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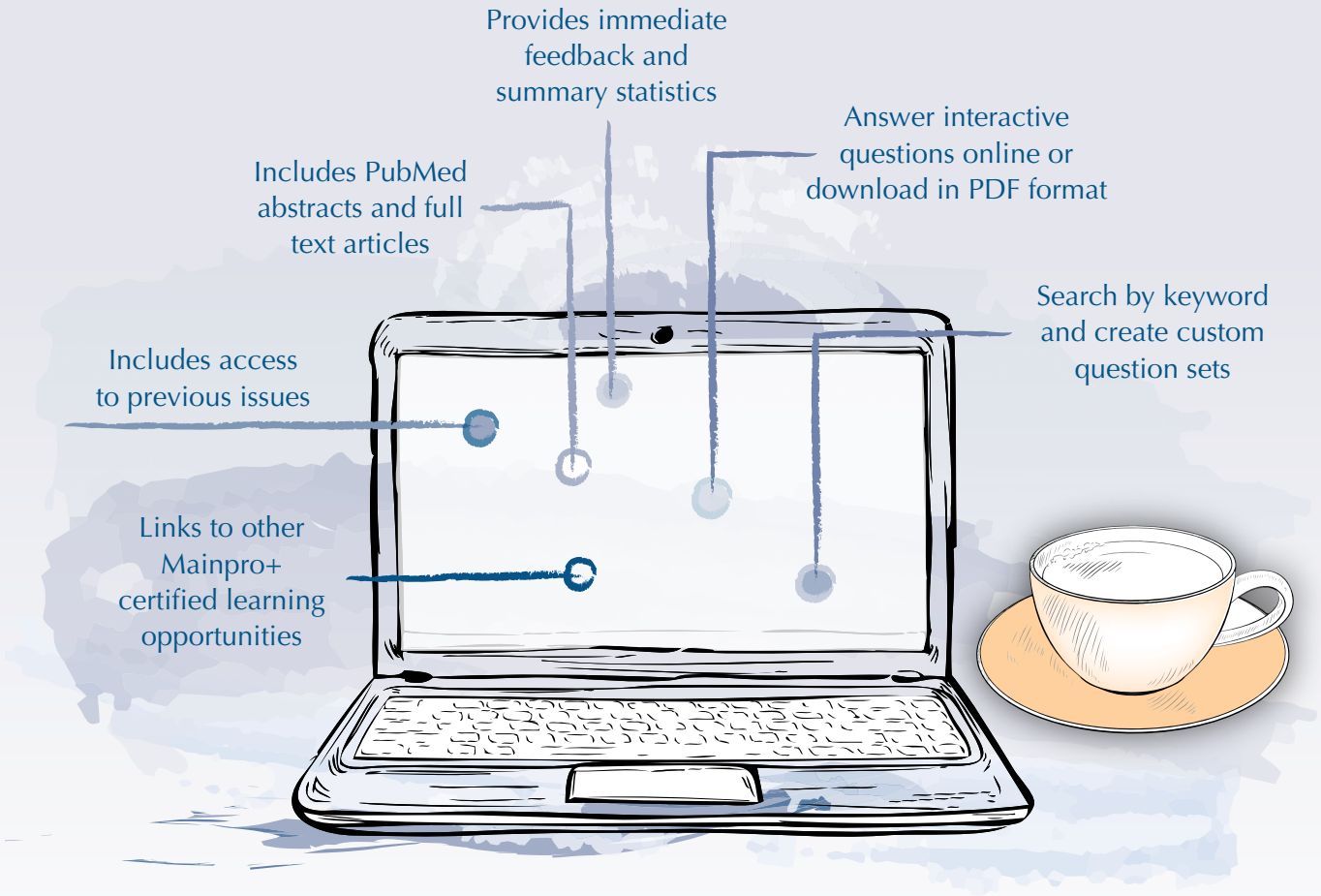

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Welcome to Self Learning™

The Self Learning Committee has created this special edition of the Self Learning Program as an educational resource available at no cost to CFPC members. We hope it serves to update you on the latest medical evidence, while introducing you to all that the Self Learning Program has to offer. Self Learning is an innovative educational program from the College of Family Physicians of Canada (CFPC). It offers subscribers the opportunity to learn any time, anywhere, with a focus on information that is timely and relevant to family medicine. Each issue contains clinical questions based on recent articles from a wide variety of peer-reviewed journals. The questions are developed by more than 50 family physician volunteers. This edition contains questions drawn from recent issues of Self Learning. 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. You are encouraged to apply the same critical appraisal to articles featured in the program as you would when reading articles in any medical journal. 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.

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*see page iv for Topics & Conflict of Interest Disclosures.
All others have no conflicts of interests to declare.

Instructions

Each question requires a selection of one best answer from either three or four possible choices, or a choice of true or false.

Educational Points and References. The specific justification for each distractor is highlighted in each Educational Point.

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Medical Journals Used

The Self Learning Program gives you access to cutting-edge information curated from more than 100 peer-reviewed medical journals worldwide.

Frequently Used Abbreviations

AIDS = acquired immune deficiency syndrome
ACE = angiotensin-converting enzyme
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
HIV = human immunodeficiency virus
HPV = human papilloma virus
HR = hazard ratio
ICU = intensive care unit
IM = intramuscularI
LFTs = liver function tests
QR = interquartile range
MRI = magnetic resonance imaging
NNH = number needed to harm
NPV = negative predictive value
NNT = number needed to treat
NSAID = non-steroidal anti-inflammatory drugs
OR = odds ratio
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
SNRI = serotonin-norepinephrine reuptake inhibitor
SSRI = selective serotonin reuptake inhibitor
STI = sexually transmitted infection
UTI = urinary tract infection
WHO = World Health Organization

Topics

This volume covers the following topics:

- Addiction Medicine
- Allergy & Immunology
- Cardiology
- Dermatology
- Diagnostic/Imaging/Laboratory
- Emergency Medicine
- Endocrinology & Metabolic
- Genetics
- Geriatrics
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- Ophthalmology
- Pediatrics
- Pharmacology & Therapeutics
- Preventive Medicine & Education
- Rheumatology
- Sexual Medicine
- Trauma
- Urology
- Women's Health

Conflict of Interest Disclosures

Name	Details
Dr. Diane Edmonds	I was an investigator in the intervention arm of the IMPACT-AF clinical trial to test web-based clinical decision support systems based on Canadian atrial fibrillation guidelines.
Dr. Grace Frankel	I will be receiving an honorarium as a book reviewer for Elsevier Canada.
Dr. Sarah Lespérance	I am the recipient of research grants from the Newfoundland and Labrador Medical Association and the College of Family Physicians of Canada.

Questions

Q1 COVID Croup

There is compelling evidence to support the hypothesis that the omicron variant causes laryngotracheobronchitis.

❍ 1. True
❍ 2. False

Educational Point: As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved, so has its effects on the pediatric population. Although early variants typically resulted in lower respiratory infections, the recently identified omicron variant may exhibit a predilection for the upper airways. The relatively smaller upper respiratory tract in children compared to adults has been thought to predispose them to more severe clinical presentations resembling laryngotracheobronchitis, or croup. Caused by viral-induced subglottic airway inflammation, croup is classically characterized by sudden onset "barking cough," inspiratory stridor, and respiratory distress. Endemic coronaviruses have been linked to croup; however, only sparse case reports have described croup specifically associated with SARS-CoV-2, and it remains unclear if croup cases constitute a causative relationship or result of coinfection with another virus. To address this knowledge gap, the authors performed a retrospective analysis of the incidence and clinical characteristics of croup associated with SARS-CoV-2 infection at a large freestanding children's hospital.

A retrospective analysis of a freestanding children's hospital found that the incidence of croup co-occurring with SARS-CoV-2 infection sharply increased in December 2021, strongly correlating with emergence of the omicron variant. Other spikes in COVID-19 were not associated with increased diagnoses of croup. Interestingly, the observed rates of hospitalization and redosing of croup-directed therapies may indicate a more severe phenotype compared to other viral etiologies. **Taken together; the authors' preliminary findings lend compelling evidence to the hypothesis that the omicron variant causes laryngotracheobronchitis.** This tropism shift may stem from differences in protein expression between cells of the lower respiratory versus upper respiratory tract, although variant-specific mechanistic studies remain an active research area.

Between March 1, 2020 and January 15, 2022, a total of 75 children were diagnosed with COVID-19–associated croup, 81% of whom presented during the omicron period. There was a significant difference in median weekly cases between the pre-omicron (0 [interquartile range (IQR) 0–0]) and omicron periods (11 [IQR 2–17]) ($P < .001$). Most patients were male (72%) and discharged from the emergency department (88%). All children tested for other viral infections were negative except for one with rhinovirus. Dexamethasone was administered to 97% of patients. Whereas 100% of hospitalized patients received racemic epinephrine, it was given to only 25% of patients treated in the emergency department. Among hospitalized patients, the median length of stay was 1.7 days (IQR 1.3–2.3 days), and the median number of dexamethasone and racemic epinephrine doses was 6 (IQR 4–9) and 8 (IQR 2–10), respectively. Four patients required intensive care, with one escalating to helium-oxygen mixture and continuous positive airway pressure. No patients required invasive ventilation or died.

Two years into the COVID-19 pandemic, the pathogenicity, infectivity, and manifestations of new variants of SARS-CoV-2 have been dynamic and unique. Croup may represent yet another such novel presentation. Further research is needed to characterize the underlying mechanisms of COVID-19–associated croup, differences in clinical features from other viral etiologies, and appropriate management strategies in the SARS-CoV-2 era.

The correct answer is 1.

Reference: Brewster RC, Parsons C, Laird-Gion J, Hilker S, Irwin M, Sommerschield A, et al. COVID-19-Associated Croup in Children. *Pediatrics*. 2022 Jun 1;149(6):e2022056492.

Available from: https://publications.aap.org/pediatrics/article/149/6/e2022056492/185378/COVID-19-Associated-Croup-in-Children?autologincheck=redirected

PMID: 35257175

Q2 Tdap in Pregnancy

Which *one* of the following statements is *true* regarding tetanus, diphtheria, and acellular pertussis (Tdap) vaccination during pregnancy?

- ❍ 1. Maternal vaccination with Tdap does not affect the incidence of pertussis in infants.
- ❍ 2. The National Advisory Committee on Immunization recommends that Tdap be administered in every pregnancy in Canada, regardless of preconception vaccination status.
- ❍ 3. The majority of pregnant patients receive Tdap vaccination during their pregnancy.
- ❍ 4. The primary reason for pregnant patients' nonvaccination is not wanting to be vaccinated during pregnancy.

Educational Point: Despite widespread vaccination, pertussis remains endemic in Canada, with incidence rates highest for infants aged <1 year: 72.5 per 100 000 population from 2013 to 2017. The 4 pertussis-related deaths reported in Canada during this period occurred in infants aged <6 months. Vaccination with the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine during pregnancy induces the production of antibodies that are transferred through the placenta to the foetus and persist in infants up to 2 – 4 months of age. **Maternal vaccination with Tdap has been shown to significantly reduce the incidence of pertussis in infants' first 2 months of life, with administration of the vaccine during the third trimester of pregnancy being significantly more effective than vaccination during the second trimester.** Tdap vaccination during the second or third trimester of pregnancy is not associated with any adverse pregnancy or birth outcomes.

For these reasons, the National Advisory Committee on Immunization recommended in February 2018 that Tdap be administered in every pregnancy in Canada, ideally between 27 and 32 weeks of gestation. In March 2018, the Society of Obstetricians and Gynaecologists of Canada issued a new clinical practice guideline on immunization in pregnancy that included a recommendation that every pregnant woman be offered Tdap, ideally between 21 and 32 weeks. This study was undertaken to measure the uptake of pertussis vaccination during pregnancy in Canada and to identify sociodemographic factors associated with nonvaccination. A sample of babies born between September 2, 2018, and March 1, 2019, was selected randomly from the list of children for whom the Canadian Child Benefit was claimed, which was estimated to include 96% of Canadian children in 2018. Data were collected from December 2, 2019, to March 6, 2020 (i.e., 9–18 months after the selected child was born). The biological mothers of these children were contacted and invited to participate in the survey, provided they had lived in Canada for most of their pregnancy. Of 9096 child/mother pairs selected from the sampling frame, 5091 completed the survey, yielding a response rate of **58.9% after removing out of scope cases. Of the mothers who participated in the survey, 39% reported having been vaccinated against pertussis during their pregnancy, 51% had not been vaccinated, and 10% did not know.** There were no significant differences among women who had received maternity care from obstetrician/gynaecologists, family doctors, nurses, or midwives with respect to advice to get vaccinated for pertussis during pregnancy. **The main reasons given by mothers for nonvaccination were not being aware that pertussis vaccination was recommended during pregnancy (60%), not wanting to be vaccinated during pregnancy (16%), and the vaccine not being offered by their maternity care provider (11%).**

More women were advised to get vaccinated in provinces or territories where Tdap was provided free of charge to pregnant women (68%) than in provinces and territories where vaccination was not funded (52%). The rate of nonvaccination was significantly higher in provinces and territories where the vaccine was not offered free of charge

(61%) than in those where it was publicly funded (46%). Other factors significantly associated with nonvaccination in simple logistic regression analyses were being born outside of Canada; lower education; lower household income; having had previous pregnancies; having had previous live births; having received maternity care from an obstetrician/gynaecologist or a midwife or having no professional care at all (compared with a family doctor); and not having been advised to get the vaccine. Being advised by the primary maternity care provider was found to be the main driver of maternal vaccination. Consistent with that observation, being unaware that pertussis vaccination during pregnancy was recommended was the number one reason mothers gave for not being vaccinated.

The correct answer is 2.

Reference: Gilbert NL, Guay M, Kokaua J, Lévesque I, Castillo E, Poliquin V. Pertussis Vaccination in Canadian Pregnant Women, 2018-2019. *J Obstet Gynaecol Can*. 2022 Jul;44(7):762-768.

Available from: https://www.jogc.com/article/S1701-2163(22)00057-3/fulltext

PMID: 35151906

Q3 Monoclonal Antibody Biologics in Pregnancy

Which *one* of the following statements about the use of monoclonal antibody biologics during pregnancy is *false*?

- ❍ 1. Most monoclonal antibody biologics readily cross the placenta.
- ❍ 2. Insufficient evidence exists to support the routine use of biologics other than anti-tumour necrosis factors (TNF) agents during pregnancy.
- ❍ 3. Maternal use of anti-TNFs is a contraindication to breast feeding.
- ❍ 4. All infants exposed to biologics during pregnancy should receive inactivated immunizations according to the routine schedule.

Educational Point: Monoclonal antibody biologics, also known as biologics, have revolutionized the treatment and quality of life of many patients with inflammatory and autoimmune conditions. Women of reproductive age are increasingly using these agents to maintain disease remission because of emerging evidence of safety before conception, during pregnancy and lactation.

Most monoclonal antibody biologics readily cross the placenta, leading to concerns regarding their use during pregnancy and their impact on the fetus and infant. However, the last decade has seen a shift in disease management toward tight disease control in pregnant patients and a goal of improving both maternal and fetal outcomes. Achieving clinical remission is recognized as one of the best predictors of favourable pregnancy outcomes, and a stable disease course, especially in the 6 months before conception, has been associated with improved maternal and fetal outcomes. This has resulted in an increased use of biologics before conception, during pregnancy and post-partum, with treat-to-target objective varying for each disease. Increasingly, cohort studies, clinical registries and systematic reviews have reported safety with the use of anti-tumour necrosis factor (TNF) biologics during pregnancy, mostly reported among patients with inflammatory bowel disease (IBD).

Insufficient evidence exists to support the routine prescribing of biologics other than anti-TNF agents during pregnancy despite emerging data. Although some prospective studies of 100-200 pregnant patients with stable IBD disease activity have reported that anti-TNF therapy can be stopped safely without adverse complications, others have reported that stopping therapy during pregnancy increases the risk of disease relapse, with associated poor outcomes for the infant, such as preterm delivery and low birth weight.

All societies agree that use of anti-TNF agents during breastfeeding presents a low risk given the minimal IgG1 secretion and biologic transfer in breast milk. In general, the use of biologics should not influence the decision to breastfeed, and breastfeeding should not influence the decision to use these medications.

Should infants exposed to biologics be immunized? **All exposed infants should receive inactivated immunizations according to the routine schedule.** Most guidelines recommend avoiding all live vaccines for the first 6-12 months of life.

The correct answer is 3.

Reference: Pham-Huy A, Top KA, Constantinescu C, Seow CH, El-Chaâr D. The use and impact of monoclonal antibody biologics during pregnancy. *CMAJ*. 2021 Jul 26;193(29):E1129-E1136.

Available from: https://www.cmaj.ca/content/193/29/E1129.long

PMID: 34312166

Q4 Rapid Diagnostic Testing (RDTs) for SARS-CoV-2

Which *one* of the following statements about rapid diagnostic testing (RDTs) for SARS-CoV-2 is *false*?

- ❍ 1. Nucleic acid amplification tests can remain positive for months after infection.
- ❍ 2. Antigen-based RDTs can detect infection within 5 to 7 days after symptom onset.
- ❍ 3. Home-based RDTs are just as accurate when performed by untrained persons.
- ❍ 4. Testing is generally not useful in the first 48 hours after exposure.

Educational Point: Limited access to diagnostic testing in underserved communities and incomplete reporting of Covid-19 data to the WHO mean that official numbers, although staggering, probably represent a fraction of total infections and deaths from the Covid-19 pandemic.

Globally, clinical laboratories have performed approximately 3 billion molecular diagnostic tests for SARS-CoV-2.

Diagnostic testing for acute SARS-CoV-2 infection can be performed with either molecular nucleic acid amplification tests (NAATs) or antigen-based assays, and both are available as rapid diagnostic tests (RDTs). Molecular NAATs detect the presence of viral gene targets, including the N, S, and E genes and the open reading frame 1ab (ORF 1ab).

Reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assays are the most widely used diagnostic SARS-CoV-2 NAATs worldwide. Antigen-based tests, also called immunoassays, detect domains of the surface proteins, including the nucleocapsid, spike, and receptor-binding domains, that are specific to SARS-CoV-2. Although both techniques are highly specific, NAATs are generally more sensitive than antigen-based tests because they amplify target genomic sequences. Tests to detect host IgG or IgM antibodies to SARS-CoV-2 should not be used to diagnose acute infection.

The clinical performance of diagnostic SARS-CoV-2 testing extends beyond pathogen targets such as viral proteins and RNA and includes clinical characteristics (e.g., the patient's viral load and the time since exposure or symptom onset), operational testing attributes (e.g., the specimen type, swab technique, transport conditions, and laboratory technique), and analytic test properties (e.g., sample preparation and signal amplification). **Although NAATs are highly sensitive and accurate, they can remain positive for weeks to months after infection.** Viral culture studies suggest that SARS-CoV-2 may be capable of replicating only for 10 to 14 days after symptom onset, so NAATs may detect remnant viral RNA well past the time period of recovering replication-competent virus. Conversely, antigen-based assays remain positive for 5 to 12 days after symptom onset and perform better in persons with a high viral load, which correlates with disease severity and death. Thus, antigen-based tests may correlate better with replication-competent SARS-CoV-2 than molecular tests and may provide information about potential transmissibility.

All antigen-based RDTs are approved for use in symptomatic persons and provide results in 10 to 30 minutes.

Although direct-comparison studies are limited and often retrospective, antigen-based RDTs have a lower sensitivity than molecular RDTs, as compared with a reference standard of laboratory-based RT-PCR tests, particularly among persons who have a low viral load or no replication-competent virus. However, **antigen-based RDTs can detect infection early in the disease course (within 5 to 7 days after symptom onset)** when viral loads are high (i.e., a low RT-PCR cycle threshold); these high viral loads account for most transmissions.

Studies have shown varying degrees of clinical accuracy (sensitivity, 36 to 82%; specificity, approximately 98 to 100%) when various antigen-based RDTs are used for screening asymptomatic persons.

Although home-based RDTs broaden the use of testing, they have been shown to be more accurate when performed by trained health care providers than by untrained persons. Persons who perform tests at home should carefully follow test kit instructions.

The appropriate interpretation of RDTs for SARS-CoV-2 testing and screening depends on the clinical indication and the pretest probability of infection. Among persons with a moderate-to-high pretest probability, which includes symptomatic persons and asymptomatic persons who have had close contact with a person with Covid-19, a positive RDT indicates a confirmed SARS-CoV-2 infection. However, RDTs may have false negative results, and repeat testing should be considered in cases of high clinical suspicion or worsening symptoms and in the serial screening or asymptomatic persons. A second negative RDT 2 days after the initial test or a negative laboratory-based NAAT would help to rule out SARS-CoV-2 infection.

In persons with exposure to SARS-CoV-2, testing is generally not useful in the first 48 hours after exposure since the virus will not have achieved a sufficient viral load. The most appropriate window for testing is generally considered to be 5 to 7 days after exposure, which is the average peak of symptoms and viral load. Therefore, for a single-test strategy, asymptomatic, exposed persons could use an RDT 5 to 7 days after exposure. For a two-test strategy, which is the FDA-approved indication for most RDTs for asymptomatic screening, a second RDT should be performed 2 days after a negative test. All symptomatic persons should be tested at the onset of symptoms and, if test results are negative, repeat testing should be considered if clinical suspicion remains high or symptoms worsen. In persons with low pretest probability of infection who have a positive RDT, a confirmatory test should be performed promptly.

The correct answer is 3.

Reference: Drain PK. Rapid Diagnostic Testing for SARS-CoV-2. *N Engl J Med*. 2022 Jan 20;386(3):264-272.

Available from: https://www.nejm.org/doi/10.1056/NEJMcp2117115?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

PMID: 34995029

Q5 Recurrent UTI

Methenamine Hippurate as a preventative treatment for recurrent UTI is non-inferior to current guideline recommended low dose prophylactic antibiotics.

❍ 1. True
❍ 2. False

Educational Point: Recurrent UTI is defined as repeated UTI with a frequency of at least two episodes in the preceding six months or three episodes in the past year. About one in four women with one UTI episode will go on to develop frequent recurrences. National and international guidelines acknowledge the need for preventive strategies, and those from the UK, Europe, and US strongly recommend the use of daily, low dose antibiotics as the standard prophylactic treatment for recurrent UTI. The urgent need for demonstration of effective non-antibiotic treatments is underlined by the UK antimicrobial resistance strategy. Methenamine hippurate is one such non-antibiotic treatment, which is hydrolysed to formaldehyde in acidic environments such as the distal tubules of the kidney. Formaldehyde is bacteriocidal and works by denaturing bacterial proteins and nucleic acids. Methenamine hippurate has been evaluated in previous Cochrane systematic reviews, which concluded that "methenamine hippurate may be effective for preventing UTI" but recognised the "need for further large well-conducted RCTs to clarify."

This pragmatic, multicentre, randomised, open label, non-inferiority trial compared clinical effectiveness of low dose antibiotic prophylaxis, the current standard treatment for recurrent UTI prevention, with the urinary antiseptic methenamine hippurate. Adult women aged 18 years and over with recurrent UTI who had decided, in conjunction with their responsible clinician, that prophylaxis was appropriate, were eligible for inclusion. The researchers excluded women with correctable urinary tract abnormalities contributory to recurrent UTI (eg, urinary tract calculi) and those with neurogenic dysfunction of the lower urinary tract. For participants assigned to antibiotic prophylaxis, the drug used was chosen from nitrofurantoin (50 or 100 mg), trimethoprim (100 mg), or cephalexin (250 mg) given orally once daily, depending on previous urine culture results and individuals' history of allergy or intolerance. Methenamine hippurate was prescribed as a twice daily oral dose (1 g). The primary clinical outcome measure was the incidence of symptomatic, antibiotic treated, UTI episodes self-reported by participants over the 12 month treatment period. Secondary outcomes were the incidence of symptomatic, antibiotic treated UTI in the six months after treatment; microbiologically confirmed UTIs; antibiotic resistance profiles in Escherichia coli isolated from urine and perineal swabs; asymptomatic bacteriuria; total antibiotic use; and hospital admissions due to UTI. Participant satisfaction with treatment was measured using the treatment satisfaction questionnaire for medication.

Between 23 June 2016 and 20 June 2018, 240 participants were recruited and randomly assigned to antibiotic prophylaxis (n=120) or methenamine hippurate (n=120). Patient follow-up was completed in January 2020. In the modified intention-to-treat population, 90 symptomatic, antibiotic treated UTI episodes were reported over 101 person years of follow-up in the antibiotic group, and 141 episodes over 102 person years of follow-up in the methenamine hippurate group. The incidence of symptomatic antibiotic treated UTI over the 12 month treatment period was therefore 0.89 episodes per person year (95% confidence interval 0.65 to 1.12) in the antibiotic group and 1.38 (1.05 to 1.72) in the methenamine hippurate group (absolute difference 0.49 (90% confidence interval 0.15 to 0.84). With the upper limit of the 90% confidence interval below the non-inferiority limit of one, the researchers concluded methenamine hippurate to be non-inferior to antibiotic prophylaxis. Overall, 183 (79%) of 231 UTI episodes reported in the modified intention-to-treat population were accompanied by a urine sample. Incidence of microbiologically confirmed UTIs was 0.41 (95% confidence interval 0.27 to 0.56) in participants allocated to antibiotic prophylaxis and 0.53 (0.34 to 0.72) for those allocated methenamine hippurate (absolute difference 0.11 (−0.12 to 0.35). The proportion of participants demonstrating resistance to at least one antibiotic in E coli isolated from perineal swabs was similar between randomised groups at baseline. At six or 12 month follow-up, this proportion was higher in the antibiotic prophylaxis group than in the methenamine hippurate group (46/64 (72%) v 39/70 (56%); $\chi 2$ test, P=0.05. On average, treatment satisfaction was high and generally comparable between treatment groups, although the antibiotic prophylaxis group reported higher scores in the convenience domain than the methenamine hippurate group

(mean 91.4 (standard deviation 12.7) v 82.2 (18.4); t test, P=0.001). Rates of adverse events and adverse reactions were low and comparable across treatment groups. Two serious adverse reactions (severe abdominal pain and raised alanine transaminase) were reported, both in participants allocated to antibiotic prophylaxis.

This trial has demonstrated that the non-antibiotic preventive treatment for UTI (methenamine hippurate) is not inferior to the current guideline recommended standard (daily, low dose prophylactic antibiotics). This trial adds to the evidence base for the use of methenamine hippurate for prophylactic treatment in adult women with recurrent UTI. Although the methenamine hippurate group had a 55% higher rate of UTI episodes than the antibiotics group, the absolute difference was just 0.49 UTI episodes per year, which has limited clinical consequence. These results could support a change in practice in terms of preventive treatments for recurrent UTI and provide patients and clinicians with a credible alternative to daily antibiotics, giving them the confidence to pursue strategies that avoid long term antibiotic use.

The correct answer is 1.

Reference: Harding C, Mossop H, Homer T, Chadwick T, King W, Carnell S, et al. Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial. *BMJ*. 2022 Mar 9;376:e068229.

Available from: https://www.bmj.com/content/376/bmj-2021-0068229.long

PMID: 35264408

Q6 Dry Eye Disease

Which *one* of the following statements regarding dry eye disease is *false*?

- ❍ 1. Aerobic exercise decreases tear secretion.
- ❍ 2. Artificial tears are the first-line treatment.
- ❍ 3. Overuse of artificial tears can cause toxic conjunctivitis.
- ❍ 4. Artificial tears with vasoconstrictors to reduce redness can cause rebound redness due to tachyphylaxis.

Educational Point: Dry eye disease (DED) is a relatively common condition characterized by abnormal tear film composition and ocular surface inflammation. Patients with DED often present with foreign body sensation and blurred vision.

DED can be categorized into 2 main groups: aqueous tear deficiency and evaporative DED. Many patients have a combination of both types. Aqueous tear deficiency is due to reduced lacrimal secretion or inadequate tear volume. Evaporative DED, which is a more common condition and develops in the setting of normal lacrimal secretion, involves excessive evaporation of the tear film, which may result from an insufficient lipid layer of the tear film.

Aerobic exercise increases tear secretion, and incorporation of light exercise and a diet with low glycemic index foods are associated with improved dry eye symptoms.

Restoration of tear film homeostasis is the primary goal when treating DED. The optimal strategy for a patient depends on specific causative factors, and multiple treatment modalities may be necessary to disrupt the cycle of DED. **Lubrication with artificial tears and ointments are first-line treatments for DED and can provide at least partial relief of symptoms.**

Patients with suspected or confirmed DED that does not adequately respond to a trial of over-the-counter treatments should be referred to an ophthalmologist. However, primary care physicians should be aware of several key concepts, including that most over-the-counter artificial tear formulations contain a preservative. **Patients should be advised to use these eye drops no more than 4 to 6 times per day because exposure to elevated amounts of preservatives can**

damage the ocular surface and cause toxic conjunctivitis, resulting in symptoms that may be similar to DED. Preservative-free artificial tears are less irritating to the ocular surface and may therefore be used more frequently, although toxic conjunctivitis is still possible.

Some artificial tear formulations contain a vasoconstrictor such as tetrahydrozoline. While these eye drops may be used occasionally for lubrication or to help reduce eye redness, regular use may lead to rebound redness from vasodilation secondary to tachyphylaxis. Lubricating ophthalmic gels and ointments are often recommended for use at bedtime as the higher viscosity results in greater contact time on the ocular surface, but they may also cause unwanted blurring of vision while patients are awake.

In addition to lubricants, ophthalmologists may recommend topical anti-inflammatory medications such as a steroid, cyclosporine, or lifitegrast. Topical steroids can cause secondary glaucoma, cataract formation, or both when used long term (>4 weeks), so these medications should only be prescribed by an ophthalmologist.

The correct answer is 1.

Reference: Hakim FE, Farooq AV. Dry Eye Disease: An Update in 2022. *JAMA*. 2022;327(5):478–479.

Available from: https://jamanetwork.com/journals/jama/fullarticle/2788545

PMID: 35103781

Q7 *Paxlovid*

Which *one* of the following statements about *Paxlovid* for treatment of COVID-19 infection is *false*?

- ❍ 1. It can reduce rate of hospitalization.
- ❍ 2. It can reduce the rate of death.
- ❍ 3. It is contraindicated for use with drugs that are highly dependent on CYP3A for clearance.
- ❍ 4. It can be started after 5 days of symptom onset.

Educational Point: On December 22, 2021, the FDA issued an Emergency Use Authorization (EUA) for the investigational antiviral drug nirmatrelvir copackaged with the HIV-1 protease inhibitor ritonavir (*Paxlovid*) for oral treatment of mild to moderate COVID-19 in outpatients ≥12 years old who weigh at least 40 kg and are at high risk of progressing to severe disease, including hospitalization or death. *Paxlovid* was the first oral antiviral drug to be authorized in the US and Canada for treatment of COVID-19.

Nirmatrelvir inhibits the SARS-CoV-2 main protease (Mpro), preventing viral replication. Ritonavir does not have any activity against SARS-CoV-2, but it increases serum concentrations of nirmatrelvir by inhibiting its metabolism by CYP3A.

Issuance of the EUA for nirmatrelvir/ritonavir was based on the results of a randomized, double-blind, placebo-controlled trial (EPIC-HR) in 2246 nonhospitalized, unvaccinated adults with laboratory-confirmed SARS-CoV-2 infection, symptom onset within 5 days of randomization, and at least one risk factor associated with progression to severe disease. Nirmatrelvir 300 mg/ritonavir 100 mg twice daily for 5 days decreased COVID-19 related hospitalization or death through day 28 by 88% compared to placebo (0.8% vs 6.3%). There were 12 deaths in the placebo group versus none in the nirmatrelvir/ritonavir group. Delta was the primary SARS-CoV-2 variant in both groups.

The most common adverse effects of nirmatrelvir/ritonavir in EPIC-HR were dysgeusia, diarrhea, hypertension, and myalgia.

Both nirmatrelvir and ritonavir are CYP3A substrates; drugs that induce or inhibit CYP3A will affect serum concentrations of both drugs. Concurrent use of *Paxlovid* and strong CYP3A inducers, such as rifampin, carbamazepine, phenobarbital, phenytoin, or St. John's wort, can decrease serum concentrations of nirmatrelvir and ritonavir and is contraindicated.

Ritonavir is a strong inhibitor of CYP3A and may increase serum concentrations of drugs metabolized by CYP3A. ***Paxlovid* is contraindicated for use with drugs that are highly dependent on CYP3A for clearance and for which elevated serum concentrations are associated with serious or life-threatening events (e.g., amiodarone, midazolam).** Recommendations for concomitant use of other CYP3A substrates are listed in the FDA Fact Sheet. Ritonavir decreases serum concentrations of ethinyl estradiol and may reduce the efficacy of combination hormonal contraceptives.

There are no data on the use of nirmatrelvir in pregnant women. Observational data from the antiretroviral pregnancy registry did not show an increase in birth defects following use of ritonavir during pregnancies resulting in more than 6900 live births.

Ritonavir is secreted into human breast milk. No data are available on the presence of nirmatrelvir in human breast milk or the effects of either drug on the breastfed infant or milk production.

Nirmatrelvir retains activity against the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) variants. According to the manufacturer, nirmatrelvir also inhibited the 3CL protease associated with the Omicron (B.1.1.529) variant in a biochemical assay.

***Paxlovid* is supplied in cartons containing nirmatrelvir 150-mg tablets copackaged with ritonavir 100-mg tablets. The recommended dosage is 300/100 mg (2 nirmatrelvir tablets and 1 ritonavir tablet taken together) twice daily for 5 days. Treatment should be started within 5 days of symptom onset.** If a dose is missed by more than 8 hours, it should be skipped and the next dose should be taken at the regularly scheduled time. In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage should be reduced to nirmatrelvir 150 mg/ritonavir 100 mg twice daily. *Paxlovid* is not recommended for use in patients with severe renal impairment (eGFR <30 mL/min) or severe hepatic impairment (Child-Pugh C).

Paxlovid, the investigational oral antiviral drug nirmatrelvir copackaged with oral ritonavir, has received an Emergency Use Authorization from the FDA for treatment of mild to moderate COVID-19 in outpatients ≥12 years old at high risk of progression to severe disease. In one trial, the antiviral combination decreased COVID-19 related hospitalization or death by 88%. It should be started as soon as possible after diagnosis and within 5 days of symptom onset. *Paxlovid* appears to be well tolerated, but ritonavir is a strong inhibitor of CYP3A and interacts with many other drugs.

The correct answer is 4.

Reference: *Paxlovid* for Treatment of COVID-19. *Med Lett Drugs Ther*. 2022 Jan 24;64(1642):9-10.

Available from: https://secure.medicalletter.org/w1642a

PMID: 35134040

Q8 Combining Antidepressants for Treatment of Patients with Acute Depression

Concerning combination treatment as compared to monotherapy for patients with acute depression, which *one* of the following is *false*?

- ❍ 1. Combination treatment with presynaptic alpha2-autoreceptor antagonists provides superior treatment outcomes in first-line treatment.
- ❍ 2. Combination treatment with presynaptic alpha2-autoreceptor antagonists provides superior treatment outcomes in nonresponders.
- ❍ 3. Combination treatment results in a higher rate of dropouts due to adverse events.
- ❍ 4. Bupropion combinations are not superior to monotherapy.

Educational Point: Despite a host of antidepressant agents, response rates to initial antidepressant monotherapy hover at 60%, and remissions occur in only up to 40% of patients, even after 12 to 24 weeks of treatment. Guidelines advocate a number of second-step treatments for patients considered nonresponders, most prominently switching to a different monotherapy, dose escalation, augmentation (eg, with lithium or second-generation antipsychotics), or combining 2 antidepressants. Combining 2 antidepressants is a common next step, particularly in primary care settings, based on the assumption that combining 2 antidepressants with different modes of action increases clinical efficacy. In a previous meta-analysis, the authors showed that, compared with monotherapy, combination therapy is more effective and comparably tolerable as a treatment for acute depression, most notably when applied as a first-line treatment. They also found that this was particularly the case for combinations that include monoamine reuptake inhibitors (SSRI, SNRI or tricyclic antidepressant) and antagonists of presynaptic α2-autoreceptor (mirtazapine, trazodone).

The authors conducted a systematic review and meta-analysis assessing the efficacy and tolerability of combination therapy. Combinations using presynaptic α2-autoreceptor antagonists or bupropion were investigated separately. MEDLINE, Embase, PsycINFO, and the Cochrane Central Register of Controlled Trials were systematically searched from each database inception through January 2020. Randomized clinical trials (RCTs) comparing combinations of antidepressants with antidepressant monotherapy in adult patients with acute depression were included. Following guidelines from Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and recommendations from the Cochrane Handbook, 2 reviewers independently performed a literature search, study selection, data extraction, and evaluation of risk of bias. Data were pooled in random-effects analyses. Primary outcome was efficacy measured as standardized mean difference (SMD); secondary outcomes were response, remission, change from baseline in rating scale scores, number of dropouts, and number of dropouts due to adverse events.

Thirty-nine RCTs including 6751 patients were eligible. **Combination treatment was statistically significantly associated with superior treatment outcomes relative to monotherapy (SMD = 0.31; 95% CI, 0.19-0.44). Combining a reuptake inhibitor with an antagonist of presynaptic α2-autoreceptors was superior to other combinations (SMD = 0.37; 95% CI, 0.19-0.55). Bupropion combinations were not superior to monotherapy (SMD = 0.10; 95% CI, −0.07 to 0.27). Numbers of dropouts and dropouts due to adverse events did not differ between treatments. Combination therapy was associated with superior outcomes when analyses were restricted to studies of low risk of bias (SMD = 0.29; 95% CI, 0.15-0.42), among nonresponder populations (SMD = 0.18; 95% CI, 0.04-0.33), and when applied as a first-line treatment (SMD = 0.52; 95% CI, 0.24-0.79).** Studies were heterogeneous, and there was indication of publication bias (Egger test result was positive; $P = .007$, $df = 36$), but results remained robust across prespecified secondary outcomes and sensitivity and subgroup analyses, including analyses restricted to studies with low risk of bias.

In this meta-analysis of RCTs comparing combinations of antidepressants with antidepressant monotherapy, combining antidepressants was associated with superior treatment outcomes but not with more patients dropping out of treatment. Combinations using an antagonist of presynaptic α2-autoreceptors may be preferable and may be applied as a first-line treatment in severe cases of depression and for patients considered nonresponders.

The correct answer is 3.

Reference: Henssler J, Alexander D, Schwarzer G, Bschor T, Baethge C. Combining Antidepressants vs Antidepressant Monotherapy for Treatment of Patients With Acute Depression: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2022 Apr 1;79(4):300-312.

Available from: https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2789300

PMID: 35171215

Q9 Epinephrine and Defibrillation in In-Hospital Cardiac Arrest

In in-hospital cardiac arrest due to a shockable rhythm, treatment with epinephrine before defibrillation is associated with worse survival.

❍ 1. True
❍ 2. False

Educational Point: Use of epinephrine for cardiac arrest remains controversial, and it is not recommended as first line treatment for cardiac arrest due to a shockable rhythm because immediate defibrillation is highly effective in achieving return of spontaneous circulation for most patients with ventricular fibrillation or pulseless ventricular tachycardia. Despite this, one Get With The Guidelines-Resuscitation study found that 51% of patients with in-hospital cardiac arrest with an initial shockable rhythm that was refractory to first defibrillation within two minutes were treated with epinephrine before the second defibrillation, contrary to current guidelines. Treatment with epinephrine in these patients was associated with 30% lower odds of survival. The authors used data from a large multicenter registry of in-hospital cardiac arrest in the US, to examine the frequency of use of epinephrine before first defibrillation in patients with a shockable in-hospital cardiac arrest; and the association between epinephrine before defibrillation with survival to discharge, favorable neurological survival, and survival after acute resuscitation. They used 2000-2018 data from 497 hospitals participating in the American Heart Association's Get With The Guidelines-Resuscitation registry. Participants were adults with an index in-hospital cardiac arrest due to an initial shockable rhythm treated with defibrillation. Propensity-matched analysis was performed to evaluate the independent association of epinephrine before defibrillation with study outcomes.

Among 34,820 patients, 9630 (27.6%) were treated with epinephrine before defibrillation, contrary to current guidelines. In comparison with participants treated with defibrillation first, treatment with epinephrine was strongly associated with delayed defibrillation (median 3 minutes v 0 minutes). **Epinephrine before defibrillation was associated with lower odds of survival to discharge (25.2% v 29.9%; adjusted OR 0.81, 95% CI 0.74 to 0.88; P<0.001),** favorable neurological survival (18.6% v 21.4%; 0.85, 0.76 to 0.92; P<0.001), and survival after acute resuscitation (64.4% v 69.4%; 0.76, 0.70 to 0.83: P<0.001).

The authors conclude that, contrary to current guidelines, more than one in four patients were treated with epinephrine before defibrillation, which is associated with worse survival.

The correct answer is 1.

Reference: Evans E, Swanson MB, Mohr N, Boulos N, Vaughan-Sarrazin M, Chan PS, et al. Epinephrine before defibrillation in patients with shockable in-hospital cardiac arrest: propensity matched analysis. *BMJ*. 2021 Nov 10;375:e066534.

Available from: https://www.bmj.com/content/375/bmj-2021-066534.long

PMID: 34759038

Q10 Empagliflozin in Heart Failure

Which *one* of the following statements about the use of empagliflozin in patients with heart failure and preserved ejection fraction is *false*?

- ❍ 1. It reduces the combined risk of cardiovascular death or hospitalization in patients with diabetes.
- ❍ 2. It does not reduce the combined risk of cardiovascular death or hospitalization in patients without diabetes.
- ❍ 3. It increases the risk of uncomplicated urinary tract infections.
- ❍ 4. It increases the risk of hypotension.

Educational Point: Patients with heart failure present with either a reduced or a preserved ejection fraction. Whereas heart failure with a reduced ejection fraction can be treated with drugs that act to attenuate the over-activation of endogenous neurohormonal systems, therapeutic options for patients with heart failure and a preserved ejection fraction are limited. Although some benefits have been reported with mineralocorticoid-receptor antagonists and neprilysin inhibitors, the magnitude of the effects has been modest and the benefits have been apparent only in subgroups of patients.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce the development and progression of heart failure in patients with type 2 diabetes and in those with heart failure and a reduced ejection fraction. However, the effect of these drugs in patients with heart failure and a preserved ejection fraction has not been well studied. Post hoc analyses of a large-scale trial of dapagliflozin in type 2 diabetes indicated that SGLT2 inhibition might not reduce the incidence of serious adverse heart failure outcomes in patients with heart failure and a preserved ejection fraction. In contrast, benefits in such patients were reported in a trial with sotagliflozin, but the number of events was too small to allow for a reliable estimate of a treatment effect.

The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) was carried out to evaluate the effects of SGLT2 inhibition with empagliflozin on major heart failure outcomes in patients with heart failure and a preserved ejection fraction.

In this double-blind trial, the authors randomly assigned 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. **The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.**

Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). **Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.**

Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes.

The correct answer is 2.

Reference: Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021 Oct 14;385(16):1451-1461.

Available from: https://www.nejm.org/doi/10.1056/NEJMoa2107038?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

PMID: 34449189

Q11 Inhaled Budosenide

Inhaled budesonide improves time to recovery, with a chance of also reducing hospital admissions or deaths, in people with COVID-19 in the community who are at higher risk of complications.

❍ 1. True
❍ 2. False

Educational Point: There is an urgent need for effective and safe community-based treatments for COVID-19, especially for older people and those with comorbidities who are at higher risk of hospital admission and death.

Inhaled corticosteroids are widely available, inexpensive, and generally safe, and have been proposed as a COVID-19 treatment because of their targeted anti-inflammatory effects in the lungs. Inhaled steroids also reduce replication of SARS-CoV-2 in epithelial cells in vitro. Early in the COVID-19 pandemic, the low prevalence of asthma and chronic obstructive pulmonary disease among people admitted to hospital with COVID-19 led to speculation that the inhaled corticosteroids used to treat these conditions might be protective. An efficacy trial of adults with early COVID-19 in the community found inhaled budesonide reduced COVID-19-related emergency assessments or hospital admissions, and time to self-reported recovery.

The authors aimed to establish the effectiveness of inhaled budesonide in reducing recovery time and rates of COVID-19-related hospital admission or death in people at high risk of an adverse outcome in the community.

PRINCIPLE is a multicentre, open-label, multi-arm, randomised, controlled, adaptive platform trial done remotely from a central trial site and at primary care centres in the UK. Eligible participants were aged 65 years or older or 50 years or older with comorbidities, and unwell for up to 14 days with suspected COVID-19 but not admitted to hospital. Participants were randomly assigned to usual care, usual care plus inhaled budesonide (800 µg twice daily for 14 days), or usual care plus other interventions, and followed up for 28 days. Participants were aware of group assignment. The coprimary endpoints are time to first self-reported recovery and hospital admission or death related to COVID-19, within 28 days, analysed using Bayesian models. The primary analysis population included all eligible SARS-CoV-2-positive participants randomly assigned to budesonide, usual care, and other interventions, from the start of the platform trial until the budesonide group was closed. This trial is ongoing.

The trial began enrolment on April 2, 2020, with randomisation to budesonide from Nov 27, 2020, until March 31, 2021, when the prespecified time to recovery superiority criterion was met. 4700 participants were randomly assigned to budesonide (n=1073), usual care alone (n=1988), or other treatments (n=1639). The primary analysis model includes 2530 SARS-CoV-2-positive participants, with 787 in the budesonide group, 1069 in the usual care group, and 974 receiving other treatments. There was a benefit in time to first self-reported recovery of an estimated 2.94 days (95% Bayesian credible interval [BCI] 1.19 to 5.12) in the budesonide group versus the usual care group (11.8 days [95% BCI 10.0 to 14.1] vs 14.7 days [12.3 to 18.0]; hazard ratio 1.21 [95% BCI 1.08 to 1.36]), with a probability of superiority greater than 0.999, meeting the prespecified superiority threshold of 0.99. For the hospital admission or death outcome, the estimated rate was 6.8% (95% BCI 4.1 to 10.2) in the budesonide group versus 8.8% (5.5 to 12.7) in the usual care group (estimated absolute difference 2.0% [95% BCI –0.2 to 4.5]; odds ratio 0.75 [95% BCI 0.55 to 1.03]), with a probability of superiority 0.963, below the prespecified superiority threshold of 0.975. Two participants in the budesonide group and four in the usual care group had serious adverse events (hospital admissions unrelated to COVID-19).

Inhaled budesonide improves time to recovery, with a chance of also reducing hospital admissions or deaths, in people with COVID-19 in the community who are at higher risk of complications.

The correct answer is 1.

Reference: Yu LM, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021 Sep 4;398(10303):843-855.

Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01744-X/fulltext

PMID: 34388395

Q12 Calcium Intake in Aged Care Residents

Using dairy foods to improve calcium and protein intake in aged care residents reduces each of the following except:

- ❍ 1. Overall fracture risk
- ❍ 2. Hip fracture risk
- ❍ 3. Risk of falls
- ❍ 4. Overall mortality

Educational Point: Loss of independence increases the number of people needing full time institutionalised care, the source of around 30% of all hip fractures in the community. The widespread use of antiresorptive therapy is unlikely to reduce this fracture burden because of a paucity of evidence of antifracture efficacy in people over 80 years of age. These people often have calcium intakes below 700 mg daily, and protein intakes below 1 g/kg body weight/day, predisposing to loss of lean muscle mass. Few studies have investigated the efficacy and safety of a nutritional approach to reduction of fracture risk in aged care residents. Chapuy and colleagues showed antifracture efficacy with pharmacological doses of calcium and vitamin D in female nursing home residents with low calcium intakes and vitamin D deficiency. No studies have examined the effects of protein supplementation on reduction of fracture risk, despite evidence of improved muscle function and reduced falls. The objective of this two year study was to assess the antifracture efficacy and safety of a nutritional intervention in institutionalised older adults replete with vitamin D but with mean intakes of 600 mg/day of calcium and <1 g/kg body weight protein/day in 60 accredited residential aged care facilities in Australia. Participants were 7195 permanent residents with a mean age of 86 years.

Thirty facilities were randomised to provide residents with additional milk, yogurt, and cheese that contained 562 mg/day calcium and 12 g/day protein achieving a total intake of 1142 mg calcium/day and 69 g/day protein. The 30 control facilities maintained their usual menus. The main outcome measures were group differences in fractures, falls, and all cause mortality. A total of 324 fractures (135 hip fractures), 4302 falls and 1974 deaths were observed. **The intervention was associated with risk reductions of 33% for all fractures (121 vs 203; HR 0.67, 95% CI 0.48 to 0.93; P=0.02), 46% for hip fractures (42 vs 93; HR 0.54, 0.35 to 0.83; P=0.005), and 11% for falls (1879 vs 2423; 0.89, 0.78 to 0.98; P=0.04).** The risk reduction for hip fractures and falls achieved significance at five months (P=0.02) and three months (P=0.004). **Mortality was unchanged (900 vs 1074, HR 1.01). The authors conclude that improving calcium and protein intakes reduces the risk of falls and fractures occurring in aged care residents.**

The correct answer is 4.

Reference: Iuliano S, Poon S, Robbins J, Bui M, Wang X, De Groot L, et al. Effect of dietary sources of calcium and protein on hip fractures and falls in older adults in residential care: cluster randomised controlled trial. *BMJ*. 2021 Oct 20;375:n2364.

Available from: https://www.bmj.com/content/375/bmj.n2364.long

PMID: 34670754

Q13 Covert Brain Infarction Discovered in Emergency Department CT Scans

Most patients with covert brain infarctions discovered after CT of the head in the emergency department are informed of these findings.

❍ 1. True
❍ 2. False

Educational Point: Covert brain infarctions are focal lesions detected on brain imaging consistent with ischemia in the absence of a history of overt stroke or neurologic dysfunction. They are the most common incidental finding on brain imaging, with a prevalence of 10% to 30% in elderly populations. Covert brain infarctions are associated with an increased risk of future stroke. Stroke prevention interventions such as further diagnostic testing and risk factor modification are indicated in these patients according to the current guidelines. Evidence regarding covert brain infarction in emergency department (ED) patients is limited. The goal of this study was to determine the prevalence of covert brain infarction in patients undergoing computed tomography (CT) in the ED who were subsequently discharged and to determine how often clinicians act on these findings or make patients aware of them.

The authors conducted a retrospective chart review of patients presenting to the ED of an urban academic medical center. Patients aged more than 50 years were identified who underwent CT of the head and were seen and discharged from the ED from January to September 2018. Patients with a history of stroke, or prior brain imaging with ischemia, were excluded. Patient data and clinician response (patient notification, neurology referral, and risk factor modification) were collected. The authors included 832 patients, with an average age of 62 years, and 50% of the patients were women. Covert brain infarctions were present in 11% of patients (n=95). **Only 9% of patients with covert brain infarctions were clearly made aware of the finding.** Of the patients with covert brain infarctions, 27% were already on aspirin and 28% on a statin. Aspirin was added for 2 patients, and statin medication was not started on any patient. The blood pressure medication was added or adjusted for 2 patients with covert brain infarctions. The neurology department was consulted for 9% of the patients with covert brain infarctions.

The authors concluded that covert brain infarction is a common incidental finding in an elderly ED population. They noted however that this is often not conveyed to the patient, and primary stroke prevention strategies are rarely implemented. Because the covert brain infarction can have significant clinical consequences, this finding, at minimum, should be treated like other incidental findings and communicated to the patient.

The correct answer is 2.

Reference: Balderston JR, Brown CK, Feeser VR, Gertz ZM. Covert Brain Infarction in Emergency Department Patients: Prevalence, Clinical Correlates, and Treatment Opportunities. *Ann Emerg Med*. 2022 Mar;79(3):265-269.

Available from: https://www.annemergmed.com/article/S0196-0644(21)01379-2/fulltext

PMID: 34955329

Q14 Influenza Vaccination after Myocardial Infarction

Influenza vaccination early after an MI results in a lower risk of all-cause death at 12 months compared with placebo.

❍ 1. True
❍ 2. False

Educational Point: Observational and small, randomized studies suggest that influenza vaccine may reduce future cardiovascular events in patients with cardiovascular disease.

The authors conducted an investigator-initiated, randomized, double-blind trial to compare inactivated influenza vaccine with saline placebo administered shortly after myocardial infarction (MI; 99.7% of patients) or high-risk stable coronary heart disease (0.3%). The primary end point was the composite of all-cause death, MI, or stent thrombosis at 12 months. A hierarchical testing strategy was used for the key secondary end points: all-cause death, cardiovascular death, MI, and stent thrombosis.

Because of the COVID-19 pandemic, the data safety and monitoring board recommended to halt the trial before attaining the prespecified sample size. Between October 1, 2016, and March 1, 2020, 2571 participants were randomized at 30 centers across 8 countries. Participants assigned to influenza vaccine totaled 1290 and individuals assigned to placebo equaled 1281; of these, 2532 received the study treatment (1272 influenza vaccine and 1260 placebo) and were included in the modified intention to treat analysis. Over the 12-month follow-up, the primary outcome occurred in 67 participants (5.3%) assigned influenza vaccine and 91 participants (7.2%) assigned placebo (hazard ratio, 0.72 [95% CI, 0.52–0.99]; *P*=0.040). Rates of all-cause death were 2.9% and 4.9% (hazard ratio, 0.59 [95% CI, 0.39–0.89]; *P*=0.010), rates of cardiovascular death were 2.7% and 4.5%, (hazard ratio, 0.59 [95% CI, 0.39–0.90]; *P*=0.014), and rates of MI were 2.0% and 2.4% (hazard ratio, 0.86 [95% CI, 0.50–1.46]; P=0.57) in the influenza vaccine and placebo groups, respectively.

The authors concluded that Influenza vaccination early after an MI or in high-risk coronary heart disease resulted in a lower risk of a composite of all-cause death, MI, or stent thrombosis, and a lower risk of all-cause death and cardiovascular death, as well, at 12 months compared with placebo.

The correct answer is 1.

Reference: Fröbert O, Götberg M, Erlinge D, Akhtar Z, Christiansen EH, MacIntyre CR, et al. Influenza Vaccination After Myocardial Infarction: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. *Circulation*. 2021 Nov 2;144(18):1476-1484.

Available from: https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.121.057042?rfr_dat=cr_pub++0pubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org

PMID: 34459211

Q15 Subarachnoid Haemorrhage

The use of non-contrast multislice CT alone is unable to rule out aneurysmal subarachnoid haemorrhage at 24 hours after headache onset.

❍ 1. True
❍ 2. False

Educational Point: Headache is a common reason for presentation to EDs causing approximately 1%–2% of attendances. While most headache presentations are due to benign pathologies such as tension headaches, subarachnoid haemorrhage (SAH) represents an important potentially life-threatening differential diagnosis. SAH has an incidence of 6–8/100 000 persons/year, and around 30% of survivors will have severe disabilities affecting their daily lives.

Historically, studies suggested that CT detects as many as 93%–95% of SAH if the scan is performed within the first 24 hours after headache onset. Given the life-threatening potential of the diagnosis, most patients therefore received a follow-up LP to bring the miss rate to within a margin that is more comfortable for most clinicians. Unfortunately, LP is unpleasant for the patient, time-consuming, procedurally difficult in some cases, requires technical skill and has potential complications such as ongoing headache and local bleeding. The historical sensitivities listed previously were based on earlier generations of CT scanners than now available, but scanner technology has continually improved to make better detection of SAH possible. In a practice-changing study by Perry *et al* in 2011 showed 100% sensitivity for the detection of SAH provided the scan was performed within 6 hours of headache onset. In this study, patients were only included in the analysis if they had a GCS of 15 and had no focal neurological deficits. This has essentially negated the need for routine LP after a negative CT, if performed within 6 hours of headache onset. Perry et al used a wide range of third-generation multislice CT (MSCT), implying a range of image qualities. Since the Perry et al study, there have been further improvements for modern MSCT in image noise reduction, resolution and motion artefact that have continued to improve image quality.

A 2021 retrospective analysis aimed to establish if modern MSCT could improve the sensitivity of SAH detection at sequential timepoints from symptom onset, as this could potentially expand the time window within which CT alone can be used to exclude aneurysmal SAH. Patients were imaged with MSCT. The primary outcome was the proportion of patients with spontaneous aneurysmal SAH (identified via coding and confirmed by clinical and radiological records) that had a positive MSCT. The secondary outcome was the proportion of patients with any type of spontaneous SAH that had a positive MSCT.

There were 347 patients with an SAH of whom 260 were aneurysmal SAH. MSCT identified 253 (97.3%) of all aneurysmal SAH and 332 (95.7%) of all SAH. The sensitivity of MSCT was 99.6% (95% CI 97.6 to 100) for aneurysmal SAH and 99.0% (95% CI 97.1 to 99.8) for all SAH at 48 hours after headache onset. **At 24 hours after headache onset, the sensitivity for aneurysmal SAH was 100% (95% CI 98.3 to 100). These data suggest that it may be possible to extend the timeframe from headache onset within which modern multislice can be used to rule out aneurysmal SAH.**

The correct answer is 2.

Reference: Vincent A, Pearson S, Pickering JW, Weaver J, Toney L, Hamill L, et al. Sensitivity of modern multislice CT for subarachnoid haemorrhage at incremental timepoints after headache onset: a 10-year analysis. *Emerg Med J*. 2022 Nov;39(11):810-817.

Available from: https://emj.bmj.com/content/39/11/810.long

PMID: 34819306

Q16 Acetaminophen and Blood Pressure

Regular daily intake of 4 g acetaminophen increases systolic BP in individuals with hypertension.

❍ 1. True
❍ 2. False

Educational Point: Acetaminophen is the most widely used analgesic globally and is generally the initial drug of choice for the treatment of chronic pain. Recent evidence, however, suggests that its role in the management of chronic pain has probably been overstated. As evidence grows to suggest regular acetaminophen use has, at best, limited benefit for chronic pain, greater emphasis on determining the harms of acetaminophen will allow more informed decision-making by clinicians and patients. The significant risks of acetaminophen in overdose are well-known. However, considerable uncertainty remains regarding the safety of chronic acetaminophen use at therapeutic doses because of reliance on observational data and cohort studies that often have conflicting results. Many observational studies suggest that acetaminophen increases BP. However, interventional data remain limited

to smaller, largely underpowered trials that have not affected clinical practice. To address this knowledge gap, the authors performed a randomized, double-blind, crossover study comparing the effects of regular acetaminophen and matched placebo on BP in individuals with hypertension.

To meet inclusion criteria for enrollment, individuals had to be aged ≥18 years of age and hypertensive. They had to either be: (1) treated for hypertension with an average daytime ambulatory BP of <150/95 mm Hg on stable doses of ≥1 antihypertensive medication; or (2) untreated with an average daytime ambulatory BP ≥135/85 mm Hg but <150/95 mm Hg. Individuals were excluded if they had a history of ischemic heart disease, heart failure, cerebrovascular disease, liver impairment (ALT [alanine aminotransferase] >50 IU/L), chronic kidney disease staged III to V, or suicidal ideation. Individuals were also excluded if they weighed <55 kg or were regularly taking acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or oral anticoagulants.

Participants were randomly assigned to receive either 1 g acetaminophen 4 x daily or matched placebo for 2 weeks. Following a 2-week washout, patients crossed over to the other treatment arm for an additional 2 weeks of treatment. 103 participants were included in the modified intention-to-treat analysis.

Using a mixed model to account for period effect, an increase in mean daytime systolic ambulatory BP of 4.7 mm Hg (95% CI, 2.9–6.6; P<0.0001) with acetaminophen compared to placebo was observed. The 4.7-mm Hg difference in BP, greater than the study was powered to detect, might be expected to translate to ≈20% more cardiovascular events during any period of chronic treatment.

The findings of this study further call into question current guidelines suggesting that acetaminophen is a safe alternative to NSAIDs. Indeed, the rise in BP seen in this study matches that seen with NSAIDs and may well explain the finding that self-reported frequent acetaminophen use in women is associated with an increase in cardiovascular events similar to that seen with frequent NSAID use. While the precise mechanism of actions of acetaminophen remains unclear, it is believed to involve COX2 (cyclooxygenase-2) inhibition which may, at least in part, explain the these similarities. These findings suggest that caution should be used when encouraging or prescribing regular use of acetaminophen, particularly in those with hypertension and otherwise at risk of ischemic heart disease and stroke. Additionally, acetaminophen should no longer be *thought* of as a "safe" alternative analgesic to NSAIDs, at least with respect to hypertension.

In summary, regular daily intake of 4 g acetaminophen increases systolic BP in individuals with hypertension by ≈5 mm Hg when compared with placebo; this increases cardiovascular risk and calls into question the safety of regular acetaminophen uses in this situation.

The correct answer is 1.

Reference: MacIntyre IM, Turtle EJ, Farrah TE, Graham C, Dear JW, Webb DJ; PATH-BP (Paracetamol in Hypertension–Blood Pressure) Investigators*. Regular Acetaminophen Use and Blood Pressure in People With Hypertension: The PATH-BP Trial. *Circulation*. 2022 Feb 8;145(6):416-423.

Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.121.056015?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

PMID: 35130054

Short Answer Management Problems

Q17 Cannabis Use Disorder

A 17 year old woman is in the office to consult you about contraception. When inquiring about medication and substance use, you find out that she smokes marijuana regularly at bedtime to help her sleep, but is concerned about health risks.

1. Adolescents are two to four times more likely than adults to develop cannabis use disorder within two years of use. True or false?

   ❍ True
   ❍ False

2. She has heard that regular cannabis use is associated with an increased risk of neurological or mental health problems. Name 3 such problems.

Your patient is now concerned about using marijuana on a daily basis and would like your help to reduce her habit. She is afraid that if she stops suddenly she may experience withdrawal.

3. What symptoms are associated with withdrawal? Name 3.

4. Large studies have shown clear benefits of pharmacotherapy for cannabis use disorder. True or false?

   ❍ True
   ❍ False

Educational Point: Cannabis use disorder develops in 19.5% of lifetime users. **Adolescents are two to four times more likely than adults to develop cannabis use disorder within two years of use.** A 2017 national survey showed that 22% of Americans incorrectly believe marijuana is not addictive, and 29% strongly believe that its use can prevent health problems.

A validated screening tool such as the Cannabis Use Disorder Identification Test-Revised (CUDIT-R) can be used to screen patients for cannabis use disorder. A positive result on CUDIT-R screening has a 91% sensitivity and 90% specificity for detecting cannabis use disorder. Diagnosis of cannabis use disorder requires fulfillment of the Diagnostic and Statistical Manual of Mental Disorders, 5th ed., (DSM-5) criteria.

Cannabinoids can potentially interact with several drug classes, such as commonly prescribed analgesic, psychotropic, and cardiovascular medications. However, the effects are not well-characterized. Both THC and CBD may alter levels of certain opioids, benzodiazepines, statins, antidepressants, and anticoagulants. THC may increase the effects of central nervous system depressants (e.g., alcohol, opioids, benzodiazepines), resulting in added impairment.

Acute cannabis intoxication can present with hunger, tachycardia, tachypnea, hypertension, ocular erythema, anxiety, and altered judgment. Acute paranoia and psychosis may occur with higher THC doses. Females may experience more intense intoxication and withdrawal.

Cannabinoid hyperemesis syndrome is more common in males and presents with cyclic vomiting, diffuse abdominal pain, and relief with hot showers. Traditional antiemetics are often ineffective for cannabinoid hyperemesis syndrome, but topical capsaicin applied to the abdomen, back, or arms and dopamine antagonists might help reduce symptoms.

Cannabis withdrawal syndrome occurs in about 47% of regular users. It presents with anxiety as early as four hours after cessation, with other symptoms manifesting one to two days later and lasting up to three to four weeks.

Cannabis withdrawal syndrome is diagnosed when more than three of the following DSM-5 criteria are present within approximately seven days of reduced use: (1) irritability, anger, or aggression; (2) nervousness or anxiety; (3) sleep difficulty (e.g., insomnia, disturbing dreams); (4) decreased appetite or weight loss; (5) restlessness; (6) depressed mood; (7) at least one physical symptom causing significant discomfort (abdominal pain, tremors, diaphoresis, fevers, chills, headache).

Cannabis can impair short-term memory, judgment, and coordination, resulting in a three to sevenfold increased risk of motor vehicle crashes. Cannabis appears to be a neurotoxin affecting brain development, and **long-term studies demonstrate associations with lower IQ, poor educational outcomes, impaired executive function, and avolition.** Adverse effects on young, developing brains appear to be driven by heavy use.

Long-term cannabis use increases the risk of future anxiety disorders in cohort studies, even with cessation. Adolescent use is associated with increased risk of self-harm, suicidality, and all-cause mortality. A large meta-analysis (n = 296,815) found moderate associations between cannabis use and risk of physical violence (odds ratio = 2.62). Cannabis use is a modifiable risk factor for psychosis, especially in those who are genetically predisposed. One observational study found a four- to fivefold increased risk of a first episode of psychosis in people who use high-potency (more than 10% THC) cannabis daily.

Other risks of long-term cannabis use include male infertility, symptoms of chronic bronchitis, and cannabis use disorder. THC crosses the placenta, and low-strength evidence links prenatal marijuana use to preterm birth, lower birth weight, and future risk of childhood psychopathology.

Psychosocial interventions are the cornerstone of treatment for cannabis use disorder. Brief counseling by primary care physicians has shown benefit for adolescents and nondaily users. Cognitive behavior therapy and motivational enhancement therapy are equally effective for reducing mean days of cannabis use, and maximal effectiveness occurs when they are used in combination.

Pharmacotherapy for cannabis use disorder, although limited and experimental, can improve withdrawal and reduce cannabis use. Small studies have shown reduced cravings and cannabis use with gabapentin in adults and acetylcysteine in adolescents. Mirtazapine and quetiapine may modestly reduce cannabis use and withdrawal symptoms.

Harm reduction strategies should be discussed with patients who use cannabis. These may include choosing products with low THC, avoiding daily use, reducing inhalation (to one puff every 15 minutes), purchasing from legal dispensaries (which have to comply with state regulations for contaminant testing, labeling, and dosing), and gradual tapering. Tapering should include education about cannabis withdrawal syndrome and a treatment plan for symptoms.

Acceptable answers:

1. **True**

2. **Neurological - lower IQ, poor educational outcomes, impaired executive function, avolition. Psychiatric- increased risk of self-harm and suicidality, anxiety disorders, psychosis.**

3. **Irritability, anger, or aggression; nervousness or anxiety; sleep difficulty; decreased appetite or weight loss; restlessness; depressed mood; physical symptoms including abdominal pain, tremors, diaphoresis, fevers, chills, and headache.**

4. **False**

Reference: Sazegar P. Cannabis Essentials: Tools for Clinical Practice. *Am Fam Physician*. 2021 Dec 1;104(6):598-608.

Available from: https://www.aafp.org/link_out?pmid=34913644

PMID: 34913644

Q18 DRESS Syndrome

A 54-year-old female presents to your rural emergency department with a complaint of a new rash. She has a history of gout and has been started on allopurinol over the last few months. She has a diffuse morbiliform rash, is febrile, and is found to have elevated LFTs and eosinophils. You suspect drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

1. DRESS can be associated with a number of medications. List 3 of the most common medications or medication categories.

2. Apart from fever and rash, what are the most common clinical manifestations of DRESS? List 2.

3. Apart from eosinophilia and elevated LFTs, what diagnostic test abnormalities are commonly seen in DRESS? List 2.

The patient has been hydrated and given antipyretics and the offending agent has been stopped.

4. What is the generally accepted treatment of choice?

5. Empiric antibiotics should be provided to this patient who is suspected of having DRESS syndrome. True or false?

   ❍ True
   ❍ False

6. What additional pharmacotherapy can be considered if there is an inadequate response? List 2.

Educational Point: A variety of adverse drug reactions were first reported in the 1930s. Then, in the 1950s, Chaiken et al. reported a case of exfoliative dermatitis, hepatitis, and fever associated with phenytoin. Following this report, several other cases were reported describing similar findings in patients taking antiepileptic medications. The term "drug rash with eosinophilia and systemic symptoms" was first used in 1996 by Bocquet et al. However, as dermatosis is not mandatory for the diagnosis of DRESS, the "R" was later modified to "reaction".

Adverse drug reactions with skin involvement can be broadly separated into severe reactions (e.g., DRESS, toxic epidermal necrolysis, Stevens-Johnson Syndrome) and more limited reactions (e.g., serum sickness-like reactions, drug-induced dermatoses). DRESS is a severe reaction that is estimated to occur in up to 2 cases per 100,000 patients per year, with a population-level risk between 1 in 1000 and 1 in 10,000 drug exposures. However, DRESS accounts for up to 20% of patients admitted with a cutaneous drug adverse event, and has a mortality rate of nearly 10%. While DRESS is more common in adults, it has also been described in pediatric patients. Numerous medications have been associated with DRESS, and a specific drug is identified as the causative agent in approximately 80% of cases. However, in 10–20% of cases, an association with a medication is unclear. **Approximately three-quarters of cases with an identified cause are associated with allopurinol, aromatic anticonvulsants (e.g., carbamazepine, lamotrigine, phenytoin), proton pump inhibitors, antibiotics containing sulfonamides, minocycline, or vancomycin.** In the United States, the increasing use of vancomycin has led to it being the most common causal agent]. Interestingly, the risk of DRESS may be dose dependent for several drugs, including allopurinol, especially in those with renal impairment.

Unfortunately, DRESS can present with myriad symptoms and can be challenging to diagnose. In light of these challenges and the significant mortality rate, it is essential that emergency clinicians are aware of this important condition.

While DRESS is believed to be a hypersensitivity reaction to a drug or its metabolites, the exact pathogenesis has not been fully elucidated.

DRESS can be challenging to detect due to the variation in clinical presentations. There is often a latency period between the initiation of the offending medication and the beginning of symptoms. Data suggest the latency period can range from 1 to 12 weeks. **The most common feature of DRESS is dermatologic findings, with a rash occurring in nearly 99% of patients. The most common manifestation is an exanthematous, macular-papular rash starting at the trunk, which can be seen in 48 to 100% of patients.** The rash is often distributed symmetrically across the body. The rash can be large, with one study reporting that 79% of patients had a rash exceeding over half of their body surface, and the majority of rashes persist for two weeks or longer. **Facial edema is also common, with one study reporting that it was present in over half of all cases (65% of major cases and 32% of minor cases). Skin involvement can also affect mucosal surfaces, leading to dysphagia in some patients.**

While the most common symptom is a rash, fever is also frequently present and has been reported in 72 to 100% of patients. Lymphadenopathy is seen in 50 to 88% of patients. Lymphadenopathy can be present in the cervical, axillary, or inguinal regions. Lung involvement is seen in 32% of patients, and can include pneumonitis, pleural effusions, pneumonia, and even acute respiratory distress syndrome (ARDS). Patients may present with symptoms such as dyspnea, cough, chest pain, or other manifestations of pulmonary disease. Cardiac involvement is seen in only 4 to 15% of patients, and can include symptoms such as chest pain, palpitations, tachycardia, and hypotension in some cases.

When considering DRESS syndrome, clinicians should obtain a complete blood count with differential, basic metabolic panel, liver function testing, urinalysis, and a chest radiograph. The most common laboratory finding is eosinophilia (defined as an eosinophil count ≥700 μL^{-1}), which can be seen in 30 to 95% of patients. One study reported that 81% of patients had an eosinophil count ≥1500 μL^{-1}. Leukocytosis was seen in 52 to 95% of patients who were diagnosed with DRESS. Similarly, thrombocytosis, an acute phase reactant, can be seen in 25% of patients.

The liver is the most commonly involved organ besides the skin, affected in 51 to 100% of cases. Elevated liver enzymes are present in over half of cases. Renal dysfunction (including elevation of creatinine or proteinuria) is also common, occurring in 11 to 53% of patients presenting with DRESS syndrome. Allopurinol specifically has been associated with an increased risk of renal dysfunction among patients with DRESS.

A chest radiograph will be abnormal in approximately half of cases, with the most common findings including interstitial infiltrates (50%), ARDS (31%), and pleural effusions (22.7%). While not generally performed by emergency clinicians, dermatologists may decide to obtain a skin biopsy.

Current recommendations involve a combination of administering supportive care, discontinuing the culprit drug, and reducing the inflammatory cascade. Early management should involve antipyretics and intravenous hydration as needed. Empiric antibiotics should be avoided as they have the potential to exacerbate the clinical condition due to cross-reactivity. If the causative medication is identified, it should be stopped as soon as possible. An 11-year retrospective study out of Thailand reported a 4% mortality rate when they removed the culprit drug, with 84.6% of medications being halted on the first day of hospitalization. Importantly, clinicians should re-evaluate for alternative causative agents if the suspected medication was stopped but symptoms have not improved.

Systemic corticosteroids are generally considered to be the treatment of choice for all cases of DRESS. Corticosteroids should be initiated when the diagnosis is considered. Data suggest that they are associated with a shortened time to resolution of symptoms (12.5 vs 14.5 days), though there was no difference in mortality. Other case reports and series have demonstrated rapid improvement in symptoms after initiation of corticosteroids. Systemic corticosteroids should be initiated at a minimum dose of 1 mg/kg/day of prednisone or an equivalent corticosteroid with a gradual taper over 3 to 6 months. Rapid discontinuation of corticosteroids has been associated with early recurrence. While the corticosteroids are frequently given orally at the aforementioned dose, pulsed dose methylprednisolone (30/mg/kg intravenous daily for three days) can be considered in refractory cases.

Intravenous immunoglobulin (IVIG) given at a dose of 1–2 g/kg for two days can be considered in cases that do not respond to corticosteroids (e.g., systemic symptoms that are worsening or not improving after initiation of corticosteroids). IVIG is proposed to work by replenishing low immunoglobulin levels, protecting against HHV-6, and by direct anti-inflammatory properties. Several case reports have demonstrated a benefit with IVIG, while others have suggested no benefit. Therefore, IVIG remains controversial but may be considered in refractory cases. However, it is not currently advised as a monotherapy for DRESS in the absence of corticosteroids. **Plasmapheresis and immunosuppressive agents (e.g., cyclophosphamide, cyclosporine, interferons, mycophenolate mofetil, rituximab) may also be considered in refractory cases. Data are limited to isolated case reports demonstrating benefit in cases that did not respond to corticosteroids alone. N-acetylcysteine (NAC) has also been reported as a potential treatment to aid in detoxification and reduction in reactive metabolites of anticonvulsant-induced DRESS, but the data are similarly limited to case reports.**

Acceptable answers:

1. **Allopurinol**
   Aromatic anticonvulsants (Lamotrigine, Phenytoin, Carbamazepine)
   Vancomycin
   Minocycline
   Proton pump inhibitors
   Sulfonamides

2. **Facial edema**
   Lymphadenopathy
   Pleuritic involvement (including pleural effusions, pneumonitis)

3. **Leukocytosis**
   Thrombocytosis
   Elevated creatinine or proteinuria
   Chest x-ray pulmonary infiltrate, pleural effusion, acute respiratory distress syndrome

4. **Systemic corticosteroids**

5. **False**

6. **Intravenous immunoglobulin**
   Plasmapheresis
   Immunosuppressive agents
   N-acetyl cysteine

Reference: Gottlieb M, Figlewicz MR, Rabah W, Buddan D, Long B. Drug reaction with eosinophilia and systemic symptoms: An emergency medicine focused review. *Am J Emerg Med*. 2022;56:1-6.

Available from: https://www.sciencedirect.com/science/article/abs/pii/S0735675722001814?via%3Dihub

PMID: 35338896

Q19 Maturity-Onset Diabetes of the Young

A 25-year-old female presents to your office for follow up on type 2 diabetes which was diagnosed three years ago and has been controlled with diet and lifestyle modifications. She has read online about maturity-onset diabetes of the young (MODY) and wonders if she could have this.

1. MODY is most often an autosomal dominant inherited disorder. True or false?

   ❍ True
   ❍ False

2. It is misdiagnosed as Type 1 or Type 2 diabetes in up to 80% of cases. True or false?

   ❍ True
   ❍ False

3. What clinical clues could suggest the patient has MODY rather than type 2 diabetes? List three.

4. What laboratory testing results would suggest MODY? List two.

Her initial history, exam and laboratory findings suggest MODY.

5. What confirmatory test should be ordered?

Her laboratory testing confirms MODY subtype 3.

6. MODY subtype 3 is the most common subtype. True or false?

   ❍ True
   ❍ False

7. Patients with MODY subtype 3 do not usually develop microvascular complications. True or false?

   ❍ True
   ❍ False

8. Metformin is not a preferred pharmacologic agent. True or false?

   ❍ True
   ❍ False

She continues lifestyle treatment and a low-carbohydrate diet, but her glycemic control worsens over the next few months. You decide to initiate an oral medication.

9. Which oral agent is preferred and what is the recommended starting dose?

Educational Point: Maturity-onset diabetes of the young (MODY) is an underrecognized type of diabetes mellitus that is usually diagnosed in young adulthood. Advances in genetic testing have led to the discovery of more subtypes of the disease. This article provides a summary of the most common subtypes of MODY to help primary care clinicians distinguish the condition from types 1 and 2 diabetes. MODY should be considered in nonobese patients who have diabetes that was diagnosed at a young age (younger than 30 years), preserved pancreatic beta-cell function, lack of pancreatic beta-cell autoimmunity, and a strong family history of diabetes.

MODY accounts for approximately 1% to 5% of diabetes cases. **Up to 80% of MODY cases are misdiagnosed as type 1 or 2 diabetes.**

MODY is most often an autosomal dominant disease and is divided into subtypes (MODY1 to MODY14) based on the causative genetic mutation. Subtypes 1 to 3 account for 95% of cases. In the most common subtype (MODY3), more than 95% of people with the mutation will develop diabetes, most by 25 years of age.

The pathophysiology of MODY involves impaired insulin secretion, whereas type 2 diabetes is a heterogeneous disease characterized by insulin resistance and a progressive loss of beta-cell function. **Clues that a patient presumed to have type 2 diabetes may actually have MODY include a lack of response to metformin, a larger drop in serum glucose level with sulfonylureas, and greater sensitivity to insulin.**

Although definitive guidelines are lacking, testing for MODY can be considered in a patient younger than 30 years who has diabetes and:

- **has a family history of diabetes in young, nonobese family members**
- **is not obese**
- **lacks signs of insulin resistance such as acanthosis nigricans, skin tags, androgenic alopecia, or markers of metabolic syndrome**
- **lacks pancreatic beta-cell autoantibodies**
- **has a fasting C-peptide level greater than 0.60 ng per mL**

Commercially available genetic testing can confirm the diagnosis of MODY. Referral to an endocrinologist and/or a clinical genetics consultant should be considered when clinical suspicion for MODY is high.

MODY1 and MODY3 are caused by mutations in transcription factors (HNF4A and HNF1A, respectively). This results in impaired insulin secretion from defective beta-cell signaling in response to glucose. These patients have glucose intolerance and may have normal fasting serum glucose levels in the early stages of the disease. Patients with MODY3 usually develop postprandial glycosuria before the onset of diabetes. **Like patients with types 1 and 2 diabetes, patients with MODY1 and MODY3 are thought to develop associated micro- and macrovascular complications caused by suboptimal glycemic control.**

There are limited data on what A1C goals are associated with the best outcomes for patients with MODY1 and MODY3. Because these patients are thought to be susceptible to micro- and macrovascular complications, it is reasonable to individualize A1C goals based on patient characteristics (e.g., comorbidities, life expectancy, risks

associated with hypoglycemia), as recommended by American Diabetes Association guidelines for patients with types 1 and 2 diabetes.

Lifestyle modification including a low-carbohydrate diet should be first-line therapy because MODY1 and MODY3 are predominantly associated with glucose intolerance. **If glycemic control worsens, sulfonylureas are the recommended pharmacologic therapy because these drugs bypass the defective glucose-mediated insulin secretion associated with HNF1A and HNF4A mutations.** Patients with MODY3 are four times more responsive to sulfonylureas than patients with type 2 diabetes and are therefore at higher risk of hypoglycemia when using these drugs. **Sulfonylureas should be started at one-fourth of the typical starting dose to avoid hypoglycemia, then slowly titrated to achieve optimal glycemic control.** Although glucose-induced insulin secretion may decline over time, most patients remain responsive to sulfonylureas for decades.

Meglitinides may be considered instead of sulfonylureas to treat postprandial hyperglycemia if sulfonylurea use is complicated by frequent hypoglycemic events. A small double-blind, randomized, crossover trial compared liraglutide, a glucagon-like peptide 1 agonist, with glimepiride, a sulfonylurea. Patients taking liraglutide had similar glycemic control as those taking glimepiride but much lower risk of hypoglycemia. Liraglutide may be considered in patients who are obese or with high rates of hypoglycemia. Limited data suggest that dipeptidyl-peptidase 4 inhibitors and sodium-glucose cotransporter 2 inhibitors may also be effective, but additional studies are needed. **Because MODY is associated with impaired insulin secretion and minimal or no defects in insulin action, metformin is not a preferred pharmacologic agent.**

Acceptable answers:

1. **True**
2. **True**
3. **Onset age less than 30 years**
   Not obese
   Lacks signs of insulin resistance such as acanthosis nigricans, skin tags, androgenic alopecia or markers of metabolic syndrome.
   Has a family history of diabetes in young, nonobese family members, a lack of response to metformin, a larger drop in serum glucose level with sulfonylureas and greater sensitivity to insulin.
4. **Absent pancreatic beta-cell autoantibodies**
   Fasting C-peptide level greater than 0.60 ng per mL
5. **Commercially available genetic testing**
6. **True**
7. **False**
8. **True**
9. **Sulfonylureas. They should be started at one-fourth of the typical starting dose to avoid hypoglycemia, then slowly titrated to achieve optimal glycemic control.**

Reference: Kant R, Davis A, Verma V. Maturity-Onset Diabetes of the Young: Rapid Evidence Review. *Am Fam Physician*. 2022 Feb 1;105(2):162-167.

Available from: http://www.aafp.org/pubs/afp/issues/2022/0200/p162.html

PMID: 35166506

Q20 Opioid-Induced Neurotoxicity

You see an 86-year-old patient who is admitted to the hospital with hypoactive delirium. His head CT is normal and no infectious cause is found. His creatinine level is 130 umol/L (baseline 95 umol/L), the rest of the blood results is unremarkable. He is followed for chronic lumbar pain for which he takes long-acting morphine 30 mg twice a day, the dose has been the same for many years. He also takes verapamil for hypertension. According to his family, he also has a history of recurrent falls, associated with involuntary muscle movements that cause him to fall without warning symptoms. On physical examination, he is irritable and inattentive. You also notice myoclonus without any focal neurological deficits. You suspect opioid-induced neurotoxicity (OIN).

1. List 4 signs or symptoms of OIN.

OIN can be difficult to differentiate from a serotonin syndrome, especially if there has been an increase or the addition of a new serotonin agent within the last 24 hours.

2. List 3 features that would lead you to suspect a serotonin syndrome instead of an OIN.

3. Which opioids are most commonly associated with OIN, considering that all opioids are at risk of causing OIN?

4. Renal failure increases the risk of OIN for this patient. List 3 other risk factors for this condition.

5. Which drugs can increase morphine bioavailability? Name 1.

6. How would you manage this patient?

7. If you choose to rotate the opioid, how would you reduce the equianalgesic dose of the new opioid?

Educational Point: Chronic pain is a costly disorder affecting 45–85% of older adults and is associated with considerable morbidity including reduced quality of life, social withdrawal, depression, sleep disturbance, cognitive impairment, disability and malnutrition. Opioids have been used for analgesia for moderate to severe cancer and non-cancer pain for many years. Opioids provide analgesia by acting as agonists at opioid receptors (mu-, delta-, and kappa-opioid receptors), which are present throughout the central and peripheral nervous system. Canada is the second-largest per capita consumer of opioids in the world. In Canada, compared with all other age groups, people over the age of 65 have consistently received more new opioid prescriptions and have a higher proportion (24.8%) that go on to long-term opioid therapy, which is defined as someone prescribed opioids for 90 days out of a 100-day period. In response to the opioid epidemic, an updated Canadian guideline for opioids for chronic non-cancer pain (CNCP) was published in 2017. Unfortunately, there were no specific recommendations for older adults. As older people are excluded from many medication trials, guidelines developed for adults cannot necessarily be applied to older populations. Several adverse drug reactions (ADRs) are associated with opioid prescription. Older adults are at increased risk for these adverse effects due to a combination of drug-drug interactions, multimorbidity, and age-related physiologic changes.

The short-term efficacy of opioids for CNCP in the elderly is established. The evidence for long-term opioid use for managing chronic pain at any age is limited. A systematic review found limited evidence supporting long-term opioid use for CNCP in community-dwelling older adults. It is also important to note that few studies on opioid efficacy are conducted in older adults with severe cognitive impairment, who are more likely to experience untreated pain. Many older adults have comorbidities (heart failure, kidney disease, liver cirrhosis) that preclude the use of many other forms of non-opioid analgesia. Therefore, opioid use for CNCP in older adults may be justifiable when less potent medications have been tried or are contraindicated. Long-term opioid use may be reasonable if it improves quality of life and functional status and is used as part of a comprehensive management plan.

While oral absorption and distribution are similar between younger and older adults, metabolism and excretion can be greatly altered with age due to decline in organ function, particularly hepatic and renal function. First pass metabolism can be significantly decreased in older adults. As a result, medications that undergo substantial first pass metabolism (i.e. morphine) will have higher bioavailability due to reduced metabolism in the elderly when compared with younger counterparts; this can affect tolerability by increasing risk of ADRs.

In general, hydromorphone has minimal drug-drug interactions. **Morphine primarily undergoes phase II metabolism via UGT2B7; however theoretically 3A4 inhibitors (amiodarone, diltiazem, verapamil, grapefruit juice, antifungals) can increase the morphine bioavailability leading to increased opioid effects. Alternatively, 3A4 inducers (anticonvulsants such as phenytoin) may reduce morphine bioavailability.**

Among older adults, enhanced pharmacodynamic sensitivity (i.e. more pronounced effects at equivalent doses used in younger adults) is seen with all opioids, which results in prolonged pain relief with lower dosages.

The most common opioid-associated adverse effects include constipation, nausea, and dizziness. Other ADRs include pruritus, dry mouth, sedation, fatigue, hot flushes, increased sweating, delirium, respiratory depression, urinary retention, hyperalgesia, and opioid endocrinopathy (hypogonadism with sexual dysfunction, dysmenorrhea, reduced bone mineral density, depression, and adrenal insufficiency). Opioids alter sleep regulation and can cause sleep disordered breathing. Opioids are also associated with falls and fractures, especially when combined with other CNS agents such as benzodiazepines (clonazepam), tricyclic antidepressants (amitriptyline) and nonbenzodiazepine receptor agonist hypnotics (zopiclone, zolpidem). The 2019 Beers Criteria® provided new strong recommendations to avoid use of opioids concurrently with benzodiazepines or gabapentinoids due to the increased risk of overdose.

Exceptions include when transitioning from the former to the latter or when using gabapentinoids to reduce opioid dose. These concerns need to be balanced with the need to treat chronic pain.

Opioid-induced neurotoxicity (OIN) is a clinical syndrome presenting with a range of cognitive, motor and sensory symptoms including hypersomnolence, delirium, hallucinations, allodynia, hyperalgesia, myoclonus, tremor, and seizures. There is some overlap between OIN and serotonin syndrome, however most cases of the latter begin within 24 hours of increasing a serotonergic agent, overdose, or addition of another serotonergic agent; additional features include autonomic hyperactivity (hyperthermia, tachycardia, mydriasis, diaphoresis, diarrhea) and neuromuscular abnormalities (tremor, myoclonus, hyperreflexia, muscle rigidity). OIN can be challenging to diagnose as it can be misinterpreted as disease progression in cancer and palliative patients. **Neurotoxicity can occur with any opioid, but it is most commonly associated with those that form active metabolites such as meperidine, morphine, oxycodone, and hydromorphone. Risk factors for OIN include high dosage of opioids, dehydration, renal failure, infection, end-stage disease and advanced age due to increased risk of metabolite accumulation.**

OIN is managed with dose reduction or discontinuation of opioids, opioid rotation (changing one opioid to another in order to improve pain control or reduce unwanted side effects), hydration and correction of underlying precipitants such as renal impairment. If performing an opioid rotation due to intolerable side effects, it is recommended to reduce the calculated equianalgesic dose of the new opioid by 25–50% to minimize the risk of inadvertent overdose.

No specific monitoring intervals were recommended in the Canadian guideline for opioid therapy and CNCP, however the CDC recommend that clinicians consider follow-up within 1– 4 weeks of dose escalation or when total daily opioid dosage is >50 morphine milligram equivalents (MME)/day.

Acceptable answers:

1. **Hypersomnolence, delirium, hallucinations, allodynia, hyperalgesia, myoclonus, tremor, and seizures.**
2. **Autonomic hyperactivity (hyperthermia, tachycardia, mydriasis, diaphoresis, diarrhea) and neuromuscular abnormalities (tremor, hyperreflexia, muscle rigidity).**
3. **Drugs that form active metabolites such as meperidine, morphine, oxycodone, and hydromorphone.**
4. **High dosage of opioids, dehydration, infection, end-stage disease and advanced age.**
5. **3A4 inhibitors (amiodarone, diltiazem, verapamil, grapefruit juice, antifungals).**
6. **Dose reduction or discontinuation of opioids, opioid rotation (changing one opioid to another to improve pain control or reduce unwanted side effects), hydration and correction of underlying precipitants such as renal impairment.**
7. **It is recommended to reduce the calculated equianalgesic dose of the new opioid by 25 – 50% to minimize the risk of inadvertent overdose.**

Reference: Godwin B, Frank C, Molnar F, Dyks D, Akter R. Identification and management of opioid-induced neurotoxicity in older adults. *Can Fam Physician*. 2022 Apr;68(4):269-270.

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