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a RECORD of MEDICAL PROGRESS

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THE ROAD TOWARD RECOVERY
A Story of Leadership and Community

Corey D. Fogleman, MD, FAAFP
Editor in Chief
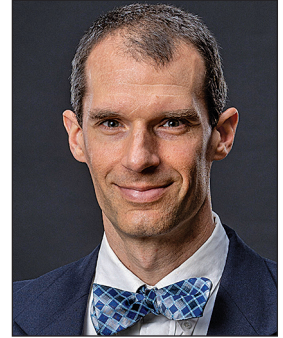
NOTES OF APPRECIATION

Thanks for picking up this issue of *JLGH*. We are excited to present several thought-provoking articles this quarter, including features on the effects of SARS-CoV-2 on placenta pathology, pediatric cardiac-related syncope, and emergency contraception. I welcome several first-time writers, their insight and comments.

This is my first issue as editor in chief, and I would like to recognize those who have contributed to this transition. First, I extend gratitude to Dr. Larry Bonchek for his years of vision and leadership at the helm of *JLGH*. His personal touches and discerning mind brought a high degree of scholarship to this endeavor, the benefits of which continue to live in the memories of all readers and in our ongoing work within the health system and community. He certainly set a high bar, and as I stand on the shoulders of his ingenuity and all he endowed, I appreciate his careful mentoring and credit his enduring vision.

I have also been fortunate for the guidance of Drs. Christine Stabler and Pamela Vnenchak, as well as Designated Institutional Officer Barbara Flory and her colleague Sara D'Ascenzo-Labinski. They have made this transition much smoother than could have been imagined.

Now, it is my pleasure to welcome Maria Boyer, managing editor of *JLGH*. She is new to Penn Medicine Lancaster General Health, but not to our area, and she brings a wealth of experience in editing and within the health care industry. She has, in turn, been mentored by Jean Korten, the outgoing managing editor, and I am excited about Maria's energy, her focus, and her many good ideas. You will find as you reach out to her regarding article proposals that she is welcoming and insightful. You can email her at maria.boyer@pennmedicine.upenn.edu. I am looking forward to a long and fruitful partnership!

LANCASTER COUNTY HEROISM

Like others, I have been struck by awesome efforts of compassion and leadership over the past two years. While there are too many to honor, this space seems perfect to recognize some who were able to rise to the occasion during the SARS-CoV-2 pandemic. I began by calling Dr. Jeffrey R. Martin, chair of the LG Health Department of Family and Community Medicine, to talk about the interface between medicine and public education. What could he tell me about the LG Health team he helped lead that was instrumental in turning Lancaster County back toward recovery?

The story of how Lancaster County schools safely reopened actually starts with the vision and insight of Lisa Riggs, president of the local nongovernmental nonprofit Economic Development Corporation of Lancaster. Recognizing that reopening our local economy would take a multipronged approach, she and her team — with input from municipal and county leadership — put out a Recovery Lancaster plan and created progress reports in conjunction with private businesses, and county and city leaders.

Riggs and LG Health's Alice Yoder soon were in touch with Hempfield School District Superintendent Michael Bromirski, who had himself been contemplating this topic. Bromirski represented many school districts in conversations with county commissioners and health system leaders. He and Riggs agreed that functioning in-person school systems are a vital part of the current business processes and the future of our economy.

Lancaster General Health opened the first Lancaster County COVID testing site on March 18, 2020, and, as most know by now, would emerge as a leader regarding mass testing, contact tracing, mass vaccination, and systematic treatments using monoclonal antibodies. Then-CEO Jan Bergen and Dr. Michael Ripchinski were, at the time, quite busy brokering many working relationships.

In the spring of 2020, after intense conversations and lacking adequate state or federal guidance, Yoder, Riggs, and Bromirski called on Martin. CARES Act funding had been approved to help school districts move toward resuming classroom-based education, and the key to getting people back to work was getting students and teachers back in person.

Martin quotes his own residency director, Dr. Nikitas Zervanos, who taught him that "care of the whole community is right there in the name." Martin is still on faculty with the LG Health Family Medicine Residency Program and a natural collaborator with a vested interest in bridging care gaps. This mentality led him, more than 10 years ago, to

initiate a working partnership with IU13 and in 2016 to help establish, along with education leaders Anna Kennedy and Sherry Zubeck, the Medical Education Coalition. Together they have developed nursing care protocols, worked to augment mental health care challenges, and continue to present a semi-annual seminar series to which health care professionals have an open invitation to meet with educators sharing a mutual interest in student health. More information about this training and a lineup of future seminar topics can be found at https://touchstonefound.org/training/

So it was that Martin was an easy choice, along with Rosemary Search and Alice Yoder, to become the face of a contingent motivated to restart the engine and get the Lancaster County education system humming again. As an arrangement between a nonprofit health system, independent public school districts, and private ventures, this collaboration appears altogether unprecedented and yet herculean in both scale and success, garnering approval by the state Department of Health and enduring gratitude on the part of Bromirski, his colleagues and coworkers.

Occupational medicine-style school building walk-throughs included personal oversight by LG Health's Nicole Meyers; each setting presented its own architectural character that helped clarify social distancing challenges and opportunities. These challenges would later explain why surging COVID diagnoses meant one school would need to close at the same time another could remain open.

The team put together nearly 20 webinars — facilitated by the strong work of Nicole Bumgardner — to describe rising and falling case counts, the science behind R values, how the vaccine manufacturing differed, and what rollout meant to different age groups. The result of this joint venture was the formulation of back-to-school protocol based on custom logarithms for each school created by the LG Health team in conjunction with local school districts.

From May 2020 to February 2022, Martin and the team conducted hour-long conference calls — usually thrice weekly — with district superintendents and principals, nurses, and school human relations representatives. Quick to give credit to Drs. Pat Moreno, Bill Fife, Fran Gross, Pia Fenimore, and Anne Reilly, among others, this team helped interpret and clarify the use of expertly crafted algorithms. Those decision trees needed constant updating and were thus housed in a "living format" that could be accessed on a website developed and maintained by Brenda Buescher.

Further, Martin, Yoder, and Search's LG Health-based team helped several school districts set up their own testing sites and facilitated the implementation of school-based contact tracing programs. These integrated systems were both elegant and unique, increasing the speed with which action plans could be carried out at the school nurse level.

Altogether this team helped field more than 950 individual nurse case calls, 95 FAQs, and an untold number of individual questions. Eventually these efforts extended to, and helped guide, an even wider circle ranging from faith-based communities to higher education institutions (Franklin & Marshall College and Millersville University).

The results were monumental: In the 2021-22 school year, while our county saw unprecedented rise in SARS-CoV-2 cases due to delta and omicron surges, most Lancaster County school districts had no COVID-protocol closures. And, in spite of the absence of a county or municipal health department, Lancaster County's case counts have been consistently lower than Berks County, our next most comparable neighbor in terms of size and resources (see Table 1).

Undeniably, there has been a tremendous loss of life and lifestyle to many here in Lancaster County, and the pandemic is not over. Yet, surely countless more individuals would have become sick and died had it not been for this tireless effort. Further, our economy would have continued to drag — every missed school day having a ripple effect on small businesses and our society — had it not been for this team of heroic Penn Medicine LG Health representatives. To you, on behalf of our community, I extend admiration and appreciation; truly, your insight into the ties that bind within our community, and your diligence and fortitude, have been life-saving and inspiring!

Table 1. COVID-19 Positivity Rates in Pennsylvania's 10 Most Populated Counties as of May 2022			
	Population	Case Total	% Positivity
*Philadelphia	1,585,480	314,253	19.8%
*Allegheny	1,212,337	268,436	22.2%
*Montgomery	842,888	156,000	18.5%
*Bucks	629,644	125,000	19.9%
**Delaware	571,295	112,000	19.6%
Lancaster	550,989	122,133	22.2%
*Chester	533,698	93,973	17.6%
#York	452,691	120,000	26.5%
Berks	423,069	103,000	24.3%
#Lehigh	372,195	90,776	24.4%

Statistics on population from https://worldpopulationreview.com/us-counties/states/pa
Statistics on COVID counts from https://www.nytimes.com/article/coronavirus-county-data-us.html
*Has county health department; **Uses neighboring county health department, announced in April 2022 the creation of their own county health department; #Has city health department within the largest municipality

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Instructions to Authors

The following is a summary of the general guidelines for submitting an article to *The Journal of Lancaster General Hospital*. Details are located on the web at www.jlgh.org.

Scientific manuscripts are typically between 2,500-4,500 words. Perspective articles are usually shorter, and photo quizzes average about 725 words plus illustrations.

Medical articles should report research, introduce new diagnostic or therapeutic modalities, describe innovations in health care delivery, or review complex or controversial clinical issues in patient care.

Reports of research involving human subjects must include a statement that the subjects gave informed consent to participate in the study and that the study has been approved by the institutional review board (IRB). Patient confidentiality must be protected according to the U.S. Health Insurance Portability and Accountability Act (HIPAA).

Please contact the Managing Editor, Maria M. Boyer (717-544-8004), Maria.Boyer@pennmedicine.upenn.edu, to discuss submitting an article or for further information.

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MOTHERS WITH FETAL DEMISE
Two Cases of SARS-CoV-2 Infection with Associated Placental Pathology

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The novel coronavirus SARS-CoV-2, responsible for the COVID-19 disease, has evolved into a worldwide pandemic. Although there has been much research on the origin, pathophysiology, treatment, and immunization of SARS-CoV-2, only a limited number of studies consider its effects on maternal health and fetal development, particularly in the second trimester of pregnancy.[1-5]

We present two similar cases of intrauterine fetal demise (IUFD) occurring during the second trimester of pregnancy in the setting of a SARS-CoV-2 positive mother.

CLINICAL PRESENTATION
Case 1

A 21-year-old unvaccinated gravida 2 para 1 woman (BMI 29.51 kg/m²) presented to Penn Medicine Lancaster General Health Women & Babies Hospital triage at 21 weeks gestational age. Her past medical history included anemia, headaches, a prior detached retina, and frequent tobacco use. (She reported quitting during the fourth week of her pregnancy.) She complained of leakage of fluid and contractions, but otherwise had no symptoms of SARS-CoV-2 infection. As part of the hospital protocol during the COVID-19 pandemic, the patient underwent a nasopharyngeal PCR screen and was found to be positive.

Although ultrasound one week prior had been normal, an ultrasound at this presentation confirmed fetal demise. She underwent induction with misoprostol and oxytocin, and she delivered a male fetus and placenta vaginally after six hours of labor without complications. Her vitals were normal following delivery. She remained asymptomatic from her SARS-CoV-2 infection during her delivery and hospitalization. At the patient's request, a fetal autopsy and placental evaluation were conducted.

Case 2

A 29-year-old G1P0 female presented to Women & Babies Hospital triage at 22 weeks gestational age with complaint of a gush of blood-tinged fluid. She was unvaccinated for SARS-CoV-2, and other noteworthy history showed that starting two weeks prior to admission she had
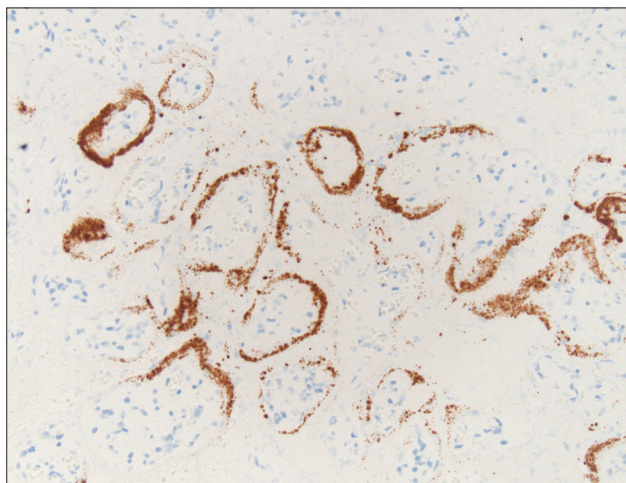
Fig. 1a. ISH for SARS-CoV-2 virus showing viral RNA within syncytiotrophoblast (Case 1).
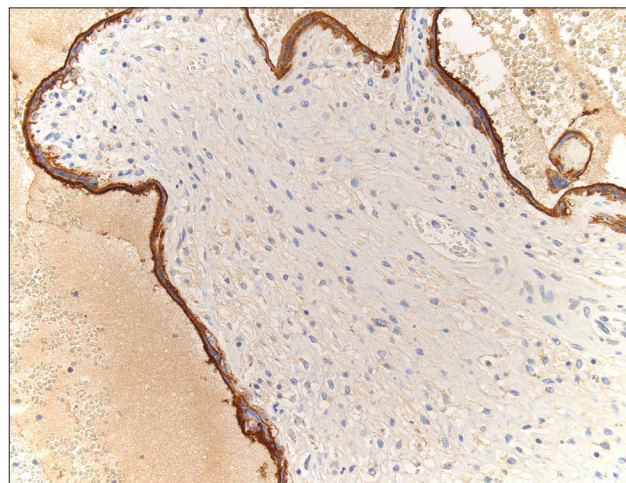
Fig. 1b. Immunostaining of C4d in syncytiotrophoblastic layer of placental villi (Case 1).

symptoms of congestion, fatigue, dry cough, diaphoresis, chills, and increased dyspnea, especially with exertion. Ten days prior to presentation to triage, the patient tested positive for SARS-CoV-2 by nasopharyngeal PCR swab. No respiratory assistance was needed to treat the dyspnea on exertion. She tested negative for SARS-CoV-2 by nasopharyngeal PCR one week later (three days prior to presentation to triage).

On presentation to triage, the patient was found to have preterm premature rupture of the membranes (PPROM); IUFD was confirmed by ultrasound. The patient underwent induction with misoprostol and delivered a male fetus and placenta vaginally after six hours of labor without complications. At the patient's request, a fetal autopsy was not conducted, however a gross external fetal evaluation was performed during the placental examination.

PLACENTAL EXAMINATION

Both placentas were submitted to the pathology laboratory in formalin and processed according to standard procedures; gross and histological examination were performed. In each case, the placental disc was at the high end of expected range (>95th percentile): the first case weighed 153 grams (96th percentile for gestational age) and the second case 175 grams (97th percentile for gestational age).

Six representative unstained placental sections of the first case were sent to the pathology laboratory at the Hospital of the University of Pennsylvania to undergo chromogenic in situ hybridization (ISH) and complement 4d (C4d) immunostaining. ISH staining confirmed the presence of SARS-CoV-2 within the syncytiotrophoblast (Fig. 1a). Complement staining of C4d was found in the syncytiotrophoblastic layer of the placental villi (Fig. 1b). This C4d staining of the placenta was much stronger and

Fig. 1c. Immunostaining of C4d in second trimester IUFD placenta (control).

more uniform in our case than in a second trimester IUFD control placenta (Fig. 1c).

In both cases, placental histology showed extensive diffuse intervillous and perivillous fibrin deposition with widespread associated villous infarction and hemorrhage (Figs. 2a and 2b on page 6). In addition, significant thrombi deep to the fetal surface and patchy hemorrhage throughout the placental parenchyma were identified in both patients (Figs. 2c and 2d on page 7). No acute or chronic inflammation was noted in either case.

FETAL EXAMINATION

A fetal autopsy of the first patient showed no developmental abnormalities; however, tissue examination revealed degenerative changes consistent with IUFD without evidence of vasculopathy. The lung sections showed scattered degenerated cells (possibly neutrophils) within alveolar spaces. The umbilical cord (aside from being slightly edematous) and fetal membranes exhibited no specific histopathologic abnormalities.

The fetuses' weights were low: in the first case, 222 grams (1.45 fetal-placental weight ratio, <5th percentile), and in the second case, 392 grams (2.24 fetal-placental weight ratio, <50th percentile). The fetal external measurements were within normal limits. The organ weights for the first case were slightly small for gestational age. In the second case, the fetus also showed no gross external abnormalities other than blood pooling in areas of the subcutaneous tissue and skin sloughing, indicating death several days prior.

No testing for SARS-CoV-2 was performed on either of the fetuses or amniotic fluids.

LABORATORY METHODS

Given the severity of the placental abnormalities observed in the first case, six representative unstained placental sections were sent to the pathology laboratory at the Hospital of the University of Pennsylvania for further analysis.

Chromogenic RNA ISH (BOND RNAscope Detection Reagents Brown; Leica Biosystems DS9790) was performed using a Leica Bond III instrument. Five-micron-thick FFPE tissue sections were stained according to manufacturer instructions with probes to SARS-CoV-2 viral RNA (Probe-V-nCoV2019-S; Advanced Cell Diagnostics 848568). Positive (PPIB; Leica Biosystems RS7755) and negative (dapB; Leica Biosystems RS77756) control probes were used to assess RNA and tissue quality.

The tissue sections were stained using polyclonal antibodies against anti-human C4d (diluted 1:100; American Research Products Inc., 12-5000). Staining performed with
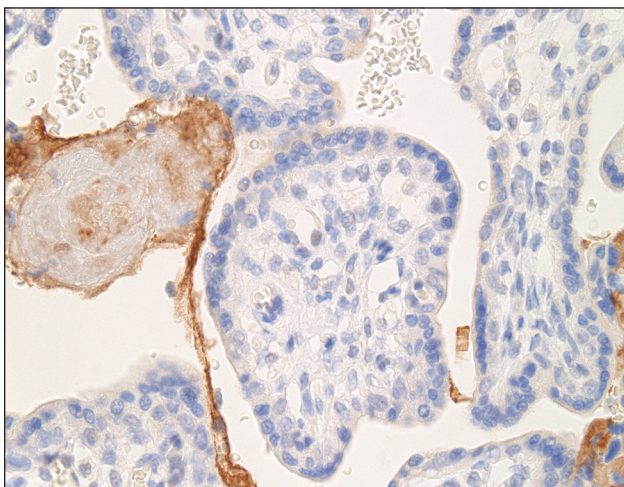
a Leica Bond III instrument used the Bond Polymer Refine Detection System (Leica Biosystems DS9800). Heat-induced epitope retrieval was done for 20 minutes in Epitope Retrieval Solution 1 (Leica Biosystems AR9961).

DISCUSSION

Although no formal diagnosis of maternal vascular malperfusion (MVM) occurred, these cases had many features consistent with MVM, such as gross findings of placental infarction and hemorrhage, and microscopic findings of extensive intervillous and perivillous fibrin deposition.[3,6] These findings align with those described in much of the literature on placental pathology associated with SARS-CoV-2 infections.[1-4] Further, although fetal vascular malperfusion (FVM) has been associated with COVID-19,[1,2,7] there was no evidence of FVM in this case.
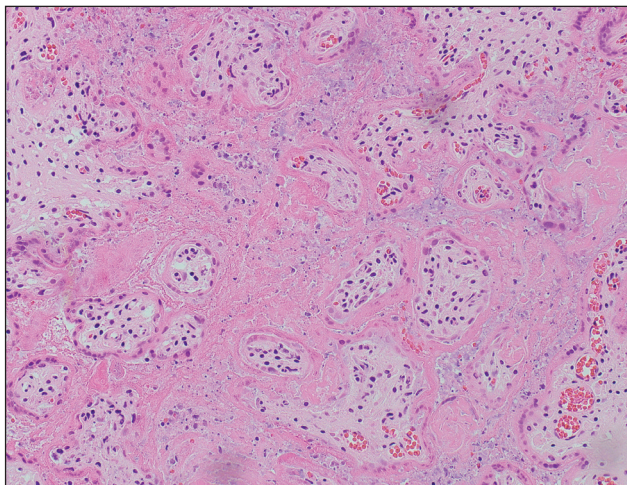
Fig. 2a. Extensive intervillous and perivillous fibrin deposition with associated villous infarction, 10X (Case 1).
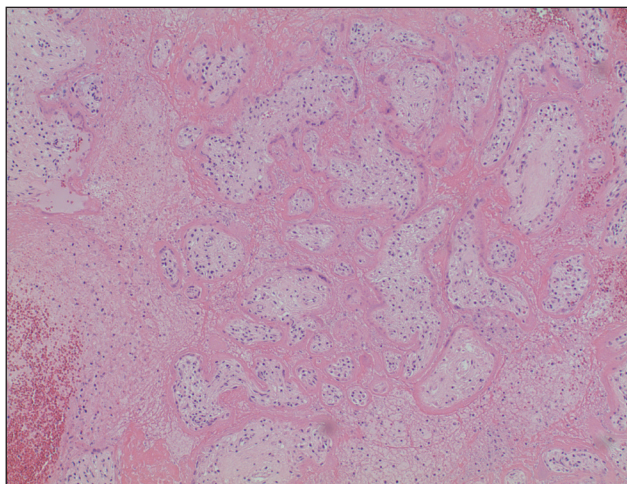
Fig. 2b. Extensive intervillous and perivillous fibrin deposition with associated villous infarction, 20X (Case 1).

In addition, there was no evidence of any vasculopathy, which has been reported to be one of the main features of MVM associated with COVID-19.[13] No acute or chronic inflammation was noted, which is consistent with a subset of SARS-CoV-2 positive pregnancies that exhibit no inflammatory response.[1,2,8] Other studies have demonstrated clear evidence of inflammation in SARS-CoV-2 infection-associated pregnancies through pathologies such as villitis, intervillositis, deciduitis, chorioamnionitis, and funisitis.[3,4,9] It is important to note that the lung sections collected during the fetal autopsy showed scattered collections of degenerated cells within the alveolar spaces, possibly representing neutrophils (and thus serving as potential evidence for inflammation).

Pregnant women have increased levels of ACE 2 receptors in the placenta to help facilitate fetal growth and regulate angiotensin-II levels. Due to the transmembrane ACE 2 providing a point of entry into cells, viruses such as SARS-CoV-2 can enter the syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle of villi where ACE 2 is significantly expressed.[10] Given this virus's association with the activation of coagulation pathways and potential progression to fibrinolysis,[11] there is enough evidence to suggest hypercoagulopathy leading to thrombosis or increased fibrin deposition resulting in associated villous infarction or hemorrhage.[1-4] These histopathological features appear to exist regardless of COVID-19 symptomatology.

Viral particles, such as SARS-CoV-2, can induce activation of the alternative and lectin complement pathways, causing the deposition of several complement proteins.[12,13] One of these complement proteins, C4d, has been used as a biomarker to detect antibody-mediated disease, and it has applications for detecting antibody-mediated injury in placental tissue.[14,15] Since covalently bound C4d has a greater chance of staying at the original site of complement activation than the antibodies themselves, and because it anchors tightly to the tissue, it was utilized for the immunostain over other complement proteins and immunoglobulins.[14] Consequently, complement staining of C4d was performed to assess for immune-complex-mediated deposition.

In case 1, the syncytiotrophoblastic layer of the placental villi had evidence of significant and uniform C4d deposition, especially when compared to the control placenta. A related study also found C4d in the syncytiotrophoblastic layer of chorionic villi, with C4d expression being more significant in preeclampsia placenta relative to placenta lacking complications.[15] It is important to note that while C4d deposition in the preeclampsia placenta was correlated with increased syncytial knots, it was not associated with any other histologic features.[15]

In addition, positive C4d staining (defined as >10% syncytiotrophoblast C4d immunoreactivity) has been associated with a lower gestational age at delivery, lower infant birth weight, and lower placental weight compared with cases showing no C4d staining.[15] These factors could help explain the significant C4d deposition we saw in our case. Our results were unlike those of researchers who found similar complement staining patterns in placentas from patients who were either positive or negative for SARS-CoV-2 infection.[12]

When SARS-CoV-2 infects cytotrophoblasts and syncytiotrophoblasts, it elicits complement activation and triggers inflammatory cytokines, which are thought to cause a procoagulant environment. More specifically, the complement fixation along the villi border might damage the microvillous syncytiotrophoblastic membrane, which is then responsible for the complement activation and subsequent C4d deposition.[16]

Other researchers postulate that the C4d deposition along the microvillous border of the syncytiotrophoblasts may be responsible for the subsequent fibrin deposition and histiocytic influx.[16] This may contribute to the histological features we saw in both cases, although only the first case underwent C4d immunostaining. Unfortunately, available literature regarding the use of C4d staining in SARS-CoV-2 affected placentas remains scarce.

CONCLUSION

ISH stain for C4d is more conclusive and widely used than C4d immunostain.[17] In our case, it confirmed the presence of SARS-CoV-2 viral antigens in the placenta and adds evidence to the possibility of vertical transmission of SARS-CoV-2. C4d present in the placenta increases the likelihood that SARS-CoV-2 could have been involved in the histopathological findings presented and the eventual fetal demise in our case.

This study is subject to some limitations. First, we were unable to perform PCR testing on either of the fetuses and amniotic fluid to confirm vertical transmission of infection.[8] In addition, the first patient's past medical history of anemia and smoking can potentially serve as a contributing factor to the fetal outcome.

The extent of placental changes seen is the most logical contributing cause of fetal demise observed in both cases. Nonspecific, extensive intervillous fibrin deposition, as well as other features of MVM, have been seen in cases of active COVID-19,[14] even in the setting of an asymptomatic mother.[1,3]

Consistent with our findings, it appears that pregnant women with SARS-CoV-2 infections, regardless of symptomatology, are more likely to exhibit adverse fetal outcomes and have more frequent placental histopathologic abnormalities.[18,19] Researchers have found that compared to controls, women who had been infected were more likely to evolve to preterm labor and infant death, and their placentas were more likely to show features of MVM and FVM.[18]

Recent publications demonstrate a greater rate of placental histopathologic abnormalities among patients with a history of SARS-CoV-2 infection compared to controls, especially FVM and villitis of unknown etiology, although they did not observe an increase in other placental histopathologic lesions.[19] Other researchers have identified similar fetal and maternal outcomes between infected and uninfected groups, as well as no significant difference in observed placental gross or microscopic morphology.[20]

Fig. 2c. Gross examination of the placenta reveals patchy hemorrhage throughout the placental parenchyma (Case 1).
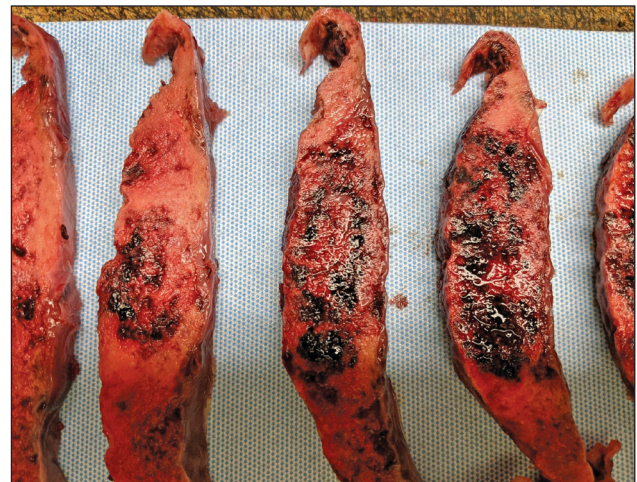
Fig. 2d. Gross examination of the placenta reveals patchy hemorrhage throughout the placental parenchyma (Case 2).

This case discussion highlights the need for more studies to further establish the clinicopathological correlations of SARS-CoV-2 infection during pregnancy. Doing so would enable providers to better understand their implications as they pertain to maternal health and fetal growth, and to help facilitate improved perinatal outcomes. Until then, increased antenatal surveillance and specialized care is needed for pregnant women diagnosed with SARS-CoV-2.

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EMERGENCY CONTRACEPTIVES
Breaking Down the Indications for Use

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CLINICAL CASE

A 19-year-old nulliparous patient you saw for well child care until the patient left for college calls your office and asks for an urgent call back. The patient had sex for the first time yesterday. The condom broke, and the patient is worried about pregnancy. The patient has been taking a combined hormonal contraceptive pill since high school and has missed a few doses. The patient's last menstrual period was two weeks ago. What options does the patient have to avoid an undesired pregnancy?

INTRODUCTION

Emergency contraception (EC) reduces the risk of pregnancy after unprotected sexual intercourse. People use EC when birth control is misused or fails, when a condom breaks, or after sexual assault. Emergency contraception does not interfere with an existing pregnancy and does not cause abortion.

Some patients may feel ambivalent about formalizing their contraception plan when asked in their physician's office, but have a clear preference to prevent pregnancy when faced with this possibility later on. Unfortunately, many sexually active people in relationships do not have full autonomy in their reproductive decision-making and are prevented from using contraception.

However, oral EC offers a way to reduce the risks for and consequences of undesired pregnancy. Emergency contraception is a critical part of sexual and reproductive health care.

Because all forms of emergency contraception must be administered soon after unprotected intercourse and because accessing EC can be time consuming, it is reasonable and recommended to provide prescriptions for oral EC in advance so patients may use emergency contraception as soon as possible when it is needed. This practice is called *advanced provision*. A 2007 Cochrane Review demonstrated that advanced provision was not associated with negative sexual or reproductive health outcomes.[1]

In 2019, the American Academy of Pediatrics released an updated policy statement on EC recommending that pediatricians provide emergency contraception to adolescents and young adults who have an urgent need and recommended advanced provision of emergency contraceptive pills. Furthermore, they recommended:

> [All] adolescents receive counseling about EC as part of routine anticipatory guidance in the context of a discussion on sexual health and family planning regardless of current intentions for sexual behavior. In addition, it is important that information about EC be included in all contraceptive and STI counseling for adolescents wherever these visits occur, including emergency departments, clinics, and hospitals. Information provided should include indications for use and options for access, including over-the-counter availability and advance prescription or supply if available in the clinic. It is important that pediatricians also provide this counseling to adolescents with physical and cognitive disabilities and their parents.[2]

They went on to suggest that regarding policy, health care professionals "should advocate for low-cost or free, nonprescription access ... for teenagers regardless of age and insurance coverage of EC without cost sharing to further reduce cost barriers."

DEMOGRAPHICS

Use of emergency contraception is increasing. In 2015, 23% of sexually active women aged 15-44 in the United States reported they had used EC, compared to 11% in 2008. Increased use of EC is seen across demographic groups — regardless of age, race and ethnicity, income level, education, religion, marital status, and women's number of births.

During the same period, the Affordable Care Act's contraceptive coverage guarantee took effect, and some forms of EC became available over the counter. Of note, this data only includes oral EC and does not include intrauterine devices (IUDs) for EC.[3]

METHODS AND CLINICAL CONSIDERATIONS

There are currently a number of safe and effective forms of EC: the Copper TCu380A IUD and levonorgestrel 52 mg IUDs, oral levonorgestrel, and oral ulipristal. Patients may also utilize large doses of combined hormonal contraceptives; this regimen is known as the Yuzpe method.

The most effective forms of EC are IUDs. The copper IUD (Paragard®) and the 52 mg levonorgestrel IUDs (Mirena® and Liletta®) can all be used for EC when inserted within five days of unprotected intercourse.[4] The pregnancy rate following IUD insertion for EC is less than 1%. IUDs work as EC regardless of BMI.[5] They are an excellent choice for anyone who wants ongoing highly effective contraception (for up to 12 years with the copper IUD and up to seven with a levonorgestrel-containing IUD). They are the most expensive form of EC — both for the device and required insertion.

The mechanism of action of an IUD for EC is thought to be inhibition of sperm function and inhibition of fertilization through direct effects on sperm, as well as thickening of cervical mucous and endometrial receptivity, thus creating an inhospitable environment. There is no evidence to demonstrate that IUDs have post-implantation effects.[6,7,8,9]

Risks of IUD insertion include pelvic pain or abdominal cramping, vaginal bleeding, and much lower risks of infection and uterine perforation.

If pregnancy occurs despite IUD as EC, the patient should receive options counseling. The IUD will need to be removed, and the patient can initiate prenatal care or abortion care.

Two oral forms of EC are currently available. Both oral levonorgestrel and ulipristal prevent ovulation. Neither method will prevent ovulation after luteinizing hormone (LH) peaks, nor will they interfere with implantation of a fertilized egg or an established pregnancy.[10]

Levonorgestrel (abbreviated LNG, brand names PlanB® or Next Choice®) is the most commonly used and most available method. It works to inhibit ovulation by blocking the luteinizing hormone surge, which subsequently prevents follicle development. LNG loses efficacy if the LH surge has started. This method will not work if fertilization has already occurred as it does not affect implantation of a fertilized egg.[11]

The efficacy decreases with increasing time between unprotected intercourse and LNG administration, thus it must be taken as soon as possible within 72 hours. Because of the urgency of medication administration, advanced provision of EC, as described above, is advisable. Evidence suggests oral LNG loses efficacy for individuals with BMI >26.[12,13] Efficacy also varies depending on the timing of unprotected intercourse within an individual's menstrual cycle; LNG is not as effective once a patient has ovulated (typically day 14 of her cycle). Another form of EC should be considered.

If a patient desires ongoing contraception at the time of LNG use, any contraceptive method can be prescribed on the same date. There is no interference between levonorgestrel EC and other birth control methods. A typical seven-day backup method or abstinence period should be recommended. Breastfeeding after use of LNG is safe.

All levonorgestrel EC products are now approved for over-the-counter sale without age or gender restrictions, but the reality of access may vary in each community. The original levonorgestrel EC was approved in 1999 as a two-dose prescription product. In 2006, LNG was approved for nonprescription sale for anyone over the age of 18. And in 2009, the limit was lowered again to age 17. The product was available to women under age 17, but required a prescription and was held behind the counter so that age restriction could be enforced prior to purchase. Plan B One-Step®, an LNG product, was approved for unrestricted sale in 2013, but the age-restricted label remained for generics until 2014.[14]

Patients should be informed that LNG is available to anyone regardless of gender or age without a prescription. They may have to talk to pharmacy staff, as some stores keep the product behind the register or in locked boxes to prevent theft. If purchased over the counter (either in stores or online), the cost can be $15 to $50. If prescribed, the medication is usually covered as part of the Affordable Care Act's contraceptive coverage guarantee. It is on Pennsylvania's Statewide Preferred Drug List and, if prescribed, is available with no co-pay.

Ulipristal (abbreviated UPA, brand name ella®) is a selective progesterone receptor modulator that works by mimicking and blocking progesterone, which can delay ovulation before and even after the LH surge has begun. There is no evidence that UPA interferes with fertilization or disrupts an established pregnancy.[15]

UPA is more effective than LNG and can work for five days after unprotected intercourse.[11,16] Patients should be counseled to take the medication as soon as

possible. UPA loses efficacy in higher BMI individuals and may be ineffective for individuals with BMI >35.[13] It is important to explain the effect larger body size may have on efficacy of ulipristal EC so a patient may make an informed choice about EC. UPA requires a prescription and is usually available for $40 to $50 with a GoodRx coupon. It can be found at low cost on-line and/or from international pharmacies. Advanced provision of ulipristal EC is advisable.

The Centers for Disease Control and Prevention's (CDC's) Medical Eligibility Criteria do not restrict UPA while breastfeeding, but do recommend expressing and discarding breast milk for 24 hours after taking UPA based on limited evidence.

Progestin-containing contraceptive methods may interfere with UPA. Any desired ongoing contraception — that is, subsequent use of progestin-containing contraceptives (including progestin-only birth control pills, combined estrogen-progestin pills, patch or ring, depot-medroxyprogesterone acetate injection, or

Fig 1. A Visual Guide to Choosing an Emergency Contraceptive Method

Urgent Need: Unprotected Intercourse <72h Prior to Encounter

Note: Both LNG and UPA are ineffective if patient has already ovulated.

If efficacy is most important factor for patient, IUD recommended.

Other considerations for specific patient:

Elevated BMI

If patient prefers most efficacious method, IUD recommended.

BMI >26: LNG may not be effective.

BMI >35: UPA may not be effective.

If patient prefers oral method regardless of BMI, offer preferred method.

Choose IUD based on patient preferences for IUD MOA or side effect profile.

Desires ongoing contraception

IUD: Choose based on patient preferences for MOA or side effect profile.

LNG: Administer, start any follow-up method with 7-day abstinence/backup method.

*UPA: Administer; can use barrier/nonhormonal method right away *or* use 5-day window if initiating progestin-containing contraception.

Cost

Determine if IUD covered by insurance plan.

LNG will have $0 copay for PA Medicaid plans.

LNG can be purchased without insurance OTC.

*UPA requires Rx, will cost $40-$50.

Preference for Yuzpe method

Can obtain combined oral contraceptives but not EC method

Worry about cost or privacy

Understands side effects and decreased efficacy

Urgent Need: Unprotected Intercourse 72-120h Prior to Encounter

Note: Both LNG and UPA are ineffective if patient has already ovulated.

Other considerations for specific patient:

Elevated BMI

If patient prefers most efficacious method, IUD recommended.

BMI >35: UPA may not be effective.

If patient prefers oral method regardless of BMI, offer preferred method.

Choose IUD based on patient preferences for IUD MOA or side effect profile.

Desires ongoing contraception

IUD: Choose based on patient preferences for MOA or side effect profile.

*UPA: Administer; can use barrier/nonhormonal method right away *or* use 5-day window if initiating progestin-containing contraception.

Cost

Determine if IUD covered by insurance plan.

LNG will have $0 copay for PA Medicaid plans.

LNG can be purchased without insurance OTC.

*UPA requires Rx, will cost $40-$50.

Non-Urgent Need: Advanced Provision

Discuss all methods, and educate that patient may present for IUD for EC.

For LNG and *UPA: — Explain cost difference.
— Explain efficacy difference with elevated BMI.
— Explain interaction of LNG with other forms of contraception.

IUD = intrauterine device
LNG = levonorgestrel
UPA = ulipristal
BMI = body mass index
MOA = mechanism of action
EC = emergency contraception
Rx = prescription
OTC = over the counter

*Local considerations — if urgent need for EC, confirm that UPA is stocked at pharmacy.

etonogestrel implant) — must be delayed at least five days following UPA administration.

Despite increased efficacy of UPA compared to levonorgestrel EC, it is not always available in pharmacies for same-day use. A number of studies have investigated accessibility of LNG and UPA in pharmacies.[17,18] A 2021 survey of southwestern Pennsylvania pharmacies revealed that only 5% of pharmacies had ulipristal in stock.[19] This author called four pharmacies in Lancaster (including one LGH Convenience Pharmacy and three retail pharmacies), and none had UPA in stock for same-day use.

For both forms of oral EC, patients may experience nausea, vomiting, headache, dizziness, abdominal pain, or breast pain.[20] Individuals should be counseled to take a home pregnancy test if they have not had a period within a week of their expected cycle.

Efficacy for both oral EC methods decreases with repeated unprotected intercourse, especially during the fertile window. The CDC's Medical Eligibility Criteria may be referenced for further questions about medication interactions, contraindications, or safety.[21]

Clinicians may be asked about the Yuzpe method — named for Canadian obstetrician-gynecologist Albert Yuzpe, MD. This method requires specific combinations of combined hormonal contraceptive pills (100 mcg ethinyl estradiol and 0.5 mg levonorgestrel) taken twice, 12 hours apart. A number of common birth control brands can be arranged in the appropriate doses; lists of these combinations can be found online.

This method is the least effective of all emergency contraceptives. Side effects including nausea, vomiting, spotting, and headaches are common. It is reasonable to offer an antiemetic to help with these side effects. With the other available and effective forms of long-acting reversible contraception and EC, the Yuzpe method has fallen out of common practice. However, for patients who already have an oral contraceptive prescription at home, it is convenient, private, and does not incur additional cost.

In-person or telehealth visits, pelvic exams, or pregnancy tests are not required for EC prescriptions. Either persistent bleeding or delayed bleeding following oral EC use should prompt an evaluation for pregnancy.[22,23]

If a patient suspects pregnancy, it is reasonable to test for pregnancy and offer options counseling. If pregnancy occurs despite use of emergency contraceptive pills (either LNG or UPA), there are no known adverse outcomes to the developing fetus. Patients should be offered options counseling and appropriate follow-up for prenatal or abortion care.

Repeated use of EC is not harmful, nor does it lead to infertility.[24,25] For a visual guide to choosing an emergency contraceptive method, see Fig. 1 on page 11.

OPPORTUNITIES

Anyone who is having sex or plans to become sexually active should have access to EC. Access to EC includes medically accurate, evidence-based counseling, same-day availability of prescriptions and procedures, advanced provision, and insurance coverage for all methods.

Emergency contraception is an appropriate topic for discussion in a variety of patient encounters (see Table 1).

Table 1. Clinical Opportunities to Discuss and/or Offer Advanced Provision of EC
Wellness exams for teenagers (in context of counseling for safe sex and healthy relationships)
Prenatal visits when discussing postpartum contraception plans
Following childbirth
Following pregnancy loss
Encounters for testing and treating sexually transmitted infections, including visits for PrEP (HIV pre-exposure prophylaxis) and PEP (HIV post-exposure prophylaxis)
Encounters where a patient discloses intimate partner violence
Encounters for any patient of reproductive age, particularly those new to your practice, so they know this is a service your office can provide

CONCLUSION

The patient described at the beginning of this article is a candidate for LNG, UPA, or an IUD for emergency contraception (see Fig. 1). Since it is approximately day 14 of their menstrual cycle, LNG may be ineffective. If they would like to use UPA and subsequently continue their oral contraceptive, there should be a five-day window before resuming their birth control pill. They could also be counseled on the Yuzpe method if desired.

Preventing an undesired pregnancy is an emergency. Patients deserve education about EC as part of their contraception counseling. Clinicians should be aware of the forms of EC, understand the indications for use, and be prepared to deliver patient-centered care including EC for our patients.

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Two Cases of Syncope in Children
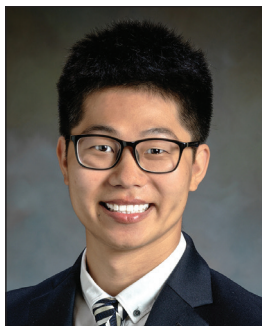
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Syncope is an acute, transient loss of consciousness associated with loss of postural tone and spontaneous recovery. Syncope is a common problem in children presenting to emergency departments. Before adolescence, about 15% of children have at least one episode. The common causes include vasovagal reactions, orthostatic reactions, breath-holding spells, and reactions to acute ingestions. Only 2% of patients have a serious underlying cardiac cause.[1] While less common, it's important to rule out insidious cardiac causes.

As is the case with all presenting chief complaints, a thorough family history is helpful in elucidating the cause. Regarding posture, timing of the event and the associated activity are important. Pallor, diaphoresis, visual or auditory changes, dizziness, palpitations, hyperventilation, nausea, incontinence, seizure-like activity (including timing of seizures), presence of a postictal state, and prodromal vision/hearing changes can be helpful. The absence of vigorous exercise or pain, and a history of skipped meals, point toward a non-cardiac cause. Exertional syncope is a good indicator that the etiology may be cardiac.

Children with mid-exertional syncope may be manifesting cardiac disease and warrant evaluation.[2] One also must be vigilant for red flags associated with events occurring during periods of high emotions, as they relate to potential catecholamine surges.

Physical examination for the undifferentiated syncopal event should include orthostatic vitals. Auscultation of murmurs is helpful, especially those consistent with left ventricular outflow tract disease and mitral regurgitation. Characterizing a particularly prominent S2 is also important, as it may indicate pulmonary hypertension.[3]

The cardiac etiologies of syncope can be grouped by the following general framework: electrical, structural, or acquired. The differential for each is broad. See Fig. 1 for common causes and their incidence.

Some important electrical etiologies to consider include Wolff-Parkinson-White (WPW), Long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), and arrhythmogenic right ventricular cardiomyopathy (ARVC). This review will focus on only a few electrical and structural syndromes.[3]

CASE 1

An otherwise healthy 12-year-old male presents to the office for pre-participation school sports screening. His mother reports one episode of syncope during a particularly hot summer day while playing soccer, which they had attributed to dehydration. On further questioning, he states that he sometimes has "a funny feeling in his chest" during other sports. There is no family history of cardiac disorders.

An EKG (see Fig. 2 on page 17) reveals a shortened PR interval and a wide QRS complex with a slurred onset of the QRS waveform, consistent with the WPW pattern. How would you counsel the patient and his parents regarding this finding, and is a cardiology consult warranted?

Pathophysiology

In the normal heart, electrical impulses travel from the atria and are delayed by the AV node before moving on to the ventricles. WPW is characterized by an accessory pathway, also known as the bundle of Kent, that bypasses all or part of the AV node. This additional conduction tissue is congenital and is the result of remnant myocardial syncytium at the annulus fibrosus that failed to resorb during fetal development. It is more conductive, and as electrical impulses take the path of least resistance, we see a preexcitation of the ventricles.[4]

When conduction bypasses the AV node, we see a shortening of the PR interval; in the case of WPW, we see a characteristic "slurred" upstroke of the QRS complex known as a delta wave. The WPW pattern on the EKG may be intermittent and may even disappear

permanently over time. In several large cohorts, the frequency of intermittent preexcitation appears to range from 10% to 40%.[5]

This accessory pathway does not lead to sudden events; however, it is a nidus for re-entrant SVTs both in children and adults. In the adult population — and rarely pediatric patients — should atrial fibrillation occur, the accessory pathway enables the arrhythmia to deteriorate to ventricular fibrillation (VF).

Wolff-Parkinson-White Epidemiology

In a review of more than 22,000 adults, the prevalence of a WPW pattern on EKG is estimated to be between 0.13% and 0.25% of the general population. Only 1.8% of those with the preexcitation pattern had

documented arrhythmias, i.e., WPW syndrome. In a study of over 430,000 children, ages 6 to 20 years, the prevalence of WPW syndrome was 0.07%. Males are more commonly affected than females. A proportion of WPW cases are due to a familial syndrome, but many have no family history of this disorder.

WPW EKG Pattern

The WPW EKG pattern has two classic components: first, a PR interval less than 0.12 seconds due to rapid conduction of the accessory pathway that bypasses the AV node; and second, slurring of the upstroke of QRS complex. It should be noted that this classic pattern occurs only when the accessory pathway conducts in an antegrade direction. If the pathway

Most Common Causes of Syncope in Children
(percentage of cases)

Major Cardiac Causes

59%	Indeterminate Cause
17%	Arrhythmia
6%	Mechanical
5%	Reflex
3%	Long QT Syndrome
2%	Sinus Node Dysfunction
1%	Third-Degree AV Block
1%	Primary Pulmonary Hypertension

2% Other*
1% Situational
1% Orthostatic Hypotension
2% Psychiatric
2% Tilt Induced
2% Breath-Holding Spell
3% Neurologic
4% Cardiac
13% POTS (postural tachycardial syndrome)
52% Vasovagal Syncope (also known as neurocardiogenic reflex/situational sycope, or common fainting)
18% Indeterminate Cause

Fig. 1. The incidence in the general population in the United States is 1:500 for HCM and 1-3.1:1,000 for WPW.

Orthostatic hypotension may include volume depletion (hemorrhage or dehydration), pregnancy (venous pooling), anemia, anorexia nervosa, and medications (calcium channel blockers, vasodilators, phenothiazines, diuretics).

*Among non-cardiac causes, "Other" can include hyperventilation, hypoglycemia, intoxication, migraine, and trauma.

Other cardiac causes include AV node reentry tachycardia, supraventricular tachycardia, exertional tachycardia, primary myocardial disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, carotid sinus hypersensitivity, and sick sinus syndrome.

Data for charts from Zavala R, Metais B, Tuckfield L, DelVecchio M, Aronoff S. Pediatric syncope: a systematic review. *Pediatr Emerg Care.* 2020;36(9):442-445. Additional references: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0227012; https://rarediseases.org/rare-diseases/wolff-parkinson-white-syndrome/

conducts retrograde, from the ventricles to the atria, there will be no delta wave.[4]

Due to the electrophysiological changes of WPW, EKG findings can be similar to those seen in myocardial infarction (MI), premature ventricular contractions (PVCs), cardiomyopathies, and bundle branch blocks. A negative delta wave may mimic a Q wave, and a positive delta wave may obscure one. Intermittent WPW is occasionally seen on alternate beats and may resemble ventricular bigeminy. If the pattern persists for several beats, it can resemble an accelerated idioventricular rhythm. Preexcited beats are sometimes confused with left or right bundle branch block. EKG changes due to congenital heart defects such as atrial enlargement or hypertrophic cardiomyopathy can sometimes be confused with WPW due to abnormal depolarization.[4]

Workup and Risk Stratification

There are differing opinions on the approach to patients with preexcitation, but there is consensus that adolescent/pediatric patients discovered to have this rhythm should be referred to a specialist in pediatric cardiology/electrophysiology (EP) to initiate risk stratification. Typically, this includes exercise testing to determine the shortest cardiac cycle length at which the accessory pathway is suppressed, if at all, and potentially requires invasive electrophysiology studies.[6]

Management

With referral, treatment, and patient education, patients with WPW syndrome can expect to have a normal life expectancy and good quality of life.[7] Patients with WPW syndrome may be treated acutely with adenosine. Caution should be used in the use of AV nodal blocking agents, as these can propagate deterioration of the arrhythmia, should the patient be in atrial fibrillation and not re-entrant SVT. Radiofrequency ablation is first-line treatment for those with symptomatic tachyarrhythmias and those deemed higher risk based on EP studies or cardiac history. Unstable patients require immediate cardioversion.[8]

Management of asymptomatic individuals is less clear given the low risk of arrhythmia and sudden death, which appeared comparable to the risk of ablation in a recent meta-analysis.[9] If episodes of SVT are infrequent but last more than one hour, a "pill-in-the-pocket" approach may be effective. These patients can self-administer an as-needed dose of non-dihydropyridine

calcium channel blockers, beta blockers, or antiarrhythmics. Effectiveness of this approach ranges from 30% to 60%.[10] Shared decision-making with input from cardiology is important in deciding what plan is most appropriate.

Summary

The WPW syndrome is due to an accessory pathway of the AV ring and causes a pattern on EKG classically described as a shortened PR interval with a slurred upstroke of the QRS complex, termed a delta wave. This pattern may be intermittent. The prevalence of the WPW pattern is estimated to be 0.13% to 0.25% and may disappear permanently over time. Most asymptomatic patients can be cautiously observed; a cardiology referral for our patient regarding risk stratification yielded this advice.

CASE 2

A 13-year-old female presented after "passing out" during gym class. She was found to be pulseless, thus her coach quickly applied an AED and gave one shock before she was transferred to the hospital where further evaluation was performed. An EKG showed left ventricular hypertrophy and demonstrated Q waves in the inferior and lateral leads. An echocardiogram confirmed left ventricular hypertrophy. The patient was diagnosed with hypertrophic cardiomyopathy.

Epidemiology of Pediatric Hypertrophic Cardiomyopathy

The incidence of cardiomyopathy in children younger than 18 years old is 0.47 to 1.5 cases per 100,000 per year.[11,12] Hypertrophic cardiomyopathy (HCM) is the most commonly inherited cardiomyopathy and can be caused by various genetic mutations. Pediatric HCM incorporates a large group of various disorders. Primary HCM is caused by a sarcomeric gene mutation and is the most common cause. Secondary HCM, or non-sarcomeric-caused HCM, includes inborn errors of metabolism, malformation syndrome, neuromuscular disease, and mitochondrial disease, which are responsible for approximately 35% of HCM in children worldwide.

Inborn errors of metabolism and malformation syndromes are common causes of HCM in infancy, and are often associated with neurological and musculoskeletal abnormalities.[12] In contrast, HCM due to sarcomeric mutations may not be diagnosed until adolescence or early adulthood, and are most commonly those identified as "familial cases." Therefore, age at presentation and the HCM
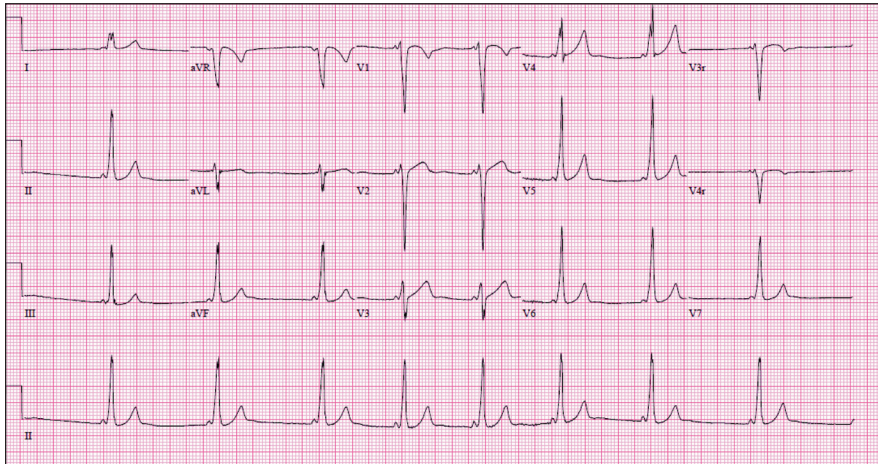
Fig. 2. EKG showing shortened PR interval and wide QRS complex.[3]

etiology are important for predicting outcomes and progression of the disease.[13]

Pediatric Hypertrophic Cardiomyopathy Pathophysiology

HCM is characterized by hypertrophy of cardiac myocytes without dilatation of the left ventricle (LV), and most commonly, normal left ventricular systolic function. The phenotype familiar to most primary care practitioners is that of hypertrophy of the basal portion of the septum causing left ventricular outflow tract (LVOT) obstruction in the setting of concurrent systolic anterior motion of the mitral valve. However, it is important to remain vigilant regarding subtle cases that involve other areas of the myocardium, including solely the apex. Cardiac myocytes are not only hypertrophied but also disorganized and separated by areas of fibrosis which can lead to arrhythmias.[14]

Arrhythmias and a primary hemodynamic mechanism in the setting of LVOT obstruction are the two underlying mechanisms for syncope in patients with HCM. Prolonged repolarization of transmembrane action potentials and changes of composition and ion channels in hypertrophic cardiac myocytes can also cause arrhythmias. Finally, repetitive microvascular ischemia can cause scarring, further precipitating ventricular tachyarrhythmias and atrial fibrillation.[14]

Clinical Presentation

Patients with HCM can have a wide range of presentations, from remaining asymptomatic to having palpitations, chest pain, cardiac arrest, and even sudden death.

Hypertrophied cardiomyocytes with an increased oxygen requirement may become ischemic because the thickened heart wall reduces blood flow by narrowing the lumen of coronary arteries. Patients may complain of exertional chest pain that improves with rest. LVOT obstruction may also lead to palpitations, exertional pre-syncope, or syncope. Palpitations in these patients need to be thoroughly evaluated as they can represent both atrial and ventricular ectopy/tachyarrhythmias.

Sudden cardiac death (SCD) is mostly caused by deterioration of a ventricular arrhythmia. Atrial fibrillation (AF) can be found in about 25% of HCM and LVOT obstruction patients. Dilation of the left atrium and LVOT obstruction are common causes of AF. In turn, AF may lead to heart failure, left ventricular end diastolic pressure elevation, and thromboemboli.[13]

On physical examination, patients with HCM may demonstrate signs of left ventricular hypertrophy (LVH), such as leftward cardiac impulse displacement, cannon A wave, prominent S4, or presystolic apical lift. The LVOT obstruction causes a murmur characterized as a harsh and mid-systolic heartbeat at the apex and left sternal border. Maneuvers that decrease LV volume will increase the intensity of the murmur. In addition, a mitral valve regurgitation murmur can be common in patients with HCM.[14]

Workup

Evaluation of suspected HCM starts with an EKG to look for pathologic Q waves and abnormal repolarizations. Signs of LVH on EKG are nonspecific and found in normal children and adolescents. While cardiac MRI is considered the gold standard for diagnosis, an echocardiogram is 80% specific.[15,16] Regarding echocardiogram, LV wall thickness greater than 15 mm that is not explained by other factors is considered diagnostic. Other echocardiogram findings suggestive of HCM include LVOT obstruction, especially in the setting of systolic anterior motion of the mitral valve leaflet.

Patients with metabolic HCM may have an echocardiogram that shows a concentric biventricular hypertrophy. In contrast, sarcomeric and syndromic HCM echocardiograms tend to have an asymmetrical septal hypertrophy. LVOT obstruction is seen in 25%

to 40% of children with HCM. Diastolic dysfunction as detected by echo can be an early indication of the development of HCM, as can the presence of Q waves on EKG or arrhythmias in those at risk of developing it.[14]

All patients with HCM should be offered genetic testing and counseling, and if a pathogenic variant is the cause, genetic testing should be offered to all first-degree relatives as well. Sarcomeric HCM is inherited in an autosomal dominant pattern with variable expression and incomplete penetrance. First-degree relatives found to be positive for the pathogenic genotype should be offered screening imaging and ongoing clinical surveillance.[14,17,18]

If a patient does not have pathologic HCM genetic variants, then first-degree relatives do not need genetic testing. However, genetic screening is evolving, thus the discussion of whether to test may be an ongoing conversation.[14]

Patients should also be screened for SCD risk factors, including previous adverse cardiac events, non-sustained ventricular tachycardia, unexplained syncope, family history of early HCM-related SCD, and extreme LVH.[16] According to the 2020 American Heart Association guidelines, further risk factors such as apical aneurysm, decreased LV systolic function, and extensive gadolinium enhancement should be considered.

Treatment

Patients should be referred to pediatric cardiology after being diagnosed with HCM or if there is high clinical suspicion. Cardiovascular magnetic resonance (CMR) may be useful in patients with inconclusive echocardiogram results, especially if suspected of having metabolic storage disorder. CMR may also assist with assessing the risk of SCD by measuring late gadolinium enhancement.[19]

ICD implant should be considered for any patient with SCD risks factors, and patients with HCM and a previous documented cardiac arrest or sustained ventricular tachycardia should consider an ICD for secondary prevention of SCD.[20]

Symptom control and prevention of SCD are the main goals of treatment. Symptomatic treatment of adult HCM is well established, however pediatric HCM is not well studied. The underlying approach is the same:

- avoid peripheral vasodilatation,
- maintain adequate intravascular volume, and

- consider beta blockers to allow increased filling time in those with severe hypertrophy or obstruction.

Beta blockers have also been shown to prevent SCD events. If beta blockers are contraindicated or do not improve symptoms, then a non-dihydropyridine calcium channel blocker like verapamil or diltiazem can be added. Disopyramide can be considered for patients with persistent symptoms. Diuretics should be avoided as they can deplete intravascular volume.[21]

An anticoagulant should be considered for stroke prevention if patients have atrial arrhythmias. Patients with AF with rapid ventricular rate (RVR) may benefit from medications that control either rate or rhythm.[21]

Septal reduction can be done by surgery or ablation. The goal of this procedure is to reduce LVOT obstruction. Mitral valve regurgitation may improve after septal myectomy, but valves can be injured during the surgery.[22] Treatment for those with severe cases can also include cardiac resynchronization, LV assistant device, or cardiac transplantation.[21]

Advice regarding exercise for children with HCM is a controversial topic. Exercise restriction for adolescents can affect their mental health and lead to social isolation and depression. Most recent information suggests that moderate-intensity exercise could be useful and does not increase the risk of arrhythmias.[22] Higher intensity exercise may be pursued if they are genotype-positive, but phenotype-negative. Most importantly, shared decision-making and multidisciplinary care are essential and can lead to better outcomes.[23]

Summary

Like all patients, pediatric patients with syncope should be evaluated for possible cardiac causes. Syncope with exertion, or soon after, is concerning, as HCM can result in LVOT obstruction or arrhythmias. An EKG and echocardiogram should be done in patients suspected of having cardiac etiology.

Returning to the patient described in the second case, initial management of HCM includes removing stressors, ensuring adequate hydration, and avoiding peripheral vasodilatation to limit symptoms. Restricting activity until further evaluation is prudent; screening and surveillance of her first-degree relatives is recommended. A referral to pediatric cardiology will assist in management, as will shared decision-making and a frank conversation about the value of exercises and the balance of lifetime risk factors.

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LIPID UPDATE
What Should Be Done About Residual Triglycerides?

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Non-high-density lipoproteins (non-HDL) is a measurement of the sum of low-density lipoproteins (LDL), intermediate-density lipoproteins (IDL), very low-density lipoproteins (VLDL), chylomicron remnants, and lipoprotein (a). Triglycerides are a portion of non-HDL, represented in VLDL and chylomicron remnants.

Triglyceride-rich lipoproteins (TRLs) are involved in the initiation and propagation of atherosclerosis through their invasion in the arterial wall.[1] They further activate inflammation in the arterial wall through the secretion of tumor necrosis factor-β and interleukin 1-β, thought to set off the process of atherogenesis via endothelial dysfunction.[2]

Recent guidelines emphasize that while the focus of atherosclerotic cardiovascular disease (ASCVD) prevention should remain on LDL, we should not ignore elevated levels of apolipoprotein B (ApoB)-containing cholesterol — of which non-HDL is a surrogate marker — and triglycerides. Retrospective data from the Framingham Offspring study and Atherosclerosis Risk in Communities study showed a linear relationship between average triglyceride level and ASCVD risk, even in those with triglyceride levels less than 150 mg/dL.[3] Thus, it would seem, lower triglyceride levels are associated with decreased coronary risk, and there does not appear to be a "safe" level.

Further, if a patient is considered "at risk" for ASCVD events and treated with statins to push the LDL to levels <70 mg/dL, individuals with triglycerides ≥150 mg/dL still have a 41% higher risk of coronary events.[4] Thus, non-HDL should be a co-target for both primary and secondary prevention.

When lipid levels are checked in the fasting state, they can provide an accurate measurement of triglycerides, especially if there is a family history of premature ASCVD or a genetic cholesterol disorder. Optimal fasting triglyceride levels should be <100 mg/dL.[4] In general, levels between 150 and 199 mg/dL are borderline high, 200 to 499 mg/dL high, and ≥500 very high. The risk for pancreatitis increases with levels above 500 mg/dL, with substantial risk ≥1000 mg/dL.[5]

PRIMARY CAUSES

Being overweight (BMI 25-29 kg/m^2) or obese (BMI ≥30 kg/m^2) raises the chance of having high triglycerides and elevated non-HDL. Dietary intake of sugar or simple, processed carbohydrates, as well as fats, can raise the levels of triglycerides. Thus, it is essential to tease out what may be considered innocuous dietary habits (e.g., use of coffee creamer), but may impart significant risk toward dyslipidemia. Oils or spreads used for cooking, specifically coconut oil or butter, can place a high burden through saturated fats.

There has been much confusion in the media about healthy behaviors in dietary preparation; providers must work to clear up misconceptions. Regular use of alcohol may exacerbate hypertriglyceridemia, but a ketogenic diet — one high in fat, but low in carbohydrates — can successfully reduce weight and improve cholesterol levels. However, if done inappropriately, this diet pattern may contribute to dyslipidemia. Further, a ketogenic diet should be avoided in those who have genetically derived cholesterol problems, such as those with familial hypercholesterolemia (FH), an inherited disorder of LDL common in the population of Lancaster County.

SECONDARY CAUSES AND GENETICS

It is widely recognized that many disease processes and medicines can contribute to increased levels of triglycerides (see Table 1). Genetics are also an important consideration.

The most common monogenic mutation causing hypertriglyceridemia is Familial Chylomicronemia Syndrome (FCS), an autosomal recessive disorder characterized by triglyceride levels >99th percentile. FCS results from mutations causing the ineffectiveness of lipoprotein lipase or alteration of ApoC-II, leading to the inability to break down triglycerides.[6] Patients with FCS have very high levels of chylomicrons, and when diagnosed may have triglyceride levels above 880 mg/dL despite medication treatment.

A hallmark of FCS is recurrent episodes of pancreatitis, although these patients do not have a higher incidence

of ASCVD. This disorder is rare, with an incidence of approximately one in a million, yet accounts for 95% of monogenic mutations. The remainder of patients with mutations have errors in genes for ApoC-II, GPIHBP1, ApoA-V, and LMF1.

Other genetic causes of hypertriglyceridemia that are recurrent fall under the umbrella of Multifactorial Chylomicronemia Syndrome, or MCS, a polygenic hypertriglyceridemia. Familial Combined Hyperlipidemia (FCH) is characterized by high triglycerides with or without high LDL. These patients have a significant amount of ApoB cholesterol particles, generally ≥130 mg/dL, which can be distributed between triglyceride and LDL burden. This can be difficult to diagnose as LDL levels can vary, although triglycerides tend to remain high. In most of these cases, the true LDL cannot be evaluated until triglyceride levels improve.

Interestingly, while FH is very common among the Pennsylvania Dutch population, there is also a mutation in the gene for ApoC-III in the Amish community that leads to abnormally low levels of triglycerides. ApoC-III acts primarily as an inhibitor of lipoprotein lipase, thereby raising levels of triglycerides.

Finally, Familial Dysbetalipoproteinemia is characterized by mutations in ApoE. This exists in about one in 10,000 people, with elevated IDL and chylomicron remnants. Those afflicted will have high levels of cholesterol and triglycerides with low LDL. Patients may demonstrate eruptive xanthomas and are at increased risk for ASCVD.

TREATMENT

Lifestyle modification is the first step in the treatment of any cholesterol disorder. Clinicians should suggest that patients bring a three-day food diary to expedite review.[5] Dietary recommendations depend on triglyceride levels, with stricter recommendations reserved for patients with the highest levels and thus the most risk (see Table 2 on page 23). These include attention to fat, alcohol, and carbohydrate intake.

Along with this recommendation, exercise in the form of at least 150 minutes of moderate or 75 minutes of vigorous exercise per week should be encouraged. Additionally, patients with BMI >25% may find that weight loss of 5% to 10% of total body weight can contribute to a 20% or more reduction in triglyceride levels.

In 2021, the American College of Cardiology (ACC) revealed its Expert Decision Pathway on the Management of ASCVD Risk Reduction in Patients with Persistent Hypertriglyceridemia.[5] Statins remain

Table 1. Secondary Causes of Hypertriglyceridemia	
Categories	**Contributing Conditions and Medications**
Diseases	• Poorly controlled diabetes mellitus • Chronic kidney disease, nephrotic syndrome • Familial partial lipodystrophy • Uncontrolled hypothyroidism • Cushing syndrome • Glycogen storage disease, acute hepatitis • Rheumatoid arthritis • Psoriasis • Systemic lupus erythematosus • Multiple myeloma • Sepsis *(repeat measurement is recommended if lipids were measured during an episode of sepsis)*
Diet/Lifestyle	• History of alcohol abuse or alcohol excess • Diets high in saturated fat, sugar, or high-glycemic-index foods • Sedentary lifestyle • Total parenteral nutrition with lipid emulsions

Drugs* (Medications)	**Anesthesia:**
	• Propofol
	Cardiology:
	• Beta adrenergic blocking agents
	• Thiazide and loop diuretic agents
	• Bile acid sequestrants (cholestyramine, colestipol, colesevelam)
	Endocrine:
	• Glucocorticosteroids
	• Anabolic steroids
	• Oral estrogens
	  — Raloxifene
	  — Clomiphene citrate
	  — Estradiol
	  — Ethinyl estradiol
	  — Conjugated estrogens
	  — Tamoxifen
	Dermatology:
	• Isotretinoin
	Infectious Disease:
	• HIV protease inhibitors
	Oncology:
	• Tamoxifen
	• l-asparaginase
	• Bexarotene
	• Cyclophosphamide
	Psychiatry:
	• Atypical antipsychotic agents (e.g., olanzapine, mirtazapine, clozapine)
	Immunosuppressive agents:
	• Tacrolimus
	• Sirolimus
	• Cyclosporine
	• Interferons

Metabolism Disorders	• Overweight and obesity • Metabolic syndrome/insulin resistance • Weight gain after weight loss • Pregnancy *(especially third trimester when triglyceride elevation associated with pregnancy is peaking)*

Triglyceride-raising medications require careful monitoring; minimizing other conditions that raise triglycerides; and, when clinically appropriate, using alternatives.

Adapted from Virani et al.[5]

the primary treatment for those with ASCVD and can lower triglyceride levels reasonably. For those with triglyceride levels above 500 mg/dL, triglycerides become a primary target to prevent complications such as pancreatitis. Clinicians may still utilize statins first, especially in the presence of ASCVD; otherwise, these guidelines suggest that if a patient's cardiovascular risk is low, the use of icosapent ethyl (*Vascepa*[1]), fenofibrate, or omega-3 acid ethyl esters (*Lovaza*[1]) should be considered.
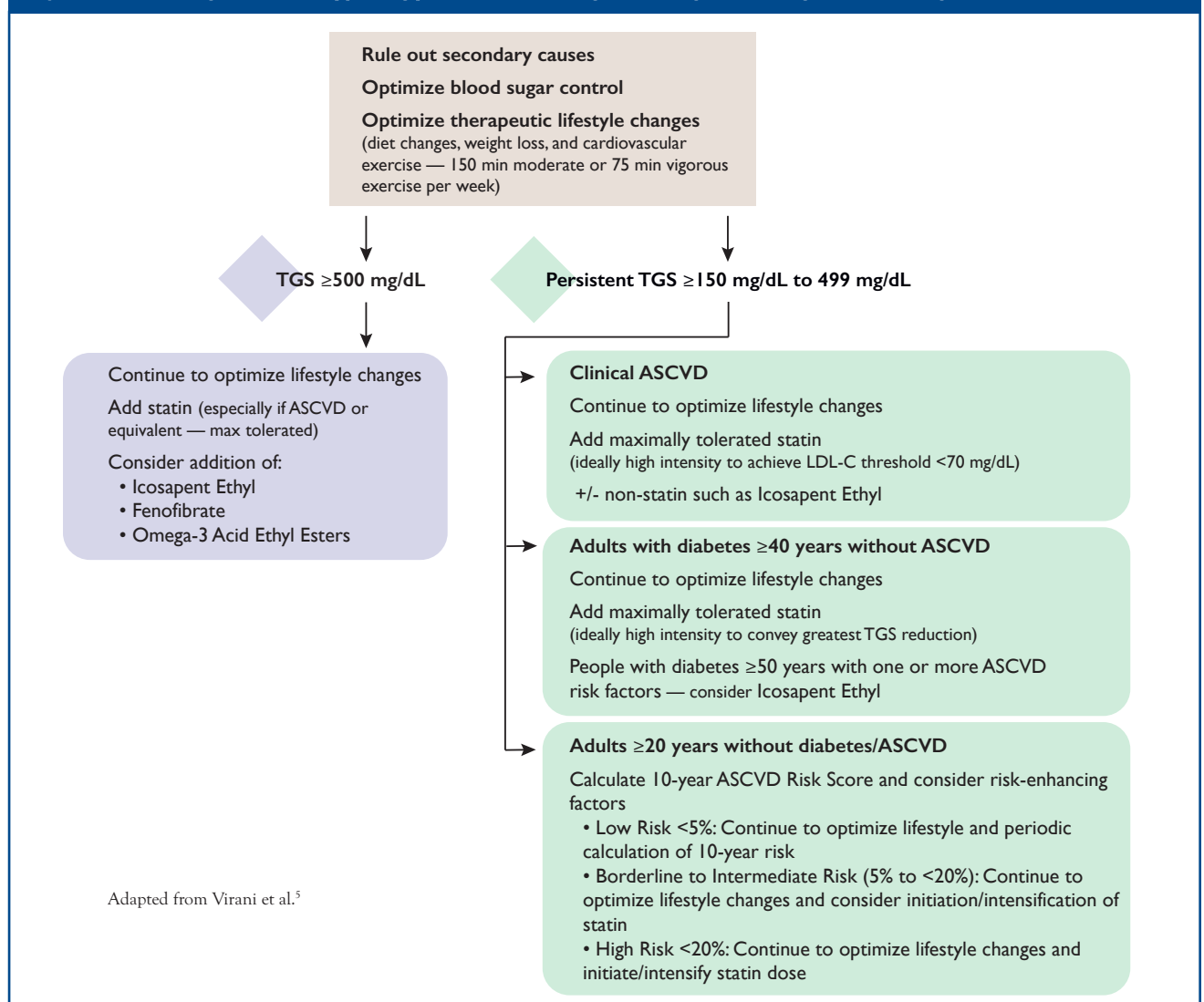
Consistent with the 2018 guidelines, the 2021 Decision Pathway indicates that if triglyceride levels are below 500 mg/dL, treatment should focus on LDL first, then on non-HDL. Further, for those patients at increased ASCVD risk who have attained an LDL goal, yet have residual triglycerides between 150 mg/dL and 499 mg/dL, clinicians should consider the addition of icosapent ethyl.

Statins

In addition to lowering the risk for ASCVD and major adverse cardiac events (MACE), statins can induce a 10% to 30% reduction in triglycerides dependent upon medication selected and dose. In adults with ASCVD and hypertriglyceridemia, or those 40 and above with diabetes and hypertriglyceridemia, maximal statin therapy is the primary treatment recommendation in addition to diet and lifestyle changes.[5] For those 20 years old or greater with persistent hypertriglyceridemia who will not become pregnant, statin therapy may be considered after lifestyle changes, elimination of secondary causes, and calculation of the 10-year ASCVD risk assessment tool.

Fig 1. Treatment Algorithm for Hypertriglyceridemia ≥150 mg/dL Fasting or ≥175 mg/dL Nonfasting

Rule out secondary causes

Optimize blood sugar control

Optimize therapeutic lifestyle changes
(diet changes, weight loss, and cardiovascular exercise — 150 min moderate or 75 min vigorous exercise per week)

TGS ≥500 mg/dL

Persistent TGS ≥150 mg/dL to 499 mg/dL

Continue to optimize lifestyle changes

Add statin (especially if ASCVD or equivalent — max tolerated)

Consider addition of:
• Icosapent Ethyl
• Fenofibrate
• Omega-3 Acid Ethyl Esters

Clinical ASCVD

Continue to optimize lifestyle changes

Add maximally tolerated statin
(ideally high intensity to achieve LDL-C threshold <70 mg/dL)

+/- non-statin such as Icosapent Ethyl

Adults with diabetes ≥40 years without ASCVD

Continue to optimize lifestyle changes

Add maximally tolerated statin
(ideally high intensity to convey greatest TGS reduction)

People with diabetes ≥50 years with one or more ASCVD risk factors — consider Icosapent Ethyl

Adults ≥20 years without diabetes/ASCVD

Calculate 10-year ASCVD Risk Score and consider risk-enhancing factors
• Low Risk <5%: Continue to optimize lifestyle and periodic calculation of 10-year risk
• Borderline to Intermediate Risk (5% to <20%): Continue to optimize lifestyle changes and consider initiation/intensification of statin
• High Risk <20%: Continue to optimize lifestyle changes and initiate/intensify statin dose

Adapted from Virani et al.[5]

Fibrates

Fibrates include gemfibrozil and fenofibrate. The VA-HIT trial studied gemfibrozil in more than 2,500 men with ASCVD, though most were not on statin therapy. While a benefit was seen, the sample size was small and there was no extensive use of statin therapy. No studies have shown a benefit of gemfibrozil in addition to statin therapy. More notable is the potential for significant interaction with statin therapy, and this combination should be avoided.

Fenofibrate has been studied in several trials, including the ACCORD trial with more than 5,000 people with diabetes on baseline simvastatin. There was no significant benefit in cardiovascular outcomes noted. The FIELD trial studied nearly 10,000 people with diabetes treated with fenofibrate who were not on baseline statin therapy. Though there was no statistical difference in coronary events compared to placebo, non-fatal myocardial infarction decreased by 24%. Most notable was improvement in albuminuria and retinopathy, suggesting benefit from microvascular complications.[7]

Omega-3 Fatty Acids

While none of the recent major studies (VITAL, ASCEND, OMEMI, and STRENGTH) using combination omega-3 fatty acids showed any clinical benefit or reduction in MACE, combination omega-3 acids are an option to treat triglycerides above 500 mg/dL. Regarding a derivative, icosapent ethyl, the results are more encouraging.

The 2019 Reduce-It trial examined the use of 2 grams twice daily (purified EPA only — *Vascepa*[1]) versus placebo in over 8,000 patients with existing cardiovascular disease or diabetes and two additional risk factors. The baseline triglyceride levels were between 135 mg/dL and 499 mg/dL, and patients were all given statin and demonstrated median LDL levels of 75 mg/dL.

Over 4.9 years of follow-up, there was a reduction in MACE by 25% (number needed to treat [NNT] = 28). Cardiovascular death improved by 20%, ischemic stroke by 29%, and improvement was seen in rates of hospitalization from heart failure as well.[5]

Side effects did include a higher risk for atrial fibrillation (5.3% vs. 3.9%), peripheral edema (6.5% vs. 5.0%), and adverse serious bleeding (2.7% vs. 2.1%), although there was no fatal bleeding. In general, anemia and gastrointestinal side effects were better in the treatment group. Thus, in 2019 the National Lipid Association endorsed the use of icosapent ethyl in statin-resistant hypertriglyceridemia, especially in patients with high or very high risk for clinical ASCVD.[8]

| Table 2. Effect of Lifestyle Modifications in Patients with Hypertriglyceridemia ||
Intervention	Reduction in Triglycerides (%)
Weight Loss	**Up to 70%** *Although most patients will likely experience reductions in triglyceride levels of 10% to 20%, evidence suggests that in some patients, a reduction of up to 70% may be achieved.*
Dietary Modifications (including restricting or abstaining from alcohol consumption)	**>70%** *Response may vary depending on patient's baseline triglyceride level and how strictly patient follows dietary recommendations.*
Physical Activity and Excercise	**Up to 30%** *Response may vary depending on the type, duration, and insensity of activity.*
	Adapted from Virani et al.[5]

Over-the-counter fish oil products are not recommended due to the differences in concentration of omega-3 fatty acids and purity, as well as the number of pills needed and gastrointestinal side effects.

Niacin

Niacin is vitamin B-3, though for cholesterol treatment it is administered in levels much higher than dietary consumption — 500 mg or higher.

While early studies with niacin alone showed cardiovascular benefit in secondary prevention, the results of the AIM-HIGH study (2011) for those with existing ASCVD on baseline statin therapy showed no benefit. After three years, the study was stopped early due to futility. Subsequently, in the HPS2-THRIVE trial (2014), extended-release niacin was studied in combination with laropiprant, an agent added to prevent flushing, in those with baseline ASCVD on statin. This trial, too, was stopped early, due to a high level of major adverse events. Niacin can cause flushing, hepatotoxicity, insulin resistance, and gout flares.[9]

In 2016, the FDA stated the risks outweighed the benefits in combining extended-release niacin with statin medication. Niacin may still be considered as monotherapy for severe hypertriglyceridemia (≥1000 mg/dL), but caution should be used and side effects considered. The 2018 ACC/AHA guidelines do not endorse the use of niacin in combination with statin therapy.[10]

CLINICAL TRIALS IN PROGRESS

There has been an advent of many new classifications of medicine treatment, including monoclonal antibodies, small interfering RNA, and antisense technology. Monoclonal antibodies are laboratory-made antibodies, similar to those occurring naturally, which can target a single site for medication benefit. Small interfering RNA

technology utilizes a small double-stranded RNA molecule that interferes with transcription or production of a gene or protein. Antisense oligonucleotide drugs are single-stranded RNA molecules that interfere with the transcription of a protein. Several phase 2 and 3 studies are currently underway.

Three companies have three different technologies against ANGPTL3, in which interference can improve both triglycerides and total cholesterol levels. These drugs include:

- evinacumab (*Evkeeza*[1]), a monoclonal antibody currently approved for LDL treatment in homozygous FH (mutations in both alleles of genes responsible for LDL processing);
- ANGPTL3-LRx, an antisense drug; and
- ARO-ANG3, an siRNA drug.

Two drugs targeting ApoC-III, which can improve triglyceride levels by increasing lipoprotein lipase levels, are available:

- AKCEA-ApoCIII-LRx, an antisense medication; and
- ARO-APOC3, an siRNA to ApoC-III.

Finally, pemafibrate is a fibrate medication that can act as an agonist to PPAR-α, reducing triglyceride levels more effectively and with fewer side effects than traditional fibrates. Kowa Pharmaceuticals recently announced they are stopping their study of pemafibrate, as cardiovascular outcomes are unlikely to be met; they may still consider it to be studied for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH). Clinicians may soon have multiple other options to reduce ASCVD risk in patients with hypertriglyceridemia, but we await the results of trials and updates of guidelines.[11]

SUMMARY

For the majority of patients with dyslipidemia, emphasis should first be placed on diet and exercise; causes of secondary hypertriglyceridemia, such as medications or underlying health conditions, should be addressed and augmented as appropriate. Medication therapy may be appropriate for those with triglycerides less than 500 mg/dL if they meet criteria and is generally recommended when values are above 500 mg/dL to prevent pancreatitis. For those who may have resistant hypertriglyceridemia, or suspicion of genetic disorders, referral to a lipid clinic is recommended.

The major challenge, of course, for use of cholesterol-lowering drugs is the problem of long-term non-adherence. Strategies to improve treatment adherence, which honor the patient's desires and wishes and which are supported by the entire health care team, will give our patients the best chance for more favorable long-term health outcomes.[1]

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A Teen with Neck and Chest Pain

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CASE HISTORY

A 13-year-old female was playing soccer during practice when she was accidentally hit in the anterior neck by a teammate's arm. She presented to Urgent Care the following day with pain in the neck and upper chest.

The patient said she had mild neck pain after being hit, but finished practice without difficulties. She said the pain was sharp, radiated into her chest, and primarily occurred when swallowing. She denied any voice changes, globous sensation, difficulties swallowing, shortness of breath, headache, vision changes, dizziness, neurologic deficit, cough, hemoptysis, abdominal pain, nausea, vomiting, and diarrhea.

On physical examination, vital signs were normal. Lungs were clear to auscultation bilaterally. The anterior neck was not tender and had normal appearance. The trachea was without deformity. The oropharynx was normal. Phonation was normal, and she had no difficulties tolerating secretions. There was no crepitus on exam and no decreased range of motion at the neck; pain was minimal with movement. A lateral soft tissue neck x-ray was performed in urgent care (Fig. 1).

QUESTIONS

1. What is your differential diagnosis?
2. What does the x-ray (Fig. 1) show?
   a. Normal x-ray
   b. Loss of normal lordotic curve
   c. Right cornu fracture of hyoid bone
   d. Prevertebral anterior soft tissue neck subcutaneous emphysema
   e. Steeple sign
3. What is the diagnosis?
4. What would you do next?

ANSWERS

1. Differential would include: muscle strain, pneumothorax, pneumomediastinum, esophageal injury, tracheal injury, laryngeal injury
2. d. Prevertebral anterior soft tissue neck subcutaneous emphysema
3. Pneumomediastinum
4. Transfer to the Emergency Department

DISCUSSION

Pneumomediastinum is a rare condition in which air is present in the mediastinum. This is due to any condition or trauma that results in air escaping from the lungs, airways, or bowel into the chest cavity. This can occur without obvious antecedent trauma (considered primary pneumomediastinum), but typical inducing factors include lung disease such as COPD or asthma, Valsalva maneuver, excessive vomiting, and trauma. It is termed a secondary pneumomediastinum when there is an identifiable cause.[1]

The condition is rare but more common in young patients. The main presenting symptom is typically chest pain that often radiates into the neck or back.
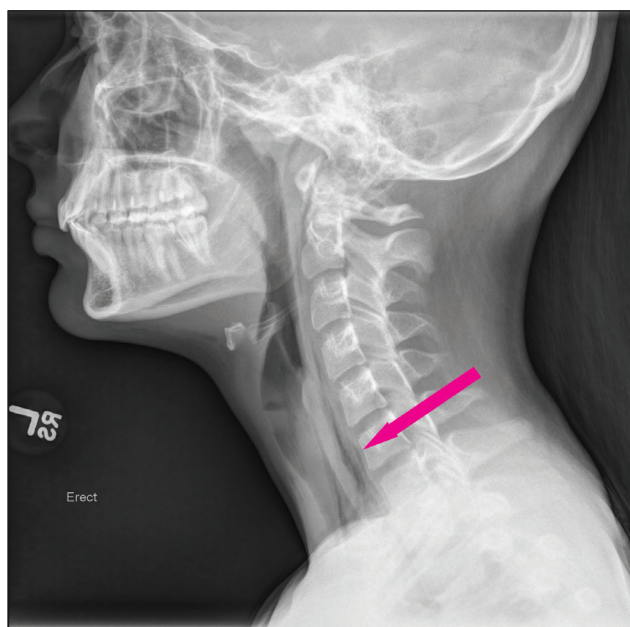

Fig. 1. Lateral soft tissue neck x-ray of 13-year-old female patient.

Other symptoms include dyspnea, coughing spells, neck pain, and dysphagia. Common signs include distorted phonation and neck swelling. Findings may include tachycardia and tachypnea. A nearly pathognomonic, yet uncommon finding, is Hamman's sign: the presence of mediastinal crunch on auscultation over the cardiac apex synchronous with the heartbeat.[1,2]

The diagnosis of pneumomediastinum is typically made on plain anterior chest film in which a positive study would illustrate lucent streaks outlining mediastinal structures and visible mediastinal pleura. Chest CT is used to confirm the diagnosis in inconclusive cases, assess extent of pneumomediastinum, and attempt to associate a causative factor. Further studies including bronchoscopy, esophagoscopy, and esophagography may be used to further identify an etiology.[1]

Fig. 2. A CT scan revealed extensive subcutaneous emphysema within soft tissues of the neck.

Pneumomediastinum is typically benign and requires no direct intervention.[3] After diagnostic workup has excluded significant pathology, treatment is directed toward symptom relief. Stability of the pneumomediastinum and treatment of any complications is generally adequate for discharge. In rare occasions in which complications or sequelae arise — such as the development of a significant amount of air in the mediastinum, tamponade, airway compression, or pneumopericardium — surgical intervention may be needed.[3]

The patient was referred to the Penn Medicine Lancaster General Hospital Emergency Department from Urgent Care for further evaluation and treatment. A CT scan was performed, revealing extensive subcutaneous emphysema within soft tissues of the neck (Fig. 2). Based on this finding, an occult perforation involving the esophagus or trachea could not be excluded. The patient was evaluated by Trauma Service and admitted.

An otolaryngology consultant was asked to evaluate for upper airway injury using nasopharyngoscopy. No significant findings were noted, and it was suspected there that the patient had a minor shear injury of one of her bronchi. Thoracic surgery was consulted, and a Gastrografin study was recommended. It did not reveal an esophageal tear.

After the second night of the patient's admission, she had no worsening symptoms and was tolerating a regular diet. She was discharged home with outpatient follow-up.
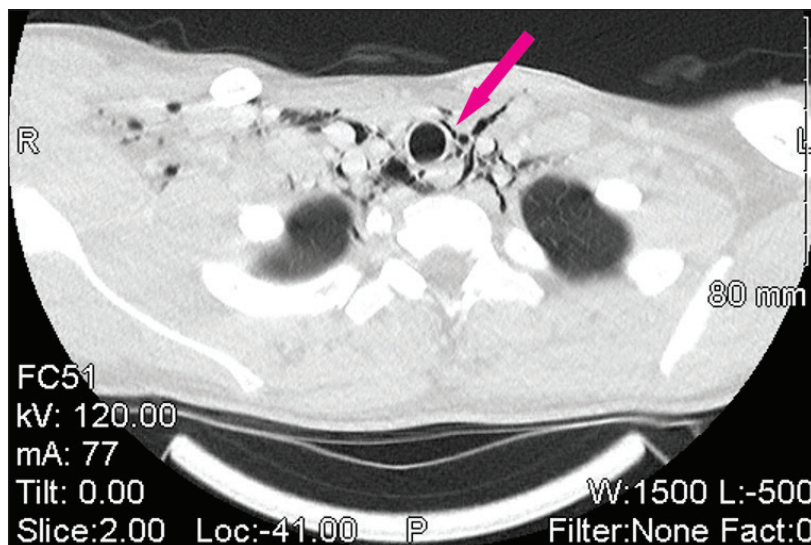
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Knee System Implants, Therapy to Slow Heart Failure, Breath Training

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Editor's note: This is the 11th in a series of articles from the Penn Medicine Lancaster General Health Research Institute that describes ongoing research studies. Other active studies have been described in previous issues of this journal. The Research Institute wishes to recognize a first-time principal investigator included in this article: Dr. Thomas Renz (Persona Revision Knee) from Lancaster Orthopedic Group.

The Lancaster General Health Research Institute encourages readers to look to the Fall 2022 journal for more information about the exciting trauma research being conducted by Dr. Lindsey Perea and Dr. Eric Bradburn. Physicians who wish to refer patients for any of the studies mentioned below are encouraged to contact the Research Institute at 717-544-1777. Other members of the Lancaster General Health staff who are conducting research and wish to have their studies described here are encouraged to contact the offices of JLGH at 717-544-8004.

SPONSORED STUDIES

Persona Revision Knee System Study

Sponsor: Zimmer Biomet
Principal Investigator: Thomas Renz, DO

This multicenter, single-arm, retrospective study evaluates the performance, clinical benefits, and safety of Persona Revision Knee System implants. Sites enroll eligible patients who previously received one of the qualifying knee systems.

Patients are split into cohorts by the method used for the implant (e.g., Revision splined constrained condylar knee [CCK], Revision cemented posterior stabilized/constrained posterior stabilized [PS/CPS]). Study sites then monitor these patients for two years post-implant, documenting any adverse events or deviations.

The study plans to assess the improvement from baseline (implant) to two years using an objective knee scoring tool that assesses the knee joint by awarding points for pain, stability, and range of motion. Specifically, these participants will be rated using the 1989 Knee Society Clinical Rating System objective knee score (KS-KS), which is a 0-100 scale score, and

the Numeric Rating Scale (NRS), which is scored on a scale of 0 to 10.

The study plans to enroll a total of 380 patients. Lancaster General Health has currently enrolled nine retrospective patients into the study. This study is being conducted by the Lancaster Orthopedic Group.

ANTHEM HFrEF: Autonomic Regulation Therapy to Enhance Myocardial Function and Reduce Progression of Heart Failure with Reduced Ejection Fraction

Sponsor: LivaNova
Principal Investigator: Roy Small, MD

The ANTHEM HFrEF trial is a multi-center, randomized, controlled trial sponsored by LivaNova. This study aims to enroll patients with New York Heart Association class II-III heart failure and reduced ejection fraction (EF ≤35%).

Participants are randomized to receive either standard guideline directed medical therapy (GDMT) or electrical vagal stimulation in addition to GDMT using the novel implanted VITARIA pacing device. The VITARIA system provides titratable, periodic stimulation of the vagal nerve to amplify parasympathetic tone. All study participants complete follow-up study visits at four weeks post-randomization, every three months for the first year, and then every four months until the study ends.

With an overall study enrollment goal of 800 participants across over 20 sites, Lancaster General Health plans to enroll at least 10 patients. While no patients have been enrolled at the time of this article, enrollment efforts continue regularly, including running study-specific reports and daily EPIC screening.

INVESTIGATOR-INITIATED STUDY

PART-HF: Parasympathetic Augmentation via Respiratory Training for Patients with Systolic Heart Failure

Grant-Funded by: Louise Von Hess Foundation
In Collaboration with: Stasis, LLC
Principal Investigator: Roy Small, MD

The primary outcome of this prospective, randomized, controlled clinical trial is to evaluate the effect of

breath training on the six-minute walk test. The study targets a population of symptomatic heart failure (NYHA Class II or III) patients with reduced Ejection Fraction (HFrEF). Participants will be randomized to one of two groups: standard guideline directed medical treatment (GDMT) (control group) or GDMT plus breath training (intervention group).

The six-minute walk test is a standard HF assessment tool used to assess aerobic and functional capacity. The walk test and additional physiologic parameters including parasympathetic tone (using heart rate variability [HRV]), quality-of-life assessment (Kansas City Cardiomyopathy Questionnaire [KCCQ]), and biomarkers will be completed at the baseline assessment, three-month assessment, and final six-month assessment.

Breath training has been shown to improve the functional capacity of heart failure patients. However, prior protocols have been too intense to allow widespread adoption. PART HF will utilize a Stasis-modified U.S. Navy SEAL respiratory training protocol to improve parasympathetic tone using diaphragmatic breathing techniques. This study aims to determine if this breath training regimen is not only beneficial to this group of heart failure patients, but also if it is easy enough to follow to promote compliance.

The participants randomized to the therapy group of the study will receive virtual breath training from a breathwork coach from Stasis. The coach will meet with participants biweekly via Zoom to promote compliance, re-educate, and answer questions. A novel "humming" practice exercise has been included, as humming has been shown to increase endogenous nitric oxide, a potent beneficial vasodilator.

Therapy arm participants will practice their breathing exercises twice a day for 15 minutes each, practice humming exercises twice a day for five minutes each, and measure their heart rate and HRV daily using a smart phone app (one minute).

Control group participants will complete clinical assessments and HRV measurements without breath training or humming exercises. At the end of their study involvement (six months), control group participants will have the option to receive the same breath training given to the therapy group participants.

The study plans to enroll 100 participants.

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Recommendations from the American Society of Nuclear Cardiology and the American Urogynecologic Society

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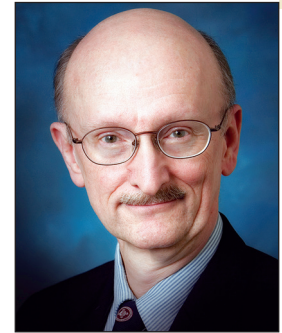
This is my 37th article on Choosing Wisely from the American Board of Internal Medicine (ABIM) Foundation. As noted in previous issues of *JLGH,* each specialty group is developing "Five or More Things That Physicians and Patients Should Question."

All items are developed to encourage discussion between physicians and their patients about which tests and procedures are best in each case. Additional resources are available online at choosingwisely.org.

I. RECOMMENDATIONS OF THE AMERICAN SOCIETY OF NUCLEAR CARDIOLOGY (ASNC)

1. Stress cardiac imaging or coronary angiography should not be performed in patients without cardiac symptoms unless high-risk markers are present. Asymptomatic, low-risk patients account for up to 45% of inappropriate stress testing. Testing should be performed only when the following findings are present: diabetes in patients older than 40 years old, peripheral arterial disease, and greater than 2% yearly coronary heart disease event rate.[1]

2. Cardiac imaging should not be performed for patients who are at low risk. Chest pain patients at low risk of cardiac death and myocardial infarction (based on history, physical exam, electrocardiograms, and cardiac biomarkers) do not merit stress radionuclide myocardial perfusion imaging or stress echocardiography as an initial testing strategy if they have a normal electrocardiogram (without baseline ST-abnormalities, left ventricular hypertrophy, pre-excitation, bundle branch block, intra-ventricular conduction delay, paced rhythm, or on digoxin therapy) and are able to exercise.

3. Radionuclide imaging should not be performed as part of routine follow-up in asymptomatic patients. Performing stress radionuclide imaging in patients without symptoms on a serial or scheduled pattern (e.g., every one to two years or at heart procedure anniversary) rarely results in any meaningful change in patient management. It could lead to unnecessary invasive procedures and excess radiation exposure. An exception to this rule would be for patients more than five years after a bypass operation.

4. Cardiac imaging as a pre-operative assessment in patients should not be performed in those scheduled to undergo low- or intermediate-risk non-cardiac surgery. In those patients or in those with no cardiac symptoms or clinical risk factors, non-invasive testing is not useful. This type of testing does not change the patient's clinical management or outcomes and may result in increased cost.

5. Whenever possible, use methods to reduce radiation exposure in cardiac imaging, including not performing such tests when limited benefits are likely. The key step to reduce or eliminate radiation exposure is appropriate selection of any test or procedure for a specific person, in keeping with medical society recommendations such as appropriate use criteria.[2]

II. RECOMMENDATIONS OF THE AMERICAN UROGYNECOLOGIC SOCIETY (AUGS)

1. Fluoroquinolone antibiotics should be avoided for the first-line treatment of uncomplicated urinary tract infections (UTIs) in women. For women with uncomplicated UTIs (defined as premenopausal, non-pregnant women with no known urologic abnormalities or comorbidities), fluoroquinolone antibiotics should not be considered first-line treatment. Although fluoroquinolones are efficacious in three-day regimens, they have a higher risk of ecological adverse events, such as increasing multidrug-resistant organisms. Therefore, use these drugs only for the treatment of acute UTIs for women who should not be prescribed first-line regimens such as nitrofurantoin, trimethoprim-sulfamethoxazole, or fosfomycin.[3]

2. Cystoscopy, urodynamics, or diagnostic renal and bladder ultrasound should not be performed in the initial workup of an uncomplicated overactive bladder patient. The initial evaluation of an uncomplicated patient presenting with symptoms should include history, physical examination, and urinalysis. In some cases, urine culture, post-void residual urine assessment,

and bladder diaries may be helpful. More invasive testing should be reserved for complex patients, patients who have failed initial therapies (i.e., behavioral therapies and medications), or patients who have abnormal findings on their initial evaluation.

3. Pessaries should not be excluded as a treatment option for pelvic organ prolapse. Non-surgical treatment options for pelvic organ prolapse include pessaries, which are removable devices that are placed into the vagina to support the prolapsed organs (i.e., uterus, vagina, bladder, and/or rectum). A pessary trial can be offered to almost all women with pelvic organ prolapse. Exceptions include women with an active vaginal infection and those who are unable to follow through with treatment.

4. Synthetic or biologic grafts should be avoided in primary rectocele repairs. Posterior vaginal repair of rectocele is performed for women with symptoms of a posterior vaginal wall bulge or difficulty with defecation. The repair involves suturing the posterior vaginal wall and perineal tissue. The addition of synthetic or biologic grafts to this repair does not improve patient outcomes.

5. Removing ovaries at hysterectomy should be avoided in pre-menopausal women with normal cancer risk. There is evidence from observational studies that surgical menopause may negatively impact cardiovascular health and all-cause mortality. This is particularly important in patients with a personal or strong family history of cardiovascular disease or stroke. Women with an average risk of ovarian cancer are defined as women who do not have a documented germline mutation or who do not have a strong family history suspicious for a germline mutation and are undergoing a hysterectomy for benign conditions.[4]

Top Tips

RECOMMENDATIONS SIMPLIFIED FOR PNEUMOCOCCAL VACCINATION

A new policy has simplified the pneumococcal vaccination recommendations of the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC). The updated recommendations were published in the CDC's *Morbidity and Mortality Weekly Report* in January of this year.[5]

Noting that the 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) were recommended for use in U.S. adults, with the recommendations varying by age and risk group, Miko Kobayashi, MD, from the CDC in Atlanta, and colleagues reviewed the evidence framework to develop recommendations for use of 20-valent PCV (PCV20) and 15-valent PCV (PCV15). PCV20 and PCV15 were licensed in 2021 by the Food and Drug Administration for adults ages 18 years and older.

As a result of this review, ACIP now recommends an only-one-PCV-in-adulthood rule (at right).

PPSV23 had been recommended for use in the United States since the 1980s for adults ages 65 years and older, and for younger adults with underlying conditions that increased their risk for pneumococcal disease. PCV13 was first recommended for use in children in the United States in 2010; indirect effects from its use in children reduced PCV13-type pneumococcal disease in all adult groups.

In 2012, ACIP recommended administration of PCV13 in series with PPSV23 for adults with immunocompromising conditions, cerebrospinal leaks, or cochlear implants, and in 2014, the recommendation was extended to all adults ages 65 and older.

GAS STOVES POLLUTING EVEN WHEN TURNED OFF

In an article published by the American Chemical Society, researchers noted that natural gas (methane) stoves in over 40 million U.S. residences release methane — a potent greenhouse gas — through post-meter leaks and incomplete combustion.[6] Almost three-quarters of the methane found was emitted from the stoves when they were not turned on.

The researchers quantified methane released in 53 homes during all phases of stove use: steady-state off (appliance not in use), steady-state on (during combustion), and transitory periods of ignition and extinguishment. They found:

> Using a 20-year timeframe for methane, annual methane emissions from all gas stones in U.S. homes have a climate impact comparable to the annual carbon dioxide emissions of 500,000 cars. In addition to methane emissions, co-emitted health-damaging air pollutants such as nitrogen oxides (NO_x) are released into home air and can trigger respiratory diseases.[6]

Other pollutants associated with gas stoves include formaldehyde, particulate matter (such as PM2.5), and

Only-One-PCV-in-Adulthood Rule

**Adults age ≥65 years and adults age 19-64 years with
underlying medical conditions (*) or risk factors (#†) should receive PCV.**

❶ If a patient has never received PCV, patient should receive PCV20 or PCV15.
   a. Upon receipt of PCV20, the patient's PCV and PPSV23 series is complete.
   b. Upon receipt of PCV15:
      i.   If they received PPSV23 ≥ one year prior, this series is complete.
      ii. If they are ≥65 years or have underlying medical conditions (*), they need one PPSV23 ≥ one year after PCV15 to complete their series.
      iii. If they have risk factors (#†), they may receive PPSV23 ≥ eight weeks after PCV15 to complete their series.

❷ If a patient already received PCV13, they should complete the series PPSV23 (**).
   a. If ≥65 years, ensure they receive PPSV23 at least one year after PCV13.
   b. If they are 19-64 years with risk factors (†):
      i.   Give a dose of PPSV23 ≥ eight weeks after PCV13 dose, and
      ii. give a second dose of PPSV23 after the patient has turned 65 years and waited ≥ five years after b.i. (above).
   c. If they are age 19-64 with risk factors (#):
      i.   Give a dose of PPSV23 ≥ eight weeks after PCV13, and
      ii. give a second dose of PPSV23 at least five years after c.i. (above).
      iii. If the patient was still not ≥65 years at the time of c.ii. (above), give a third dose of PPSV23 at least five years after c.ii. and after age 65.

*Underlying medical conditions: alcoholism; chronic heart, liver, or lung disease; diabetes mellitus; cigarette smoking

#Risk factors of chronic renal disease; nephrotic syndrome; asplenia; generalized malignancy, including leukemia or lymphoma; multiple myeloma; hemoglobinopathy; immunodeficiency; history of solid organ transplant

†Risk factors of cochlear implant or cerebrospinal fluid leak

**Note: If PPSV23 is unavailable, it is considered acceptable to give one dose of PCV20 to complete the pneumonia vaccination series.

carbon monoxide. A significant amount of nitrogen oxides entering the homes of people with asthma and other health conditions is obviously not a good finding.

In 32 homes, the researchers measured NO and NO_2 emissions and found them to be linearly related to the amount of natural gas burned. Their data suggest that "families that don't use their range hoods or who have poor ventilation can surpass the [one-hour] national standard of NO_2 (100 ppb) within a few minutes of stove usage, particularly in smaller kitchens." And even when U.S. gas stoves are not running, they are emitting 2.6 million tons of methane into the air each year.

We don't need to fix every gas stove to eliminate this source of emissions, as there is already a better solution: replace these with stoves that run on electricity. The best contender to replace the gas stove is the induction stove, which uses a magnetic field to heat pans. But this transition to electric-powered cooking without city, state, and even federal policy will be difficult.

Why is this important to our patients? Researchers in a toxicology article published in 2020 concluded that exposure to ambient air pollution contributed to autism spectrum disorders and that oxytocin receptor protein may serve as part of the mechanism linking them.[7]

It has even been suggested that airborne particulate matter may act like a trojan horse, representing an effective delivery system for diverse environmental toxicants to reach the brain. Previous studies reported that simultaneous exposure to particulate matter and gaseous pollutants during pregnancy have been associated with autism spectrum disorder.[8,9]

AMERICAN COLLEGE OF PHYSICIANS (ACP) RELEASES NEW CLINICAL GUIDELINES ON DIVERTICULITIS[10,11]

Acute diverticulitis is usually uncomplicated, causing only localized inflammation. However, in about 12% of cases, there can be complications.

Complicated diverticulitis is an inflammation association with an abscess, a phlegmon, a fistula, an obstruction, bleeding, or perforation. The chance of recurrence is approximately 22%.

Approximately 95% of patients with diverticula have sigmoid diverticula, and 5% to 10% of those with diverticulosis may develop acute diverticulitis, increasing with age.

Due to recent theory that diverticulitis may be more inflammatory than infections, the ACP in early 2022 released new guidelines as follows:

- Use abdominal CT imaging when there is diagnostic uncertainty with suspected acute diverticulitis (conditional recommendation: low-certainty evidence).
- Manage most patients with acute uncomplicated diverticulitis in an outpatient setting (conditional; low-certainty).
- Characterize uncomplicated diverticulitis by absence of frank perforation, obstruction, fistula, or abscess on CT.
- Initially manage select patients with acute diverticulitis without antibiotics (conditional; low-certainty).

For adults with recent episodes of acute left-sided colonic diverticulitis:

- Refer for a colonoscopy after an initial episode of complicated diverticulitis for those who have not had recent colonoscopy (conditional; low-certainty).
- Do not use mesalamine to prevent recurrent diverticulitis (strong; high-certainty).
- Discuss elective surgery to prevent recurrence after initial treatment in those who have either uncomplicated diverticulitis that is persistent or recurs frequently, or complicated diverticulitis (conditional; low-certainty).
- Personalize the decision on whether to treat with surgery based on a discussion of potential benefits, harms, costs, and patient preferences.

If antibiotics are indicated in the ambulatory setting, amoxicillin-clavulanate (Augmentin®) alone should be favored over a combination of fluoroquinolones and metronidazole due to Food and Drug Administration advisement regarding reserving fluoroquinolones for conditions with no alternative treatment options.

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