.

5. What form of psychotherapy is the most effective treatment?

After several weeks, her symptoms have not improved, and she has lost an additional 5 pounds.

6. What are the acute indications for hospitalisation for atypical anorexia nervosa? List five.

Educational Point: Anorexia nervosa (AN) and atypical anorexia nervosa (AAN) are serious, potentially life-threatening illnesses that are best addressed through early detection and treatment. Recent studies suggest that the global COVID-19 pandemic has contributed to an increase in the incidence of eating disorders (EDs), particularly among teenagers. Primary care providers (PCPs) play an important role in addressing screening, diagnosis, and treatment of adolescents with AN or AAN.

Anorexia nervosa is a restrictive ED that often begins in adolescence. **The term atypical anorexia nervosa is used to describe an individual with a history of living in a larger body who becomes preoccupied with weight or shape and loses a considerable amount of weight but nonetheless remains in a range considered healthy (e.g., dropping from the 95th percentile to the 50th percentile).** Recently, an increased prevalence of patients with AAN (who would not meet the underweight criteria but meet all other criteria) has been observed. Weight loss in this population may not always be recognized as problematic. This is concerning, as studies suggest that patients with AAN exhibit serious psychological distress and demonstrate similar risks related to malnutrition. Equally concerning are reports by patients with AAN that health-related counselling contributed to illness onset and progression.

An initial visit should contain a focused history and physical examination with emphasis on ED symptoms (restricting, bingeing, purging, overexercising) and the patient's safety. Subsequent visits should involve more discussion with respect to daily nutritional intake and weight history as well as a focused mental health review involving stressors, self-critical thoughts, mood, suicidality, self-harm, sleep, substance use, energy level, and concentration. If applicable, a menstrual history should be obtained. **Common physical symptoms of EDs should also be asked about, including reflux esophagitis, constipation, nausea, presyncope, palpitations, chest pain, weakness, fatigue, lanugo, dry skin, hair loss, muscle cramps, joint pain, pallor, easy bruising, and cold intolerance.** Signs of severe purging may include abrasions on knuckles, poor dentition, halitosis, and salivary gland hypertrophy.

Physical examination should include measurement of weight, height, temperature, and postural vital signs (heart rate and other vital signs measured after lying horizontally for 5 minutes and then again after standing for 2 minutes). When providing a patient or their family members with a diagnosis of AN or AAN, the seriousness should be underscored. Families and patients should be informed that these diagnoses are often due to a combination of genetic, environmental, and social factors. Providers should emphasize the need for weight restoration, including a discussion of the medical and psychological effects of insufficient nutrition and the long-term health outcomes. When appropriate, providers should empower caregivers to take control of nutrition. When available, patients should be referred to the nearest specialized ED program, and families should be provided with psychoeducational resources and directed to a therapist and a dietitian with relevant expertise.

At an early visit, a treatment goal weight (TGW) should be determined. **The authors recommend, when possible, using a patient's prior growth curve to project weight as if they had continued to grow along their curve without weight loss.** In younger teenagers, TGW should be reassessed at least every 6 months. Return of regular menstrual function, if applicable, may also serve as an indication that a patient is approaching their TGW. In patients with AAN, it is important

that issues related to weight bias and stigma do not influence the determination of an optimal TGW, which will be higher than the 50th-percentile body mass index for age. **Depending on the degree of clinical concern, initial blood work may include complete blood count; assessment of renal function; and measurement of electrolyte, extended electrolyte, liver enzyme, albumin, vitamin B12, ferritin, and lipid levels. Other investigations can also be considered to rule out other causes of symptoms, including measurement of thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, estradiol, androgen, and C-reactive protein levels and erythrocyte sedimentation rate.** Urinalysis can assist with assessment for hydration status, the presence of ketones, and proteinuria. An electrocardiogram should be done to rule out bradycardia, arrhythmias, and corrected QT interval prolongation. Providers should be aware that certain symptoms (such as purging) also require specific ongoing monitoring.

Assessment and management of patients with EDs require regular in-person visits given the need for physical examination and measurement of weight and vital signs. Further, assurance of a confidential setting is paramount. If patients do not meet any of the criteria for inpatient management, then outpatient weight restoration is the treatment of choice. **The core components of treatment are renourishment and psychotherapy, with family-based psychotherapy being the most effective treatment.** Family-based therapy involves a multidisciplinary team including a PCP as well as a psychologist or psychotherapist and, if available, a dietitian experienced in treating EDs. Ensuring an open line of communication between team members is essential to maintaining a uniform approach.

In family-based therapy, the entire family supports recovery. Initially, caregivers should be encouraged to oversee 3 meals and 3 snacks per day. If a patient is unable to complete their nutrition plan, they may be offered supplements and progress toward full intake of solid food. During this phase, the ED can be externalized, meaning that it is discussed as an external force that is putting thoughts into a patient's head and compelling them to behave in ways that jeopardize their health. As a patient improves and reaches their TGW, they can transition to taking on more independence in eating. For older teens or those without families who are able to support them, cognitive-behavioural therapy for EDs is the recommended treatment.

If weight or overall status continue to decline, patients should be referred to a specialized program. As nutrition increases, care should be taken to evaluate risk of refeeding complications. Blood work should be checked monthly, at minimum, during the initial renourishment stage and more frequently if a patient is actively purging or if there are concerns about medical stability. Regular electrocardiographic monitoring may also be required. Clinicians could also suggest initiating a multivitamin with iron and vitamin D. Patients at acute risk of refeeding syndrome, generally those with a higher degree of malnutrition at presentation (ie, 75% TGW), should be admitted for renourishment. Gastrointestinal complaints are common during the acute phase of refeeding and will likely resolve with continued feeding; these can be quite distressing, however, and may require symptomatic treatment.

Box 1. Acute indications for hospitalization for AN or AAN in a young person

The following indicate a need for hospitalization:

- <75% of treatment goal weight
- Arrested growth or development
- Core temperature <35.6°C (<96.0°F)
- Heart rate <50 BPM in the daytime or <45 BPM overnight
- Blood pressure <90/60 mm Hg or orthostatic hypotension (sustained increase in pulse of >40 BPM or a sustained decrease in blood pressure of >10 diastolic or >20 systolic mm Hg/min from lying to standing)
- ECG showing arrhythmia, prolonged QTc interval, or severe bradycardia
- Electrolyte abnormalities (eg, hypoglycemia, hyponatremia, hypophosphatemia, hypokalemia, hypomagnesemia)
- Uncontrolled bingeing or purging
- Dehydration
- Poorly controlled mental health or other medical diagnosis that is resulting in a barrier to care for the eating disorder (eg, severe depression, obsessive compulsive disorder, type 1 diabetes mellitus, etc)
- Active suicidal ideation

AN—anorexia nervosa, ANN—atypical anorexia nervosa, BPM—beats per minute, ECG—electrocardiogram, QTc—corrected QT.

Data from van der Leer et al and the Society for Adolescent Health and Medicine.[26,27]

Acceptable answers:

1. Reflux esophagitis
   Nausea
   Palpitations
   Weakness
   Dry skin
   Muscle cramps
   Pallor
   Cold intolerance
   Constipation
   Presyncope
   Chest pain
   Fatigue
   Hair loss
   Joint pain
   Easy bruising
   Lanugo
2. The term atypical anorexia nervosa is used to describe an individual with a history of living in a larger body who becomes preoccupied with weight or shape and loses a considerable amount of weight but nonetheless remains in a range considered healthy (eg, dropping from the 95th percentile to the 50th percentile).
3. Complete blood count
   Electrolytes
   Liver function tests
   Vitamin B12
   Lipid levels
   Luteinizing hormone
   Estradiol
   C-reactive protein levels
   Assessment of renal function
   Extended electrolytes
   Albumin
   Ferritin
   Thyroid-stimulating hormone
   Follicle-stimulating hormone
   Androgen
   Erythrocyte sedimentation rate
4. True
5. Family-based psychotherapy
6. <75% of treatment goal weight
   Arrested growth or development
   Core temperature <35.6°C (<96.0°F)
   Heart rate <50 BPM in the daytime or <45 BPM overnight
   Blood pressure <90/60 mm Hg or orthostatic hypotension (sustained increase in pulse of >40 BPM or a sustained decrease in blood pressure of >10 diastolic or >20 systolic mm Hg/min lying to standing)
   ECG showing arrhythmia, prolonged QTc interval, or severe bradycardia
   Electrolyte abnormalities (eg, hypoglycemia, hyponatremia, hypophosphatemia, hypokalemia, hypomagnesemia)
   Uncontroled bingeing or purging
   Dehydration
   Poorly controlled mental health or other medical diagnosis that is resulting in a barrier to care for the eating disorder (eg, severe depression, obsessive compulsive disorder, type 1 diabetes mellitus, etc)
   Active suicidal ideation

Reference: Parpia R, Spettigue W, Norris ML. Approach to anorexia nervosa and atypical anorexia nervosa in adolescents. *Can Fam Physician*. 2023 Jun;69(6):387-391.
Link: https://www.cfp.ca/content/cfp/69/6/387.full.pdf
PMID: 37315981

Q7 Dilated Cardiomyopathy

A 50-year-old man comes to the ER complaining of recent onset chest heaviness, leg swelling and trouble breathing at night. He is referred urgently to the cardiology service where he undergoes angiography. This reveals "normal coronary anatomy and no evidence of valvular disease, but there appears to be an element of left ventricular dilatation, in keeping with dilated cardiomyopathy". The cardiologist recommends that the patient be investigated for his dilated cardiomyopathy.

1. What are possible etiologies for his dilated cardiomyopathy? List three.

2. Which initial laboratory tests should be ordered? List four.

3. Beyond laboratory testing, which additional cardiac testing could be considered? List two.

You speak with his family and find out that two of his uncles had a similar problem.

4. Dilated cardiomyopathy is rarely familial.
   - ❍ True
   - ❍ False

Investigations confirm dilated cardiomyopathy with an ejection fraction of 30%, possibly related to viral infection.

5. What initial pharmacologic treatments are recommended? List three pharmacologic classes.

6. All patients with dilated cardiomyopathy and low ejection fraction should have an implantable defibrillator placed.
    - ❍ True
    - ❍ False

You see him for follow up two weeks later, and he is feeling much better and wants to "start getting fit".

7. What advice would you give about exercise?

Three months later you see him for follow-up. He recently saw the cardiologist and his echocardiogram showed normal cardiac function indicating reverse remodelling. He has no cardiac symptoms. He wonders if he "really needs all these pills".

8. Would you recommend weaning off cardiac medication at this time?

Educational Point: Dilated cardiomyopathy is conventionally defined as the presence of left ventricular or biventricular dilatation or systolic dysfunction in the absence of abnormal loading conditions (eg, primary valve disease) or significant coronary artery disease sufficient to cause ventricular remodelling. This definition has been recognised as overly restrictive, as left ventricular hypokinesis without dilation could be the initial presentation of dilated cardiomyopathy.

Direct causes of dilated cardiomyopathy include likely pathogenic or pathogenic gene variants, infections, autoimmunity, toxins (eg, ethanol, recreational drugs, and cancer therapy), endocrinopathies, and tachyarrhythmias. Some conditions can also act as modifiers, aggravating cardiomyopathy without being directly causal, such as the haemodynamic and hormonal changes of pregnancy leading to the clinical manifestation of previously asymptomatic dilated cardiomyopathy. In some patients, it is the combination of genetic susceptibility and exposure to myocardial stressors, infections, or toxins that leads to the development of dilated cardiomyopathy, with a more severe phenotype and a worse related outcome. For example, truncating variants in TTN (TTNtv), affecting the giant sarcomere protein titin, are the most common genetic cause of dilated cardiomyopathy. Moreover, TTNtv are present in approximately 0.5% of the general population, many of whom will not develop dilated cardiomyopathy without a second environmental or genetic trigger. A concerted interaction between a monogenic risk and an acquired cause is an important consideration directing the diagnostic tests. For example, the identification of an acquired cause of dilated cardiomyopathy such as myocarditis, anthracyclines, or alcohol abuse does not exclude underlying or another likely pathogenic or pathogenic gene variant.

Genetic causes of dilated cardiomyopathy have been pursued due to the highly heritable nature of this disease, which is recognised as familial in 30–40% of cases. The inheritance pattern of familial dilated cardiomyopathy is typically autosomal dominant, suggesting monogenic or mendelian cause, although X-linked, autosomal recessive, and mitochondrial inheritance are observed, particularly in paediatric populations.

Toxins, mainly anthracyclines, immune checkpoint inhibitors, ethanol, and recreational drugs (e.g., amphetamines and cocaine) might cause dilated cardiomyopathy through direct cardiomyocyte toxicity, or indirectly by causing myocarditis or microvascular injury. In alcohol-induced cardiomyopathy, the direct toxic effect of long-standing high alcohol intake on the myocardium is mediated by high oxidative stress, apoptosis, and upregulation of the innate immune system and the neurohumoral axis. Chronic alcohol intake can cause increased cardiac fibrosis, iron deposition, and epicardial fat along with cardiac dysfunction. Indulgent drinking induces cardiac oedema, suggestive of inflammation. However, abstinence or significant reduction of alcohol intake might result in a reversal of systolic dysfunction.

Recreational drugs, methamphetamines in particular, have been increasing in popularity, availability, and purity in recent decades. Cardiovascular disease is the second most common cause of death in people who use these drugs. Methamphetamines and cocaine can induce direct cardiomyocyte toxicity by chronic, malignant overactivation of the sympathetic nervous system, generalised endothelial dysfunction, and activation of reactive oxygen species and the innate immune system. The damage to the heart and vessels is less likely to be reversible.

The diagnostic tests for all patients with known or suspected dilated cardiomyopathy include clinical history, laboratory tests, electrocardiogram (ECG), and cardiac imaging.

Detailed questions should be asked on systemic diseases, toxic agents (chemotherapy, alcohol, and drugs), and a familial history of cardiac or neuromuscular disease or sudden cardiac death at a young age (<50 years). Dilated cardiomyopathy can be considered familial if two or more first-degree or second-degree relatives have a history of the disorder, or a first-degree relative has autopsy-proven dilated cardiomyopathy and sudden death aged younger than 50 years. **A 12-lead ECG should be performed to look for electrical abnormalities.** In view of the high arrhythmogenic risk, inclusive of both atrial and ventricular arrhythmias, in patients with variants in certain genes, **ambulatory electrocardiographic monitoring might be prudent.**

Echocardiography is central for the diagnosis and monitoring of cardiac systolic function, whereas cardiac magnetic resonance (CMR) imaging provides more detailed morphological and prognostic information and should be performed early in the diagnostic investigation. Genetic testing and counselling should be considered in all patients with a diagnosis of dilated cardiomyopathy independent of their family history, in view of its high prevalence and clinical relevance for the patients and their family members.

Positron emission tomography (PET) is used to evaluate myocardial metabolism and blood flow. The radiotracer [18 F] fluorodeoxyglucose ([18 F]FDG), a glucose analogue, is the most frequently used tracer for the assessment of tumour, cardiac viability, brain function, and active inflammation. **Combined PET and CT scanning is an alternative to CMR to detect cardiac inflammation.** A full body PET-CT scan might also be required in patients with suspected sarcoidosis to identify extra-cardiac organ involvement.

Routine laboratory examinations include cardiac and muscular enzymes, liver and renal function, haemoglobin, white blood cell count (including differential white blood cell count to detect eosinophilia), natriuretic peptides, thyroid function tests, iron status, and markers of systemic autoimmune diseases. Natriuretic peptides (B-type natriuretic peptide and N-terminal-proBNP) are the most widely adopted biomarkers for diagnosis and prognostication of heart failure. Increased creatine kinase could indicate overt or subclinical skeletal muscle involvement in muscular dystrophinopathies (Duchenne, Becker, and limb girdle muscular dystrophy), mitochondrial cardiomyopathies, glycogen storage diseases, and sarcomeric cardiomyopathies.

High-sensitivity troponin is a representative biomarker for myocardial injury due to acute myocarditis or myocardial stress in dilated cardiomyopathy, associated with adverse clinical outcomes and cardiac remodelling. Patients with recurrent increased high-sensitivity troponin levels and excluded coronary artery disease should be investigated for myocarditis and cardiac inflammatory diseases.

To evaluate the etiopathogenesis of dilated cardiomyopathy, endomyocardial biopsies are decisive in the differentiation of inflammatory and non-inflammatory cardiac diseases, distinguishing different types of myocarditis, storage disorders (including amyloidosis, glycogenosis, Fabry disease, or haemochromatosis), and genetic heart diseases. According to the intersociety position statement, endomyocardial biopsies should be considered in patients with suspected fulminant myocarditis or acute myocarditis with acute heart failure, left ventricular dysfunction or rhythm disorders, suspected myocarditis (in haemodynamically stable patients), autoimmune disorders with progressive heart failure, dilated cardiomyopathy with recent onset heart failure and moderate-to-severe left ventricular dysfunction, suspected immune checkpoint inhibitor-mediated cardiotoxicity, high-degree atrioventricular block, syncope or unexplained ventricular arrhythmias, myocardial infarction with non-obstructive coronary arteries or takotsubo syndrome with progressive left ventricular dysfunction, and unexplained restrictive or hypertrophic cardiomyopathy. An endomyocardial biopsy is also required to identify the cause of cardiac inflammation, thus guiding immunosuppressive treatment in non-infectious cases especially with giant cell myocarditis, eosinophilic myocarditis, and cardiac sarcoidosis. Patients with dilated cardiomyopathy should be treated with guideline-directed medical therapy for heart failure with reduced ejection fraction, as it has been proven to decrease morbidity and mortality and impact cardiac remodelling. **Such treatments include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, mineralocorticoid receptor antagonists and SGLT2 inhibitors. An angiotensin-converting enzyme inhibitor or angiotensin receptor blocker can be replaced by sacubitril–valsartan in patients with dilated cardiomyopathy who remain symptomatic despite optimal treatment.**

Medical therapy should not be withdrawn from patients with dilated cardiomyopathy who experience reverse remodelling, including normalisation of cardiac function. A randomised pilot study, TRED-HF, in 51 patients investigated the possibility of withdrawing medical treatment in those patients with non-ischaemic dilated cardiomyopathy who had partial-to-complete recovery of LVEF (>40% with normal natriuretic peptide concentration). However, relapse of dilated cardiomyopathy within 6 months was observed in 44% of

patients. Rapid left ventricular remodelling with early tissue and functional changes was found, even among patients who did not relapse. Whether patients with recovered ejection fraction following acute myocarditis without underlying immune disease will require lifelong heart failure treatment remains unclear. Current guidelines advise a 6-month treatment period after recovery from systolic dysfunction.

Exercise training improves functional capacity and quality of life in patients with dilated cardiomyopathy. Low-to-moderate intensity recreational exercise or guided exercise training should be considered as an integral part of the management of affected individuals. However, high intensity exercise and competitive sports could trigger sudden cardiac death in dilated cardiomyopathy, and shared decision-making regarding risks and values should precede such participation. In particular, an LVEF lower than 45%, unexplained syncope, extensive cardiac fibrosis at CMR or endomyocardial biopsy, high-risk genotype, or frequent ventricular tachyarrhythmias on ambulatory Holter monitoring or exercise testing are negative prognostic markers in patients considering high intensity activities. However, risk scores for sudden cardiac death developed for specific activities are scarce and will require large, collaborative, international dilated cardiomyopathy cohorts to be developed.

The indication for placement of a primary prevention implantable cardioverter defibrillator in dilated cardiomyopathy has been a major topic of discussion since the publication of the DANISH trial. This study revealed that prophylactic cardioverter defibrillator implantation in patients with symptomatic systolic heart failure not caused by coronary artery disease was not associated with a significantly improved all-cause survival. However, younger patients in this study did benefit from prophylactic cardioverter defibrillator implantation. Long-term follow-up of patients younger than 70 years in the DANISH trial revealed that cardioverter defibrillator implantation was associated with a lower incidence of all-cause mortality, cardiovascular death, and sudden cardiovascular death. Although the DANISH trial did not show a significant benefit from implantable cardioverter defibrillator therapy in patients with dilated cardiomyopathy, certain genetic or inflammatory subgroups are at higher risk of sudden death and therefore merit careful consideration of cardioverter defibrillator implantation.

Cardiac resynchronisation therapy is indicated for patients with symptomatic dilated cardiomyopathy with sinus rhythm, an LVEF of 35% or more despite optimal medical therapy, and a QRS duration of greater than 130 ms with left bundle branch block. In response to cardiac resynchronisation therapy, patients with dilated cardiomyopathy experienced greater improvements in LVEF and left ventricular cavity size coupled with a greater survival benefit than ischaemic cardiomyopathy.

Acceptable answers:

1. Likely pathogenic or pathogenic gene variants, infections, autoimmunity, toxins (eg, ethanol, recreational drugs, and cancer therapy), endocrinopathies, and tachyarrhythmias.
2. Cardiac and muscular enzymes, liver and renal function, haemoglobin, white blood cell count (including differential white blood cell count to detect eosinophilia), thyroid function tests, iron status, markers of systemic autoimmune diseases, natriuretic peptides (B-type natriuretic peptide and N-terminal-proBNP), creatine kinase, high-sensitivity troponin, possible genetic testing.
3. EKG, ambulatory EKG monitoring, echocardiography, cardiac magnetic resonance (CMR) imaging, CT/ PET scan, Combined PET and CT scanning, endomyocardial biopsies.
4. False
5. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, mineralocorticoid receptor antagonists and SGLT2 inhibitors.
6. False
7. Low-to-moderate intensity recreational exercise or guided exercise training should be considered as an integral part of the management of affected individuals. However, high intensity exercise and competitive sports could trigger sudden cardiac death in dilated cardiomyopathy.
8. No

Reference: Heymans S, Lakdawala NK, Tschöpe C, Klingel K. Dilated cardiomyopathy: causes, mechanisms, and current and future treatment approaches. *Lancet*. 2023 Sep 16;402(10406):998-1011.
Link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01241-2/fulltext
PMID: 37716772

Q8 Food Allergy

You are seeing a 21-year-old patient with known peanut and shellfish allergy. Up until this age, they have strictly avoided food triggers, though unfortunately they have required the use of epinephrine via autoinjector a couple of times. They are seeing you today as they have heard there may be other treatment options available for their food allergies.

1. In addition to oral immunotherapy (OIT), several other treatments targeting the immune response to a food allergen have emerged in recent years. List two.

Your patient is interested in OIT, but is worried about the potential of an allergic reaction by being exposed to increasingly larger daily doses of the food allergen.

2. At what point in therapy do allergic reactions mostly occur?

3. What "safe dosing" rules exist for OIT? Name two recommendations.

4. In what other situations may dose adjustments be required? List three.

Your patient returns after having tried OIT, but finds the daily regimen very difficult to adhere to. They have also unfortunately had an allergic reaction during OIT.

5. What treatment may be the preferred option at this time?

6. Immunotherapy demonstrates equal efficacy in younger and older individuals.
   - ❍ True
   - ❍ False

Educational Point: The traditional management approach for food allergy involves strict avoidance of the food trigger, education on how to recognize signs and symptoms of allergic reactions and how to treat them, and training on the use of epinephrine autoinjectors in case of anaphylaxis. **In addition to this approach, multiple treatments specifically targeting the immune response to a food allergen have emerged in recent years in both clinical and research settings, including various forms of food allergen immunotherapy (oral immunotherapy [OIT], sublingual immunotherapy [SLIT], and epicutaneous immunotherapy [EPIT]) and biologics, such as omalizumab.** Rates of accidental exposures vary across different studies, and strict allergen avoidance may be challenging for some patients.

OIT involves the oral administration of increasingly larger daily doses of the food allergen. The dose is increased usually every 2 to 4 weeks during the build up phase, with the aim to reach a target daily maintenance dose that will protect individuals with food allergy from accidental exposures and reduce severity of allergic reactions. The efficacy of OIT is high (roughly 60% to 80% may achieve desensitization, with some studies suggesting higher or lower rates in specific populations), but the therapy is associated with potentially burdensome adverse effects and limitations. **Allergic reactions mostly occur during the build up phase and are often mild or moderate in severity (often involving oral/pharyngeal or gastrointestinal symptoms) though anaphylaxis across all stages does occur.**

To help limit dose-related adverse effects, "safe-dosing" rules have evolved. These include taking doses on a full stomach and avoiding or altering doses when reaction-augmentation factors may be present, such as avoiding dosing around the times of exercise or passive warming (eg, hot showers). In addition, dosing adjustments may need to be made at times of illness (eg, viral infection), sleep deprivation, menstruation or whether the patient is also taking nonsteroidal anti-inflammatory medications. Across studies, a small percentage of individuals may be able to achieve remission; however, protection tends to wane with dose interruption or discontinuation, and long-term regular exposure is necessary to maintain dose tolerance for most individuals. Multiple studies generally reveal that OIT results in a level of challenge-proven desensitization that should offer protection from accidental exposures after 6 to 12 months of therapy.

SLIT refers to tablets or liquid drops, typically containing a few milligrams of the allergen which are placed under the tongue and held. The dose is 100 to 1000 times smaller compared with OIT and targets submucosal Langerhans cells. Common SLIT adverse effects may include oropharyngeal symptoms (mostly pruritus and lip swelling). Anaphylaxis is rarely reported in SLIT studies. A recent study suggests that remission may be possible with SLIT (at least in younger children), with rates similar to OIT, but more studies are needed to confirm this finding.

EPIT is a therapy in which the allergen is continuously applied to intact skin, which is currently in phase III development using a proprietary technology. The dose is administered in the form of a patch that is placed on the skin and changed every 24 hours.

In general, research regarding "early life" immunotherapy (preschool OIT, SLIT, or EPIT) has revealed a better efficacy and safety profile for all forms compared with similar studies in older individuals, suggesting that intervention during periods of increased immune plasticity may offer a valuable opportunity for potential disease modification, though comparative efficacy studies definitively supporting an optimal age for intervention are lacking.

Omalizumab is FDA approved for "IgE-mediated food allergy in adult and pediatric patients aged 1 year and older for the reduction of allergic reactions (type I), including anaphylaxis, that may occur with accidental exposure to 1 or more foods. To be used in conjunction with food allergen avoidance." **Patients for whom omalizumab may be the preferred option include those who desire any or all of the following: a non-daily or non-oral treatment, did not tolerate previous immunotherapy, have multiple food allergies and/or multiple allergic disorders (eg, allergic asthma, chronic rhinosinusitis with nasal polyps, and chronic spontaneous urticaria).**

Omalizumab treatment is intended to be of long term, as treatment effects are expected to wane if omalizumab is discontinued, although longer-term treatment outcomes are lacking, but being studied. Importantly, the FDA approval for omalizumab in food allergy indicates that it is to be used in conjunction with food allergen avoidance. Omalizumab is intended to increase allergen threshold of a moderate-to-severe reaction, but it does not eliminate risk of an allergic reaction. Data have revealed omalizumab can be used to reduce OIT-related dosing adverse events and speed the build up phase (both single and multiple foods), can increase thresholds of tolerance for single or multiple different foods and enable reintroduction of varying doses of these foods into the diet regularly (while remaining on continuous omalizumab therapy), and is associated with improvements in quality of life.

Acceptable answers:

1. Sublingual immunotherapy
   Epicutaneous immunotherapy
   Biologics (such as omalizumab)
2. During the build-up phase
3. Taking doses on a full stomach
   Avoiding or altering doses when reaction-augmentation factors may be present (times of exercise or passive warming (e.g., hot showers)).
4. Times of illness (e.g., viral infection)
   Sleep deprivation
   Menstruation
   If the patient is also taking nonsteroidal anti-inflammatory medications
5. Omalizumab
6. False

Reference: Anagnostou A, Greenhawt M, Shaker M, Vickery BP, Wang J. Food allergy yardstick: Where does omalizumab fit? *Ann Allergy Asthma Immunol*. 2024 Aug 24: S1081-1206(24)00494-0.
Link: https://linkinghub.elsevier.com/retrieve/pii/S1081-1206(24)00494-0
PMID: 39182580

Q9 Food Allergies

A 30-year-old mother is at your office today because she suspects her 4 year-old daughter has food allergies. Her daughter experiences wheezing, diarrhea, and hives when she eats shellfish.

1. What are risk factors for food allergies? List three.

2. The rates of food allergies are overestimated because of self-reported food allergies that may be food intolerances.
   - ❍ True
   - ❍ False

3. What tests can be performed to confirm food allergies? List two.

4. What is the primary treatment for food allergies?

5. Oral and sublingual desensitization immunotherapies may induce tolerance to an allergenic food by gradually increasing the dose of the allergenic extract.
   - ❍ True
   - ❍ False

She also has a newborn son. She has been exclusively breastfeeding for the past 4 months. She is planning to start to expose her newborn son to some allergenic foods, which may contain peanuts, cow's milk, wheat, and cooked eggs.

6. Exclusively breastfeeding for the first three to four months has been shown to reduce the development of food allergies.
   - ❍ True
   - ❍ False

7. Infants with early sequential exposure to allergenic food (peanuts, cow's milk, wheat, and cooked eggs) between four and six months of age are less likely to develop food allergies at 36 months than unexposed infants.
   - ❍ True
   - ❍ False

8. Tree nut, peanut and shellfish allergies are more likely to be lifelong.
    - ❍ True
    - ❍ False

Educational Point: In the United States, approximately 2% to 3% of adults and 8% of children have a food allergy, and 40% of those children have multiple food allergies. About 40% of food allergies in children are reported as severe, which can lead to significant costs and anxiety for parents and caregivers. Common foods that produce allergies are peanuts, cow's milk, shellfish, tree nuts, egg, fish, soy, and wheat. Peanut allergy, the most common (2%), is the leading cause of life-threatening anaphylaxis. **Children are likely to outgrow allergies to egg, cow's milk, wheat, and soy, whereas peanut, tree nut, fish, and shellfish allergies tend to persist throughout life.** Peanut allergy resolves in approximately 1 in 5 children in the first four years of life.

Children with asthma, allergic rhinitis, atopic dermatitis, or an allergy to insect venom, medications, or latex are at an increased risk of developing food allergies. Children with vitamin D insufficiency, a history of antibiotic use in the first two years of life, or a family history of atopy also have an increased risk of developing food allergies. Other factors, including exercise, emotional stress, menses, alcohol consumption, and having a viral infection, can lower the reaction threshold and increase the risk of having an allergic reaction to food.

Food allergies are classified as immunoglobulin E (IgE)- and non–IgE-mediated. IgE-mediated allergies typically have a rapid onset, within seconds to minutes (e.g., pruritus, anaphylaxis). Non–IgE-mediated food allergies are characterized by delayed reactions, within hours to several days (e.g., food protein allergy–induced colitis). The severity of the reaction is influenced by the amount of food ingested, form of the food (i.e., how it was prepared), and presence of other ingested foods.

The rates of food allergies are overestimated because of self-reported food allergies that may be food intolerances. Food intolerances are adverse reactions without an immunologic cause (e.g., lactose intolerance) and can be mistaken for food allergies.

Diagnosis starts with a detailed history from the parent, caregiver, or patient. The amount and type of food that was eaten, form of the food (e.g., raw, extensively baked), time from ingestion to symptoms, presence of symptoms not associated with food, presence of risk factors that increase the likelihood of an allergic reaction (e.g., exercise), and number of reactions are essential components of an allergy-focused history. Non–IgE-mediated food allergies should be considered in children without an adequate response to treatment for atopic dermatitis, gastroesophageal reflux disease, and chronic gastrointestinal symptoms, including chronic constipation.

Serum IgE or skin prick testing (SPT) should be performed only in patients whose allergy-focused history indicates a high pretest probability of a food allergy. Doing so promptly can prevent unnecessary food avoidance and strain for patients and their families. SPT should be performed only in facilities equipped to handle anaphylactic reactions and interpreted by clinicians with an adequate knowledge of history, clinical findings, and allergen pathology. SPT can be performed on patients of any age and has high sensitivity and high negative predictive values. Children younger than two years and adults older than 70 years may have smaller positive results. The likelihood of allergy reactivity can be estimated with correlation of wheal size.

SPT has greater sensitivity than serum IgE testing. Drawbacks of SPT include the lack of standardization of the extracts used and the interference of antihistamine and certain antidepressant medications. Before SPT, patients should abstain from the use of high-potency topical steroids on test sites for three weeks and discontinue any antihistamines and antidepressants with antihistamine properties (e.g., tricyclic antidepressants) for one week. It is not necessary to stop leukotriene receptor antagonists, which are often used in the treatment of asthma.

Serum IgE testing is preferable to SPT in patients at high risk of anaphylaxis. Patients who cannot tolerate the SPT procedure, have uncontrolled medical conditions (e.g., uncontrolled asthma), take essential medications (e.g., beta blockers for coronary artery disease), or have skin conditions that could interfere with SPT should instead undergo serum IgE testing. Widely available serum IgE tests provide reliable measures with standardization of accurate laboratory techniques and specified 95% positive predictive values of reactivity within a population. Serum IgE testing can indicate sensitization to a specific allergen. Care is necessary when interpreting serum IgE results. A positive test result does not necessarily indicate the existence of a food allergy, and the level of specific IgE does not correlate to symptom severity. A negative test result may indicate that a patient has not been sensitized (i.e., exposed) to the allergen, leading to an incorrect dismissal of a food allergy.

Less commonly used allergy testing is typically done by an allergist and includes intradermal tests, atopy patch tests, and basophil activation tests. The preferred method of food allergy diagnosis is a double-blind oral food challenge. An oral food challenge can reliably disprove a previously diagnosed nonsevere food allergy or confirm an already diagnosed food allergy. It should be done under physician supervision and in a setting capable of managing severe reaction. If a child has severe allergic symptoms after a known ingestion and an oral food challenge is not feasible, having no further symptoms after elimination of the food is sufficient for diagnosis.

The primary treatment for a food allergy is elimination of the offending food from the diet. Nutrition counseling and regular growth monitoring are warranted when multiple foods are eliminated. The U.S. Food Allergen Labeling and Consumer Protection Act of 2004 requires food labels to list when any of the nine major food allergens (i.e., milk, egg, peanuts, tree nuts, soy, wheat, fish, crustacean shellfish, and sesame) are present as ingredients in prepared foods. However, including warning labels such as "may contain trace amounts of nuts" or "may be prepared in a facility that also uses nuts" is voluntary.

No medications are effective for preventing IgE- or non–IgE-mediated allergic reactions to food. **Oral and sublingual immunotherapies are methods of desensitization therapy. These treatments induce tolerance to an allergenic food by gradually increasing the dose of the allergenic extract. Patients receiving oral immunotherapy for peanut, egg, and milk allergies are more tolerant of the allergenic food in oral food challenges than patients receiving placebo.** Local gastrointestinal and systemic reactions requiring epinephrine have been reported with oral immunotherapy. Patients are more likely to achieve clinical desensitization with oral immunotherapy, but there is a higher risk of adverse effects. Peanut desensitization therapy increases the risk of anaphylactic reactions compared with placebo or avoidance. Immunotherapy (oral and sublingual) with cross-reacting allergens is not recommended to treat food allergies.

Although exclusive breastfeeding for three to four months reduces the likelihood of the child developing eczema and asthma, it has not been shown to reduce the development of food allergies. Evidence does not support restricting a mother's diet during pregnancy or while breastfeeding to reduce the risk of food allergies. Restricting cow's milk supplementation for the first three days of life is associated with a significantly lower risk of developing cow's milk, egg, and wheat allergies by 24 months of age in infants who have an increased risk of atopy. **Evidence indicates that infants with early sequential exposure to allergenic foods (peanuts, cow's milk, wheat, and cooked eggs) between four and six months of age are less likely (number needed to treat = 63) to develop food allergies at 36 months than unexposed infants.**

Guidelines for the prevention of peanut allergies recommend that infants with severe eczema, egg allergy, or both be introduced to age-appropriate, peanut-containing food as early as four to six months of age. Other solid foods should be introduced before peanut-containing foods to confirm that the infant is developmentally ready.

Most children with food allergies will eventually tolerate cow's milk, egg, soy, and wheat. **However, tree nut, shellfish, and peanut allergies are more likely to be lifelong.** Most children (75%) with egg and cow's milk allergies can often tolerate baked forms of these foods. The time course of food allergy resolution in children varies by food and may occur as late as their teenage years. An initial high level of allergen-specific IgE against a food is associated with a lower rate of resolution of the allergy over time.

Acceptable answers:

1. Children with asthma, allergic rhinitis, atopic dermatitis, or an allergy to insect venom, medications, or latex are at an increased risk of developing food allergies. Children with vitamin D insufficiency, a history of antibiotic use in the first two years of life, or a family history of atopy also have an increased risk of developing food allergies. Other factors, including exercise, emotional stress, menses, alcohol consumption, and having a viral infection, can lower the reaction threshold and increase the risk of having an allergic reaction to food.
2. True
3. Serum IgE or skin prick testing (SPT) should be performed only in patients whose allergy-focused history indicates a high pretest probability of a food allergy. Less commonly used allergy testing is typically done by an allergist and includes intradermal tests, atopy patch tests, and basophil activation tests. The preferred method of food allergy diagnosis is a double-blind oral food challenge. An oral food challenge can reliably disprove a previously diagnosed nonsevere food allergy or confirm an already diagnosed food allergy. It should be done under physician supervision and in a setting capable of managing severe reactions.
4. Elimination of the offending food from the diet.
5. True
6. False
7. True
8. True

Overuse Alert!
This practice question aligns with the Canadian Society of Allergy and Clinical Immunology's Choosing Wisely Canada recommendation: **Don't order specific immunoglobin E (IgE) tests (skin or serum) unless indicated by the patient's history specific to that food.**

Reference: Bright DM, Stegall HL, Slawson DC. Food Allergies: Diagnosis, Treatment, and Prevention. *Am Fam Physician*. 2023 Aug;108(2):159-165.
Link: https://www.aafp.org/pubs/afp/issues/2023/0800/food-allergies.html
PMID: 37590855

Q10 Recurrent Bacterial Vaginosis

A 30-year-old female patient presents to your office with complaints that "I have BV again." She is requesting treatment for bacterial vaginosis (BV) and expresses her frustration at how frequently this occurs. She would like to know if there is anything that could be done to prevent infection.

1. Thirty-day cure rates approach 80% in BV infected women treated with metronidazole.
   - ❍ True
   - ❍ False

2. What is the difference between recurrent and refractory BV?

Your patient asks about possible causes for BV. She is sexually active with one male partner. This is her fourth suspected episode of symptomatic BV this year.

3. Name three possible contributors to overall risk of recurrent and refractory BV.

4. Providing intra-vaginal probiotics in recurrent or refractory BV is recommended.
   - ❍ True
   - ❍ False

You examine the patient. On examination, you note a thin vaginal discharge smoothly coating the vaginal walls, the presence of a fishy odor of the vaginal discharge, and there are >20% clue cells per high power field on microscopic examination. You diagnose her with recurrent BV. She was last treated with oral metronidazole twice daily for 7 days.

5. What is the initial recommended treatment approach for recurrent BV?

6. Should the initial treatment of recurrent BV fail, what treatment is recommended?

Educational Point: Bacterial vaginosis (BV) is the most common vaginal infection in reproductive-age women. While it is known that BV is a dysbiosis characterized by a shift in the vaginal microbiota from *Lactobacillus* species (spp.) dominance to a dramatic increase in facultative (ie, *Gardnerella vaginalis*) and strict anaerobic bacteria, the inciting agent(s) are not yet clearly defined. During BV, a polymicrobial biofilm containing *G. vaginalis* and other BV-associated bacteria (BVAB) forms on vaginal epithelial cells, providing an antibiotic impregnable sanctuary to protect this pathologic community of microorganisms. Desquamation of these cells coated with biofilm results in clue cells seen on wet mount of vaginal fluid.

Despite 30-day cure rates approaching 80% in BV-infected women treated with 7 days of oral metronidazole (MTZ), BV recurrence within 12 months is common (i.e., 58% in one study). While the BV biofilm likely contributes to high recurrence rates after therapy by reducing antimicrobial

penetration, antimicrobial resistance in BV-associated bacteria (BVAB), both within the biofilm and the vaginal canal, may also play a role. For the purpose of this article, **recurrent BV is defined as ≥3 annual episodes of symptomatic BV requiring antimicrobial therapy. This is in contrast to refractory BV, in which short-term conventional antimicrobial therapy fails to achieve a positive response in terms of resolution of vaginal symptoms and/or resolution of a BV Nugent score ≥7[20] (this score is obtained by determining the relative concentration of lactobacilli (ie, long, Gram-positive rods), small Gram-negative and Gram-variable rods (*G. vaginalis* or Bacteroides spp.), and curved Gram-negative rods (*Mobiluncus* spp.)or Amsel criteria ≥3/4, (homogeneous, thin vaginal discharge smoothly coating the vaginal walls, vaginal pH >4.5, presence of a fishy odor of the vaginal discharge before and/or after addition of 10% KOH [whiff test], and >20% clue cells [vaginal epithelial cells with a grainy border and speckled appearance due to adherent bacteria] present per high power field on microscopic examination).**

A large majority of women (50–80%) with BV are asymptomatic. Routine screening for BV among asymptomatic women (including pregnant women) is controversial and is not currently recommended, as treatment has not been found to reduce adverse outcomes in multiple studies.

Other studies have found that women with an intrauterine device (IUD) have an increased risk of BV, particularly those with copper IUDs (a non-hormonal long-acting reversible contraceptive device). Two hypotheses have been proposed for the elevated risk of BV among women with copper IUDs. The first is that the presence of an IUD, a foreign body, in the female genital tract may facilitate the overgrowth of BVAB. In addition, use of a copper IUD can be associated with an increased volume and duration of menses, potentially allowing heme-stimulated growth of *G. vaginalis*, a common, key BVAB, to the point of vaginal dysbiosis and development of BV.

The pathogenesis of recurrent BV is likely multifactorial and complex and remains incompletely understood. **While persistence of the BV biofilm and/or antimicrobial resistance among key BVAB (ie, *G. vaginalis*, *F. vaginae*) are thought to play a role in recurrent and refractory infection, a significant body of data also suggests that ongoing exchange of pathogenic BVAB between sexual partners occurs which may also be contributing.** The penile microbiota of male sexual partners has been found to be significantly more similar to the vaginal microbiota of their female sexual partners compared to the vaginal microbiota of non-partner women. In addition, uncircumcised men with community state types 4–7 (ie, those associated with a high prevalence and abundance of BVAB) in their penile microbiota were significantly more likely to have a female sexual partner with a high Nugent score ($p = 0.03$).

In another study of 43 BV patients (18 refractory, 16 recurrent, and 11 remission patients) by Turner et al, persistently high titers of Gardnerella Gsp07 were associated with refractory treatment responses while persistently low abundance of Gardnerella Gsp07, *G. swidsinskii*, and *G. leopoldii* were associated with remission. **Thus, the presence of Gardnerella Gsp07, *G. swidsinskii*, and *G. leopoldii* may be markers of a poor clinical outcome among women with BV and future therapies targeting these strains could improve treatment outcomes.**

It is essential to identify patients with recurrent BV, as opposed to refractory BV, as treatment regimens can be different. A refractory response differs from relapse in that the major causative pathogens are not eradicated but persist in high numbers. **Providing oral or intra-vaginal probiotics in either of these situations is not recommended.**

In cases of refractory BV, switching of the class of therapeutic drug should be performed (ie, 5-nitroimidazole to clindamycin or vice versa) as should the route of therapy (ie, oral to vaginal therapy or vice versa). Change in drug class exploits subtle differences in antimicrobial activity and pathogen susceptibility. If treatment failure continues despite these measures, a 7-day trial of high-dose intra-vaginal metronidazole 750 mg-1000 mg daily is reasonable. It is also reasonable to use combination therapy with an oral 5-nitroimidazole for 7 days in addition to daily intra-vaginal boric acid 600 mg for 7–21 days. Unfortunately, randomized controlled trials have not yet been performed including women with refractory BV. The above recommendations are thus based upon the authors' clinical experience and extrapolated from studies targeting women with recurrent BV. It is also important to recognize that patient tolerance and toxicity set a low ceiling for the use of high 5-nitroimidazole doses.

In the management of women with recurrent BV, reversible factors should initially be considered. First, identifying reinfection from a sexual partner as a cause of recurrence should be investigated. For women diagnosed with recurrent BV, the authors recommend mandatory and consistent use of condoms for a period of at least 3–4 months after treatment, aimed at preventing reinfection from an asymptomatic partner who may be colonized with BVAB. Condom use has been shown to provide some benefit in prior studies although the optimal duration of use is unknown. It is hypothesized that BVAB

residing in the male urethra or under the prepuce might resolve over time without additional re-population from a female sexual partner. A similar concern applies to female sexual partners of women with recurrent BV, in which celibacy is advocated together with female partner evaluation and avoidance of sex toys and other sexual practices which may transmit infected vaginal fluids. Unfortunately, partner treatment trials of women with BV have yet to show a significant effect although an additional trial is currently enrolling. Data from a prior literature review and meta-analysis of 55 studies found that hormonal contraceptive use was significantly associated with a reduced risk of BV, regardless of the type of contraception. Overall, more recent data suggest that re-infection from an untreated regular sexual partner may overwhelm the potential benefits of combined oral contraceptive pill on the vaginal microbiota.

Given the association between copper IUD use and BV recurrence, the authors advocate for removal of copper IUDs among women with recurrent BV. Whether or not other types of IUDs should also be removed in this setting is controversial due to lack of data. Other behavioral risk factors for BV recurrence undoubtedly exist (i.e., chronic smoking) but are not part of the currently recommended management process.

With regard to specific therapeutic measures for women with recurrent BV, following switching of antibiotic drug classes similar to what is recommended for refractory BV, the authors generally proceed to the use of combination therapy with oral metronidazole 500 mg twice daily for 7 days in combination with an anti-biofilm agent such as intravaginal boric acid 600 mg daily, to be used for 7–30 days. The rationale for use of combination therapy with an oral 5-nitroimidazole and intra-vaginal boric acid is based on the presence of the polymicrobial BV biofilm. Boric acid, a widely available antiseptic agent, serves as a potent method of biofilm removal in addition to providing broad-spectrum bacteriostatic activity. However, the optimal duration of intra-vaginal boric acid use remains unknown. Boric acid monotherapy, in spite of its dual activity, does not exert the same successful antimicrobial therapeutic efficacy.

Another advance in the understanding of recurrent BV pathogenesis is that acquired antimicrobial resistance constitutes a major contributor to recurrent BV. Dose of antimicrobial does appear to matter, but additional controlled studies are needed and surprisingly missing. Schwebke et al previously demonstrated that simply prolonging standard antibiotic therapy beyond 1 week afforded little advantage. Accordingly, next steps in managing women with recurrent BV should include higher drug dose and drug combination therapy.

Another step in the management of recurrent BV is the introduction of long-term maintenance suppressive or prophylactic antibiotic regimens following a course of induction or short-term antibiotic therapy. In the first maintenance therapy trial utilizing twice weekly intra-vaginal metronidazole gel 0.75%, protective efficacy was shown but overall cure was not apparent. Miscellaneous prophylactic regimens are now widely used, including intermittent twice weekly intra-vaginal boric acid, but not compared scientifically or subject to robust evaluation. Results are only modestly successful, with occasional breakthrough recurrences of symptomatic BV, much to the distress and disappointment of patients. Unfortunately, reoccurrences also occur following cessation of the maintenance regimen. Another problem is that frequent episodes of symptomatic vulvovaginal candidiasis complicate the use of maintenance antibiotic regimens and can occur in excess of 50% of women.

Acceptable answers:

1. True
2. Recurrent is ≥3 annual episodes of symptomatic BV.
   In refractory BV, short-term conventional antimicrobial therapy fails to achieve a positive response in terms of resolution of symptoms and/or resolution of BV Nugent score or Amsel criteria.
3. IUDs, particularly copper
   Persistence of the BV-associated bacteria (BVAB) biofilm
   Antibiotic resistance
   Ongoing exchange of pathogenic BVAB between sexual partners
   Presence of Gardnerella Gsp07, G. swidsinskii, and G. leopoldii
4. False
5. Switching of the class of therapeutic drug (ie, 5-nitroimidazole to clindamycin or vice versa).
   Removal of copper IUDs
6. Oral metronidazole 500 mg twice daily for 7 days in combination with an anti-biofilm agent such as intravaginal boric acid 600 mg daily, to be used for 7–30 days.

Reference: Muzny CA, Sobel JD. Understanding and Preventing Recurring Bacterial Vaginosis: Important Considerations for Clinicians. *Int J Womens Health*. 2023 Aug 9;15:1317-1325.
Link: https://www.dovepress.com/understanding-and-preventing-recurring-bacterial-vaginosis-important-c-peer-reviewed-fulltext-article-IJWH
PMID: 37581202

Q11 Ulcerative Colitis

A 36-year-old man presents to your clinic with bloating, loose/watery stools with mucus, and fatigue for the past 3 months. He has experienced two episodes of blood in his stool last week without any anal pain.

He has lost 3 kg since you've seen him 6 months ago. He has diffuse abdominal tenderness and a normal rectal examination. Your patient is worried that he has ulcerative colitis (UC).

1. What dermatological conditions are associated with UC? List two.

You order blood work and stool samples. His liver function tests are abnormal.

2. Which liver condition is associated with UC?

3. Which stool samples would you order given a suspicion of UC? List two.

Testing is suggestive of UC. You refer the patient to gastroenterology.

4. What is the first-line therapy for induction and maintenance of remission of mild to moderate ulcerative colitis?

5. For those whose disease extends beyond the rectum, when should screening for colorectal cancer begin?

Educational Point: Ulcerative colitis (UC), 1 of the 2 major forms of inflammatory bowel disease (IBD), is a chronic inflammatory condition of the colon. In North America, the prevalence of UC in 2023 is estimated to be 0.4% of the population, which represents approximately 1.5 million people living with UC in North America. UC has a relapsing-remitting course, which necessitates different therapeutic approaches to induce and maintain remission. There is no known cure for UC and, thus, the goals of treatment are resolving symptoms, improving quality of life, and preventing and treating complications. Natural history studies demonstrate that within 5 years of diagnosis approximately 20% of those with UC are hospitalized and 7% require colectomy. Understanding of the pathogenesis of UC has led to the development of different classes of biologics and oral small molecules that have expanded treatment options for UC.

The pathogenesis of UC is driven by gene-environment interactions leading to an abnormal immune system response to the intestinal microbiome. More than 200 genetic loci have been associated with UC. A classic symptom of UC is rectal bleeding, which is reported by more than 90% of patients and varies by disease severity from trace to frank bleeding. More than 90% of patients experience a decrease in stool consistency (ie, loose to watery stools) and/or **increased stool frequency**

(ie, passage of stool, mucus, and/or blood) occurring more than 3 times per day. Individuals with severe inflammation throughout the colon may also experience systemic symptoms such as fatigue, fever, dehydration, and weight loss.

A meta-analysis of 14 studies (N = 8925 patients with UC) estimated that extraintestinal manifestations (EIMs) occur in approximately 27% of people with UC, with one-quarter of EIMs occurring prior to the diagnosis of UC. Sacroiliitis and ankylosing spondylitis occur in 4% of patients with UC and are independent of bowel disease activity. People with UC and chronic low back pain should receive plain film radiography of the lumbar spine, or magnetic resonance imaging when plain films are not diagnostic. Peripheral arthritis occurs in approximately 11% of patients with UC. Joint arthropathy may present with involvement of fewer than 5 asymmetrical large joints (eg, ankle, knee) associated with bowel disease activity (type 1 arthritis) or 5 or more bilateral symmetrical small joints (eg, hands) independent of bowel disease activity (type 2 arthritis). Ocular manifestations of UC occur in 2% of patients and may precede bowel inflammation. Painless red eye may be due to episcleritis; however, pain, impairment in vision, and/or headaches may indicate anterior uveitis, which is reported more commonly in women (2.8%) than in men (1.1%) with UC. Erythema nodosum and pyoderma gangrenosum both occur in approximately 1% of people with UC. **Erythema nodosum is characterized by raised, tender nodules occurring with bowel inflammation, whereas pyoderma gangrenosum is a deep skin ulceration independent of bowel disease. Primary sclerosing cholangitis (PSC) should be investigated in people with UC who have elevated liver enzymes because a meta-analysis of 43 studies (N = 566 178 patients with UC) estimated that approximately 2.5% of those with UC will be diagnosed with PSC.** Patients with a new diagnosis of PSC without a diagnosis of UC should be screened for asymptomatic UC with colonoscopy, as bowel inflammation may be subclinical.

Diagnosis of UC is based on a combination of gastrointestinal symptoms, biochemical markers, colonoscopy, and pathology. Blood work results may be normal, but with more severe disease activity, anemia, leukocytosis, thrombocytosis, and an elevated C-reactive protein level can be detected. **Stool biomarkers, such as calprotectin, a protein released by neutrophils, can distinguish UC from functional disorders such as irritable bowel syndrome. Fecal calprotectin has a sensitivity of 0.89 (95% CI, 0.86-0.91) and specificity of 0.81 (95%CI, 0.78-0.84) in differentiating IBD from non-IBD diagnoses when using a 50-µg/g cutoff. Less than 1% of individuals presenting with symptoms consistent with irritable bowel syndrome have IBD when the fecal calprotectin level is 40µg/g or less.**

Biopsy of inflamed mucosa demonstrates chronic architectural changes such as distorted crypts and branching glands. **Due to lack of a pathognomonic characteristic, the diagnosis of UC requires ruling out alternate causes of colitis** including infectious (e.g., salmonella, shigella); ischemic, though ischemic colitis rarely involves the rectum; radiation (e.g., treatment of prostate cancer); and medications (e.g., nonsteroidal anti-inflammatory drugs, checkpoint inhibitors). **Approximately 3% to 6% of adults diagnosed with UC have coexisting Clostridioides difficile. Thus, infectious stool studies are ordered as part of the diagnostic evaluation.**

Colonoscopy with inspection of the terminal ileum, pathology, and small bowel imaging (eg, intestinal ultrasound) can differentiate UC from Crohn disease. Serological testing is not recommended to differentiate UC from Crohn disease. When Crohn disease cannot be distinguished from UC, the diagnosis is IBD-unclassified.

Acute severe UC (ASUC) is the most severe form of UC and can be life threatening. Individuals with ASUC require hospitalization. Complications of ASUC include toxic megacolon, peritonitis/perforation, hemorrhage, venous thromboembolism, and secondary infections such as C difficile or cytomegalovirus for example. *C. difficile* is also diagnosed in approximately 3% of patients with ASUC.

The primary objectives of treatment are to maintain health-related quality of life and prevent complications such as colorectal cancer. Treatment goals include inducing clinical remission (ie, induction) and preventing future flares of disease activity (ie, maintenance). Drugs in different classes have been developed because a number of patients do not respond to drugs and/or lose response over time.

Treatment of mild to moderate disease activity is directed by disease location and activity. Induction of remission is typically attempted with 5-aminosalicylic acid (5-ASA) such as mesalamine. Topical 5-ASA is recommended for the induction of remission of isolated proctitis. Individuals with procto-sigmoiditis or more extensive forms of UC benefit from a combination of oral and topical 5-ASA therapy for induction of remission. Proctitis resistant to topical mesalamine may benefit from topical steroids to induce remission. Remission can be induced in mild to moderate active disease not responding to oral 5-ASA with colonic-release corticosteroids using once-daily budesonide, 9mg, multimatrix for 8 weeks.

Due to the absence of high-quality evidence, guidelines do not make recommendations for the use of probiotics, curcumin, or fecal microbial transplantation in the treatment of mild to moderate UC.

Individuals whose condition flares on steroid tapering or those needing more than a single course of systemic steroids per year are considered steroid dependent and should be considered for steroid-sparing agents such as thiopurines, biologics, or oral small molecules.

Once an individual with UC transitions to a state of clinical remission, primary care clinicians in partnership with gastroenterologists should focus on monitoring patient-reported outcomes, health maintenance, and surveillance for colorectal cancer. Clinicians should monitor bowel symptoms (eg, frequency and consistency of bowel movements, presence of blood, urgency, incontinence, and abdominal discomfort) and systemic symptoms (eg, fatigue and weakness). Individuals with UC reporting no symptoms with a fecal calprotectin level of less than 50 µg/g correlate (false-negative rate <5%) to a Mayo Endoscopic Score of 0 or 1 and thus do not require alteration in treatment. Patients reporting diarrhea and rectal bleeding with a fecal calprotectin level greater than 250 µg/g correlate (false-positive rate <5%) to a Mayo Endoscopic Score of 2 or 3 and thus may not require endoscopic confirmation of disease activity. Sigmoidoscopy or colonoscopy can assess disease activity in patients between these end points.

The first colonoscopy for surveillance of dysplasia should commence 8 to 10 years after diagnosis for those whose disease extends beyond the rectum; with a concomitant diagnosis of PSC, colonoscopy should be initiated regardless of disease duration. Following a negative surveillance colonoscopy, the next colonoscopy should be repeated 1 to 5 years later based on the presence of risk factors including disease extent, duration, and activity; cigarette smoking; PSC; family history of colorectal cancer; and prior dysplastic lesions.

Colectomy with permanent end ileostomy or intestinal pouch anal anastomosis (IPAA) are options for patients with UC who do not respond to medical management or experience a complication such as colorectal cancer.

Acceptable answers:

1. Erythema nodosum and pyoderma gangrenosum.
2. Primary sclerosing cholangitis.
3. Fecal Calprotectin and infectious stool studies including *C. difficile*.
4. Oral and/or topical 5-aminosalicylic acid.
5. 8 to 10 years after diagnosis for those whose disease extends beyond the rectum; (with a concomitant diagnosis of primary sclerosing cholangitis, colonoscopy should be initiated regardless of disease duration).

Reference: Gros B, Kaplan GG. Ulcerative Colitis in Adults: A Review. *JAMA*. 2023 Sep 12;330(10):951-965.
Link: https://jamanetwork.com/journals/jama/article-abstract/2809412
PMID: 37698559

Q12 Essential Tremor

A 72-year-old woman presents for a general checkup. She mentions that she is bothered increasingly by shaking of her right hand and her head. It interferes with her ability to eat, drink and write. She is concerned that she may have Parkinsons disease. You make a diagnosis of essential tremor which is considered an action tremor.

1. What are the 3 types of essential action tremor?

2. What other medical conditions should be considered when assessing tremor? List three.

3. First-line pharmaceutical treatment includes which medications? List two.

4. What treatment options can be considered if oral medications are not effective? List two.

Educational Point: Essential tremor (ET) presents with involuntary, rhythmic, oscillatory movements of a body part in motion (action tremor). ET is not associated with a shorter life expectancy, but may cause difficulty with activities of daily living such as eating, drinking, and writing, which can result in functional disability and cause social embarrassment. Patients with ET are at increased risk of being diagnosed with Parkinson disease. A study of 3813 individuals in Spain reported that 12 of 207 patients (5.8%) with ET developed Parkinson disease compared with 56 of 3606 controls (1.5%) after a median follow-up of 3.3 years. ET is one of the most common movement disorders worldwide and is estimated to affect approximately 7 million individuals in the US. ET is frequently diagnosed by primary care clinicians based on history and physical examination, which typically reveal upper extremity tremor but may also involve tremor of the head, jaw, neck, or voice.

Patients with ET have an action tremor, which occurs with any voluntary movement of the body and includes postural, kinetic, and intention tremors. Postural tremor can be assessed by having patients hold a position against gravity (such as outstretched arms). Finger-to-nose testing can identify kinetic tremor, which does not change throughout the phases of movement, and intention tremor, which increases as the target is reached. Individuals with ET rarely have a resting tremor, defined as a tremor in a fully supported unmoving body part, and, if present, it is suppressed by performing a mental task such as counting backward. In contrast, **a resting tremor is common in Parkinson disease and is accentuated with mental tasks.**

Masked facies, hypophonic speech bradykinesia, rigidity, and asymmetrical arm swing or stride length are also suggestive of Parkinson disease. Patients with any type

of tremor should be assessed for focal neurologic signs of weakness, reflex asymmetry, hemiataxia, and spasticity that may be caused by structural lesions from stroke, malignancy, posttraumatic brain injury, or demyelinating plaques (multiple sclerosis). When evaluating an individual with a tremor, clinicians should also assess for symptoms of hyperthyroidism (eg, palpitations, unintentional weight loss) and screen for use of medications or illicit drugs that may cause or worsen tremor, including antiepileptics (depakote valproic acid), neuroleptics, lithium, selective serotonin reuptake inhibitors, ß-agonists (albuterol), central nervous system stimulants (methylphenidate), and cocaine. Caffeine can increase tremor and alcohol typically decreases tremor in patients with ET.

There are no blood or urine tests that confirm the diagnosis of ET. Brain imaging (head computed tomographic imaging MRI) is not indicated in patients with isolated ET, but should be performed in patients with focal neurologic deficits to assess for a structural cause of tremors. Nonpharmacological therapies for ET include occupational therapy and adaptive devices (e.g. weighted or oscillating utensils, metal cups, wrist weights), which can help manage mild symptoms. Lifestyle modifications, including caffeine cessation and avoidance of alcohol overuse, can also decrease tremor. **First-line pharmacologic treatment includes propranolol and primidone, and propranolol is the only US Food and Drug Administration–approved treatment for ET. Use of propranolol decreased limb tremor in 50% to 70% of patients from 13 randomized clinical trials (255 patients). Primidone improved tremor severity, task performance, and activities of daily living in 8 randomized clinical trials that included 274 patients with ET.** The combination of propranolol and primidone may be more effective than either medication alone; however, 30% to 50% of patients with ET do not improve with these medications. Topiramate decreased tremor and improved activities of daily living in 3 of 4 randomized clinical trials of 322 patients with ET, although adverse effects such as difficulty concentrating, paresthesia, and nausea with doses greater than 200 mg per day often limit treatment adherence. **Botulinum toxin type A injection may be effective for ET that affects the voice, chin, and jaw. In addition, 3 randomized clinical trials that included 168 patients with ET refractory to oral medications reported that botulinum toxin injection into forearm or neck muscles decreased upper limb tremor but did not result in functional improvement and had no benefit for horizontal head tremor. Patients with ET who have severe symptoms that do not substantially improve with medications may be considered for stereotactic surgical procedures that target the thalamus.**

Acceptable answers:

1. Postural tremor, intention tremor, kinetic tremor
2. Stroke, malignancy, post traumatic brain injury, multiple sclerosis, hyperthyroidism, Parkinsons, medications, illicit drugs
3. Propanolol, primidone
4. Botulinum toxin, stereotactic surgical procedures that target the thalamus.

Reference: Elias WJ, Shah BB. Essential Tremor. *JAMA*. 2024 Aug 6;332(5):418-419.
Link: https://jamanetwork.com/journals/jama/fullarticle/2820853
PMID: 38976274

Q13 Obesity Management

Your next patient is a 38-year-old woman. After several years of struggling with obesity, she wishes to address this issue. The patient is healthy, with no known medical conditions.

You question your patient about her eating habits and physical activity. She has a very healthy lifestyle. You complete a physical examination. In addition to measuring the patient's body-mass index, you also measure the patient's waist circumference.

1. Why is a waist circumference measurement more accurate indicator of obesity than BMI?

Your physical examination confirms Class II obesity. You have eliminated secondary causes of obesity. The patient hesitates with starting a pharmacological treatment to help lose weight. She wishes to know more about obesity and its comorbidities in order to make an informed decision.

2. What are complications of obesity? List three.

You initiate semaglutide. She is very hopeful that she will lose at least twenty pounds.

3. After 12 weeks of a medication at a maximum tolerated dose, an alternative medication should be recommended if 10% of weight loss is not achieved. True or false?
   - ❍ True
   - ❍ False

The patient leaves your office with her prescription. Eventually, your patient loses 15 pounds and is satisfied with the results.

4. How can clinicians celebrate non-scale related weight loss benefits with patients? List three non-scale related weight loss benefits.

Educational Point: Obesity is a chronic, multifactorial condition that has genetic/epigenetic, metabolic, hormonal, cultural, socioeconomic, and neurobehavioral causes.

Obesity was recognized as a chronic disease by the American Medical Association in 2013 and contributes to several conditions, including hypertension, hyperlipidemia, type 2 diabetes mellitus, coronary artery disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, and cancers (e.g., endometrial, breast, prostate, colon).

Clinical guidelines recommend screening at least annually for obesity in all adults. Clinicians should always start by asking permission to discuss weight management with a patient before moving on to the next step, assessing readiness for change. Assessment involves evaluating a patient's readiness for change and includes the patient's history. Clinicians should then advise patients on the risks associated with excess weight and the benefits of modest weight loss. Patients and clinicians should use shared decision-making to agree on realistic treatment strategies and goals.

The family history should focus on obesity and related metabolic conditions. The social history should include tobacco, alcohol, and illicit drug use and the availability of social support. Clinicians should ask about previous treatment with anti-obesity medications. It is also important to review the patient's past and current medications to determine if prescribed weight-promoting medications may have contributed to the patient's weight gain.

The nutrition history should include questions about meal timing, content, portions, and preparation methods, which can help identify eating habits that might benefit from change. Consideration should also be given to performing appropriate screening for disordered eating such as binge-eating disorder, bulimia nervosa, or nighttime eating disorder.

Barriers to engaging in physical activity are common and unique to each patient. Clinicians should assess for physical limitations and mood disorders that may influence physical ability or motivation to exercise. Clinicians should also seek to better understand each patient's lifestyle or work schedule to identify barriers and develop appropriate strategies for increasing physical activity if needed.

While health care professionals are screening their patients for disordered eating and mood disorders, they should also evaluate them for learned eating behaviors. These include an individual's habitual patterns of food and beverage consumption. Clinicians should also evaluate patients for life stressors, emotional triggers, and associated reward responses to eating.

Following an examination of the patient's general physical health, their waist and neck circumference should be measured and their BMI should be calculated to quantify the degree of obesity. Physicians should measure waist circumference because central adiposity (35 inches or greater for women; 40 inches or greater for men) is related to an increased incidence of metabolic disease. **Waist circumference can be a more accurate indicator of obesity than BMI, particularly in older adults, because they can have a normal BMI due to decreased muscle mass (sarcopenia) and loss of bone density despite excess adipose tissue.** Physicians should measure neck circumference because an increased circumference is often found in patients with sleep apnea, which is associated with obesity.

During the initial evaluation, recommended laboratory studies include a complete blood count, comprehensive metabolic panel, lipid profile, and thyroid-stimulating hormone and A1C levels. These values can be used with additional testing to evaluate secondary causes of obesity and other risk stratification.

The Obesity Medicine Association recommends treatment that involves five pillars: (1) behavioral counseling, which can include motivational interviewing and referral to an intensive weight-management program, (2) nutrition counseling, including a focus on eating habits that might benefit from change, (3) increasing physical activity, including helping patients to address barriers, (4) pharmacotherapy, and (5) bariatric procedures, when appropriate. **Clinicians should celebrate weight loss with patients, but also non–scale-related benefits such as increased energy, having clothing fit better, improved sleep, increased physical activity, and the ability to reduce medication use.**

Pharmacologic treatments for obesity are indicated in conjunction with lifestyle measures. Pharmacotherapy should be offered to patients with a BMI of 30 kg per m^2 or greater and those with a BMI of 27 kg per m^2 or greater with any metabolic comorbidities (e.g., hypertension, type 2 diabetes, dyslipidemia). Pharmacologic therapies for obesity should not be used during pregnancy. **If 5% weight loss is not achieved after 12 weeks of a medication at a maximum tolerated dose, an alternative medication should be recommended.** Current guidelines do not specify which medications are indicated for first-line management of obesity. Pharmacotherapy should be individualized for each patient, considering factors including comorbidities, insurance coverage, and medication availability. Newer anti-obesity medications have variable insurance coverage and may be cost prohibitive.

Acceptable answers:

1. Waist circumference can be a more accurate indicator of obesity than BMI, particularly in older adults, because they can have a normal BMI due to decreased muscle mass (sarcopenia) and loss of bone density despite excess adipose tissue.
2. Hypertension
   Hyperlipidemia
   Type 2 diabetes mellitus
   Coronary artery disease
   Stroke
   Gallbladder disease
   Osteoarthritis
   Sleep apnea
   Cancers (e.g., endometrial, breast, prostate, colon).
3. False: If 5% weight loss is not achieved after 12 weeks of a medication at a maximum tolerated dose, an alternative medication should be recommended
4. Clinicians should celebrate weight loss with patients, but also non–scale-related benefits such as increased energy, having clothing fit better, improved sleep, increased physical activity, and the ability to reduce medication use.

Reference: Keating MK, Woodruff RK, Saner EM. Management of Obesity: Office-Based Strategies. *Am Fam Physician*. 2024 Aug;110(2):145-156.
Link: https://www.aafp.org/pubs/afp/issues/2024/0800/obesity-management.html
PMID: 39172672

Q14 Mastitis

A 33-year-old mother has an erythematous, focally tender, and indurated segment in her left breast. She is breastfeeding her newborn infant and is also experiencing fatigue, fever, body aches, and headache. You suspect that she has lactational mastitis.

1. When does lactational mastitis occur in the postpartum period?

2. What are the risk factors for developing lactational mastitis? List three.

3. Laboratory tests, including white blood cell count, white blood cell differential, and C-reactive protein, are useful for diagnosis.
   - ❍ True
   - ❍ False

4. What are the new recommended lifestyle and behavior interventions that can be done to manage lactational mastitis? List three.

5. Conservative therapy may be used initially, and if symptoms have not improved within 24 to 48 hours or are worsening, antibiotics may be considered.
   - ❍ True
   - ❍ False

6. What is the recurrence rate for lactational mastitis?

Educational Point: Mastitis can occur in lactating and nonlactating individuals, but lactational mastitis is the most common, with an incidence of 2% to 33% worldwide and approximately 10% in the United States. The wide range of incidence is due to differences in the definition of mastitis, which can impact the frequency of reporting, level of breastfeeding support, and rates of mastitis across different populations worldwide. Low socioeconomic status and lack of studies in low-resource settings also play a role. **Lactational mastitis may occur within the first 2 to 3 weeks postpartum; however, 75% to 95% of patients will present within the first 3 months postpartum.**

Risk factors for developing lactational mastitis include over-stimulation of milk production (from hyperlactation or excessive pumping) and recent antibiotic use that may disrupt the normal balance of bacterial flora. Hyperlactation is less likely to occur when the infant is fed directly from the

breast compared with pumping. **Other factors that may contribute to the development of lactational mastitis include the use of nipple shields; poor infant latch (e.g., due to a cleft lip and palate or ankyloglossia [tongue-tie]) that results in inadequate feeding technique and possible nipple trauma; wearing tightly fitted clothing or bras; history of mastitis; primiparity; poor maternal nutrition; and tissue trauma from aggressive breast massage.** Milk stasis (i.e., lack of milk flow that results in the buildup of milk in the breast) and occasional missed feedings were previously identified as risk factors for lactational mastitis but are no longer thought to be as strongly correlated. There is also no good evidence for yeast as a causative organism. Nonlactational mastitis is rare and more often associated with immunosuppressive conditions and Hispanic ethnicity. It is also linked to a possible increased risk of breast cancer.

Few trials have examined mastitis prevention strategies. Based on expert opinion, it is thought that optimizing infant latch and feeding the infant from the breast may prevent mastitis. This can be accomplished by working with a lactation consultant. Most cases of mastitis are caused by hyperlactation or oversupply, which is often associated with excessive pumping. Experts suggest encouraging patients to get enough sleep, use stress reduction techniques, consume an adequate amount of fluids, and wear loose fitting clothing and bras. In cases of subacute mastitis, an observational study found that an anti-inflammatory plant- and oil-based diet rich in antioxidants, minerals, and vitamins, such as the Mediterranean diet, may be beneficial to help prevent the progression to fulminant mastitis. Whenever possible, physiologic feeding (i.e., feeding the infant from the breast rather than pumping) should be used because it discourages hyperlactation and disrupted mammary bacterial balance. Pumping should be reserved for times when the mother is separated from the infant, and the volume of milk removal should be limited to only what the baby would consume.

With the exception of postpartum engorgement, which is most often bilateral and non-segmental and encompasses the entirety of each breast, patients typically present with an erythematous or hyperpigmented, focally tender, indurated segment in a unilateral breast. Some patients may also experience systemic symptoms including fatigue, fever greater than 38.3°C (100.9°F), malaise, body aches, headache, and flulike symptoms.

Diagnosis is clinical and laboratory tests and imaging are not needed except in patients with severe disease or those who are immunocompromised. **Laboratory tests, including white blood cell count, white blood cell differential, and C-reactive protein, are rarely useful because leukocytosis and elevated C-reactive protein levels occur almost universally in patients with conditions on the mastitis spectrum, and they do not differentiate a systemic inflammatory response from a bacterial infection.** Common pathogenic organisms in bacterial mastitis include *Staphylococcus* (e.g., *S. aureus*, *S. epidermidis*, *S. lugdunensis*, *S. hominis*) and *Streptococcus* (e.g., *S. mitis*, *S. salivarius*, *S. pyogenes*, *S. agalactiae*), which are part of the usual skin flora. Milk cultures are rarely needed. False-positive cultures are common due to normal bacterial colonization, and negative cultures do not definitively rule out bacterial mastitis. Consider ultrasonography of the breast if the condition does not improve as expected, within 48 hours, or if there is a high suspicion for abscess.

In 2022, based on expert opinion, the Academy of Breastfeeding Medicine updated their recommendations for the management of mastitis spectrum disorders after several traditional treatment methods were found to worsen the condition by increasing underlying inflammation and decreasing feedback inhibition. These treatments include heat application, breast massage or vibration, and frequent, complete emptying of the breast, especially if using a breast pump.

New recommendations for treatment emphasize ice or cold application to vasoconstrict the blood vessels and the use of oral nonsteroidal anti-inflammatory drugs. For most patients, continuing to feed the infant directly from the breast should be encouraged, but pumping should be limited or stopped until symptom resolution. Complete breast rest for 24 to 48 hours should be recommended only if the area around the areola is so edematous that no appreciable milk can be expressed because continued stimulation of the area will worsen the problem. Patients should be counseled to expect a drop in milk supply on the affected side, but that it can be recovered at a later time by increasing milk removal from the breast after the inflammation has subsided.

Because hyperlactation or oversupply is the underlying etiologic factor in most instances of lactational mastitis, patients should be counseled on pump overuse. Use of nipple shields should be avoided. When possible, physiologic breastfeeding without pumping is optimal. If engorgement is present, lymphatic drainage maneuvers and reverse pressure softening may be used to reduce nipple and areolar swelling and to help with infant latch. Block feeding for 24 to 48 hours should be considered to decrease oversupply. This involves feeding only from one breast for a discrete period to allow the engorged breast to get the signal to make less milk.

For nonlactational mastitis, conservative treatment (e.g., nonsteroidal anti-inflammatory drugs, ice) should be emphasized and may be adequate treatment alone; however, there is a lower threshold for antibiotic treatment, incision and drainage, and imaging, with possible tissue biopsy to rule out malignancy. Systemic steroids may also be prescribed.

Not all episodes of mastitis warrant the use of antibiotics. Patients may have fever and other systemic symptoms from the inflammatory response that is seen almost universally across the mastitis spectrum, and this does not always signify infection. **Conservative therapy may be used initially, and if symptoms have not improved within 24 to 48 hours or are worsening, antibiotics may be considered.**

Narrow-spectrum antibiotics are the preferred treatment for bacterial mastitis and should be targeted to the most common organisms of usual skin flora, *Staphylococcus* and *Streptococcus*. Antibiotics in the macrolide class may be the most effective (intracellular mechanism of action) for subacute mastitis.

If a multidrug-resistant organism is suspected or the patient has hemodynamic instability, hospital admission for intravenous antibiotics may be required. Patients with breast abscesses should always be referred to a breast surgeon for drain placement. For recurrences of mastitis in the same location, imaging should be obtained to rule out structural abnormality, an underlying mass, granulomatous mastitis, or inflammatory breast cancer.

Prognosis is good for lactational mastitis, but it has an 8% to 30% recurrence rate. Breast abscess is the most concerning complication of mastitis and occurs in approximately 3% to 11% of patients with acute mastitis; milk fistulas occur in less than 2% of patients. Interruption of breastfeeding during acute mastitis, including when an abscess is present or being treated with antibiotics, is not warranted and may impede long-term feeding goals.

Acceptable answers:

1. Lactational mastitis may occur within the first 2 to 3 weeks postpartum; however, 75% to 95% of patients will present within the first 3 months postpartum.
2. Overstimulation of milk production (from hyperlactation or excessive pumping), recent antibiotic use, the use of nipple shields, poor infant latch, wearing tightly fitted clothing or bras, history of mastitis, primiparity, poor maternal nutrition, and tissue trauma from aggressive breast massage.
3. False
4. Ice or cold application, oral nonsteroidal anti-inflammatory drugs, complete breast rest for 24 to 48 hours especially if the area around the areola is edematous, avoiding pump overuse, avoiding the use of nipple shields, lymphatic drainage maneuvers and reverse pressure softening may improve infant latch. Block feeding for 24 to 48 hours should be considered to decrease oversupply. Complete breast rest for 24 to 48 hours should be recommended only if the area around the areola is so edematous that no appreciable milk can be expressed because continued stimulation of the area will worsen the problem.
5. True
6. 8 to 30%

Reference: Morcomb EF, Dargel CM, Anderson SA. Mastitis: Rapid Evidence Review. *Am Fam Physician*. 2024;110(2):174-182.
Link: https://www.aafp.org/pubs/afp/issues/2024/0800/mastitis.html
PMID: 39172675

Q15 Pruritus in Pregnancy

A 28-year-old pregnant G1P0 patient at 31-weeks of gestation attends your office and describes two weeks of palm and sole pruritus. The patient notes that the pruritus is worse at night. Further history-taking does not reveal any other significant symptoms. The patient's past medical history and antepartum course have been uncomplicated. Physical examination does not reveal any dermatologic findings save excoriations. You suspect a disease unique to pregnancy.

1. What is your presumptive diagnosis?

2. Which laboratory test can confirm the diagnosis?

The laboratory test result confirms the diagnosis.

3. What is the mainstay of symptomatic treatment for this patient's pruritus?

4. Does this treatment reduce the risk of stillbirth?

Using the patient's laboratory results as a guide for timing delivery, you arrange for the patient to undergo an induction of labour at an appropriate gestational age. An uneventful spontaneous vaginal delivery ensues.

At a six-week postpartum follow-up appointment with you, your patient confirms resolution of their pruritus. You counsel them about the risk of future diagnoses.

5. Due to the gestational diagnosis aforementioned, for which future diagnoses is this patient at elevated risk? List three.

6. Genetic testing should be considered for this patient.
   - ❍ True
   - ❍ False

Your patient enquires about hormonal contraception options at this postpartum appointment.

7. Progestin-only contraceptives are associated with the lowest risk of recurrence of this diagnosis in a non-gestational state.
   - ❍ True
   - ❍ False

Educational Point: Intrahepatic cholestasis of pregnancy (ICP) is the most common hepatic disease unique to pregnancy, with wide-ranging incidence from 0.1% to >27% in certain populations. This multifactorial disease manifests in the late-second or third trimesters of pregnancy. The most common presenting symptom of ICP is pruritis of the palms of the hands and soles of the feet that is often reported as worse at nighttime. Pruritis usually occurs in the latter half of the second trimester or early in the third trimester and may appear 3-4 weeks prior to any abnormal laboratory findings. Other uncommon symptoms could include nausea, fatigue, abdominal pain, pale stool or steatorrhea, dark urine, and malaise; however, systemic complaints are atypical and would indicate the need for further evaluation for other differential diagnoses. There are no primary dermatological lesions associated with ICP; however, secondary excoriations and prurigo nodules resulting from scratching by the patient are common. Jaundice may be present in up to 10%-15% of patients with ICP, with an onset of approximately 3-4 weeks after pruritis occurs. Elevation of serum bile acids is the most common laboratory abnormality in ICP. Although serum bile acids may be normal at first presentation with pruritus, subsequent elevations are common, justifying ongoing surveillance. Other common laboratory abnormalities include elevated serum aminotransferases (alanine aminotransferase / aspartate aminotransferase). Gamma-glutamyl transferase may be normal or moderately elevated. **Once ICP is suspected in a pregnant person with pruritus (particularly of the hands and feet) in the second or third trimester, diagnosis is confirmed by an elevation of total serum bile acids with or without an elevation in liver transaminases.**

Bile acids are produced in the liver in a highly regulated manner due to their cytotoxicity, and pregnancy is believed to have a cholestatic effect. Bile acids within the fetal compartment result from fetal production, which starts as early as 12 weeks gestation, as well as from transplacental transfer. Pregnancies without a diagnosis of ICP have a fetal to maternal gradient to facilitate clearance of bile acids and protect the fetus from their cytotoxic effects. In ICP, a significant increase of maternal bile acid reverses this gradient, resulting in accumulation within the fetal compartment.

The perinatal sequelae of intrahepatic cholestasis of pregnancy includes increased risks of preeclampsia, gestational diabetes, preterm birth, neonatal respiratory distress, and neonatal intensive care unit admission. Patients with intrahepatic cholestasis and bile acids 100 mmol/L have a significantly increased risk of stillbirth compared with the general population. The goal of treating ICP has two aims: to ameliorate maternal symptomatology of pruritus and to improve fetal outcomes. **The mainstay of symptomatic treatment of pruritus is with ursodeoxycholic acid (10-15 mg/kg/d), given daily in 2-3 divided doses, which may also reduce the risk of preterm birth, but not stillbirth.** Other therapies that may be used for pruritic relief include topical emollients and antihistamines, such as hydroxyzine; these are safe in pregnancy; however, they have not been specifically evaluated for efficacy in the treatment of ICP.

Symptoms as well as ICP-associated biochemical abnormalities are expected to resolve within 1-2 weeks postpartum, although they may persist up to 4 weeks in some individuals. It is important to confirm resolution of symptoms at a follow-up visit around 6 weeks postpartum and repeat bile acid and liver transaminase testing for those whose symptoms persist. The postpartum encounter also provides an opportunity to discuss the risk of ICP in family members, particularly female siblings. **If ICP has developed before 32 weeks gestation, there is a 20% chance that the patient has a pathologic genetic variant in the *ABCB11/ABCB4* genes.** These genes have been associated with other forms of hepatobiliary disease including benign recurrent hepatic cholestasis and cholelithiasis. **In these individuals, consultation with a specialist in clinical genetics, internal medicine, or maternal-fetal medicine is recommended for consideration of genetic testing.**

Individuals who have been diagnosed with intrahepatic cholestasis are at increased risk of future cholecystitis, cholelithiasis, pancreatic disease, goiter, and hypothyroidism. The increased likelihood of hepatobiliary disease may, in part, be secondary to shared genetic risk factors. **Overall, the recurrence risk of ICP in future pregnancies is around 70%, and up to 90%, if genetic predispositions are present.**

Individuals with prior ICP should also be advised that they are at risk of non-pregnant cholestasis with use of combined hormonal contraception, and that this risk can be reduced using lower dose estrogen formulations. **In patients with a history of intrahepatic cholestasis of pregnancy choosing hormonal contraception, progestin-only options are associated with the lowest risk of non-pregnant cholestasis.**

Acceptable answers:

1. Intrahepatic cholestasis of pregnancy
2. Serum bile acid level
3. Ursodeoxycholic acid
4. No
5. Recurrence of intrahepatic cholestasis of pregnancy in future pregnancies, cholecystitis, cholelithiasis, pancreatic disease, goiter, and hypothyroidism.
6. True
7. True

Reference: Hobson SR, Cohen ER, Gandhi S, Jain V, Niles KM, Roy-Lacroix MÈ, et al. Guideline No. 452: Diagnosis and Management of Intrahepatic Cholestasis of Pregnancy. *J Obstet Gynaecol Can*. 2024 Aug;46(8):102618.
Link: https://www.jogc.com/article/S1701-2163(24)00441-9/abstract
PMID: 39089469

Q16 Chronic Urticaria

A 34-year-old patient presents to your office with a 3 month history of "hives". There is a history of asthma but there are otherwise no medical concerns. After examination you diagnose chronic urticaria.

1. How long must urticaria persist to be termed chronic?

2. Type 2 chronic inflammatory diseases such as asthma, allergic rhinitis, and atopic dermatitis are present in about 25% of patients with chronic urticaria.
   - ❍ True
   - ❍ False

You wonder about chronic inducible urticaria and ask about triggers.

3. List five forms of chronic inducible urticaria.

4. The mainstay of management of chronic inducible urticaria is identification and avoidance of triggers.
   - ❍ True
   - ❍ False

After performing history and physical, you do not identify any forms of chronic inducible urticaria and you diagnose chronic spontaneous urticaria.

5. What are the two subtypes of chronic spontaneous urticaria?

The patient has tried several second generation antihistamines at standard dosages with minimal effect. You discuss the possibility of off label use of increased dosages.

6. What is the recommended maximum to which the standard dose can be increased?

There is no response to increasing second generation antihistamine. The patient is frustrated and wonders if the symptoms will persist forever.

7. About 50% of patients with chronic urticaria experience spontaneous remission within 5 years.
   - ❍ True
   - ❍ False

You order some laboratory tests and her total IgE level is quite elevated.

8. What treatment is associated with early and complete response in this clinical scenario?

Educational Point: Chronic urticaria is a prevalent skin disease lasting more than 6 weeks, characterised by the development of wheals, angio-oedema, or both. Activation of skin mast cells with release of histamine and other mediators leads to wheals and angio-oedema. Chronic urticaria is spontaneous (ie, chronic spontaneous urticaria) if symptoms appear in the absence of specific triggers, and inducible (ie, chronic inducible urticaria) if it is elicited reproducibly by specific stimuli. **Nine chronic inducible urticaria forms exist, including symptomatic dermographism, cold, cholinergic, delayed pressure, solar, heat, aquagenic, contact urticaria, and vibratory angio-oedema;** these forms are listed in reducing frequency. Chronic urticaria is a debilitating disease associated with autoimmune and psychiatric comorbidities, high economic costs, and consequences on patient quality of life and performance at work and school. **Spontaneous remission is seen within 5 years in around 50% of patients with chronic urticaria, with many needing long-term treatment.**

Chronic urticaria treatment remains a challenge, with several patient-reported outcome measures used to assess disease activity, impact, and control. At least a quarter of patients with chronic urticaria have uncontrolled disease despite up-dosing of second-generation antihistamines; 296 (32%) of 921 second-generation antihistamine non-responders or partial responders are also non-responders or partial responders to omalizumab. This finding is, in part, due to the heterogeneity of chronic urticaria pathophysiology, resulting in distinct endotypes. Treatments that prevent, delay, or slow the progression of chronic urticaria and induce disease remission are needed.

Several initiatives, including the current international guidelines for the management of urticaria published in 2022, and other guidelines published between 2020 and 2024, address these challenges. **The international guideline treatment algorithm recommends first-line second-generation antihistamines, with dosage ranging from the approved dose to four-fold up-dosing (off-label),** followed by omalizumab (monoclonal anti-IgE) and ciclosporin (immunosuppressive), in alignment with French and South Korean guidelines. However, differences between guidelines exist, for example the UK and Australian–New Zealand guidelines recommend prescribing montelukast before omalizumab.

Several drugs have been used with varied success for chronic urticaria over the last three decades, especially before the licensing of omalizumab. These include H2-antihistamines, montelukast, azathioprine, dapsone, doxepin, and methotrexate; however, there is little high-quality evidence for their use in urticaria. These drugs are available worldwide and are relatively cheap with long-term experience of use in other dermatological disorders. They can be useful when there are financial or other limitations for the recommended management algorithm or if patients do not respond to urticaria guideline-recommended treatments

Type 2 chronic inflammatory diseases, such as allergic rhinitis, atopic dermatitis, and asthma, are present in up to 20–30% of patients with chronic urticaria. Type 2 comorbidities might favour therapies that manage the symptoms of both chronic spontaneous urticaria and other type 2 chronic inflammatory diseases. For example, omalizumab is also approved in asthma, food allergy, and chronic rhinosinusitis with nasal polyps and can therefore provide additional benefit in patients with chronic urticaria with these comorbidities.

Chronic spontaneous urticaria pathogenesis is complex with interplay between autoimmunity, complement, coagulation, and inflammation. **Two chronic spontaneous urticaria endotypes are emerging, both of which are mediated by mast cell-activating autoantibodies: autoimmune chronic spontaneous urticaria (also known as type IIb autoimmunity) mediated by IgG autoantibodies; and autoallergic chronic spontaneous urticaria mediated by IgE autoantibodies.** Autoimmune chronic spontaneous urticaria is present in 8–40% of patients with chronic spontaneous urticaria

and is linked to high disease activity, autoimmune comorbidities (eg, autoimmune thyroid disease), no, partial, or slow response to second-generation antihistamines and omalizumab, and a good response to ciclosporin. Autoallergic chronic spontaneous urticaria is present in over 50% of patients with chronic spontaneous urticaria.

Several autoimmune chronic spontaneous urticaria markers associated with no or slow response to omalizumab have been reported, including a positive autologous serum skin test, low serum total IgE, low FcεRI expression on basophils, eosinopenia, and a positive basophil activation test or basophil histamine release assay. By contrast, **high serum concentrations of total IgE were associated with a complete response and early response to treatment with omalizumab.** The predictive values, sensitivity, and specificity of available biomarkers to predict autoimmune chronic spontaneous urticaria diagnosis and to differentiate from autoallergic chronic spontaneous urticaria need further study.

The landscape of urticaria drugs is evolving rapidly. The years ahead will undoubtedly present major advancements in chronic urticaria therapy as novel small molecules and biologics become available, with some of the current unresolved needs being addressed. The use of emerging targeted treatments for chronic urticaria will lead to a personalised therapeutic approach for patients and support endotype characterisation and biomarker development with the final goal of disease modification and remission. Furthermore, their use can improve understanding of disease mechanisms, including the pathophysiological roles of mast cells, basophils, B cells, and other inflammatory cells in urticaria.

Acceptable answers:

1. Six weeks
2. True
3. Symptomatic dermographism, cold, cholinergic, delayed pressure, solar, heat, aquagenic, contact urticaria, and vibratory angio-oedema
4. True
5. Autoimmune chronic spontaneous urticaria (also known as type IIb autoimmunity) and autoallergic chronic spontaneous urticaria.
6. Four-fold increase above standard dosages
7. True
8. Omalizumab

Reference: Chronic urticaria: unmet needs, emerging drugs, and new perspectives on personalised treatment Torsten Zuberbier et al. *Lancet*, The, 2024-07-27, Volume 404, Issue 10450, Pages 393-404.
Link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)00852-3/fulltext
PMID: 39004090

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