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Adolescent Sexual Health: A Focus on the Sexual Health Portion of HEADSS Examination

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EDUCATION GAPS

- An estimated 16% to 25% of adolescents are identified as having special health care needs, including physical and developmental disability and medically complex illness. Sexuality and sexual health care needs are often overlooked in this population, but data show that adolescents with chronic illness have similar levels of sexual behaviors and sexual health outcomes as healthy adolescents.
- There are many potential gaps and challenges in privacy and confidentiality for adolescents. Electronic health records present challenges with parental access to patient portals, automated discharge summaries, appointment notifications, and medication lists including contraception. These issues can negatively affect ability to care for minors even when state laws allow confidential reproductive care of adolescents.

OBJECTIVES *After completing this article, readers should be able to:*

1. Explain that despite making up only 13% of the population, adolescents from 15 to 24 years of age account for approximately half of all new sexually transmitted infections in the United States every year.
2. Explain that adolescents consider their primary care or pediatric practitioner a highly trusted source of sexual health information.
3. Explain that nearly a quarter of adolescents are identified as having special heath care needs, and further, in this population, sexuality and sexual health care needs are often overlooked.
4. List potential gaps and challenges in privacy and confidentiality for adolescents.
5. Provide an introduction to sex-positive parenting to caregivers.

ABSTRACT

Sexual exploration is a natural part of adolescence, and most individuals will initiate sexual activity in their adolescent years. Privacy, confidentiality,

AUTHOR DISCLOSURE: Drs Barrett, Shih, and Warren have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

and consent are crucial considerations in providing sexual health care to adolescents, with laws varying by state. References to gender in this article are primarily limited to the binary male-female due to lack of data representing the gender spectrum. We aim to reframe the conversation and offer tools to share with parents for productive conversations with their teens. Sex-positive parenting and the involvement of parents in promoting healthy sexual development through ongoing conversations is emphasized. Primary care practitioners have a vital role to play in providing sexual health education and services to adolescent patients, and this article offers practical tips and tricks in engaging this population.

BACKGROUND

Adolescents are sexually active in ways that primary care practitioners (PCPs) may not be routinely asking about. Sexual exploration is a natural part of adolescence, and most patients will initiate sexual activity in their adolescent years (Figure 1).[1,2] "Sexually active" can have multiple definitions, including penile-vaginal intercourse (commonly referred to as "sexual intercourse"), oral sex, and anal sex.[3] From the analysis of the 2015 to 2019 National Survey of Family Growth (NSFG), 40.5% of female and 38.7% of male teenagers reported ever having had sex, down from greater than 45% in 2002. When surveyed, 29.8% of female and 24.9% of male teenagers report having had sex in the last 3 months.[4] Sixty-five percent of teens have had penile-vaginal intercourse by age 18 years (Figure 1).[3]

In the 2017 to 2019 section of the NSFG analysis, 38.7% of females 15 to 19 years of age were currently using contraception methods (it was not specified whether hormonal methods were used for noncontraceptive medical indications),[5] with 98.9% of sexually active females having used contraception at some point.[4] Use of contraception at first intercourse is higher than might be expected, with 77.3% of female and 92.1% of male teenagers. The most common contraceptive method reported is the male external condom, followed by combined oral contraceptives (COCs)[4] (Table 1). Rates of contraception at first sex event are lower in female teenagers who initially have sex at a younger age. For female patients who first had sex at 14 years of age or younger, 56.3% used contraception vs 82.9% of adolescents who initiated sexual activity between 15 and 17 years and 83.9% between 17 and 19 years of age.[4]

Withdrawal as a primary method is used at an alarming rate, given its limited effectiveness (22% failure rate among all users) and lack of protection against sexually transmitted infections (STIs) (Table 1).[4] PCPs should be educating patients about the limitations of this method while also encouraging high-reliability contraceptive options,[6] specifically long-acting reversible contraception (LARC) methods. LARC methods are minimally dependent on patient use factors, changing insurance or requiring transportation (ie, for Depo-Provera injections or pharmacy pick-up). The rate of

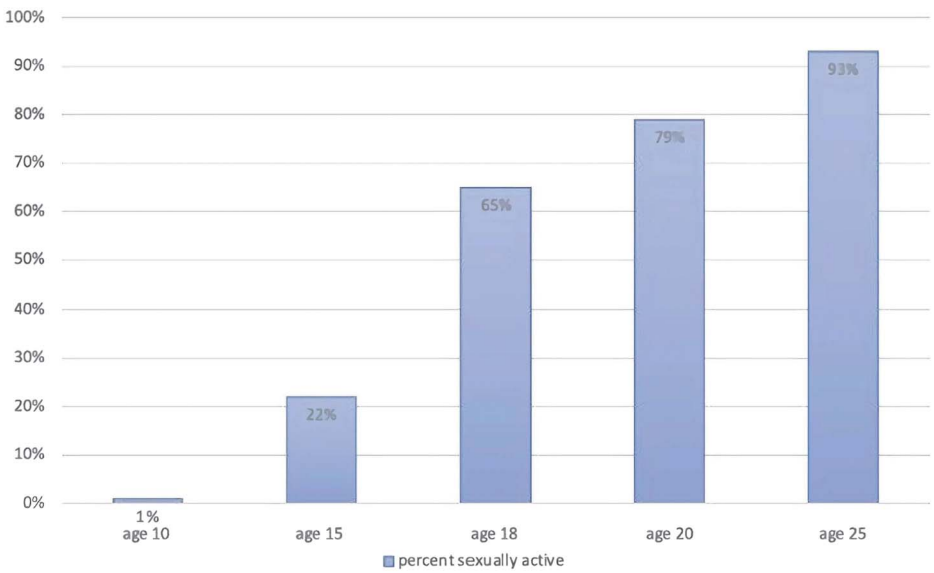

FIGURE 1. Ages of sexual debut.[1,2] Adapted from Keller L. Reducing STI cases: young people deserve better sexual health information and services. The Guttmacher Institute. April 20, 2020;[1] and Boyer, J. The Guttmacher Institute. New name, same harm: rebranding of federal abstinence-only programs. The Guttmacher Institute. 2018.[2]

TABLE 1. Contraceptive Use Methods Among Teens, 2015 to 2019[4]

Method	Frequency of Use
Condom	95.4%
Withdrawal	64.8%
Pill	52%
Implant	13.3%
Emergency contraception	8.1%
Intrauterine device	6.1%
Other	2.2%

Adapted from Teenagers in the United States: sexual activity, contraceptive use, and childbearing, 2015 to 2019. Centers for Disease Control, National Health Statistics Report.[4]

implant use is highest among 15 to 19-year-olds (16%), and 25 to 29-year-olds have the highest use rate of intrauterine devices (IUDs).[7] Over 90% of teenagers used a contraceptive method of some type at last sexual encounter, most commonly condoms.[4] Condoms have several advantages including male involvement in contraception, low cost, easy/confidential accessibility, and STI prevention.[6]

Data from the Youth Risk Behavior Surveillance System has demonstrated that condom use is lower in adolescents using LARC (16.4%) compared with COCs (37.3%). This survey result serves as a reminder to PCPs to discuss the importance of condoms for STI prevention,[8] even for patients using reliable forms of contraception. Other contraceptive methods (female/internal condom, fertility awareness/rhythm method, spermicide, diaphragm, and cervical cap) are all used less commonly by adolescents, following similar patterns seen with adult patients.[6]

Contraceptive insurance coverage and over-the-counter (OTC) availability varies widely across the United States. Only 7 states have Medicaid coverage for OTC contraception (typically emergency contraception or condoms). Six states require private insurance to provide OTC contraceptive options without a prescription; many more states require coverage for OTC contraception with a prescription. Seven states allow pharmacists to distribute emergency contraception without a prescription (not all overlapping with OTC Medicaid coverage). Thirty states require insurance coverage for contraceptive options.[9] The Food and Drug Administration (FDA) approved the first OTC oral contraceptive, norgestrel, in July 2023,[10] although access will likely be challenging for years to come given impact of insurance coverage and local politics on price and ease of availability.

Adolescents comprise only 13% of the population[11] yet account for half of new STIs in the United States every year.[12,13] One in four sexually active adolescent females has had an STI, most commonly chlamydia, human papilloma virus (HPV), or gonorrhea.[13] Females ages 15 to 24 years have had the greatest increase in rates of both syphilis and gonorrhea,[12] although genital herpes simplex virus and *Trichomonas vaginalis* are also increasingly common.[13]

Multiple factors contribute to disproportionate rates of STIs in the adolescent population. Physiologically, a lower production of cervical mucous and increased cervical ectopy causes increased biologic susceptibility to STIs in adolescent females.[13] Adolescents are less likely than adults to access and use sexual health services, partly influenced by confidentiality concerns while on a parent/guardian's health insurance (ie, bills and explanation of benefits may disclose care provided). Although confidential services are available at locations such as county clinics and Planned Parenthood, barriers such as the lack of independent transportation and clinic availability after school hours persist. The prefrontal cortex is still developing throughout adolescence, thus influencing the adequacy of executive function and safe decision-making. Adolescents are more likely to engage in high-risk sexual behavior such as multiple partners, unprotected sex, and substance use prior to sex. Among sexually active teens, 19% used alcohol or substances before their last sexual activity. Structural barriers that prevent equitable access to health care, such as racism, discrimination, and poverty, contribute to particularly high rates of STIs among some groups, especially black adolescent men who have sex with men.[1] Youth experiencing homelessness or incarceration and who have substance use disorder are additional high-risk populations. Of note, broadly adverse experiences in childhood are associated with increased risk for STIs in adolescence,[13] which is reminiscent of conclusions from the Adverse Childhood Experience Study[14] and subsequent research.

Vaccinating adolescents against HPV before initiation of sexual activity is highly effective at reducing HPV transmission. However, only half of all 13 to 17-year-olds in the United States were fully vaccinated against HPV in 2018.[12] This finding identifies a large opportunity for education of adolescents and their parents about the benefits of this vaccine.

SEXUAL EDUCATION

Research on sexual education has been focused on prevention programs aimed at reducing STI and pregnancy rates. The Future of Sex Education (2012, updated 2020), a partnership among 3 leading national sex education organizations: Advocates for Youth, Answer, and Sex Ed for Social Change, released the National Sexuality Education Standards (NSES), which are aimed at providing "clear, consistent, and straightforward guidance on the essential, minimum, core content, and skills needed for sex education that is age-appropriate for

students in Grades K-12 to be effective."[15] The 7 content areas are as follows: "Consent and Healthy Relationships," "Anatomy and Physiology," "Puberty & Adolescent Sexual Development," "Gender Identity and Expression," "Sexual Orientation and Identity," "Sexual Health," and "Interpersonal Violence."[15] Forty percent of school districts in the United States have adopted NSES.[16] For sexual education to be most effective, it must occur before adolescents begin having sex. Eighty-three percent of younger adolescents report not having received sex education before they first had sex.[17]

Differences in the implementation of sex education leave many adolescents without access to accurate information. Peers, social media, and mass media fill in the educational gaps when information is not forthcoming from schools or parents.[18,19] Multiple factors influence sexual education including gender, race, and ethnicity of students and teachers. The location of instruction and local politics can significantly impact the comprehensiveness of education.[20]

Comprehensive sex education leads to reductions in STI rates.[21] However, stigma surrounding STIs continues to thwart frank, open conversations, and education about how to have a safe and healthy sex life. Sexual education should normalize sexual development and relationships, be evidence-based, and be provided to adolescents across the population spectrum.[12]

Abstinence education can have a strong negative connotation in health care settings. However, because abstinence/postponement of sex is 100% effective in preventing pregnancy and has a role in developmentally informed sexual education, teens should be encouraged to abstain from or postpone sex until they feel emotionally ready and have a partner they trust and with whom they feel safe. Abstinence/postponement has a role in developmentally informed sexual education. Abstinence has not been shown to be an effective long-term contraceptive method and strict adherence rates are low.[6] Abstinence-only programs do not lower adolescent birth rates, STIs, or sexual activity (oral, anal, or penile-vaginal). States with policies emphasizing abstinence-only teaching do have higher incidences of adolescent pregnancy.[22–25] Studies surrounding virginity pledgers show that pledgers have similar rates of premarital sex, lifetime sexual partners, age of first sex, or STI rates and are less likely to use protection against STI transmission or pregnancy.[23] Adolescents experiencing abstinence-only teaching have lower rates of contraceptive use and higher risk for HPV infection.[24,25]

Practitioners caring for adolescents should provide all adolescents, of all gender identities and sexual orientations, access to comprehensive sexual health education and services. This includes STI prevention and screening, contraception method consultations, initiation of contraception, adherence check-in, management of side effects,[6] and counseling regarding safe relationships and consent. Education regarding safety decreases incidence of intimate partner violence among youth.[16]

SEX-POSITIVE PARENTING

Parents play a significant role in their children's decisions and knowledge about sex, sexuality, and relationships. Most adolescents talk to their parents at some point about sexual health.[17] However, many parents have not been educated on how to effectively talk about sex (inclusive of puberty, sexual orientation, and healthy relationships) with their children. The concept of sex-positive parenting is teaching youth in developmentally appropriate ways about sex and being open to what can be typically considered challenging topics. Youth are taught that having and asking questions about their bodies, relationships, gender identity, sexual identity, consent, and sex itself is normal and healthy. Open communication teaches youth that parents are trustworthy and safe sources for information and guidance. Parenting with this mindset includes the goal of youth becoming whole, fully formed, independent adults who have thought about and found their own sexual orientation, gender identities, and relationships. Continual conversations across childhood and adolescence are a shift from the one-time "talk" practice. Ongoing conversation can significantly improve a child's development of a healthy relationship with their body and sexual health (Table 2).[26] In well child visits, practitioners should encourage parents to engage in these conversations with their children and offer tools and suggestions.

TABLE 2. Characteristics of Sex-Positive Parenting

Characteristics
Children want to talk with their parents about sex; 76% of children have talked with their parents about birth control or sexual health decisions[17]
Parents support broad sexual education including STIs, healthy relationships, puberty, abstinence birth control, sexual orientation[24]
Teaching children in age-appropriate and developmentally appropriate ways that learning about bodies, relationships, and eventually sexuality, is natural, normal and healthy[26]
Answering questions as they come up, normalizing conversations about gender and sexuality—allowing parents to develop into trusted sources of information[26]
Knowing that children will become their own autonomous selves with their own gender identities, gender expression, and sexualities[26]

Abbreviation: STI, sexually transmitted infection.

PRIVACY AND CONFIDENTIALITY

Privacy, confidentiality, and consent are particularly important when providing sexual health care to adolescents.[27] Laws surrounding confidentiality and consent for adolescent health care are primarily determined at the state level.[28] About half of US states explicitly allow minors to consent for contraceptive services.[9,29] Thirty-nine states and the District of Columbia allow all individuals to consent for STI services without stipulation to age or condition.[29] Since adolescents are able consent to contraceptive and STI services, during sexual health and well child visits, adolescents should have one-on-one time with the practitioner without a parent or guardian present.[28]

Although many states allow adolescents to consent for sexual health care at a younger age, the right to consent does not guarantee confidentiality. Despite the goal of treating adolescent sexual health care as confidential, there are pragmatic complications.[8] In addition to confidentiality concerns with the use of parental/guardian insurance, additional system-level constructs such as patient portal access, documentation of after-visit summaries, medication lists, and appointment notifications can undermine confidentiality. These concerns can curtail the ability to provide confidential comprehensive sexual health services, even when state laws allow for it.[8,27] There is valid concern that confidentiality concerns lower adolescent access to sexual and reproductive health services.[8,27] The Title X Family Planning Program allows adolescents to provide independent consent for reproductive health care and does not provide a detailed bill of services.[8] This serves as a model for an improved billing practice that supports confidentiality. However, due to Department of Health and Human Services information blocking penalties with the 21st Century Cures Act, there remains additional concern for breach of confidentiality with the use of electronic medical records.[30]

Although not universal, parents are frequently not in opposition of sexual health care for their children.[24] Similarly, they are often supportive of minor consent and confidentiality for sexual health services. Adolescents should be encouraged to involve parents or trusted adults, barring significant concerns.[6] If parents are participating in part of an adolescent well child check, it can be useful to introduce the topic of adolescent sexual health while both the adolescent and parent are in the room and ask the parent if they are open to their child talking to them about sexual health as questions arise. Creating a space for a general discussion of sexual health with both the parent and adolescent can serve as a powerful conversation opener in their relationship. Unless brought up by the adolescent, specific details about the adolescent's sexual health should be avoided until the parent has stepped out of the room.

UNIQUE ADOLESCENT POPULATIONS

An estimated 16% to 25% of adolescents have special health care needs including physical and/or developmental disability and medically complex illnesses. Addressing sexual development and sexual health needs and care are often missed for these patients. Although not commonly discussed, data show that these adolescents have similar rates of sexual activity, STIs, and pregnancy as other adolescents.[6] In addition to routine sexual health care, medically complex adolescents may need contraception while taking therapeutic medications that have teratogenic effects or may need menstrual suppression for a multitude of reasons (ie, clotting disorders, gender dysphoria, obsessive compulsive disordered thought patterns related to menses). Safe contraceptive prescribing necessitates evaluating safety of hormone use, medication interactions, and use of contraceptive methods in the setting of chronic disease management and trajectory of disease.[6] The US Centers for Disease Control and Prevention website "U.S. Medical Eligibility Criteria for Contraceptive Use, 2024 (U.S. MEC)" has additional details on specific populations and conditions and is a free tool available to all clinicians.

Adolescents with obesity have parallel sexual health care needs compared to their peers. When choosing contraception methods, it is important to review effects of weight and related endocrine effects on the efficacy and side effect profile of each method. Weight gain after starting contraception is a common concern. Data suggest adolescents with obesity are more likely to gain weight with depot medroxyprogesterone acetate (DMPA) than normal weight peers, but not with other methods (COCs, vaginal ring, IUD, implant).[6] Of note, average weight gain associated with hormonal contraception is significantly less than average weight gain should a patient complete a pregnancy. Patients who have undergone bariatric surgery, a procedure increasing in frequency among adolescents, are at risk for decreased efficacy of oral contraceptives due to malabsorption, diarrhea, and vomiting. There is increasing frequency of placing a hormonal IUD at the time of bariatric surgery. Outside of the concern for additional weight gain with DMPA and decreased absorption of COCs after procedures known to result in malabsorptive dysfunction, all other contraceptive options are safe after bariatric surgery.[6]

ADOLESCENT INTERVIEW

Pediatric practitioners have a strong role to play in preventing undesired pregnancy, preventing STIs, and promoting

healthy sexual lives in adolescent patients.[17,31] Pediatric practitioners see patients annually at preventive visits, sports physicals, chronic health follow-ups (ie, mood disorders, attention-deficit hyperactivity disorder, asthma, acne), and acute illness visits. These visits provide a unique opportunity to be a trusted source of information in adolescents' lives. Practitioners offer factual information, respond to sensitive questions, and initiate conversations regarding sexual health.[6] Adolescents lean on their practitioners for support regarding their sexual health needs. After initiating contraception for an adolescent, a practitioner should consider scheduling a follow-up visit to address use, adherence, and any side effects. These visits are an opportunity to reassess and further discuss relationship dynamics, sexual behaviors, condom use, STI testing, and catch-up HPV vaccination. Risk of STIs in both penetrative and nonpenetrative sex should be discussed.[28] Motivational interviewing approaches can increase healthy and safe sexual practices and encourage patients to involve their parents in their sexual health care when safe to do so.[6,28] Bright Futures recommends that PCPs begin discussing with parents during prenatal visits the concepts of assigned gender at birth vs development of gender after birth and to continue to discuss with parents developmentally appropriate sexual behaviors, gender identity, and sexuality throughout their child's growth.[32] Guidelines recommend reproductive health visits begin for patients between 11 and 14 years old and continue throughout adolescence.

Adolescent sexual interviews should be developmentally appropriate and begin in a broad manner. Taking a sexual history should begin with a reminder of confidentiality parameters. It is helpful to normalize sexual interest and exploration in their age group, followed by an introduction that several questions will be asked to help them have positive and healthy experiences with sex. The HEADSS assessment (Table 3) is a framework for clinicians to address psychosocial development and well-being of adolescents across broad categories. HEADSS stands for Home, Education, Activities, Drugs, Sexuality, and Suicide (Table 3).[33,34]

TABLE 3. HEADSS: Sexual Behavior Assessment[34,35]

Questions
Have you ever been attracted to anyone? Boys, girls, or both?
Have you ever had sex? Oral sex? Anal sex?
How many sexual partners have you had?
How old were you when you first had sex?
Has anyone ever touched you in a way you did not want to be touched or forced you to do something you did not want to do sexually?
Are you dating anyone now? How old is he or she?
Do you like your boyfriend or girlfriend? Do you feel safe with him or her?
Are you in a relationship now?
Do you have sex or sexual contact with a partner or friend?
Did you use a condom with your last sexual contact?
Have you ever had a sexually transmitted infection?

Adapted from Sexual and reproductive health toolkit for adolescent providers: taking a client centered sexual history. Adolescent Health Working Group. 2010.[34]

TIPS/TRICKS WITH EXAMINATIONS/VISITS

Many adolescents fear health care visits due to not knowing what will occur during the visit. Staff should be trained how to interact with adolescents, which includes training to be comfortable regarding sexual and gender diversity.[28] Pelvic examinations are a frequent point of concern. Practitioners should let patients know at the beginning of a sexual health visit that an examination will only happen if both the patient and practitioner agree an examination is necessary, and an examination will usually happen only if there are symptoms. Normal anatomy of the external genitalia should be confirmed, but internal examinations of patients in female bodies are not indicated in a screening capacity.[36] These authors assert that once normal anatomy/pubertal development is confirmed by a clinician, the clinician does not need to do a pelvic examination without additional indication. Indications for pelvic examination of a patient in a female body could include persistent vaginal discharge, abnormal vaginal bleeding/amenorrhea, pregnancy, suspected abuse or assault, need to perform a pap smear or place an IUD, and need to evaluate lower abdominal/pelvic pain.[35] Patients and parents should be advised that cervical cancer screening routinely starts between ages 21 to 25 years for average risk individuals.[28,36] One should establish a connection with the patient and talk through what a speculum examination is before proceeding. Clinicians should use positive pain language, with words like "pressure" rather than "sharp." The patient's face should be kept in sight so that one can respond to nonverbal reactions that can help guide the need to pause or stop an examination before completion.

REFERRALS

Sometimes PCPs need assistance from gynecologists; a few tips can help those referrals be more efficient. When an examination or IUD insertion cannot be completed by the PCP, one should be specific in the referral about what was tried, what tools were used, and what part of the examination or procedure could not be completed. For difficulty managing hormones for contraception or menstrual suppression (ie, ongoing breakthrough bleeding), delineating the

specifics of what has been tried will help the consulting gynecologist take the appropriate next step (ie, estrogen dose, cyclically vs continuously, monophasic vs triphasic). Before referral of medically complex patients, specialists appreciate knowing in advance the verbal and developmental capacity of the patient they will see. It can also be beneficial for specialists to know how involved parental figures are in the care of the patient.

CONCLUSION

A healthy understanding by adolescents of relationships, sexuality, gender identity, and sexual intimacy begins with early education that continues throughout adolescence. Pediatric practitioners are considered trusted health professionals by both parents and adolescents for the gamut of sexual health care and education.[6] These practitioners can take advantage of the relationships they have with adolescents to routinely check in on sexual health topics during clinic visits, including at chronic illness follow-ups, sick visits, and preventive examinations. The practitioners' special role in children's lives provides them with a unique position to help shape the development of an adolescent's lifelong relationship and sexual health. A healthy understanding of one's body, sexuality, gender identity, and relationships can have a profound benefit on a person's lifelong health—this is not an opportunity that should be squandered.

Summary

- Sexual exploration is a natural part of adolescence, and most individuals will initiate sexual activity in their adolescent years.[1–3] "Sexually active" can have multiple definitions, including penile-vaginal intercourse, oral sex, and anal sex.[3] (Category B, based on clinical and observational studies)
- Despite making up only 13% of the population,[11] adolescents (15–24 years old) account for approximately half of new STIs in the United States every year,[12,13] with 1 in 4 sexually active females having had an STI.[13] (Category B, based on clinical and observational studies)
- Nearly a quarter of adolescents are identified as having special health care needs, and these adolescents have similar rates of sexual activity, STIs, and pregnancy as other adolescents. Further, in this population, sexuality and sexual health care needs are often overlooked.[6] (Category C, based on observational studies and studies with limitations)
- The need for privacy and confidentiality for adolescent sexual health care can be complicated by electronic health records, insurance billing, and state laws.[8,9,28,29] (Category C, based on observational studies and studies with limitations)
- Sex-positive parenting and the involvement of parents can help promote healthy sexual development through ongoing parent-child conversations.[26] (Category D, based on expert opinion, case reports, reasoning from first principles)

Take the quiz! Scan this QR code to take the quiz, access the references and view and save images and tables (available May 1, 2025).

PIR QUIZ

1. A pediatric resident proposes a quality improvement (QI) initiative aimed to increase the rates of condom education for adolescents seen in the ambulatory clinic. In support of the initiative the resident presented data highlighting rates of gonorrhea and syphilis and the multiple factors associated with a disproportionate burden of sexually transmitted infections (STIs) among adolescents and young adults. Whereas those aged 15 to 25 years represent approximately 13% of the population, this population annually accounts most closely for which of the following proportions of new STIs?

   A. 1 in 2
   B. 1 in 4
   C. 1 in 5
   D. 2 in 3
   E. 3 in 4

2. A 9-year-old girl is seen in the clinic for a health maintenance visit. The mother has noticed that the child has some breast development. The mother expresses that she is nervous about having the "talk" about menstrual periods and sex. The mother placed a call to the nurse at her daughter's school to learn about school resources and sex education; a return call with the nurse is scheduled for next week. At this time in the girl's development which of the following is the most appropriate next step to be taken by the provider to address the mother's concern?

   A. Introduce the mother to the concept of sex positive parenting that includes developmentally appropriate sexual health conversations that span childhood and adolescence.
   B. Introduce the mother to the concept of virginity pledgers that have a historic track record for paternal participation and substantially reducing age of first sex.
   C. Reassure the mother that most public schools provide a comprehensive and adequate sex education curriculum that begins in the 3rd grade.
   D. Reassure the mother that there is no hurry for the "talk'; her daughter's menarche will be close to the typical age of 13 years.
   E. Recommend that the mother joins a social media or community based "mom-teen" parenting support group.

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3. A 16-year-old girl is being seen alone for a health maintenance visit and makes a request for contraception. She is healthy and has no contraindications for hormonal contraception and expresses a preference for oral contraceptive pills. She has been sexually active for 3 months with 1 male partner, and they have consistently used condoms. She has had conversations with her parents about sexual health and understands the role of effective contraception and condoms. However, at this time, she is not ready to disclose her sexual activity to her parents and requests that this information remains strictly confidential. At age 14 years her parents initiated and established a private password for their daughter to have confidential access to her health visit records. The parents have never asked to use the passcode or to review her health record. The clinician discusses all contraception options and recommends continued condom use. Which of the following is the best next step to meet this patient's confidentiality needs?

    A. Discuss her accessibility to a clinic with Title X services (eg, school clinic, federally qualified health care clinic) and its associated privacy and confidentiality safe guards.
    B. Offer "depo" a hormonal birth control injection (medroxyprogesterone acetate) that can be given every 3 months in the privacy of the same clinic.
    C. Prescribe an oral contraceptive pill with the reassurance the parents are not likely to learn about her prescription.
    D. Recommend the over-the-counter progesterone pill until she is ready to disclose her sexual activity to her parents.
    E. Recommend an implantable progestin contraceptive as the most discreet and effective contraceptive method; additionally, placement services are available in the same clinic.

4. A 16-year-old girl with a history of Type 1 Diabetes and a well-controlled seizure disorder presents to the clinic for her health maintenance visit. During the HEADSS interview she shares that she has been in a sexual relationship with a 16-year-old male partner and they have had intercourse only twice in the past 2 months. She requests initiation of an oral contraceptive. The Center for Disease Control US Medical Eligibility Criteria for Contraceptive Use tool is consulted to inform contraceptive choices. Which of the following factors is most likely to influence the provision of sexual health services for the almost 20% of the adolescent population with special health needs compared to otherwise healthy adolescents?

    A. Higher rates of STIs
    B. Lower rates of "ever had sex"
    C. Similar rates of pregnancy
    D. Substantially higher contraindication(s) for their use of Emergency Contraception
    E. Substantially higher contraindication(s) for a confidential portion of the heath visit

5. While preparing to see a young adolescent for a health maintenance visit, the precepting pediatrician shares with the medical student the plan to ask permission for them to "spend time alone" with the patient. The pediatrician anticipates that, like many, the parent and patient will be agreeable. They also review the HEADSS framework and limits of confidentiality. The medical student expresses a hesitancy to ask "S" - sexual behavior questions. After validating the medical student's hesitancy, further discussion most appropriately includes which statement about sexual health inquiry?

   A. Among adolescents ages 11 to 14 years only those with other risky behaviors or adverse childhood events are asked sexual health questions.
   B. If the adolescent is not sexually active no further "S" questioning is pursued.
   C. Only adolescents ages 15 years and older are routinely asked sexual health questions.
   D. The responsibility to ask sexual health questions is supported by rising rates of adolescents reporting "ever had sex" and rising adolescent pregnancies rates.
   E. "S" questions are an opportunity for the primary care pediatrician to address their patient's sexual health needs and to provide a trusted source of sexual health information.

Balancing Digital Media Exposure: Enhancing Language and Social Development in Early Childhood

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EDUCATION GAP

Many health care providers may not be fully aware of the nuanced effects that digital media exposure can have on early childhood language, social, and cognitive development. Although there is an understanding that excessive screen time can be harmful, the potential benefits of high-quality, interactive, and educational content are often overlooked in clinical advice. Furthermore, health care providers may not be familiar with the available tools and resources, such as the American Academy of Pediatrics' 5 C's framework, that can help families choose appropriate media. Additionally, epidemiological data showing the increasing prevalence of digital media use among young children, particularly because of the shifts in behavior brought on by the COVID-19 pandemic, may not be fully appreciated. Clinicians need to provide informed, balanced guidance that promotes both safe and effective media use for optimal developmental outcomes.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the epidemiological trends in digital media exposure among young children, including changes influenced by recent global events such as the COVID-19 pandemic.
2. Describe the impact of digital media exposure on early language, highlighting both potential risks and benefits.
3. Explain the importance of quality over quantity in digital media use, understanding how different types of media influence language development.
4. Provide practical strategies for health care providers to guide families toward balanced digital media use to support optimal language, cognitive, and social development in early childhood.

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ABBREVIATIONS

AAP American Academy of Pediatrics
QI quality improvement

ABSTRACT

In recent years, the widespread integration of digital media into early childhood has significantly influenced the landscape of language development. Traditional speech and language acquisition is deeply rooted in social interactions and environmental stimuli; however, the increasing exposure to digital media introduces new variables into this developmental process. Research indicates that excessive or inappropriate use of digital media can impede language development. Conversely, high-quality educational content, when used appropriately, can support language acquisition and vocabulary growth. This review examines the complex effects of digital media exposure on early language development and related cognitive and social domains, highlighting both potential risks and benefits. It underscores the pivotal role of health care providers in guiding families toward balanced and evidence-based media use. By synthesizing current research and offering practical recommendations, this article aims to assist providers in supporting such development trajectories in young children within our increasingly digital world.

INTRODUCTION

In recent years, the widespread integration of digital media into children's lives has significantly influenced the landscape of childhood development. Rapid advancements in technology have led to the proliferation of interactive devices, including smartphones, tablets, smart toys, and educational apps, that are now integral to many children's daily experiences.[1–4] This trend has only intensified after the COVID-19 pandemic because lockdowns and social distancing measures increased reliance on digital devices for education, communication, and entertainment.[5] This shift in how children interact with their environment and access information has raised important questions about digital media's impact on early childhood development. Researchers are therefore actively investigating how this increased digital media exposure affects developmental trajectories, particularly concerning language acquisition and cognitive skills.[5–7] Although this review primarily addresses the impact of digital media on language development, it also considers associated cognitive and social benefits and risks because of their interconnectedness in early childhood development when appropriate.

Speech and language development in early childhood follows a well-established sequence of milestones, beginning with cooing and babbling in infancy, progressing to single words and phrases, and culminating in complex sentences by the age of 5.[8,9] This developmental trajectory is fundamentally rooted in direct social interactions, environmental stimuli, and caregiver responsiveness, which collectively form the foundation for linguistic competence. With the increasing exposure to digital media, traditional pathways of language development may be influenced as children engage with new forms of communication and content delivery.

Research suggests that although digital media can offer opportunities for learning and engagement, excessive or inappropriate usage may have detrimental effects on language development (Table 1). Studies have highlighted cofounding potential risks such as decreased parent-child interaction, reduced attention spans, and poorer executive functioning in young children, which are factors that can indirectly impact language acquisition.[6,7,10–15] Some theories propose that increased screen time may lead to children missing opportunities to practice developmentally appropriate skills and tasks, particularly those involving direct social interaction and language practice.

Conversely, higher-quality screen time has been positively associated with language skills.[10,16] Media that is educational, interactive, and developmentally appropriate can support language acquisition when used appropriately. Therefore, in an age of inevitable screen use, encouraging parents to focus on the quality of screen time rather than solely on quantity may be more beneficial when discussing this topic.

It is imperative to equip ourselves with strategies to offer families proactive guidance within a collaborative, family-centered framework for decision-making. By adopting an informed and balanced approach and leveraging technology as a tool for enhancing language learning experiences and promoting meaningful interactions, we can harness its potential to enrich rather than impede the language development of young children.

FOUNDATIONS OF SPEECH AND LANGUAGE DEVELOPMENT IN EARLY CHILDHOOD

Learning speech and language is a critical task of childhood, and yet it is one that most children accomplish effortlessly, regardless of which language(s) they need to learn, the complexity, and the sheer volume of sounds, words, and meanings encompassed in human language.

Children progress through language and speech development in a stepwise fashion, regardless of child-level differences including sex, bilingualism, birth order, and

TABLE 1. Citation Summary of Benefits and Harms of Media Use on Child Development

Benefits of Media Use	Findings
Madigan et al (2020)[10]	Limit screen exposure to high-quality programming and co-viewing; High-quality media use is associated with increased language skills.
Anderson et al (2001)[29]	Viewing educational programs as preschoolers correlated with higher grades, reading more, greater creativity, and less aggression.
Christakis et al (2013)[30]	Increasing exposure to prosocial media can positively impact children's behavior.
Ricci and Beal (2002)[28]	Presenting content with stable, slow-paced visuals supports sustained attention and deeper cognitive engagement.
Calvert et al (1982)[38]	Including prosocial themes with salient auditory features (sound effects) positively influence children's social and emotional growth.
Lavigne, Hanson, and Anderson (2015)[51]	Co-viewing increases parent language quality through labeling objects and narrating actions.
Linebarger and Vaala (2010)[52]	Infants and toddlers are capable of learning from high-quality, age-appropriate digital media, particularly when co-viewing is involved.
Linebarger and Walker (2005)[42]	Age-appropriate and educational media may be associated with higher expressive language and vocabulary.
Kirkorian, Wartella, and Anderson (2008)[37]	Early exposure to age-appropriate and educational media is associated with cognitive and academic achievement.
Thakkar, Garrison, and Christakis (2006)[39]	Educational media can help broaden young children's knowledge and imaginativeness.
Huber et al (2018)[43]	Interactive and educational content may have positive impacts on young children's executive functioning.
Roseberry, Hirsh-Pasek, and Golinkoff (2014)[40]	Toddlers were able to learn novel verbs in socially contingent interactions through video chat.
Gaudreau et al (2020)[44]	Children can comprehend books over video chat
Anderson and Subrakhmanyam (2020)[24]	Digital screen media, including television, has varying impacts on cognitive development, with educational programming positively impacting development for preschool-aged children and computer games and educational programs enhancing skills.
Nobre et al (2019)[23]	Quality interactive media use in early childhood positively and significantly impacts child development, particularly in language.
Harms of Media Use	
Hudon, Fennell, and Hoftyzer (2013)[16]	Poor quality television viewing was related to lower vocabular outcomes (especially in bilingual toddlers).
Thakkar, Garrison, and Christakis (2006)[39]	Viewing cartoons may have a negative impact on children's attention capacity.
Madigan et al (2020)[10]	Greater quantity of screen use was associated with lower language skills.
McHarg et al (2020)[11]	Increased screen time at 2 y of age was negatively associated with executive function in toddlerhood.
Brushe et al (2024)[6]	Increased screen time decreases the amount of parent-child talk and interaction; promote a language-rich home environment.
Zimmerman, Christakis, and Meltzoff (2007)[53]	Increased infant viewing of baby digital video discs/videos was associated with decreased language development.
Karani, Sher, and Mophosho (2022)[13]	Screen time during early child development has negative impacts on language development; encourage parents to prioritize content and co-viewing when possible.
Bhutani et al (2024)[14]	Increased screen time may have negative impacts on language development.
McArthur, Tough, and Madigan (2022)[7]	Children engaging in media use for more than 2 h daily had increased behavioral problems, delayed developmental milestones, and decreased vocabulary.
Radesky and Christakis (2016)[31]	Increased screen time in young children may negatively impact cognitive, language, literacy, and social-emotional development.

frequency of otitis media infections.[8,9] Language and communication milestones have been extensively studied. The most recent milestone checklist was revised for the Centers for Disease Control's "*Learn the Signs. Act Early*" program by an American Academy of Pediatrics (AAP) expert workgroup, with findings published in 2022.[17] Notably, these milestones, revised to reflect expectations for 75% of children by a given age, serve as crucial indicators for developmental surveillance during pediatric visits (Table 2). If a child fails to reach these milestones, further evaluation is warranted, because factors such as media exposure can influence speech and language development.

DEFINING DIGITAL MEDIA

Digital media refers to "digitized content that can be transmitted over the internet or computer networks,"[18] including formats such as podcasts, e-books, and streaming TV

TABLE 2. Seventy-Fifth Percentile Language and Communication Milestones by Age, Adapted From Zubler et al[17]

Age	Language/Communication Milestones
2 mos	Makes sounds other than crying
	Reacts to loud sounds
4 mos	Makes sounds like "ooo," "aahh" (cooing)
	Makes sounds back when you talk to them
	Turns head toward the sound of your voice
6 mos	Takes turns making sounds with you
	Blows "raspberries"
	Makes squealing noises
9 mos	Babbles (makes a lot of different sounds like "mamamama" and "babababa")
	Lifts arms up to be picked up
12 mos	Waves "bye-bye"
	Calls a parent "mama" or "dada" or another special name
	Understands "no" (pauses briefly or stops when you say it)
15 mos	Tries to say one or 2 words besides "mama" or "dada"
	Looks at a familiar object when you name it
	Follows directions given with both a gesture and words
	Points to ask for something or to get help
18 mos	Tries to say 3 or more words besides "mama" or "dada"
	Follows one-step directions without any gestures
2 y	Points to things in a book when you ask
	Says at least 2 words together
	Points to at least 2 body parts when you ask them to show you
	Uses more gestures than just waving and pointing (like blowing a kiss or nodding yes)
30 mos	Says about 50 words
	Says 2 or more words together, with one action word
	Names things in a book when you point and ask, "What is this?"
	Says words like "I," "me," or "we"
3 y	Talks with you in conversation using at least 2 back-and-forth exchanges
	Asks "who," "what," "where," or "why" questions
	Says what action is happening in a picture or book when asked
	Says first name, when asked
	Talks well enough for others to understand most of the time
4 y	Says sentences with 4 or more words
	Says some words from a song, story, or nursery rhyme
	Talks about at least one thing that happened during their day
	Answers simple questions like "What is a crayon for?"
5 y	Tells a story they heard or made up with at least 2 events
	Answers simple questions about a book or story after you read or tell it to them
	Keeps a conversation going with more than 3 back-and-forth exchanges
	Uses or recognizes simple rhymes (like bat-cat, ball-tall)

shows or movies. Traditional media, on the other hand, encompasses live TV, radio, newspapers, and books. When both digital and traditional forms are considered together, they are often simply referred to as "media," a term we will use throughout this paper. The vast landscape of media has undergone a significant transformation with the proliferation of interactive devices, such as smartphones, tablets, smart toys, and "educational" applications (referred to as "apps"), driven by rapid technological advancements.

Distinguishing Types of Digital Media and Screen Time

The well-known "screen time" is defined as the amount of time spent using devices with screens, including smartphones, tablets, computers, and televisions. This term is used irrespective of the content quality or engagement type, encompassing both passive and interactive uses. Screen time can vary widely in its educational value and impact on development, depending on the nature of the media consumed and the context in which it is used. As screen time becomes both more prevalent and more complex, it is important to evaluate the quantity, quality, and context of screen time use and how these relate to developmental outcomes.

Quantity of screen time use includes both time spent directly using the device (watching TV, interacting with a tablet or touch screen phone) and time spent with background screen exposure (typically TV).[10] Quality of screen time is more complex and considers the context, content, and design elements of the media, which will be discussed further in the following sections.

Research suggests that different contexts of screen use have varying impacts on child development, with factors like co-use (or co-viewing) positively associated with cognitive outcomes, whereas background television and program viewing were associated with poorer cognitive outcomes.[19] In addition, excessive caregiver screen use during child routines was linked to negative psychosocial outcomes.[19] These findings highlight that not only the amount of screen time but also how and with whom screen time is used significantly affects children's cognitive and psychosocial development. Therefore, context, quantity, and quality should all be considered when evaluating the impact of screen time.[5,6,10,19] Additionally, caregivers can improve the quality of screen use by co-viewing the media along with the child.[20] While co-viewing, the caregiver can enhance the cognitive fit and interactive nature of the media by providing scaffolding, which is temporary support provided by an expert (eg, caregiver or educator) to help develop new skills, such as using gestures, providing verbal cues or prompts, or repeating or expanding the child's language to facilitate learning.[21]

TABLE 3. Digital Media Definitions

Term	Definition	References
Screen time	The amount of time spent using devices with screens, including smartphones, tablets, computers, and televisions. This term encompasses both passive and interactive uses, irrespective of content quality or engagement type. Screen time can vary widely in its educational value and impact on development, depending on the nature of the media consumed and the context in which it is used.	Common Sense Media (2013)[3]
Digital learning media	All forms of digital content that can be used for educational purposes, encompassing interactive, educational, and high-quality digital media. This includes apps that require active engagement and provide learning opportunities, as well as passive educational shows designed to teach without interaction. The intent is to enhance developmental outcomes, such as language acquisition and cognitive skills, through engaging content.	Hirsh-Pasek et al (2015)[25]; Zero to Three (2018)[26]
Interactive media	Digital platforms that require user engagement and input, such as video games, interactive story apps, or e-books that prompt users to tap the screen in response to questions or to reveal content. Interactive media responds to the user's actions but does not inherently include educational content. Not all interactive media is educational.	Madigan et al (2020)[10]; Meyer et al (2021)
Educational media	Content specifically designed to foster learning and development, often validated by educational standards set by reputable organizations like the NAEYC and reviewed for content quality by agencies such as Common Sense Media. Educational media is characterized by its intent to teach and may or may not be interactive. Examples include programs like *Sesame Street* and platforms like Khan Academy.	Anderson et al (2001); Hirsh-Pasek et al (2015); Common Sense Media (2013)
High-quality digital media	Digital media that adheres to developmental principles, promoting positive social skills, language development, and cognitive growth while avoiding overstimulation or inappropriate content. Often evaluated by frameworks like the "Four Pillars of Learning" or "E-AIMS" model, and reviewed by agencies such as Common Sense Media.	Hirsh-Pasek et al (2015); Meyer et al (2021); Zero to Three (2018)[33]
Scaffolding	Temporary support provided by an expert (eg, caregiver or educator) to help develop new skills. In the context of media use, this involves caregivers enhancing the cognitive fit and interactive nature of media by using gestures, providing verbal cues or prompts, and repeating or expanding the child's language to facilitate learning. Co-viewing media allows for effective scaffolding.	Wood, Bruner, and Ross (1976)[21]; Roseberry, Hirsh-Pasek, and Golinkoff (2014)[40]

Abbreviation: NAEYC, National Association for the Education of Young Children.

In distinguishing between "interactive media" and "educational media," it is crucial to understand that not all interactive media serve educational purposes (Table 3). Interactive media refers to digital platforms that require user engagement and input, such as video games or interactive story apps,[22,23] which may not inherently include educational content. Research highlights mixed outcomes associated with interactive media use. For instance, studies show that interactive media can support cognitive and language development, especially when used alongside parental guidance to help scaffold learning experiences.[4] However, the benefits of interactive media are highly dependent on content quality and the context of use, with some research indicating that not all interactive platforms provide significant developmental advantages.[24] Therefore, it is essential to consider both the quality of interactive media and the role of caregiver involvement to maximize interactive media's potential benefits. Further research is needed to clarify interactive media's long-term effects on cognitive and language development in early childhood, especially as new interactive platforms and applications continue to emerge.[22,23]

Conversely, educational media is specifically designed to foster learning and development, with guidance provided by organizations like the National Association for the Education of Young Children (NAEYC) and content quality reviews by agencies such as Common Sense Media.[3] Although these standards help shape what qualifies as educational media, the exact definition of educational content remains somewhat elusive.[10] For instance, studies often rely on author determination to label content as educational, and criteria can vary widely. In Madigan et al's meta-analysis of 42 studies, only 10 studies separated out "educational programming," and only one study16 cited a quantitative measure—programs previously correlated with increased vocabulary scores.[10,16] Recognizing the need for clearer standards, Hirsh-Pasek et al developed the "Four Pillars of Learning" framework based on learning science to evaluate whether apps are educational.[25] These 4 pillars have been adapted by the child development organization Zero to Three into the "E-AIMS" model to help parents and providers evaluate the quality of media content.[26] E-AIMS stands for engaging, actively involved, meaningful, and social.

Educational programs and apps designed with developmental principles in mind can support language skills, whereas passive consumption of entertainment-oriented content may not offer the same benefits.[6,27,28] For example, *Sesame Street* exemplifies traditional (one-way) educational media that delivers educational content without interactive components, and has been linked to improved developmental outcomes, including literacy[29] and social development.[30] In contrast, newer

educational digital media platforms, such as Khan Academy, offer interactive, curriculum-based learning experiences. When educational media is designed to encourage active engagement and upholds high-quality educational standards, it shows promise in promoting early literacy and language skills. However, excessive use or overstimulation from poorly designed apps may counteract these benefits.[31]

Because the Federal Communications Commission does not regulate marketing claims of the educational benefits of digital media products for children,[32] it is especially important that caregivers be educated on how to evaluate these applications themselves. Notably, an analysis by Meyer et al found that of the 124 most downloaded children's educational apps, most scored low on all 4 of Hirsh-Pasek et al's "Four Pillars," with free applications scoring significantly lower than paid apps.[25,33]

EVOLUTION OF SCREEN TIME RECOMMENDATIONS AND EPIDEMIOLOGICAL TRENDS

The AAP recommendations on media use for children have continuously evolved in response to the rapidly changing media landscape and increasing digital media exposure among young children. In its 1999 policy statement, the AAP initially emphasized the importance of direct interaction with parents and caregivers over screen time for infants under 2 years old.[15] However, with the proliferation of media—particularly television aimed at infants—the AAP updated its stance in 2013 to acknowledge the ubiquity of media while still advocating for parental involvement in content consumption.[27] The emergence of interactive media and the widespread use of digital devices prompted the AAP to publish an updated policy statement in 2016.[34]

The 2016 policy statement recognized the potential benefits of interactive media, particularly video chatting for infants under 18 months, acknowledging that such interactions could support social connections and learning when facilitated by caregivers.[34] The 2016 policy statement underscored the importance of caregiver scaffolding to facilitate learning during media use. While acknowledging the value of high-quality programming like *Sesame Street*, the AAP recommended that screen time for children aged 2 to 5 years be limited to no more than 1 hour per day, with an emphasis on co-viewing with parents to maximize educational benefits.

In contrast to the AAP's recommendation of ideally 1 hour of co-viewed screen time, epidemiological data indicate that children are exposed to significantly more screen time.[35] As of 2020, children aged 2 to 4 years used screen media for an average of 2.5 hours per day.[3] This trend intensified during the COVID-19 pandemic, with lockdowns and social distancing measures increasing reliance on digital devices for education, communication, and entertainment.[5,36] A 2022 meta-analysis found that screen time for children aged 0 to 5 years increased by an additional 0.6 hours per day during the pandemic (95% CI, 0.3–0.9 h/d).[36] Children are increasingly exposed to digital devices from infancy, interacting with touch screen devices and engaging with multimedia content tailored to their age group.[1–4,10]

Although the AAP's evolving recommendations address the quantity of screen time and emphasize parental involvement, it is equally important to consider the quality of the content consumed. As children's exposure to digital media continues to grow, the design and nature of the media itself play a critical role in shaping developmental outcomes. Beyond limiting screen time, understanding how thoughtfully crafted media can influence speech, cognitive, and emotional growth is essential. In the following section, we explore the psychological principles behind quality content design.

THE PSYCHOLOGY BEHIND QUALITY CONTENT DESIGN

The psychological aspects of media consumption, particularly for children, emphasize the importance of content design in influencing speech, cognitive, and emotional development (Figure 1). In crafting children's television programming, thoughtful consideration of visual and audio design can significantly enhance cognitive and sensory development. Programs using subdued color schemes and natural tones are less likely to cause visual strain, thus maintaining a calm environment that fosters focused attention in young viewers.[37] Additionally, presenting content with stable, slow-paced visuals supports sustained attention and deeper cognitive engagement, as opposed to fast-paced, frequently changing scenes that might promote shorter attention spans.[38] The narrative content of these programs is equally crucial; rich storylines not only boost vocabulary and language comprehension but also provide immersive experiences that aid cognitive development. The inclusion of prosocial themes—such as kindness, empathy, and friendship—plays a vital role in influencing children's social and emotional growth by imparting lessons on social norms and the importance of community.[39] Educational value is further amplified through educational dialogues woven into the storyline, making learning seamless and memorable. Moreover, carefully incorporated interactive elements can stimulate critical thinking and enhance information retention.[40] The role of parents and educators is also pivotal; co-viewing sessions offer a guided viewing experience that helps relate the

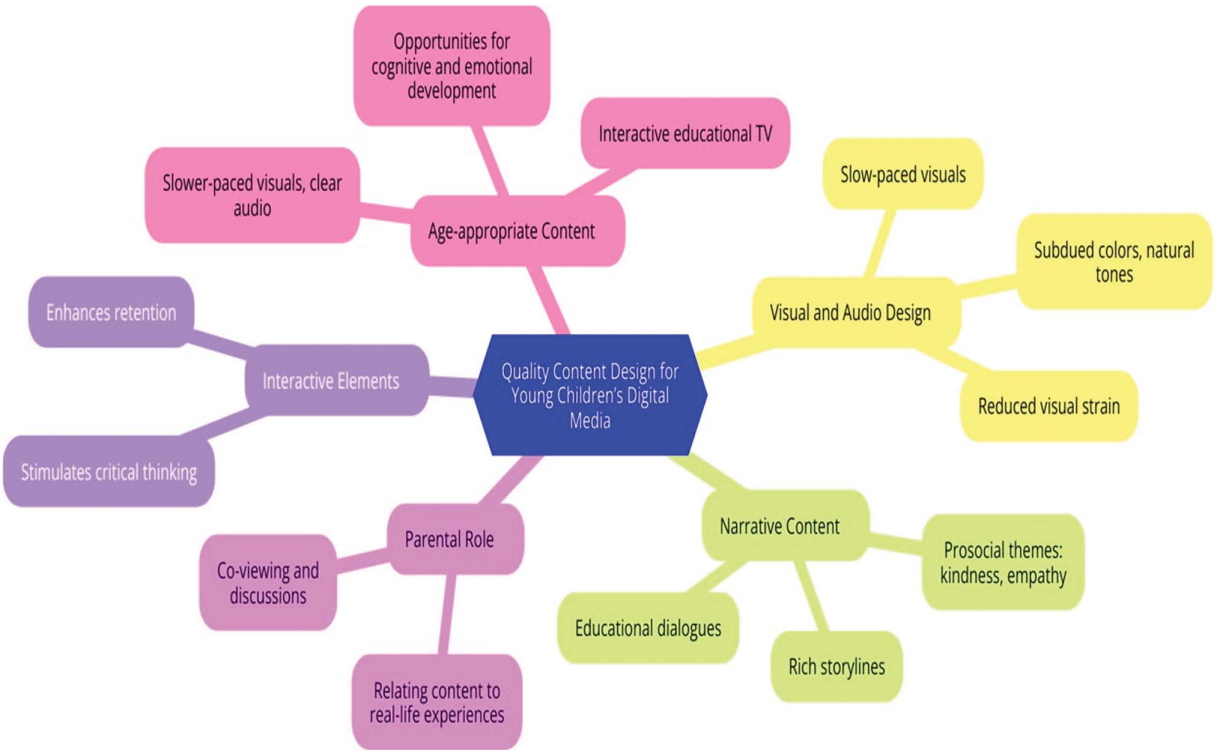

FIGURE 1. Quality content design for young children's digital media. Interactive elements—enhances retention: interactive features that help children retain information; stimulates critical thinking: activities that encourage problem-solving and decision-making. Age-appropriate content—opportunities for cognitive and emotional development: content designed to support children's learning and emotional growth; interactive educational TV: programs tailored to be both age-appropriate and educational. Parental role—co-viewing and discussions: encouraging parents to watch with children and discuss content; relating content to real-life experiences: helping children connect on-screen content to everyday situations. Narrative content—educational dialogues: conversations within media that provide learning opportunities; rich storylines: complex narratives that engage children in a meaningful way; prosocial themes: emphasis on kindness, empathy, and cooperation.Visual and audio design—reduced visual strain: visuals and sounds designed to be gentle on young eyes and ears; slow-paced visuals: content that moves at a pace suitable for young children's comprehension; subdued colors, natural tones: colors and visuals that are easy on the eyes and support focus.

content to real-world scenarios, whereas discussions post viewing reinforce the material learned and encourage reflection and critical thinking. Each of these components is essential for creating engaging and developmentally beneficial children's programming that educates while it entertains.

Higher-quality screen time includes age-appropriate interactive educational TV content, shared screen time, active apps/games, interactive video chats, and virtual story times. These tools can serve as additional opportunities for children to practice language skills but should not be used as alternatives to live and direct social interaction.[41,42] Age-appropriate educational TV content typically involves an integrative narrative, language, and auditory and visual simulation paced to the developmental level of the child.[42] Parents should be encouraged to prioritize videos that are slower paced, with less flashing/changing images, and audio with a clear cadence and softer tone. These programs typically give the child an opportunity to respond verbally or with gestures and model other aspects of cognition (attention, memory, planning) and emotional development (kindness, empathy, friendship, and prosocial skills).[11,37,39,43] Shared or co-viewing screen time can serve as an opportunity for singing, labeling, playing games, asking questions, or reading together.[10] Interactive video chats have been particularly beneficial since the beginning of the COVID-19 pandemic, allowing children to engage with individuals outside of the household and to practice social and language skills.[25,40,44]

ANTICIPATORY GUIDANCE

Health care providers should be familiar with the impact that media exposure has on developmental outcomes and provide anticipatory guidance for families. The AAP's HealthyChildren emphasizes the importance of carefully managing screen time in early childhood.[45] For infants under 18 months of age, media should be avoided, except for video chatting, to prevent potential negative impacts on attention spans and developmental milestones.[34] When

TABLE 4. Resources for Families and Providers

Resource	Description
Common Sense Media	Nonprofit that reviews media including TV, apps, YouTube channels, and more for children ages 2 to 18 y old.
Zero to Three	Nonprofit, research-based resource focusing on child development for children 0 to 3 y of age.
	"E-AIMS" Model helps caregivers evaluate the quality of screen experiences for their child.
Pathways	Nonprofit that shares free resources to support the early detection and intervention of developmental delays. Milestones are validated by AAP findings, and resources are developed by medical providers, physical and occupational therapists, and speech-language pathologists.
	Explains AAP recommendations in easy-to-understand terms, including definitions of interactive and educational content and co-viewing. Offers many alternative activities to screen time for children <5 y.
CDC's "Learn the Signs. Act Early" website and Milestone Tracker application	Government website and application to facilitate family-engaged developmental monitoring (surveillance).
Vroom® website	Set of free tools and resources, including a mobile app, that provide easy access to daily "brain-building" activities to incorporate into existing routines for children ages 0 to 5 y. Includes communication, literacy, and listening "tip sheets." Funded by the Bezos Family Foundation, developed with the Harvard University Center on the Developing Child. (Does not include restricted, paid content or advertising).
AAP's HealthyChildren website	Parenting website by the AAP, which includes specific guidance on media use for children ages 0 to 18 y.
	Family Media Plan: a customizable online tool to assist families in setting media priorities for children ages 0 to 18 y and adult caregivers.

Abbreviations: AAP, American Academy of Pediatrics; CDC, Centers for Disease Control and Prevention.

introducing screen time to children aged 18 to 24 months, it is vital to choose high-quality, educational content and engage in co-viewing to enhance understanding and interaction. Parents can find age-appropriate, high-quality content through resources such as Common Sense Media,[46] which offers detailed reviews and ratings based on age appropriateness and educational value (Table 4).

The AAP recommends limiting screen time to 1 hour per day for children aged 2 to 5 years, with a focus on content that supports learning and development.[34] This emphasis on content quality aligns with study findings, which suggest that stable, slow-paced narratives and visuals help maintain children's attention and deepen cognitive engagement.[10,37,42] Parents are encouraged to be present during screen time to discuss the content, thereby reinforcing language skills and real-world application. Establishing a personalized family media plan can help balance screen use with physical activities and unstructured play, which are crucial for healthy psychological and emotional development. The AAP family media plan allows families to set goals and rules for media use, including:

- Designated media-free times, such as during family meals and at least 1 hour before bedtime, to promote better sleep hygiene.
- Media-free zones, particularly in bedrooms, to reduce distractions and encourage other activities.
- Choosing appropriate media content that supports learning and development.
- Ensuring that media use does not displace sleep, physical activity, or face-to-face interactions.

An example of a family media plan and an online tool to create one can be found on the AAP's website: www.healthychildren.org/MediaUsePlan.

In addition to established guidelines, the AAP has introduced the "5 C's of Media Use"—child, content, context, critical thinking, and creating balance—as a framework to help providers discuss digital media use with families effectively[47] (Table 5). The "5 C's of Media Use" emphasizes tailoring media use to the child, selecting appropriate content, fostering engagement, promoting critical

TABLE 5. The 5 C's of Media Use

5 C's of Media Use	Description
Child	Tailor media use to the individual child's age, temperament, and developmental needs.
Content	Focus on high-quality, educational, and age-appropriate media that supports learning and development.
Context	Consider the environment in which media is used; promote co-viewing and active engagement to enhance learning.
Critical thinking	Encourage children to think critically about the media they consume, fostering media literacy and discernment.
Creating balance	Ensure that media use does not crowd out essential activities like sleep, physical activity, family interaction, and homework.

thinking, and ensuring a balanced lifestyle. This approach encourages mindful media choices that enhance development and prevent digital habits from displacing crucial activities such as family interaction, outdoor play, and adequate sleep. By discussing the "5 C's" with families, health care providers can offer practical strategies to manage media use effectively.

These guidelines not only promote healthier screen habits but also encourage parents to model these behaviors, as parental involvement and example-setting are instrumental in fostering appropriate screen interactions and overall healthy development in children.

CONCLUSIONS

Digital media has become an integral part of early childhood, influencing how children interact with the world and acquire language. This review highlights the nuanced impact of digital media exposure on early language development, emphasizing that although excessive or inappropriate use may impede language acquisition, high-quality educational content—used judiciously and with caregiver involvement—can support and enhance language skills. Early language development is not only foundational for communication but also a key predictor of cognitive growth and emotional understanding.

Health care providers, educators, and parents play pivotal roles in shaping the quality and quantity of digital media exposure for young children. By focusing on the quality of digital media content and fostering co-engagement through co-viewing and scaffolding, caregivers can mitigate potential negative effects and promote language development. Implementing practical strategies, such as creating individualized family media plans and using resources such as the AAP's "5 C's of Media Use" framework, can help families navigate the media landscape effectively. Collaborative efforts in research, clinical practice, and policy development are necessary to refine guidelines and support families in integrating digital media into a broader framework of developmental support.

As we continue to understand the complexities of digital media's impact on development, it is imperative to adopt a balanced approach that leverages the benefits of technology while safeguarding against its potential drawbacks. By prioritizing high-quality, educational, and developmentally appropriate digital media, and by emphasizing the irreplaceable value of direct human interactions, we can harness the benefits of technology for educational purposes while promoting healthy language and cognitive development in young children.

HOW TO COUNSEL AND GUIDE APPROPRIATE SCREEN TIME USE TO ENCOURAGE LANGUAGE AND SOCIAL DEVELOPMENT

Setting realistic expectations:

- Guidance: Clinicians should educate parents on the AAP's stance that children under 18 months should avoid media, except for video chatting. For children aged 18 to 24 months, if screen use is introduced, content should be high-quality, and caregivers should co-view to ensure understanding and engagement.
- Rationale: Early screen exposure can negatively affect attention spans and development.[1,10] However, when high-quality content is introduced with co-viewing, the social interaction helps mitigate these effects.[4] (Evidence Level B: Based on observational studies and AAP recommendations.)
- Psychological context: Some research indicates that co-viewing may turn screen time into an interactive, socially enriching experience that promotes social development.[25] (Evidence Level C: Based on observational studies and studies with limitations.)

Choosing appropriate content:

- Guidance: For children aged 2 to 5 years, the AAP recommends limiting screen time to 1 hour per day, focusing on high-quality, educational content. Parents should actively select programs that are interactive and support learning.
- Rationale: Strong evidence supports the recommendation that educational programs with slow-paced narratives help maintain attention and deepen cognitive engagement.[10,34] (Evidence Level A: Based on well-designed, conducted trials and meta-analyses.)
- Psychological context: Programs designed with children's cognitive development in mind can enhance learning by using stable visuals and structured content that supports attention.[25] (Evidence Level B: Based on clinical and observational studies.)

Encouraging parental involvement:

- Guidance: The AAP encourages parents to be present during screen time to interact with their children, discuss the content, and relate it to real-world experiences. This helps reinforce learning and ensures content is understood.
- Rationale: Studies show that parental involvement in media use improves comprehension and application of content.[10,25] Co-viewing encourages language skills and

meaningful interactions.[19] (Evidence Level B: Based on clinical and observational studies.)
- Psychological context: Active parental involvement enhances educational value and encourages children to apply what they learn to their environment, improving language and social skills.[37] (Evidence Level C: Based on observational studies and studies with limitations.)

Developing a family media plan:

- Guidance: Each family should have a personalized media plan that considers the needs of all family members. The plan should outline what kind of media is appropriate, how much time should be spent on screens, and what kind of interactions will accompany screen use.
- Rationale: The AAP recommends personalized family media plans to balance screen time and other critical activities, emphasizing age-appropriate interactions and developmentally suitable content. (Evidence Level C: Based on observational studies and studies with limitations.)
- Psychological context: Structured media plans promote balanced screen use and ensure time for physical play and other activities that are essential for psychological and emotional development.[34] (Evidence Level C: Based on observational studies and studies with limitations.)

Promoting media-free times and zones:

- Guidance: The AAP recommends establishing regular media-free times, such as during family meals or bedtime, and media-free zones, particularly in bedrooms.
- Rationale: Media-free times help improve family communication and reduce the negative effects of media use on sleep and emotional health.[34] (Evidence Level C: Based on observational studies and studies with limitations.)
- Psychological context: Media-free zones can promote better sleep hygiene and provide opportunities for family bonding, reducing emotional dependence on screens.[47] (Evidence Level C: Based on observational studies and studies with limitations.)

Leading by example:

- Guidance: Parents are encouraged to model good screen habits, such as limiting their own screen use in front of children and engaging in alternative hobbies.
- Rationale: Children often imitate parental behavior, so modeling appropriate screen habits is crucial in developing their own healthy relationship with media.[47] (Evidence Level C: Based on observational studies and studies with limitations.)
- Psychological context: Children learn behaviors through observation, and when parents model good media habits, children are more likely to adopt healthy screen behaviors themselves.[37] (Evidence Level D: Based on expert opinion, case reports, and reasoning from first principles.)

QUALITY IMPROVEMENT SUGGESTIONS

Quality improvement (QI) collaboratives have demonstrated significant benefits, such as those seen in a study where a collaborative focused on early childhood screenings led to improved processes and outcomes in the development and social determinants of health screenings.[48] In this era of widespread digital, interactive media use, pediatric practices should undertake QI projects to support caregivers in optimizing children's speech and language development.

One potential QI project involves integrating individualized family media plans into routine pediatric visits for children aged 18 months and older when screen time becomes more relevant. The AAP provides resources such as the "Beyond Screen Time: A Parent's Guide to Media Use,"[49] which can serve as foundational material for families. Implementing this project can follow the Plan-Do-Study-Act cycle:

Plan: Develop a protocol for introducing the family media plan during well-child visits for children aged 18 months to 5 years. Determine the workflow for when and how the plan is discussed and documented, such as during the visit using "smart phrases" or flowsheets within the electronic medical record.

Do: Pilot the protocol with a select group of providers or clinics. Distribute the AAP guide to parents and assist them in creating family media plans during the visit.

Study: Evaluate the implementation by collecting data on process metrics, such as:

- The percentage of eligible families who created a family media plan.
- The percentage of plans reviewed with a provider.
- The frequency of follow-up discussions at subsequent visits.

Act: Based on the findings, refine the protocol to address challenges such as workflow integration or staff training needs. Expand the initiative to more clinics or providers and consider additional strategies to support families.

Identifying key drivers specific to the practice and patient population is crucial for the project's success. Considerations

include language interpretation and translation needs, staffing availability, and standardization of workflow to ensure the project is family-centered and practical.

To address the measurement of the quality of screen time, practices could use validated tools such as the ScreenQ. The ScreenQ is a structured questionnaire used to evaluate screen use in children, assessing 4 key domains: access to screens, frequency of use, media content, and interactivity/co-viewing.[50] It includes 15 items, each scored to reflect the degree of developmental and health risks associated with screen exposure. A higher total score (maximum of 26 points) suggests greater potential risk.

Other QI projects could focus on curating and disseminating lists of age-appropriate, high-quality educational media content. Providers can develop strategies to help families effectively use these programs as tools for speech and language development. Collaborating with community organizations may enhance these efforts, especially in identifying families with limited access to speech therapy services. By providing additional support and alternative strategies—such as interactive TV viewing and language learning applications—health care providers can help mitigate health disparities associated with reduced exposure to spoken language.

Take the quiz! Scan this QR code to take the quiz, access the references and view and save images and tables (available May 1, 2025).

PIR QUIZ

1. A 4-year-old typically developing child is brought to the clinic by his mother for an annual health maintenance visit. As the mother is providing the interim history, the child is engrossed in watching something on the mother's cell phone. When asked about "screen time," the mother insists that she limits screen time to 2 half-hour television programs per evening. The clinician clarifies to the mother that most parents may not be aware that screen time includes the total amount of interactive or passive time spent using which of the following devices?

   A. Television and computers
   B. Television, computers, and tablets
   C. Television, computers, tablets, and smartphones
   D. Television only
   E. Television, videogames, and computers

2. The parents of a 3-year-old boy call your office because they are concerned about their son's fixation on tablets and smartphones. They also acknowledge that they are relying on devices at times to keep their son busy while they tend to their newborn daughter. Their call seeks to get some guidance on how to discern "better" or more educational apps to optimize the quality of device use. You explain that the "Four Pillars of Learning" framework to evaluate the educational value of apps has been adapted by the "Zero to Three" organization to an "E-AIMS" model that assesses programs available in early childhood. "E-AIMS" stands for which of the following?

   A. Educational Activities and Interactive Media Standards
   B. Educational Activities for Minors
   C. Educational apps in minors
   D. Engaging, Actively Involved, Meaningful, and Social
   E. Engaging Apps and Meaningful Social skills

3. You are precepting first-year pediatric residents in the continuity clinic and teaching on topics of anticipatory guidance for infants and toddlers. One of the residents has read that screen time for infants should be limited to only interactive video chats but wonders how to introduce screen time for toddlers. You explain that programs should be high quality, slow paced, rich in vocabulary and language, and have prosocial themes. In addition to this guidance, an important component of the screentime for toddlers includes:

   A. Choosing high-activity programs to maintain attention
   B. Choosing noise-generating programs to maintain interest
   C. Co-viewing programs to enhance understanding and interaction
   D. Repeating presentations to optimize learning opportunities
   E. Selecting colorful presentations to maintain visual interest

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This journal-based CME activity is available through Dec. 31, 2027, however, credit will be recorded in the year in which the learner completes the quiz.

2025 *Pediatrics in Review* is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics (ABP) through the AAP MOC Portfolio Program. *Pediatrics in Review* subscribers can claim up to 30 ABP MOC Part 2 points upon passing 30 quizzes (and claiming full credit for each quiz) per year. Subscribers can start claiming MOC credits as early as October 2025. To learn how to claim MOC points, go to: https://publications.aap.org/journals/pages/moc-credit.

4. In your role as an advisor to a local early childhood learning center, the faculty and staff have requested guidance on resources that might provide families of children at the center with reasonable recommendations for engaging in screen time with their children. Your first recommendation is the AAP "5 C's of Media Use" framework. The 5 C's promote considerations of the child, the media content and context, critical thinking, and creating balance. In addition to critical consideration about the content and context of media engagement, the 5 C's framework aims to prevent media use from serving which of the following roles?

    A. As an alternative displacing essential activities such as family time, outdoor play, and appropriate sleep
    B. As an alternative to a conventional learning medium
    C. As a reward for positive behaviors
    D. As a soporific to encourage independent sleep onset
    E. As a way to keep children from arguing with their siblings

5. When providing anticipatory guidance to parents about media use in young children, it is important to encourage parental involvement during screen time so parents can discuss the content and apply it to real-world experiences with their children. The rationale for recommending parental involvement during screen time for young children is that it improves which of the following?

    A. A child's attention to the learning materials
    B. A child's comprehension and application of content to the real world
    C. Parental satisfaction with the content viewed by their child
    D. Parental selection of diversity of content of the screentime
    E. Parental supervision of the child's social media skills

Diagnosis and Management of Acute Osteoarticular Infections: Summary of New Guidelines

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EDUCATION GAP

Acute osteoarticular infections are among the most common invasive bacterial infections affecting immunocompetent children. Pediatricians need to be familiar with the first North American guidelines for the diagnosis and management of acute hematogenous osteomyelitis and acute bacterial arthritis published in 2021 and 2024, respectively.

OBJECTIVES *After completing this article, readers should be able to:*

1. Appropriately diagnose acute hematogenous osteomyelitis and acute bacterial arthritis in children 1 month to 18 years of age based on clinical manifestations and noninvasive (laboratory and radiographic) and invasive (bone and synovial fluid sampling) investigations.
2. Manage acute hematogenous osteomyelitis and acute bacterial arthritis, including the need for surgical intervention, and selection, route of administration, and duration of empiric and definitive antibiotics.
3. Identify complications and treatment failure and manage them appropriately.

ABSTRACT

Acute hematogenous osteomyelitis (AHO) and acute bacterial arthritis (ABA) are among the most common invasive bacterial infections in otherwise healthy children. The diagnosis of AHO and ABA requires a high index of suspicion in children presenting with fever and musculoskeletal pain and judiciously chosen laboratory and imaging studies. Choosing the appropriate empirical antibiotic requires familiarity with local susceptibility patterns, especially for *Staphylococcus aureus*. Typical antibiotic duration for osteoarticular infection is 2–4 weeks depending on the type of infection, response to therapy, and presence of complications. Transitioning from parenteral to oral antibiotics is guided by clinical and laboratory evidence of resolving infection. This review will provide an overview of the recommendations contained in the 2 recently published guidelines for the management of AHO and ABA.

AUTHOR DISCLOSURE: Drs Shapiro, Carrillo-Marquez, and Arnold have no financial relationships relevant to the article. This article does contain a discussion of unapproved used of commercial products.

ABBREVIATIONS

ABA	acute bacterial arthritis
AHO	acute hematogenous osteomyelitis
CBC	complete blood count
CRP	C-reactive protein
CT	computerized tomography
ESR	erythrocyte sedimentation rate
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IDSA	Infectious Diseases Society of America
IV	intravenous
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
OAI	osteoarticular infection
OPAT	outpatient parenteral antibiotic therapy
PCR	polymerase chain reaction
PCT	procalcitonin
PIDS	Pediatric Infectious Diseases Society
TMP-SMX	trimethoprim-sulfamethoxazole
US	ultrasonography
WBC	white blood cell

INTRODUCTION

The Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) recently released the first North American guidelines addressing the diagnosis and management of acute (<4 weeks after onset of symptoms) osteoarticular infections (OAIs) in immunocompetent children 1 month to 18 years of age. Acute hematogenous osteomyelitis (AHO) guidelines were published in 2021,[1] followed by acute bacterial arthritis (ABA) guidelines in 2024.[2] AHO is a commonly used term for acute bone infection, reflecting the pathogenesis of the infection and distinguishing it from surgical or traumatic osteomyelitis. ABA is the term for joint infections, selected by the panel to indicate application of guidelines to infections caused by typical bacterial pathogens only. These guidelines represent an important step in reducing variability in the care of children with these infections, which can be life-threatening and affect long-term growth and function.

The guidelines were created using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to summarize evidence obtained from a systematic review of the literature.[3] In GRADE, the term "recommend" means a strong recommendation, applying to all patients. The term "suggest" means a conditional recommendation, one in which the recommendation applies to many, but not all, patients and may require shared decision-making. There was little high-quality evidence (from randomized trials) available for making strong recommendations. This review summarizes the guideline recommendations.

CLINICAL FEATURES

OAIs are clinical diagnoses. AHO should be suspected in the presence of fever with localized musculoskeletal pain, refusal to bear weight, or pseudoparalysis. Swelling and erythema may be present over the affected bone. In ABA, joints will show signs of effusion and inflammation with swelling and erythema on physical examination except for the hip and shoulder, which are deeper joints, making signs of inflammation less apparent. Pain with motion of the joint, however, will always be present. AHO and ABA may occur alone or together, with approximately 32% of cases of ABA having adjacent AHO, most commonly involving the humerus.

NONINVASIVE DIAGNOSTIC TESTING

The guidelines define blood testing and diagnostic imaging as noninvasive testing. Invasive diagnostic testing is reserved for percutaneous or open surgical procedures performed for diagnostic or therapeutic purposes.

Blood Testing

Blood culture is *recommended* in the diagnosis and management of all OAIs. Blood cultures are positive in approximately 30% of cases of AHO and 20% of cases of ABA.[4,5] A positive blood culture result eliminates the need for bone aspiration in AHO if the bone aspiration is being performed solely for diagnostic purposes. In children with suspected ABA, a positive blood culture result does not preclude the need for joint needle aspiration or joint irrigation as these procedures are therapeutic as well as diagnostic. Persistently positive blood cultures should prompt a search for complications including septic thrombophlebitis, reaccumulation of abscess following surgery, or identification of additional sites of infection. A positive blood culture result allows for definite pathogen identification and antibiotic sensitivity testing to guide antibiotic therapy.

C-reactive protein (CRP) measurement is *suggested* in the initial evaluation of OAIs, serving as a baseline for subsequent monitoring and decisions about parenteral to oral antibiotic transitions and duration of therapy.[6] Although there are no established cut-off values for ruling OAIs in or out, a normal or only mildly elevated CRP level should prompt an investigation of alternative diagnoses. CRP is typically higher in patients with bacteremia,[5,7] those with *Staphylococcus aureus* infections,[8] and those with infections complicated by an abscess or septic thrombophlebitis.[4,9,10] CRP is typically lower in patients with AHO compared with those with ABA.[6,11,12] CRP also has value in distinguishing transient nonbacterial synovitis of the hip from ABA, a situation in which a combination of low CRP level (<10–20 mg/L) together with the ability to weight bear on the affected hip (or to move the leg in children of non–weight-bearing age) rule out ABA.[13] CRP is lower in Lyme arthritis, which should be suspected in a weight-bearing patient with large-joint arthritis (typically knee) in a Lyme endemic area.[14,15] CRP cannot be used to distinguish ABA from other types of inflammatory arthritis, such as reactive arthritis or acute rheumatic fever.

Measurement of procalcitonin (PCT) is *suggested against doing* in the diagnosis of OAIs. Although the PCT level rises and falls more rapidly than CRP and is purported to be more specific for bacterial infection, studies of PCT in children with suspected OAI are few and have small sample sizes. The validity of the studies is uncertain, and PCT has shown low sensitivity in the diagnosis of OAIs.[16] There are no published studies of PCT for follow-up of patients as there are for CRP. Currently, there is no advantage of PCT over CRP, and there is limited experience with PCT's use.

No GRADE recommendation is made for either the complete blood count (CBC) or the erythrocyte sedimentation rate (ESR) because of a lack of evidence on which to base recommendations; however, there was consensus among the panelists that obtaining a CBC is useful in assessing severity of infection and suggesting alternate diagnoses, such as leukemia. The ESR is slower to rise and may remain abnormal at the end of therapy and, thus, is not useful in the diagnosis or management of OAIs.

Diagnostic Imaging

OAIs are clinical diagnoses, and diagnostic imaging is not required in all cases. Plain radiographs are *recommended* as an initial image in both suspected AHO and ABA. The sensitivity of plain radiographs for AHO is 16%–20%,[1] depending on the duration of symptoms. Early changes include soft tissue swelling and periosteal thickening with osteopenia and osteolysis occurring up to 10–20 days after the onset of infection. Early changes seen on plain radiograph in ABA include blurring of fat planes or joint widening from effusion, whereas later changes, after 10–14 days, include joint narrowing with cartilage and subchondral bone destruction. The greatest utility of plain radiographs is in excluding conditions that mimic OAIs, such as bone tumors or fractures.[4,17]

In AHO, ultrasonography (US) can detect a subperiosteal abscess, but it cannot provide evaluation of the bone or marrow. Erosion of cortical bone may be detectable if symptoms have been present for more than 1 week. US is *not recommended* in the evaluation of AHO but may be useful when magnetic resonance imaging (MRI) availability is lacking. In ABA, US is *recommended* as the imaging modality of choice to detect effusion that cannot be confirmed by examination, particularly of the hip and shoulder. The guidelines do not specifically recommend or suggest US for other joints in which effusion is more easily detected by physical examination. However, depending on the extent of the image, US may visualize extra-articular pathologies such as a subperiosteal or soft tissue abscess adjacent to a focus of AHO. The pooled sensitivity of US for effusion is 90%, and its absence rules out ABA unless negative in the first 24 hours of symptoms, in which case it should be repeated if suspicion for infection persists.[2,13,18,19] US is inexpensive, useful to guide joint aspiration, and does not require sedation. However, US requires trained staff.

MRI is *suggested* as the advanced imaging modality of choice for AHO as bone marrow edema can be detected at the time of clinical presentation. MRI can differentiate between bone, joint, and muscle infections and provides anatomic detail to detect a subperiosteal and soft tissue abscess, sinus tracts, necrotic bone, and deep vein thrombosis, which may require procedural intervention. The pooled sensitivity and specificity of MRI for AHO are 80%–100% and 67%–94%, respectively.[1,20–22] The utility of MRI in suspected ABA is in the detection of adjacent AHO. The primary risk of MRI is the need for sedation in young children. MRI is not required for patients with suspected uncomplicated AHO unless they fail to respond to medical therapy within 48 hours.

Additional modalities available, but not routinely recommended, are Technetium Tc 99m bone scintigraphy (bone scan) and computerized tomography (CT). Bone scanning is not always available, is less sensitive than MRI, does not provide anatomic detail, and cannot distinguish infection from other etiologies. Its main benefit is that it does not require sedation. CT is not sensitive for early infection because it does not demonstrate bone marrow edema; however, CT scans can detect subperiosteal abscess so, if MRI is not available, CT is an option.

INVASIVE PROCEDURES AND TISSUE TESTING

Source Control

In OAIs with sepsis or rapid disease progression, debridement of infected bone and abscesses is *recommended* and preferred to antibiotic therapy alone. Delayed surgical source control has been associated with worse outcomes.[23,24] In stable children with AHO, debridement of large abscesses (>2 cm) is *suggested* to promote faster recovery and to reduce length of hospitalization and duration of antibiotic therapy.[25]

In ABA, arthrocentesis and/or arthroscopy is performed to optimize microbiological diagnosis and to reduce joint damage. Drainage of synovial fluid may reduce the risk for cartilage erosion and avascular necrosis associated with increased intracapsular pressure, particularly in the shoulder and hip.[19,26–28]

Synovial Fluid Cell Count and Chemistry

When joint fluid is obtained by arthrocentesis, white blood cell (WBC) count with differential, aerobic bacterial culture and Gram stain are *recommended*. Synovial fluid WBC count is helpful in determining the cause of acute arthritis. Higher WBC counts are seen in ABA compared with other conditions (reactive arthritis and juvenile idiopathic arthritis), although there is substantial overlap (Table 1). Other joint fluid studies such as lactic dehydrogenase, pH, and protein are *not recommended* because they do not provide additional diagnostic utility. Cell counts and chemical testing of bone specimens have no diagnostic utility in suspected AHO.

Microbiologic Testing

In children with suspected AHO or ABA, diagnostic bone aspiration or arthrocentesis, respectively, are *suggested* to maximize microbiological diagnosis and optimize choice

TABLE 1. Typical Synovial Fluid WBC Counts for Selected Etiologies of Acute Arthritis

Synovial WBC Count/μL, Range	Predominant WBC	Pathologic Process
>50 000	Neutrophils	ABA
25 000–75 000	Neutrophils	Lyme arthritis
<50 000	Neutrophils > mononuclear	JIA
<15 000	Mononuclear	Transient nonbacterial synovitis

Abbreviations: ABA, acute bacterial arthritis; JIA, juvenile idiopathic arthritis; WBC, white blood cell.

and duration of antimicrobial therapy.[5,10,22,29–32] If diagnostic aspiration is performed in OAIs, aerobic culture with Gram stain is *recommended*.[1] Synovial fluid, rather than swabs, should be collected for microbiological analysis in ABA. Culture on solid media as well as inoculation of fluid into a blood culture bottle maximizes the yield of organism recovery, especially of fastidious pathogens such as *Kingella kingae*. Anaerobic, fungal, and mycobacterial pathogens are not typically implicated in AHO or ABA, and cultures for these pathogens should not be routinely obtained.

Molecular Testing

For both AHO and ABA, subperiosteal abscess fluid or synovial fluid (not swabs), respectively, can be subjected to molecular testing, such as polymerase chain reaction (PCR), if cultures are negative. Molecular studies using multiplex or single-target platforms (including 16S ribosomal RNA amplification and sequencing), in addition to culture, can improve the rate of pathogen identification for fastidious organisms like *K. kingae*.[33,34]

ANTIBIOTIC ADMINISTRATION BEFORE INVASIVE PROCEDURES

For both suspected AHO and ABA it is *suggested* that bone aspirates or biopsies, or synovial fluid, be obtained before initiating antibiotics. However, the patient's clinical status is an important consideration. Data extrapolated from children with sepsis (regardless of infection source) demonstrate that early antibiotic therapy is associated with improved outcomes.[35] Although there are no specific data for children with suspected OAIs, for those who are ill-appearing or have signs suggestive of rapidly progressive infection, it is *recommended* to start empirical antibiotics immediately.

In stable children with AHO or ABA who are not ill-appearing, and for whom an invasive diagnostic or therapeutic procedure is planned, it is *suggested* to withhold antibiotics up to 72 hours to preserve the yield of cultures.[31,32,36,37] This was *suggested* rather than *recommended* because studies did not demonstrate a difference in culture yield based on the timing of antibiotic administration; however, most of these studies were deemed biased because they did not control for important confounders such as disease severity. For non–ill-appearing children with suspected ABA, there is no upper limit of time specified for withholding antibiotics before joint aspiration. The decision to withhold antibiotics is conditional on accessibility to surgical procedures and the ability to monitor the patient.

SELECTION OF EMPIRICAL ANTIBIOTICS

It is *recommended* that initial antibiotic therapy for OAI should include antimicrobials with activity against the most common causative pathogen, *S. aureus*.[12] For methicillin-susceptible *S. aureus* (MSSA), this antimicrobial is typically an antistaphylococcal penicillin (oxacillin or nafcillin) or cefazolin. Empirical treatment with an antibiotic with activity against methicillin-resistant *S. aureus* (MRSA), typically clindamycin or vancomycin, should be considered in regions where MRSA accounts for more than 20% of *S. aureus* isolates. Resistance to clindamycin is variable across the United States and has been increasing. If clindamycin resistance in MRSA is greater than 20% of isolates, vancomycin is the preferred empirical agent.

For children 6 months to 4 years of age, *K. kingae* is another important pathogen. Empirical therapy for *K. kingae* is *suggested* for ABA in this age group. *K. kingae* is encountered less commonly in AHO, but empirical therapy can be considered. Cefazolin has activity against *K. kingae* and can be used as a single agent for empirical therapy in areas with a low incidence of MRSA. Ampicillin or a cephalosporin can be added to clindamycin or vancomycin that is being used for MRSA treatment. *Streptococcus pyogenes*, a frequent pathogen in OAIs, is universally susceptible to penicillin and is treated by β-lactams and vancomycin but may be resistant to clindamycin.

ADJUVANT THERAPIES

Surgical site (instilled or implanted) antibiotics are *not recommended* in patients with OAIs. Patients treated with systemic antibiotics have excellent outcomes, and there is no evidence that local antibiotics provide incremental benefit.[1] In addition, there is potential for systemic toxicity, joint irritation, and need for additional surgery for removal of nonbiodegradable materials.[38]

The efficacy of adjuvant systemic steroids has been evaluated in ABA, and their use is *not recommended* owing to limited evidence suggesting only a possible minimal effect on time to normal joint function, defervescence, normalization of CRP, and length of parenteral antibiotics and hospital

stay.[2,39] The main concern with steroid use is suppression of fevers and temporary improvement in signs of inflammation that may mask progression of infection.

DEFINITIVE THERAPY

Definitive antibiotic therapy (Table 2) for OAI should be the narrowest spectrum agent that is active against the identified pathogen, has the lowest risk of adverse effects, and is most tolerable to the patient. If no bacterial etiology is identified, the selection of definitive therapy should be based on the most likely causative pathogens, local resistance patterns, response to empirical therapy, and the child's age.

Definitive therapy is initially given parenterally with transition to oral antibiotics near the time of discharge (see the "Parenteral vs oral therapy" section). For MSSA, the most common OAI pathogen, a first-generation cephalosporin (eg, intravenous [IV] cefazolin or oral cephalexin), or an antistaphylococcal penicillin (eg, IV oxacillin or IV nafcillin) is recommended. Clindamycin (IV or oral) may be used in the case of a cephalosporin allergy.[40,41] IV clindamycin is preferred to IV vancomycin for susceptible MRSA isolates because of its safety, tolerability, and easy transition from parenteral to oral therapy. For MRSA isolates resistant to clindamycin, IV vancomycin or IV ceftaroline is preferred. Other parenteral antibiotics that have been used with less experience include IV daptomycin, linezolid, and trimethoprim-sulfamethoxazole (TMP-SMX). Linezolid and TMP-SMX also have oral formulations and may also be used when transitioning to an oral antibiotic.

K. kingae and *S. pyogenes* are susceptible to β-lactam antibiotics, including ampicillin/amoxicillin and cephalosporins. *K. kingae* is also susceptible to TMP-SMX. OAIs caused by *S. pneumoniae* and *Haemophilus influenzae* are uncommon but can be treated with a penicillin or cephalosporin depending on susceptibilities.

Despite clinical findings consistent with OAI, cultures and molecular testing results may be negative because of the presence of fastidious organisms, antibiotic administration before operative procedures, low microbial density, or noninfectious etiologies. Because of the benefits of treatment in the prevention of long-term complications of an untreated OAI,[1,2] antimicrobial therapy should be continued unless an alternative diagnosis has been identified. Consideration of adverse effects is important because OAI treatment duration is longer than other common infections. For vancomycin, monitoring of serum creatinine and drug levels should be obtained weekly once the patient is clinically stable. For β-lactams and linezolid, CBC with differential could be performed every 2 weeks to identify reversible bone marrow suppression. Linezolid may cause optic and peripheral neuropathy, especially if antibiotic therapy duration is longer than 4 weeks. Optic and peripheral neuropathies may be difficult to detect in young children. Although serotonin syndrome is rare with linezolid, it should

TABLE 2. Suggested Parenteral and Oral Antibiotics for Osteoarticular Infections by Pathogen

	Parenteral		Oral Convalescence	
Pathogen	**Preferred**	**Alternative**	**Preferred**	**Alternative**
Methicillin-susceptible *Staphylococcus aureus*	Cefazolin, oxacillin, or nafcillin	Clindamycin[a] or vancomycin	Cephalexin	Clindamycin[a]
Methicillin-resistant *Staphylococcus aureus*	Clindamycin[a]	Ceftaroline, vancomycin, daptomycin, or linezolid[b]	Clindamycin[a]	Linezolid,[b] doxycycline,[c] minocycline, or TMP-SMX
Streptococcus pyogenes	Penicillin G or ampicillin	Cefazolin, ceftriaxone, or clindamycin	Amoxicillin	Penicillin V, clindamycin, cephalexin
Kingella kingae	Ampicillin	Cefazolin, ceftriaxone, ceftaroline, or ciprofloxacin	Amoxicillin	Cephalexin, ciprofloxacin, or TMP-SMX
Neisseria meningitidis	Penicillin G or ampicillin	Ceftriaxone	Amoxicillin	Penicillin V
Neisseria gonorrhoeae	Ceftriaxone		Cefixime	
Streptococcus pneumoniae MIC for penicillin <2.0 mcg/mL	Penicillin G or ampicillin	Ceftriaxone, levofloxacin,[d] linezolid,[b] or clindamycin[a]	Amoxicillin or penicillin V	Cephalexin, levofloxacin,[d] linezolid,[b] or clindamycin[a]
Streptococcus pneumoniae MIC for penicillin ≥2.0 mcg/mL	Ceftriaxone (if ceftriaxone MIC ≤1 mcg/mL)	Clindamycin,[a] levofloxacin,[d] or linezolid[b]	Clindamycin[a] or levofloxacin[d]	Linezolid[b]

Abbreviation: MIC, minimum inhibitory concentration.
[a]Increasing resistance to clindamycin is observed and susceptibility should be confirmed.
[b]Linezolid can cause reversible bone marrow suppression and potentially irreversible optic and peripheral neuropathy with durations longer than 4 weeks.
[c]Doxycycline has not been shown to have the same adverse effects of tetracycline and is used in children (<8 years of age) with suspected or proven tickborne infections routinely. However, it is recommended that doxycycline not be used in this age group if duration of therapy is longer than 21 days.
[d]There is an increased risk of tendonitis and tendon rupture with all fluoroquinolone antibiotics. Patients should be warned to discontinue if pain or inflammation in a tendon occurs.

be used cautiously in patients taking certain serotonergic drugs, especially citalopram, escitalopram, and methadone. For gram-negative infections, fluoroquinolones may be associated with tendonitis and tendon rupture. Like most antibiotics, TMP-SMX may cause rash and inflammatory reactions; however, TMP-SMX has a stronger association with Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms compared with other antibiotics.[42] Finally, gastrointestinal distress and diarrhea may occur with any antibiotic. Clindamycin is most notably associated with *Clostridium difficile*–associated colitis, but any antibiotic may increase this risk.[43]

ASSESSING RESPONSE TO THERAPY

Fever, when present, usually resolves within 3–5 days for uncomplicated cases of AHO and ABA.[44] Improvement in swelling, erythema, pain, range of motion, and use of the affected limb should also occur. The response to appropriate therapy will vary depending on the pathogen, site of infection, severity of disease, and the need for surgical intervention.[45] Along with daily evaluation for signs of clinical improvement, serial CRP measurement is *recommended* to monitor response to therapy along with serial clinical examinations. Typically, the CRP level peaks after 2–4 days of treatment and normalizes between days 9 and 12.[46] Rapid decline in CRP level is clinically useful for timing the switch to oral therapy and avoiding prolonged therapy.[6] Higher peak and slower normalization of CRP values have been observed in patients with complications such as subperiosteal abscess, pyomyositis, and prolonged bacteremia.[6,10,11,21] Prolonged elevation of CRP suggests inadequate antimicrobial therapy (antibiotic choice, dosing, or nonadherence) or a need for additional imaging to evaluate the extent of infection and possible complications,[27] surgical intervention,[28] or reconsideration of the diagnosis, such as malignancy or autoimmune disorder.[29,30] Persistently elevated CRP may also be caused by a concurrent infection (eg, catheter-associated infection, thrombophlebitis, or *C. difficile*–associated colitis). No threshold CRP value has been validated for decisions on surgical interventions or duration of therapy. CRP concentrations can be measured every 2–3 days at the beginning of therapy and then weekly or every 2 weeks until normalization. It is not recommended to use normalization of ESR to guide duration of therapy as ESR takes longer to normalize and may unnecessarily prolong therapy.

PARENTERAL VS ORAL THERAPY

Transition to oral therapy is *recommended* over outpatient parenteral antibiotic therapy (OPAT) in cases when there is an appropriate oral option. Treatment outcomes are comparable for oral and parenteral therapy with respect to treatment failure, and oral therapy is associated with fewer harms.[1,2,41,47] There is no minimum duration of parenteral therapy required for patients who are initially bacteremic (excluding patients with concurrent endocarditis). Timing of the transition to oral therapy is driven by signs of clinical improvement (resolution of fever and other signs of sepsis, reduction in pain, and increased use of the affected limb) and a consistent downward trend in CRP level, typically to a 50% reduction from the peak CRP level.[6] In cases when oral therapy is not an option, OPAT is *suggested* so as not to prolong inpatient stay.

DURATION OF THERAPY

For common pathogens, such as *S. aureus, S. pyogenes, S. pneumoniae, H. influenzae* type b, and *K. kingae*, a duration of 3–4 weeks of antibiotics is *recommended* for uncomplicated AHO and 10 to 14 days for uncomplicated ABA.[29,30,48,49] For both AHO and ABA, a longer duration of treatment may be required for patients with slower response to treatment, complications, or uncommon pathogens, such as gram-negative bacilli, for which there are no data on optimal duration. Complications include multifocal infection, soft tissue or subperiosteal abscesses, prolonged bacteremia (≥3 days), or multiple surgical interventions for source control. Associated endovascular infection (endocarditis or septic thrombophlebitis) requires prolonged therapy per American Heart Association guidelines.[50]

END-OF-THERAPY IMAGING

The use of end-of-therapy imaging with plain radiographs is *suggested* in children with complicated AHO or ABA or AHO involving the physis. In complicated infection a plain radiograph may identify sequestrum or other abnormalities, such as lesions at risk for pathologic fracture. A plain radiograph can also be used as a baseline for monitoring growth abnormalities in children with infection of the physis. In patients with uncomplicated, metaphyseal AHO, end-of-therapy imaging is *not recommended*. Similarly, for uncomplicated ABA with full clinical recovery, end-of-therapy imaging is *not recommended* unless there is clinical concern for previously undetected adjacent osteomyelitis, in which case a plain film may be considered just before cessation of antimicrobial therapy.

MANAGEMENT OF TREATMENT FAILURE OR RELAPSE

There are many potential causes of primary or secondary treatment failure in OAIs. Primary treatment failure, that is, lack of

improvement during the initial treatment, may occur for reasons related to antibiotic therapy (nonsusceptibility to prescribed antibiotic, inadequate dose, or nonadherence) or need for surgical intervention (subperiosteal abscess, sequestrum, or adjacent or metastatic focus with abscess). Treatment failure could also occur because the patient does not have an OAI (eg, chronic nonbacterial osteomyelitis, bone tumor, other inflammatory arthritis). Addressing primary treatment failure involves reviewing and correcting issues with the antibiotic regimen and obtaining additional cultures if possible, especially if a pathogen had not previously been identified. If problems with the antibiotic regimen cannot be identified, additional imaging (MRI) is necessary.

Secondary treatment failure, late relapse of OAI following successful antibiotic and surgical therapy, is unusual (<2%).[6,11,41,51] Similar steps to those taken when there is poor response to therapy should be followed to identify if the patient has chronic osteomyelitis or if there is an alternate etiology (eg, chronic nonbacterial osteomyelitis or inflammatory arthritis). Repeat imaging with possible biopsy may help direct diagnosis and management including further debridement.

LONG-TERM FOLLOW-UP AND SEQUELAE

It is *suggested* that children at risk for long-term adverse outcomes be followed up for at least 1 year by a specialist with experience in managing children with OAIs. Most children with OAIs have return to normal function within 4–6 weeks, at which time follow-up is complete. Fewer than 1% of children with ABA and up to 10% of children with AHO have sequelae such as articular cartilage damage, chronic osteomyelitis (progressive bone destruction owing to unresolved infection, with formation of sequestrum [necrotic bone] and involucrum [periosteal new bone formation around the sequestrum] caused by persistent, indolent infection), avascular necrosis, and pathologic fracture. Sequelae are more frequent in children with prolonged symptoms before treatment, delayed response to therapy, disseminated/multifocal infection, multiple surgical interventions, involvement of the hip or shoulder, and imaging indicating risk for pathologic fracture.[6,11,23,41,47]

CONCLUSIONS

Bone and joint infections are among the most common invasive bacterial infections seen in children. The recently published PIDS/IDSA guidelines provide recommendations for the diagnosis and empirical and definitive management (both medical and surgical) of children with these infections. The recommendations were made based on mostly observational studies with variable validity. Additional research is needed with prospective studies to provide data to validate and improve the confidence with which these recommendations are made.

Summary

- All children with suspected OAIs should have a blood culture performed, preferably before the administration of antibiotics.[4,5] In AHO, cultures of bone aspirates or subperiosteal abscess fluid are recommended. In ABA, synovial fluid should be collected for culture.[5,22,30] (Based on observational studies)
- If imaging is required, the radiographic studies of choice are MRI and US for AHO and ABA, respectively.[13,19–22] (Based on observational studies)
- Surgical intervention for source control should be undertaken in patients with AHO with rapidly progressive or severe infection, including subperiosteal abscess.[31] All children with ABA should have arthrocentesis or arthrotomy.[19] (Based on observational studies)
- Empirical antibiotics should always provide coverage for *S. aureus*.[5,8,31,33] (Based on observational studies) The need for an antibiotic with activity against MRSA should be based on local susceptibility data. (Based on consensus)
- Definitive therapy should be chosen based on culture results and susceptibility testing. When no pathogen is isolated, continued therapy should have a comparable spectrum of activity to the regimen on which the patient demonstrated clinical improvement. (Based on consensus)
- For uncomplicated infections caused by common pathogens, the total duration of therapy for AHO is 3–4 weeks and 10–14 days for ABA. Once clinical improvement has occurred, oral antibiotics to complete the course of therapy are preferred to IV antibiotics.[29,30,41,47] (Based on strong evidence from 1 clinical trial and observational studies)

Take the quiz! Scan this QR code to take the quiz, access the references and view and save images and tables (available May 1, 2025).

PIR QUIZ

1. A previously healthy 7-year-old girl was seen in the emergency department (ED) yesterday for a 3-day history of right knee pain and 2 days of fever. An magnetic resonance imaging (MRI) scan of the right leg noted bone marrow edema of the right distal femur metaphysis but no abscess, and there was no increased effusion of the right knee joint. A blood culture obtained in the ED is growing gram-positive cocci at 8 hours incubation and a multiplex polymerase chain reaction on the blood culture is positive for methicillin susceptible *Staphylococcus aureus* (MSSA). Which of the following is the most appropriate next step in management?

   A. Bone aspiration of the right femur metaphysis and intravenous (IV) vancomycin and clindamycin
   B. Bone aspiration of the right femur metaphysis and IV vancomycin and ceftriaxone
   C. IV cefazolin
   D. IV vancomycin and clindamycin
   E. Open surgical bone biopsy of the right femur metaphysis and arthrocentesis of the right knee joint

2. A previously healthy 12-year-old girl is admitted to the pediatric inpatient unit after being seen in the ED for 2 days of increasing left elbow pain and swelling. She is febrile. An arthrocentesis of the left elbow joint obtained cloudy fluid, and the Gram stain noted gram-positive cocci in clusters. She is started on the appropriate antimicrobial therapy. Which of the following is the most appropriate initial laboratory test or imaging to perform as a baseline for subsequent monitoring to help guide management?

   A. Absolute neutrophil count
   B. C-reactive protein (CRP)
   C. Computerized tomography scan of the left elbow
   D. Erythrocyte sedimentation rate
   E. Procalcitonin

3. A previously healthy 18-month-old boy is brought to the ED by his parents with a 4-day history of increasing right knee pain and swelling. He now refuses to bear weight on his right leg. His temperature is 38.2 °C and his other vital signs are normal. After receiving pain medication, he is alert and not ill-appearing. A blood culture is obtained and is pending. An MRI scan showed right knee effusion but no evidence of osteomyelitis. Arthrocentesis of the right knee is obtained with cloudy fluid. In addition to Gram stain and culture on routine bacterial solid media, which of the following should also be performed on the synovial fluid specimen?

   A. Acid fast bacteria smear and culture
   B. Anaerobic culture
   C. Fungal smear and culture
   D. Inoculation into a blood culture bottle
   E. LDH level

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4. For the same patient in question #3, the hospital antibiogram notes that 41% of *Staphylococcus aureus* cultures from sterile sites were methicillin-resistant *Staphylococcus aureus* (MRSA) and 33% of the MRSA isolates were clindamycin resistant. Pending culture results, which of the following is the most appropriate empirical antimicrobial management for the patient in question #3?

   A. Cefazolin plus ampicillin
   B. Cefazolin plus clindamycin
   C. Ceftriaxone plus vancomycin
   D. Clindamycin
   E. Vancomycin

5. A 7-year-old boy was hospitalized 5 days ago for fever and increasing right upper leg pain. A radiograph of the right leg showed no abnormality. An MRI scan showed right distal femur bone marrow edema at the metaphysis and a subperiosteal abscess. Surgical drainage was performed. The culture grew MSSA resistant to penicillin and susceptible to first-generation cephalosporins, trimethoprim-sulfamethoxazole, doxycycline, and vancomycin. Blood culture showed no growth. He initially was on IV vancomycin and, based on his culture, was changed to IV cefazolin. He has been doing well and is afebrile for the past 36 hours. His CRP decreased from 123 mg/L on admission to 41 mg/L today. His pain is significantly decreased, and he has started to bear weight on his right leg. Which of the following is the most appropriate management?

   A. Continue IV cefazolin as an outpatient to complete 42 days of treatment
   B. Continue IV cefazolin as an outpatient to complete 14 days of treatment
   C. Discharge on oral cephalexin to complete 28 days total of antimicrobial therapy
   D. Discharge on oral doxycycline to complete 14 days total of antimicrobial therapy
   E. Repeat the MRI scan on day 10 of IV cefazolin and, if improved, change to oral amoxicillin for an additional 11 days

INDEX OF SUSPICION

Acute Respiratory Distress and Oxygen Refractory Hypoxemia in a Term Newborn

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CASE PRESENTATION

A full-term boy is born to a 28-year-old gravida 1 para 1 mother at 39 weeks 3 days' gestational age via normal spontaneous vaginal delivery. Pregnancy was complicated by gestational diabetes managed with metformin. The mother has no known history of nonsteroidal anti-inflammatory drug (NSAID) or corticosteroid use during the pregnancy. Prenatal anatomy scan with ultrasonography and laboratory findings are unremarkable. The mother's blood type is O+ and she is negative for group B streptococcus carriage. Membranes ruptured 7 hours prior to delivery and the mother is afebrile. The community pediatrician is asked to attend the delivery due to meconium-stained fluids and category 2 fetal heart rate tracing showing minimal variability.

At birth, the patient is in immediate respiratory distress characterized by chest wall retractions with an initial oxygen saturation of approximately 75% in room air. Temperature is 36.8 °C, heart rate is 133 beats/min, and respiratory rate is 100 breaths/min. Birth weight is 3.24 kg (56th percentile) and length is 50 cm (52nd percentile). Apgar scores are 4 (0 = skin color, 1 = heart rate, reflex irritability, muscle tone, and respiratory effort), 7 (1 = skin color, reflex irritability, and muscle tone), and 7 (1 = skin color, reflex irritability, and muscle tone) at 1, 5, and 10 minutes of life, respectively. Gentle oropharyngeal suctioning is performed and is notable for a small number of clear secretions. Supplemental oxygen is initiated at 2 L per minute (50% FiO_2) with resolution of chest wall retractions but continued tachypnea. At 10 minutes of life the patient's oxygen saturation while on low-flow nasal cannula remains in the 70s and is refractory to increased titration of supplemental oxygen. Pre- and postductal saturations are equivalent.

On physical exam, the patient does not demonstrate dysmorphic features. His anterior fontanelle is open, soft, and flat. Mucus membranes are moist. He is tachypneic. His lungs are clear to auscultation, and there is good air movement throughout the lungs without crackles, wheezing, or rhonchi. There are no murmurs, rubs, or gallops. Femoral pulses are palpable, equal, and strong bilaterally. Capillary refill is less than 2 seconds. The abdomen is soft, nondistended, and nontender without organomegaly. Neurologic examination is appropriate for his age and gestation. There is acrocyanosis limited to the extremities.

The initial blood glucose level is normal at 30 minutes of life at 89 mg/dL (8.9×10^{-5} kg/L). Blood glucose is repeated within the hour and is 25 mg/dL

AUTHOR DISCLOSURE: Mr Jenson and Drs Gregory, Taggart, and Penfold have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

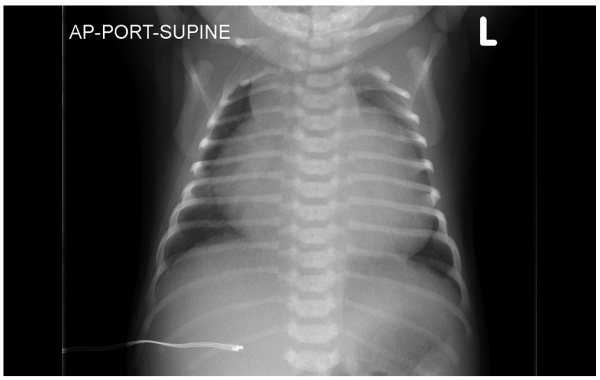

FIGURE 1. Chest radiograph demonstrating enlarged cardiac silhouette with normal lung fields.

(2.5×10^{-5} kg/L). A bolus of dextrose 10% in water is administered intravenously over 3 minutes, and a continuous infusion of dextrose 10% in water is initiated. Blood glucose 30 minutes later is 45 mg/dL (4.5×10^{-5} kg/L).

Initial peripheral venous blood gas is pH 7.33, pCO_2 49 mm Hg, pO_2 30 mm Hg, $pHCO_3$ 25 mm Hg, and BE −1. Initial laboratory results include a normal hemoglobin of 18.0 g/dL (1.8×10^{-1} kg/L) with a reference range of 13.9 to 19.1 g/dL ($1.39–1.91 \times 10^{-1}$ kg/L), a normal hematocrit of 53.5% with a reference range of 39.8 to 53.6%, and low platelet count of 187×10^9/L with a reference range of 218 to 419×10^9/L. The total white blood cell count is reassuring at 8.3×10^9/L with a reference range of 8.0 to 15.4×10^9/L with 47% neutrophils, 43% lymphocytes, 5% monocytes, 4% eosinophils, and 1% basophils. Blood cultures are obtained, and the patient is started on empirical ampicillin and gentamycin. C-reactive protein is below 3.0 mg/L ($<3.0 \times 10^{-6}$ kg/L) with a reference range less than 8.0 mg/L ($<8.0 \times 10^{-6}$ kg/L). The patient's respiratory support is escalated to nasal continuous positive airway pressure (NCPAP) with a positive end-expiratory pressure of 5 cm H_2O (25% FiO_2) with oxygen saturations remaining around 70%. A chest radiograph demonstrates an enlarged cardiac silhouette with normal lungs (Figure 1). Given the patient's continued oxygen saturation of 70% after initiation of supplemental oxygen, he is started on empirical alprostadil (prostaglandin [PG] E1 analog), and an echocardiogram is performed.

DISCUSSION

Differential Diagnosis

The differential for hypoxemic respiratory distress in a newborn can be split into 2 general categories: respiratory and nonrespiratory causes. The most common respiratory causes include transient tachypnea of the newborn, respiratory distress syndrome in the newborn, pneumonia, pneumothorax, and meconium aspiration syndrome.[1] Transient tachypnea of the newborn classically presents with prominent perihilar interstitial edema that usually resolves within 48 to 72 hours.[2] Respiratory distress syndrome is typically characterized by diffuse, bilateral, granular opacities with air bronchograms and hypoaeration.[3] Neonatal pneumonia is often seen with either infiltrate, consolidation, cavitation, and/or pneumatocele.[4] Pneumothorax is frequently identified with a visible pleural edge with no lung markings past this line.[5] Meconium aspiration syndrome is associated with hyperinflated lungs with patchy atelectasis on chest radiograph.[6] Pulmonary causes are typically responsive to oxygen administration. Given that our patient's chest radiograph demonstrated cardiomegaly without significant pulmonary findings and the lack of clinical improvement with oxygen initiation, the most likely etiology was a nonrespiratory cause.

Nonrespiratory causes of hypoxemic respiratory distress in a newborn include congenital heart disease, tracheoesophageal fistula, persistent pulmonary hypertension of the newborn, sepsis, and diaphragmatic hernia.[1]

When hypoxemia is refractory to oxygen therapy, a cardiac etiology or persistent pulmonary hypertension of the newborn should be suspected and the hypoxemia should be further evaluated with an echocardiogram to determine the diagnosis. Neonates with congenital heart disease may be asymptomatic, present with progressive heart failure symptoms, or develop acute heart failure with cardiogenic shock.[7] Generally, cyanosis in the neonate is caused by either right-to-left shunting and/or inadequate pulmonary blood flow.[8] The volume of intra- and extracardiac shunting and the amount of intracardiac mixing of deoxygenated and oxygenated blood are dynamic and may lead to slow but progressive worsening or rapid deterioration in clinical status.

Common cardiac causes of neonatal cyanosis within the first hours of life include tetralogy of Fallot with severe right ventricular (RV) obstruction, transposition of the great arteries, Ebstein malformation, pulmonary atresia, and obstructed total anomalous pulmonary venous return. Tetralogy of Fallot is characterized by 4 components: aorta that overrides the ventricular septum, RV outflow tract obstruction, RV hypertrophy, and a ventricular septal defect. The clinical presentation varies with the severity of the RV outflow obstruction, the most severe form being pulmonary atresia causing complete separation from the pulmonary artery, which presents with severe cyanosis. In such cases, PGE1 is required to keep the ductus patent while preparing for surgical correction.[7]

Neonates with transposition of the great arteries have 2 independent cardiac circuits with the aorta arising from

the right ventricle and the pulmonary artery from the left ventricle (LV). These parallel circuits require an intracardiac shunt for adequate mixing of deoxygenated and oxygenated blood. In the absence of a large atrial or ventricular septal defect, neonates can be profoundly cyanotic, which requires administering PGE1 to maintain ductal patency or performing an urgent balloon atrial septostomy.[7]

In patients with Ebstein anomaly, there is apical displacement of the tricuspid valve leading to a decrease in the size of the RV chamber. When the RV chamber size is significantly diminished, the effective pulmonary circulation is limited and deoxygenated blood begins shunting into the systemic circulation through either a patent foramen ovale or atrial septal defect, causing cyanosis.[9]

Pulmonary valve atresia is a ductal dependent lesion that requires a ductus arteriosus (DA) for adequate pulmonary blood flow in order to maintain appropriate oxygen saturations. In patients with total anomalous pulmonary venous return, oxygenated blood leaves the lungs through the pulmonary veins, either draining directly into the right atrium, or, after first entering the coronary sinus, into a systemic vein or a confluence adjacent to the posterior wall of the left atrium. When these abnormal connections are significantly narrowed or obstructed, oxygenated blood is unable to drain into the right heart. Therefore, the systemic circulation is primarily composed of deoxygenated blood that reenters the right heart through the systemic veins and across an obligatory right-to-left shunt.[10]

When patients are born with ductal dependent systemic circulation, a patent ductus arteriosus (PDA) is essential to maintain adequate perfusion and end organ function. A PDA maintains perfusion with left-sided heart defects including abnormalities of the aortic arch such as coarctation of the aorta and interrupted aortic arch, aortic valve stenosis, or hypoplastic left heart syndrome.[8] Without an adequate LV outflow tract, the systemic circulation is supplied by blood pumped through the DA from the right ventricle. However, these patients typically have some form of intracardiac mixing of oxygenated and deoxygenated blood with either a large atrial or ventricular septal defect.[7] Therefore, the blood shunted through the DA is relatively high in oxygen concentration, and cyanosis may not be present at birth. However, as the DA begins to close, there is a disruption in systemic blood flow, and cardiovascular collapse may acutely occur. Given that closure of the DA can take weeks to months to occur, patients may present with signs of inadequate perfusion well after hospital discharge if ductal dependent pathology is not diagnosed prenatally.[11]

Patients with ventricular septal defects, atrioventricular defects, or a large PDA are typically asymptomatic at birth without any appreciable cyanosis.[12] As pulmonary vascular resistance decreases and the pressure gradient between the RV and LV increases, there will be increased blood flow across the defect, which can be detected by auscultation. In these patients, the left-to-right shunting of blood causes pulmonary overcirculation, leading to elevated LV end-diastolic pressure and pulmonary edema. This manifests clinically as symptoms of congestion including tachycardia, tachypnea, increased work of breathing, sweating with feeds, and poor weight gain.[13]

Actual Diagnosis

An electrocardiogram at 4 hours of life demonstrated right atrial enlargement and RV hypertrophy (Figure 2). An echocardiogram at 5 hours of life while receiving an infusion of alprostadil demonstrated an absent DA, which was replaced with fibrous tissue indicating premature closure of the DA (Figure 3). The RV chamber was severely enlarged with severely decreased systolic function and hypertrophy. The LV was noted to have moderately decreased systolic function with an ejection fraction of 44%. A small secundum atrial septal defect with bidirectional shunting and right-to-left bowing of the atrial septum was noted and was consistent with the restrictive RV physiology. Taken together, these findings were highly suggestive of premature DA closure with the development of subsequent pulmonary hypertension and right heart failure.

The Condition

In fetal circulation, the DA acts as a right-to-left shunt allowing RV outflow to bypass the higher-resistance pulmonary circuit in favor of the lower-resistance systemic circulation.[14] With birth and the initiation of ventilation, there is an abrupt drop in the pulmonary vascular resistance resulting in left-to-right shunting through the now patent DA.[15] Low partial pressure of oxygen (pO_2) in fetal circulation and high levels of PGE1 and PGE2 in utero have been established as primary factors in maintaining the DA during the prenatal period.[16,17] At birth, there is an increase in the pO_2, and the remaining PGE, which was previously supplied by the placenta, is quickly metabolized by enzymes within the lungs.[18] These factors contribute to the functional closure of the DA shortly after birth. Within the first month of life, endothelial proliferation of fibrotic material within the ductal lumen leads to permanent anatomical closure of the DA.[19]

In the absence of another shunt, premature closure of the DA in utero forces all the RV outflow to enter the high-resistance pulmonary fetal circuit. Increased flow through the pulmonary arteries causes increased pulmonary artery wall stress and elevated pressure within the arterioles, leading

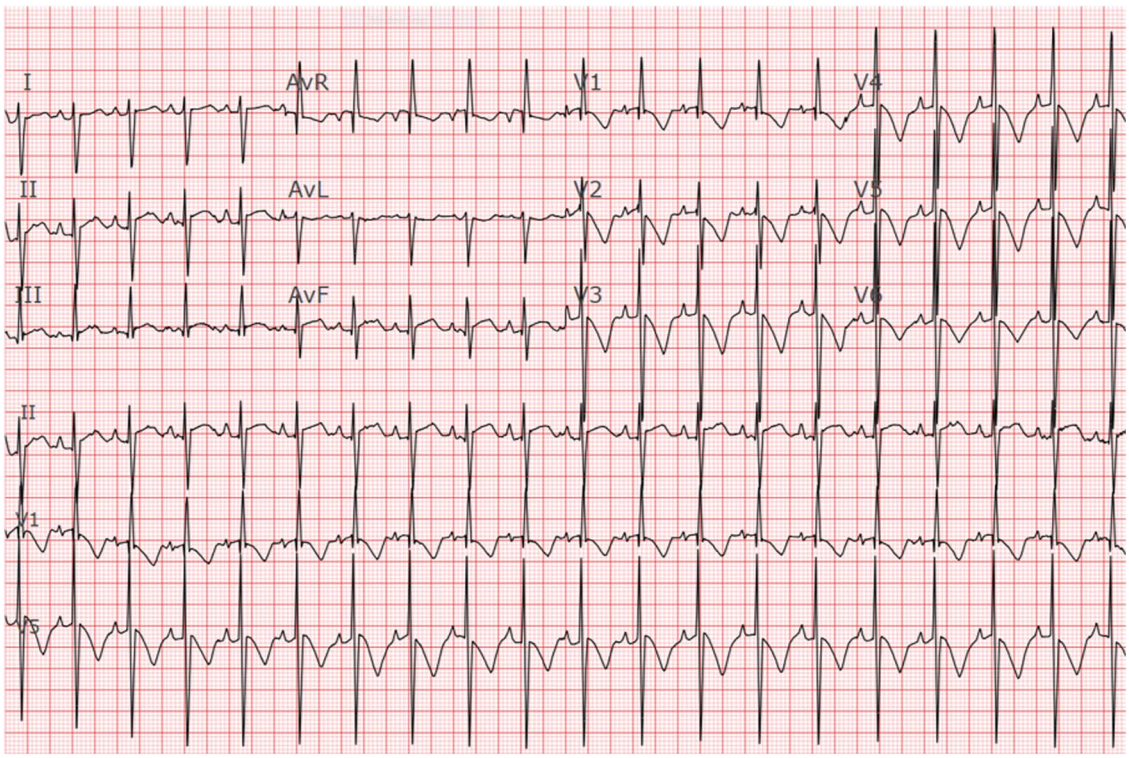

FIGURE 2. Electrocardiogram demonstrating right atrial enlargement and right ventricular hypertrophy.

to intimal fibrosis and the development of pulmonary hypertension. This increased afterload can result in RV dilation and hypertrophy.

There is a wide range of presentations for premature DA closure associated with the timing and severity of ductus closure (complete vs partial). Presentations include no symptoms, tachypnea and cyanosis related to pulmonary hypertension and right heart failure, fetal hydrops, and stillbirth.[20]

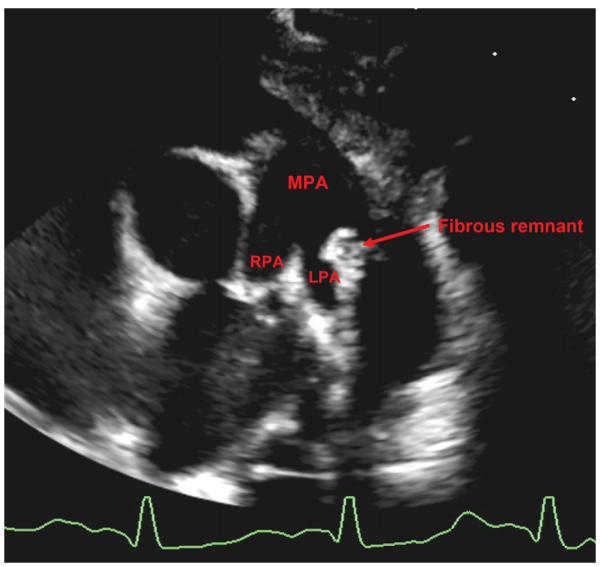

FIGURE 3. Echocardiogram demonstrating fibrous remnant in place of the ductus arteriosus, near the left pulmonary artery (LPA), right pulmonary artery (RPA), and main pulmonary artery (MPA).

Premature closure of the DA can be associated with other structural cardiac defects but may also be an isolated finding. Administration of drugs that inhibit PGE synthesis, such as NSAIDs and corticosteroids, are a known cause of premature DA closure and thus are often contraindicated during pregnancy.[21,22] Additionally, excessive consumption of sources of polyphenol (such as fruit tea and maté, a herbal tea) during pregnancy has been considered a potential risk factor, as polyphenol is believed to inhibit cyclooxygenase-2 (COX-2) through a mechanism like that of NSAIDs.[23,24] COX-2 is an enzyme responsible for converting arachidonic acid to PGH2, which can then be converted into a variety of products including PGE.[25] Finally, factors that alter the pO_2 and PGE balance during pregnancy, such as smoking, which disrupts PGE synthesis, have also been proposed as potential causes.[26,27]

Treatment/Management

When premature closure of the DA is diagnosed in utero via fetal echocardiogram, early delivery is critical if there is complete DA closure, heart failure, and/or hydrops fetalis, as they portend a significantly increased risk of mortality.[20,26,28] If

TABLE 1. Hemodynamic Findings of Echocardiograms within the First 180 Days of Life

DOL	LV Size	LV EF	RV Size	RV Function	ASD Shunt Direction	Intraventricular Septum Motion
1	Normal	44%	Severely enlarged chamber size with hypertrophy	Moderately severe decreased systolic function	Bidirectional	Bowing into LV
3	Normal	65%	Severely enlarged chamber size with hypertrophy	Mildly reduced	Bidirectional	Flattening
5	Normal	56%	Severely enlarged chamber size with hypertrophy	Mildly reduced	Predominately left to right	Flattening
9	Normal	53%	Moderate-severely enlarged chamber size with hypertrophy	Mildly reduced	Predominately left to right	Mild flattening
30	Normal	63%	Mildly enlarged chamber size with hypertrophy	Normal	Predominately left to right	Normal
180	Normal	65%	Normal chamber size without hypertrophy	Normal	Left to right	Normal

Abbreviations: ASD, atrial septal defect; DOL, day of life; EF, ejection fraction; LV, left ventricle; RV, right ventricle.
Note that reliable tricuspid regurgitation jet was not available in the echocardiograms.

premature DA closure is identified prior to viable delivery, serial fetal echocardiograms can be performed to monitor right heart function and patency of the DA. Early delivery should be considered in all patients with premature DA closure to reduce and avoid sustained pressures in the pulmonary arteries, which is known to cause pulmonary hypertension, RV remodeling, right heart failure, and in severe cases lead to death.[20] In all cases, physicians should recommend that mothers avoid NSAIDS, polyphenol-containing foods, and smoking.

Identification of premature DA closure is most likely to occur during the evaluation of a symptomatic neonate. After initial resuscitation, care should be focused on inotropic support if RV dysfunction is present, on supplemental oxygen to promote pulmonary vasodilation, and on pulmonary vasodilators if pulmonary hypertension is severe. Successfully correcting RV dysfunction and pulmonary hypertension has been shown to be a good prognostic indicator.[28]

There are currently no guidelines for the long-term care of patients with premature DA closure. However, once RV function has returned to normal and there is no longer evidence of pulmonary hypertension, patients can expect a full recovery.[28]

Patient Course

Within a few hours of NCPAP and the initiation of alprostadil, the patient's oxygen saturations improved to 95%. An echocardiogram was then performed and was notable for premature closure of the DA; therefore, the alprostadil infusion was discontinued without issue. Findings of this echocardiogram and subsequent studies are summarized in Table 1. Given our patient's severe RV dysfunction, he was initially treated with intravenous milrinone for inotropic support and pulmonary vasodilation. Supplemental oxygen and nitric oxide were also administered to support pulmonary vasodilation. A follow-up chest radiograph at 2 days of life noted improvement in cardiomegaly. Blood cultures were monitored, and after 48 hours without bacterial growth, empirical antibiotics were discontinued. Pulmonary hypertension improved over the first 3 days of life, and the patient was slowly titrated off CPAP to room air while maintaining adequate oxygen saturations. Given the improvement in RV function on echocardiogram on day of life (DOL) 3, the patient was transitioned from nitric oxide to oral sildenafil, an oral pulmonary vasodilator, in preparation for hospital discharge. The patient was tapered off milrinone as the LV function returned to normal by DOL 5 and he was able to trial small volumes of bottled breast milk and formula without issue. The patient advanced to 50% of feeds by mouth and the remainder gavaged by DOL 9, and to 90% oral feeds by DOL 14 without tachypnea, sweating, or changes in color. Given continuing improvement in biventricular function and RV hypertrophy, he was discharged home on sildenafil on DOL 14.

A repeat echocardiogram at the patient's 1-month follow-up showed normal biventricular function with mild RV enlargement and severe hypertrophy. At 5 months of age, the patient was weaned off sildenafil given his stable clinical status and in anticipation of an upcoming echocardiogram at his 6-month follow-up. The repeat echocardiogram at 6 months of age and in the absence of sildenafil was notable for normal biventricular function with resolution of RV hypertrophy and no evidence of pulmonary hypertension.

LESSONS FOR THE CLINICIAN

- Neonates in hypoxemic respiratory distress refractory to supplemental oxygen should raise the physician's

suspicion for congenital heart disease or persistent pulmonary hypertension of the newborn.

- Premature DA closure is an uncommon cause of hypoxemic respiratory distress in the newborn, with signs and symptoms due to right heart failure driven by pulmonary hypertension.
- Corticosteroids, NSAIDs, and foods rich in polyphenol are associated with a decrease in PGE synthesis, and thus premature DA closure in the fetus; therefore, these substances are not recommended in pregnant patients.
- The treatment of premature DA closure is supportive and involves inotropic support for the dysfunctional RV and supplemental oxygen and pulmonary vasodilators for pulmonary hypertension.

References for this article can be found at
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INDEX OF SUSPICION

Deadly Duo: A Common Infection and an Undiagnosed Medical Condition

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PRESENTATION

A 7-year-old boy with a past medical history of bicuspid aortic valve, multiple congenital physical anomalies and Hirschsprung disease status postcolostomy presents with 2 weeks of a diffuse petechial rash and daily fevers greater than 100.4 °F. His rash was initially erythematous and papular in nature but then became smooth and macular. The rash started on his forearms then quickly spread to involve his entire body, sparing the palms and soles (Figures 1 and 2). His mother gave diphenhydramine at home without noticeable improvement. The evening prior to presentation, he complained of abdominal pain, refused food and water, and began vomiting, which was nonbloody and nonbilious. Review of systems was otherwise negative for altered mental status, headache, rhinorrhea, sore throat, difficulty breathing, muscle aches, swelling of hands or feet, and dysuria. He had no recent travel or trauma.

In the emergency department, he was noted to be febrile (temperature 38.3 °C), tachycardic (heart rate 155), blood pressure 101/59, and hypoxic in the low 90s on room air. His physical exam was notable for microcephaly, hypertelorism, low-set ears, micrognathia, and symbrachydactyly of his hands and feet bilaterally. There was a diffuse petechial rash over his face, extremities, and trunk that spared his palms and soles. He had bilateral conjunctivitis, dry and cracked lips, and a delayed capillary refill of 3 seconds. His breathing was unlabored, and he was alert in no acute distress. Complete blood cell count with differential was normal, but inflammatory markers were elevated (erythrocyte sedimentation rate [ESR] 68, C-reactive protein [CRP] 3.2, procalcitonin 1.25). A complete metabolic panel was significant only for creatinine of 0.55 (baseline 0.3) and low bicarbonate of 18. A clean catch urinalysis was unremarkable. A chest radiograph showed diffuse bilateral patchy interstitial and airspace opacities.

Notably, the patient had been admitted twice in the past 6 months for recurrent right upper lobe pneumonia. During these hospitalizations, he was found to be adenovirus and respiratory syncytial virus positive, but other infectious labs at the time were negative, including Epstein-Barr virus immunoglobulin (Ig) G/IgM, *Coccidioides* IgG/IgM enzyme immunoassay, cryptococcal antigen blood, *Legionella* urinary antigen, cytomegalovirus (CMV) IgG/IgM, and toxoplasmosis. He had numerous genetic tests done throughout his life given his dysmorphic facies and syndactyly, including whole exome sequencing; however, no underlying genetic condition was identified.

AUTHOR DISCLOSURE: Drs Shim, Lin, and Sarhangian and Mr Vankawala have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

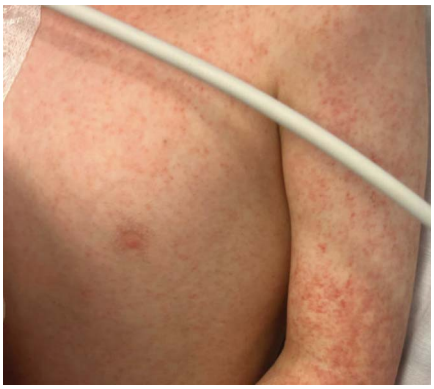

FIGURE 1. Petechial rash of the patient's torso and upper extremities.

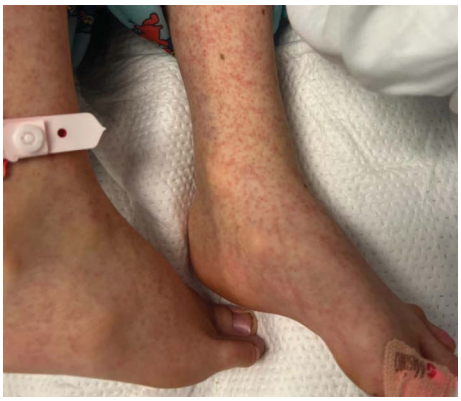

FIGURE 2. Petechial rash of the patient's lower extremities and symbrachydactyly of the feet.

DISCUSSION

Differential Diagnosis

Initial differential was broad considering the patient's congenital abnormalities and chronicity of symptoms, including rheumatological/vasculitis etiology, hematological process, and infectious causes. With his fever of 2 weeks and rash as well as bilateral conjunctivitis on initial presentation, Kawasaki disease was suspected. However, he did not meet other clinical criteria. Additionally, apart from his CRP of 3.2 and ESR of 68, the remainder of his lab values did not meet supplemental laboratory criteria. The primary team also considered multisystem inflammatory syndrome in children; however, the patient had no recent history of COVID exposure and tested COVID negative upon admission. Scarlet fever was part of the differential considering the diffuse rash and persistent fever, but *Streptococcus* throat culture and *Streptococcus* antistreptolysin O were negative. Interestingly, throat culture resulted in *Staph aureus*, but his symptoms were inconsistent with Staphylococcal scalded skin syndrome or Staph-mediated toxic shock syndrome. Henoch-Schonlein purpura was also considered because the patient initially complained of abdominal pain and had a petechial rash without thrombocytosis, but the diagnosis was less likely because his rash was not raised and did not start in the lower extremities/buttock area and patient had no history of arthralgias.

The initial leading differential was a viral pneumonia or an atypical bacterial pneumonia based on the findings from his chest radiograph. His rash was thought to be a viral exanthem.

Actual Diagnosis

Early infectious disease workup was significant for positive CMV IgM. Subsequent initial CMV quantitative DNA polymerase chain reaction (PCR) resulted in a high viral load of 202 494 IU/mL. Curiously, petechial rashes are rarely reported as viral exanthems specific to CMV and more commonly reported in congenital CMV infections.[1] Therefore, the diagnosis came as a surprise to the medical teams. A computed tomography (CT) angiogram of the chest showed diffuse septal thickening and multifocal ground glass as well as hilar engorgement of his lungs, consistent with pulmonary edema. The CT also confirmed a persistent right upper lobe segmental area of atelectasis. As the patient's daily fevers persisted and he required increasing amounts of supplemental oxygen, CMV pneumonitis became the leading diagnosis.

Patient Course

The patient was initially stable on room air but shortly thereafter required nasal cannula oxygen because of prolonged oxygen desaturation less than 90%. Transthoracic echocardiogram performed on hospital day 2 showed no intracardiac vegetations or mobile masses. His abdominal pain prompted an abdominal ultrasonography and abdominal radiograph that were also without acute findings.

Given the persistent fever and chest radiograph findings that were indicative of a viral or atypical pneumonia, he was started on ceftriaxone and azithromycin. Subsequent tests were positive for *S aureus* via throat culture and CMV IgM. Chest CT and angiogram were obtained because of concern for pulmonary anatomical abnormalities in the setting of multiple prior hospital admissions for pneumonia. On hospital day 7, CMV PCR was positive with high viral load, and ganciclovir was started.

Although the patient's petechial rash improved and, later, resolved after initiation of ganciclovir, he continued to worsen from a respiratory, infectious, and hematologic standpoint. An immunology workup was initiated and showed nonprotective antibody titers despite vaccine

boosters administered before admission (absent tetanus, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type b titers), suggesting there was high suspicion for a humoral deficiency. His opportunistic CMV infection, low natural killer cell count, and abnormal T-cell proliferation studies indicated additional deficiencies in cell-mediated immunity. Therefore, there was highest suspicion for a combined immune deficiency (CID). Intravenous immunoglobulin (IVIG) 400 mg/kg/dose was initiated on hospital day 12 and given over 4 days (1.6 g/kg total) to augment treatment of the CMV viremia and decrease the inflammatory response. This combined therapy decreased his viral load seen on PCR by 98%. In the subsequent days, the patient's primary problem became respiratory decompensation. A repeat CT chest showed interval increase in the diffuse ground glass opacities of the lungs. He was transferred to the Pediatric Direct Observation Unit (an intermediate level of care) given his increasing work of breathing, and a 3-day methylprednisolone course was started. Despite this intervention, the patient continued to decompensate, prompting transfer to the pediatric intensive care unit (PICU) on hospital day 30.

In the PICU, the patient's respiratory status severely deteriorated, requiring venovenous extracorporeal membrane oxygenation (ECMO) cannulation for acute-on-chronic hypoxic and hypercapnic respiratory failure hospital day 32. On hospital day 66, he began to require increasing fraction of inspired oxygen up to 100%, and ECMO settings were maximized. He had new bleeding from his endotracheal tube, and subsequent chest radiograph showed evidence of pulmonary hemorrhage and pneumothorax. The following day, the patient's family opted for palliative extubation and removal of life-sustaining measures; the patient died quickly thereafter. An autopsy was performed and revealed lungs that were grossly, bilaterally extremely enlarged and hemorrhagic and microscopically had evidence of diffuse alveolar damage and intra-alveolar hemorrhage. Immunohistochemistry highlighted rare positive CMV in the lung, thus confirming the immediate cause of death as hypoxic respiratory failure from CMV pneumonitis with the underlying cause of death from combined immune deficiency.

The Condition

CMV viremia is often a self-limiting disease in immunocompetent patients, and antivirals are not usually indicated. Common manifestations may include fever, sore throat, or hepatitis on lab results. Immunocompromised hosts, most commonly transplant patients or HIV/AIDS patients, tend to have the most severe outcomes from primary CMV infections,[2] including CMV retinitis, pneumonitis, and encephalitis/myelitis.[2] Even with available treatment, CMV infections in immunocompromised patients have been associated with a high mortality rate or relapse.[2]

CMV pneumonitis is a difficult diagnosis to make because symptoms and radiographic evidence are vague.[3] Standard treatment consists of the antiviral ganciclovir, with or without immunoglobulins, although concurrent therapy with Ig has been shown to significantly reduce mortality in immunocompromised patients.[4] Foscarnet, another antiviral, can be used as an alternative therapy, notably in patients who are neutropenic.[2] Our patient was started on ganciclovir 5 mg/kg twice daily, and the need for concurrent IVIG was determined by his abnormal immunology workup. Given his phenotype of speech delay, bicuspid aortic valve, micrognathia, cleft palate, hypertelorism, and symbrachydactyly, a genetic etiology was reconsidered. Genome analysis during this hospitalization did not elucidate any pathogenic variant associated with his phenotype. One may also argue that the sequelae of his underlying pneumonia from the year prior predisposed him to lung tissue involvement with primary CMV infection. Although the specific etiology of his immunodeficiency was never determined, IVIG 400 mg/kg/dose was administered to adjunct his antiviral therapy for 4 separate treatments because of evident CID.

Children with primary immunodeficiencies are at a substantial risk of morbidity and mortality due to CMV disease.[5] Risk of transmission is highest in neonates because CMV can be transmitted transplacentally through genital secretions during delivery and postnatally via maternal oral secretions and breast milk.[6] The rapid and relatively inexpensive T-cell recombinant excision circle (TREC) screening at birth has been beneficial in diagnosing severe congenital immunodeficiencies (SCIDs) characterized by low T cells and is becoming standard practice in US states.[7] However, combined immunodeficiencies may not be identified through TREC-based SCID newborn screening programs, and a high degree of suspicion must be present for patients with persistent, recurrent, or severe infections. In the case that immunodeficiency is discovered, there may be a role for CMV prophylactic therapy because it has proven beneficial in pediatric transplant patients[8]; however, pediatric data are limited for nearly all aspects of CMV diagnosis and treatment.

LESSONS FOR THE CLINICIANS

- CMV is often an asymptomatic or mild self-limiting disease in immunocompetent patients; however, it can cause severe and life-threatening infection in patients with immunocompromised conditions.

- CMV can present as a petechial rash in an immunocompromised patient.
- Combined immunodeficiencies may not be identified through TREC-based SCID newborn screening programs, and a high degree of suspicion must be present for patients with persistent, recurrent, or severe infections.
- The treatment for suspected CMV pneumonitis in an immunocompromised patient should include early initiation of both ganciclovir and IVIG.

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INDEX OF SUSPICION

Persistent Hypoxemia in a COVID-Positive Patient With Systemic Lupus Erythematosus

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CASE PRESENTATION

A 17-year old girl with systemic lupus erythematosus (SLE) and class IV lupus nephritis presents to the emergency department with lower extremity and periorbital edema, which is concerning for a lupus flare. Medical history also includes chronic leukopenia, microcytic anemia, anxiety, and gastroesophageal reflux disease (GERD). She has been taking mycophenolic acid at home but reports missing most doses of methylprednisolone, dapsone, and ferrous sulfate during the last 2 weeks. She is afebrile with a heart rate of 93 beats/min, blood pressure 128/69 mm Hg, and oxygen saturation (SpO_2) 97%. Laboratory studies are notable for white blood cells 4400 μL^{-1} (4.40×10^9 L^{-1}; reference range 4500–10 000 μL^{-1}), hemoglobin 9.5 g/dL (95 g/L; reference range 12.0–14.6 g/dL), platelets 206 000/μL (206×10^9 L^{-1}; reference range 160 000–360 000/μL), potassium 5.4 mEq/L (5.4 mmol/L; reference range 3.6–5.1 mEq/L), phosphorus 5.7 mg/dL (1.84 mmol/L; reference range 2.4–4.7 mg/dL), albumin 1.1 g/dL (11.0 g/L; reference range 3.5–4.8 g/dL), creatinine 1.19 mg/dL (90.74 μmol/L) from a baseline of 0.5 mg/dL (38.13 μmol/L), and urine protein 300 mg/dL on urinalysis. She tests positive for COVID-19, and she recalls having congestion and a cough 10 days prior. She is admitted for intravenous diuretics, albumin, and methylprednisolone 30 mg twice per day. Her home medications are continued; enoxaparin for thromboprophylaxis and remdesivir are started. Concerned that the patient's use of immunosuppressive agents increases her risk for severe COVID, we delay administration of a steroid pulse.

On the third day of her hospitalization, the patient experiences chest heaviness and pressure. She has no dyspnea or pleuritic chest pain. At the onset of symptoms, she is afebrile and normotensive with a heart rate of 125 beats/min and respiratory rate of 22 breaths/min. SpO_2 on room air is 96%. She appears uncomfortable but in no acute distress and with capillary refill less than 2 seconds. Chest auscultation reveals regular heart rhythm and no murmurs or abnormal breath sounds. She has facial fullness, but the periorbital edema has resolved. Bilateral lower extremities have trace pitting edema, and the right calf is slightly larger than the left. An electrocardiogram was obtained, at which time her heart rate had spontaneously decreased to 75 beats/min. It demonstrated normal sinus rhythm and no ST segment changes. Troponin was less than 0.010 ng/mL (<0.010 μ/L; reference range ≤0.028 ng/mL). An echocardiogram shows normal function and no pericardial effusion or right heart strain. Lower extremity venous duplex ultrasonography does not detect any

AUTHOR DISCLOSURE: Ms Riley and Dr Gustafson have no conflicts of interest to disclose. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

thrombosis. The following day, her chest discomfort and tachycardia partially improve, but her SpO_2 decreases to 92% on room air.

On hospital day 5, her SpO_2 continues to fluctuate between 92% and 96%. She has no dyspnea or chest pain but feels fatigued. A chest radiograph does not show evidence of cardiopulmonary disease. An additional laboratory test is drawn and reveals the diagnosis.

DISCUSSION

Differential Diagnosis

Chest discomfort, tachycardia, tachypnea, hypoxemia, and lower extremity swelling all supported the diagnosis of pulmonary embolism (PE). The concern for PE was heightened by the patient's hypercoagulability risk factors associated with SLE, nephrotic-range proteinuria, COVID-19 infection, and immobilization. However, considering the patient's poor kidney function and hemodynamic stability, in discussion with Pediatric Cardiology, Nephrology, and Rheumatology, the risk of contrast administration outweighed benefit of a computed tomography. We did not order a d-dimer because a negative result would not have assuaged our concerns, and a positive result could be explained by her multiple comorbidities.[1] Normal troponin, chest radiograph, ECG, and echocardiogram provided further evidence against an acute cardiopulmonary issue, such as PE, pleuritis, pneumonia, carditis, myocardial ischemia, or pericardial effusion. Moreover, these considerations seemed less likely because she remained afebrile and without cough or dyspnea. We considered GERD, anxiety, deconditioning with atelectasis, and musculoskeletal pain as possible contributors, but none of these fully explained her symptoms and persistently low SpO_2.

Actual Diagnosis

Suspicion was raised for methemoglobinemia in the setting of dapsone use because dapsone is a common cause of methemoglobinemia, and venous blood gas co-oximetry analysis revealed a methemoglobin (MetHb) level of 15.7% (0.157) and mixed venous oxygen tension (PvO_2) 42 mm Hg (5.59 kPa), confirming the diagnosis.

The Condition

Dapsone can induce methemoglobinemia through a series of oxidative reactions, causing respiratory distress and neurologic symptoms. However, less-severe cases may present with subtle signs and symptoms that can pose diagnostic uncertainty. In healthy individuals, most hemoglobin exists with heme iron in the reduced ferrous state (Fe^{2+}). Oxidation to the ferric state (Fe^{3+}) forms MetHb, which has decreased oxygen-carrying capacity, and causes a left shift in the oxygen dissociation curve. As a result, the remaining heme moieties have a higher affinity for oxygen and decreased delivery to tissues. Under normal conditions, a small fraction (<1%) of hemoglobin exists as MetHb because of auto-oxidation. Constitutive actions of reducing enzymes associated with nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate as well as the nonenzymatic compounds glutathione and ascorbic acid constantly convert MetHb back to hemoglobin, thus maintaining low levels of MetHb. However, these regulatory processes can be overwhelmed in settings of increased oxidative stress.[2]

Medications may cause methemoglobinemia either directly via oxidation of hemoglobin or indirectly through creation of superoxide free radicals. Common MetHb-inducing medications include phenazopyridine, primaquine, benzocaine, and nitrite derivatives.[3] Dapsone can produce dapsone hydroxylamine through cytochrome P450, leading to formation of reactive oxygen species that oxidize heme iron from the ferrous to the ferric state, resulting in methemoglobinemia.[3–5] Hereditary methemoglobinemia due to mutations causing NADH cytochrome *b*5 reductase deficiency is less common.[6]

Preexisting anemia, likely coexisting anemia of chronic inflammation and iron deficiency anemia in this case, can worsen one's symptoms.[2] For example, our patient's measured hemoglobin of 9.4 g/dL (94 g/L) in the setting of 15.7% (0.157) MetHb suggests a concentration of functional hemoglobin of only 7.9 g/dL (79 g/L). Cyanosis is uncommon in methemoglobinemia, particularly if patients are anemic, highlighting the importance of a blood gas test as soon as methemoglobinemia is suspected.[7] With higher levels of MetHb, SpO_2 is inaccurate because of the light absorption pattern interfering with the calculation of the oxyhemoglobin-to-deoxyhemoglobin ratio. At high levels of MetHb, the SpO_2 reading is fixed around 85%.[6] Commonly reported symptoms of methemoglobinemia include dyspnea and fatigue.[2,8–11] Given that our patient had not been taking her medications consistently, she likely had not been exposed to such significant levels of dapsone prior to hospitalization. However, on admission, we ensured she received dapsone daily.

Concomitant COVID-19 infection may have increased her susceptibility to methemoglobinemia. Scholkmann et al discuss dozens of cases in which patients with COVID-19 also had elevated MetHb levels, often when they were given hydroxychloroquine. It is possible that COVID-19 infection predisposes to methemoglobinemia.[12] A review of other case reports of adolescents and young adults (ages 15–28 years) who developed methemoglobinemia secondary to dapsone

use revealed a variety of presentations. The duration of dapsone use prior to diagnosis ranged from days to months, and patients had a variety of medical conditions (acne, Hansen disease, SLE, leukemia).[8–11,13–15] As we continue to treat COVID-positive patients, it is important to keep methemoglobinemia as a differential for those with persistent hypoxemia despite receiving standard care.

To our knowledge, this is the first report that discusses a patient with inconsistent dapsone use at home who likely developed methemoglobinemia, in part because of regular dosing while hospitalized. Medication adherence, especially among pediatric patients, can be challenging. A recent study of adolescents with SLE found that 65% were nonadherent with at least 1 component of their treatment.[16] Providers should be aware that new side effects and adverse events may arise in admitted patients who receive medications more often and at different doses than they had been taking at home.

Management

Patients with medication-induced methemoglobinemia should stop the offending drug. Supportive care, as needed, includes supplemental oxygen and intravenous hydration. Additional treatment, typically reserved for symptomatic patients with MetHb of 20% or more or asymptomatic patients with MetHb of 30% or more, involves administration of a reducing agent. First-line therapy is methylene blue, a rapid-acting medication that facilitates electron transfer to Fe^{3+} iron. However, toxic side effects occur with repeated dosing.[2] Alternative treatment with ascorbic acid is used when methylene blue is unavailable or contraindicated. The water-soluble vitamin directly reduces MetHb, but it may take up to 24 hours to exert its effects.[17]

Patient Course

Dapsone is discontinued immediately and replaced with atovaquone for *Pneumocystis jirovecii* prophylaxis given her use of immunosuppressive medications and chronic leukopenia. In patients with SLE, dapsone and atovaquone are preferred over trimethoprim-sulfamethoxazole, to which there is a high prevalence of allergies among those with SLE.[17,18] Given that the patient is hemodynamically stable and MetHb is less than 20%, she does not receive additional treatment. Overnight, her SpO_2 drops to 90%, and supplemental oxygen improves her SpO_2 to 95%. Two days after discontinuing dapsone, repeat venous blood gas analysis shows improvement in MetHb to 4.7% (0.047). PvO_2 is 54 mm Hg (7.18 kPa), and SpO_2 ranges from 94% to 97% with intermittent supplemental oxygen for patient's comfort. Her intermittent chest pressure continues for several days after resolution of methemoglobinemia, raising suspicion for a multifactorial cause, including contributions from musculoskeletal pain and anxiety. On her eighth day of hospitalization, COVID IgG is reported to be positive, indicative of time passed since acute infection, so we initiate a 3-day course of methylprednisolone 1000 mg per day. She requires continued hospitalization for electrolyte abnormalities and labile renal function. She remains hemodynamically stable for the remainder of her hospital stay without oxygen requirement and with improvement in intermittent chest pain.

LESSONS FOR THE CLINICIAN

- Providers should be aware of drug-induced methemoglobinemia and maintain suspicion for this adverse event in patients prescribed multiple medications who present with fatigue, dyspnea, and hypoxemia.
- Patients receiving medications associated with methemoglobinemia who are also diagnosed with COVID-19 may have a higher risk of developing methemoglobinemia.
- Methemoglobinemia causes inaccurate pulse oximetry readings due to interference with the calculation of the oxyhemoglobin-to-deoxyhemoglobin ratio, necessitating cooximetry for a diagnosis.

References for this article can be found at
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INDEX OF SUSPICION

An Unusual Cause of Status Epilepticus in a 2-Year-Old Boy

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PRESENTATION

A 2-year-old boy presents to the emergency department in status epilepticus with acute respiratory failure. He has no past medical history aside from language delay. He has received all recommended routine pediatric immunizations and screening laboratory tests results, including normal hemoglobin and normal lead screening 1 year prior to admission. The day prior to admission, he was in his usual state of health without any recent history of fever, trauma, or travel. On the day of admission, he was irritable on waking, and shortly thereafter had a generalized tonic clonic seizure. The seizure stopped 10 minutes later when emergency medical services gave intranasal midazolam, but seizures recurred en route to the hospital for an estimated total duration of greater than 30 minutes, accompanied by respiratory failure. On arrival, Glasgow Coma Scale score is 6. He is intubated after several attempts and has severe bradycardia requiring cardiopulmonary resuscitation with chest compressions and several rounds of atropine, epinephrine, and sodium bicarbonate infusion, with return of spontaneous circulation after 30 minutes. Initial laboratory evaluation reveals a leukocytosis of 21.9 $10^3/\mu L$, microcytic anemia, and elevated lactate of 3.0 mmol/L; complete blood count (CBC), complete metabolic panel, and urinalysis are otherwise normal. He is treated with a dose of levetiracetam and transported to a tertiary care center, where electroencephalogram initially shows burst suppression with evolution into frequent brief generalized tonic clonic seizures that resolve with repeated doses of levetiracetam 50 mg/kg and phenobarbital 20 mg/kg. Magnetic resonance imaging (MRI) shows restricted diffusion in the posterior right cerebral hemisphere with T2/FLAIR hyperintensity (Figure 1a).

Urine drug screen results and blood cultures are normal. Lumbar puncture is technically challenging; an opening pressure cannot be obtained, and a small amount of cerebrospinal fluid shows one nucleated cell. Viral and bacterial polymerase chain reaction study results are negative, and a culture shows no growth. Ophthalmologic examination is unremarkable. A skeletal survey shows no fractures but notes increased opacification of the metaphases of the femur and humerus bilaterally and abdominal intraluminal radiopaque material (Figure 1b). The patient's family reports that they are renting an old house with chipping paint. Additional review of the CBC reveals basophilic stippling (Figure 2), and a zinc protoporphyrin-to-heme ratio is 426 (normal <70).

AUTHOR DISCLOSURE: Drs Berry, Glanz, and Knox and Ms Piciw have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

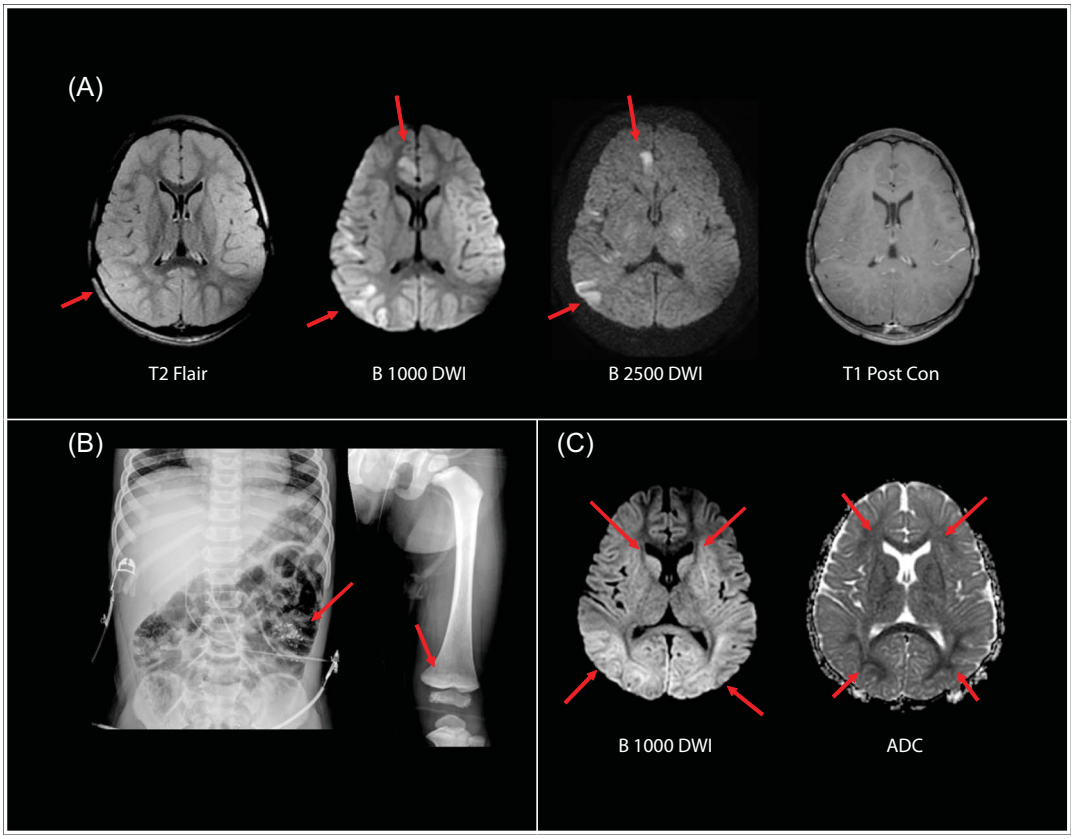

FIGURE 1. (A) MRI of the brain on day of admission shows T2/FLAIR hyperintensity with diffusion restriction in the right posterior occipital cortex, with additional diffusion restriction in the right occipital and perisylvian cortex as well as medial right frontal lobe, consistent with acute injury (red arrows). No enhancement was noted. (B) Skeletal survey shows no acute fracture. There is radiopaque material mixed with the stool in the left lower quadrant (red arrow, left) on abdominal radiograph, suggesting ingestion of a foreign substance. Long-bone radiograph shows lead lines with increased opacification at the metaphases (red arrow, right). (C) Repeat MRI of the brain 4 days after admission shows additional diffusion restriction on DWI/ADC maps within the bilateral occipital cortices, basal ganglia, periventricular white matter and corpus callosum, compatible with a combination of lead toxicity, evolving hypoxic ischemic injury, and possible superimposed postictal changes (red arrows). ADC, apparent diffusion coefficient; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging.

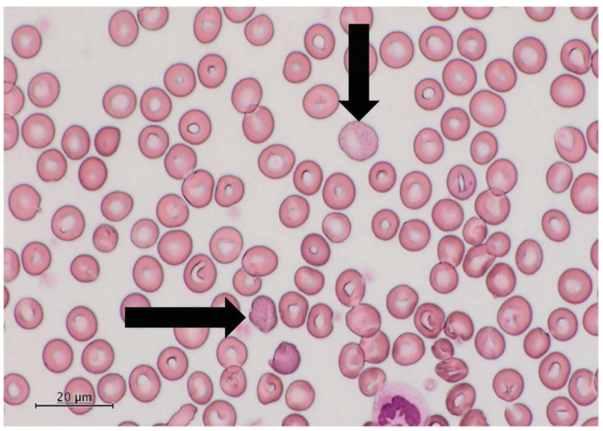

FIGURE 2. Large and small red blood cells of unequal morphology and transformation. Some of the red blood cells exhibit basophilic stippling (black arrows). (May Giemsa stain; magnification ×400).[17] Obtained for use as part of Creative Commons Attribution-NonCommercial 4.0 License.

DISCUSSION

Differential Diagnosis

It is important to consider a broad differential diagnosis for patients presenting with new onset status epilepticus, including central nervous system infection, metabolic disturbances, stroke, mass lesion, traumatic brain injury, drug or toxin ingestion, drug withdrawal, and hypoxic injury.[1] Patient history, physical examination, social history, and nonneurologic ancillary studies, such as abdominal radiograph and skeletal survey, can prove essential clues for making a correct diagnosis. Identifying an underlying etiology of status epilepticus allows the clinician to provide better prognostic information, informs selection of antiseizure medications, and has the potential to identify life-saving treatments that improve long-term outcomes.[2]

Actual Diagnosis

Although hypoxic ischemic encephalopathy initially appeared to be the cause for ongoing seizures and encephalopathy, additional history and testing suggested lead toxicity as a potential etiology for the patient's seizures and encephalopathy. A venous lead level was sent; results were delayed for 5 days because of laboratory processing with a remarkably high level of 263 μL/dL (reference <1), confirming a diagnosis of lead toxicity as the mostly likely cause of encephalopathy and seizures.

The Condition

Lead encephalopathy is a life-threatening condition characterized by altered mental status, vomiting, ataxia, seizures, and coma, which may be associated with increased intracranial pressure.[3] Cerebral imaging findings for patients with lead encephalopathy are varied and nonspecific. Chronic cases of lead toxicity in adults have reported varied T2 hyperintensities, as well as decreased white matter volume and cortical volume.[4–7] In acute lead encephalopathy, endothelial cell dysfunction may compromise the blood brain barrier and result in vasogenic edema, and mitochondrial dysfunction may lead to energy failure and diffusion restriction, as are seen in this case (Figure 1c). With increased intracranial pressure, ventriculomegaly or effacement of cisterns and herniation may be seen.[8] Diffusion restriction on this patient's MRI suggests lead toxicity, although similar findings may also be seen due to hypoxic ischemic injury.

Lead is one of the earliest recognized human toxins. Its oxidation state of 2+ allows it to masquerade as calcium in the body, explaining many of the mechanisms by which it causes pathology. It affects nearly every organ system, including the central and peripheral nervous system. It crosses the blood brain barrier, in which it causes neuronal apoptosis, excitotoxicity, mitochondrial dysfunction, disruption of second messenger signaling cascades, endothelial cell dysfunction, and demyelination. It can be sequestered for decades in glial cells and bone, compounding its long-term toxicity.[9] Lead affects both children and adults, although the developing brain is more susceptible to its effects.

Individuals with a serum lead level less than 50 μg/dL are often asymptomatic. However, there is no safe serum lead level; even levels as low as 2–5 μg/dL are associated with neurocognitive deficits and increased mortality.[10,11] Patients with a serum lead level less than 50 μg/dL may present with chronic intermittent stomach pain, anorexia, anemia, and developmental delay or neurocognitive decline. Long-term exposure is associated with psychiatric disorders, permanent neurocognitive deficits, distal motor greater than sensory neuropathy, tremor, and hearing loss. Patients with a lead level greater than 70 μg/dL are more likely to present with subacute onset of irritability, somnolence, abdominal pain and anorexia; over days to weeks, these symptoms may progress to lead encephalopathy.

Treatment/Management

Lead encephalopathy is treated with chelation. Use of calcium disodium ethylenediamine tetraacetate (CaEDTA) reduces mortality to 25%,[12] and dual chelation therapy with CaEDTA and dimercaprol or succimer further reduces mortality.[13] Hospitalization for treatment with dual chelation therapy is recommended for patients who are encephalopathic or have a lead level greater than 70 μg/dL.[14] In a study from Nigeria, treatment with succimer alone during hospitalization was also effective, yielding a mortality rate of 2%.[15] However, although chelation therapy is life-saving, it does not improve long-term neurodevelopmental outcomes.[16] The only intervention that has been shown to improve the neurodevelopmental outcomes for those with lead exposure is prevention of further lead exposure.[14] This is achieved through education, removal of lead sources from the home, notification of public health officials, hospitalization for lead levels greater than 70 μg/dL, and in some cases emergent relocation of the patient and family. Patients with a lead level less than 70 μg/dL with no encephalopathy on examination can generally be managed safely at home.[14]

Patient Course

Polyethylene glycol was given to expedite clearance of radiopaque material seen on abdominal imaging, and he passed paint chips in his stool. Poison Control recommended dual chelation therapy with CaEDTA and dimercaprol. The patient began empirical therapy with dimercaprol on hospital day 3 while the lead level was pending, but CaEDTA initially could not be obtained commercially or from other hospitals in the region. When the elevated lead level was confirmed, oral succimer and zinc supplementation were added to the chelation regimen. Dimercaprol was stopped on hospital day 10 with a repeat lead level of 69 μl/dL and then was restarted several days later because of an increase in blood lead level to 76 μl/dL. Although CaEDTA remained commercially unavailable, pharmacy was able to create a nonformulary alternative, and he completed a full 5-day course of CaEDTA (hospital days 28–32). The patient's lead level at discharge was 47 μL/dL.

On hospital day 5, the patient again had clinical seizures that were treated with lacosamide. Repeat brain MRI showed evolving injury in the bilateral occipital cortices, basal ganglia, and subcortical structures, with no evidence of increased intracranial pressure (Figure 1c). Throughout his

4-week hospitalization, the patient worked with physical, occupational, and speech therapy. He gradually became more alert, made some vocalizations, and began to raise his head. Phenobarbital and lacosamide were weaned and he was discharged on levetiracetam monotherapy. At the time of discharge, he was left with profound axial hypotonia, spastic quadriplegia with no purposeful movements, no visual tracking and paroxysmal sympathetic hyperactivity.

LESSONS FOR THE CLINICIAN

- The differential diagnosis for new-onset status epilepticus is broad. Completing a thorough workup, including a detailed medical and social history, can provide clues and assist with targeted treatment of the underlying cause.
- Thanks to heroic public health efforts, lead encephalopathy, once an all-too-common cause of neurologic devastation, has been all but forgotten in clinical practice. However, because lead is still present in the environment, it is important that pediatric providers remain vigilant and consider lead intoxication in children with unexplained altered mental status.

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IN BRIEF

Antenatal Hydronephrosis

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Before the mid-1980s, diagnosing hydronephrosis was a postnatal occurrence, and pediatricians were forced to be reactive in our evaluations and therapy. With the advent of improved ultrasonography (US) equipment prenatally, pediatricians working alongside radiologists, obstetricians, and urologists were tasked with prenatal abnormalities and determining what was pathologic and what was developmentally typical for a fetus. One such abnormality is antenatal hydronephrosis (AHN), which is the dilatation of the renal collecting system. Routine maternal US detects AHN after the first trimester in 1%–5% of all pregnancies, rendering AHN as the leading cause of abnormal prenatal US.

Although the condition is most frequently transient or physiologic (50%–75% cases), it can also be representative of obstructive or nonobstructive abnormalities, including ureteropelvic junction obstruction (UPJO), ureterovesical junction obstruction, vesicoureteral reflux, posterior urethral valves (PUVs), and multicystic dysplastic kidney as well as syndromic and/or genetic conditions. These causes, which may be associated with significant morbidity, are typically confirmed postnatally with examination and additional imaging including renal-bladder US, voiding cysto-urethrography, and diuretic renography, with additional investigations offered for specific causes. Many cases that persist postnatally will be low grade, of these some will resolve during infancy and others will require intervention to mitigate complications of AHN like urinary tract infections, urinary stones, and significant renal dysfunction. The grading systems we will discuss along with appropriate communication among the obstetrician, pediatrician, and potentially a urologist will aid to differentiate between physiologic and pathologic AHN, as this early identification is critical in ensuring rapid identification and intervention.

The simplest grading system uses anteroposterior renal diameter (APD) along with gestational age to risk stratify urinary tract dilatation (UTD) as mild, moderate, or severe. The APD, measured in the transverse plane, determines degrees of renal pelvis dilatation. Abnormal values indicative of prenatal HN (PHN) are generally accepted as at least 4 mm in the second trimester and at least 7 mm in the third (Table 1).

Another classification system was developed at a multidisciplinary consensus meeting, held in March 2014 resulting in the UTD classification system. For prenatally detected hydronephrosis, UTD classification uses US findings including APD, caliectasis, parenchymal thickness/appearance, ureterectasis, bladder abnormalities, and unexplained oligohydramnios to stratify fetuses into low or increased risk categories based on the presence of the most concerning finding (Table 2).

The UTD classification is divided into low risk (UTD A1) and increased risk (UTD A2–A3). According to UTD A1, for those diagnosed before 32 weeks, follow-up

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TABLE 1. PHN APD Severity Classification vs SFU Grading System

APD Classification			SFU Grading	
Severity	**Diameter, mm**		**Grade**	**US Findings**
Mild	2T	4 to <7	0	Normal kidney (resolved PHN)
	3T	7 to <9	1	Pyelectasis
Moderate	2T	7 to ≤10	2	Pyelectasis with dilation of ≥1 major calyces
	3T	9 to ≤15	3	Pyelectasis with dilation of all 3 major calyces
Severe	2T	>10	4	Pyelectasis with parenchymal thinning compared with contralateral kidney
	3T	>15		

Abbreviations: APD, anteroposterior renal diameter; PHN, prenatal hydronephrosis; SFU, Society of Fetal Urology; T, trimester; US, ultrasonography.
Comparison of APD and SFU systems for assessment of PHN, where 2T is indicative of the second trimester and 3T is indicative of the third trimester.

TABLE 2. UTD Risk Stratification for Prenatal Hydronephrosis

	UTD A1 Low Risk		UTD A2–3 Increased Risk	
Gestational age at detection	16–27 weeks	≥28 weeks	16–27 weeks	≥28 weeks
Anteroposterior renal diameter	4 to <7 mm	7 to <10 mm	≥7 mm	≥10 mm
Calyceal dilation	Central or no dilation		Peripheral dilation	
Parenchymal thickness	Normal		Abnormal	
Parenchymal appearance	Normal		Abnormal	
Ureters	Normal		Abnormal	
Bladder	Normal		Abnormal	
Oligohydramnios	No unexplained oligohydramnios		Unexplained or suspected GU cause	

Abbreviations: GU, genitourinary; UTD, Urinary Tract Dilatation.
The UTD Classification System involves consideration of findings used in both APD and Society of Fetal Urology classification systems, such as ultrasonography findings and anteroposterior renal diameter.

prenatal US can be done after 32 weeks to monitor progression. However, this raises the question, "If resolution of PHN is demonstrated, is cessation of further follow-up appropriate?" There are mixed recommendations for postnatal follow-up in the transient group, with some suggesting that as the risk of postnatal pathology is low for prenatally resolved HN cessation of follow-up is reasonable, and others citing that, despite this, all patients should be provided with postnatal US.[1] Ultimately, there is yet to be an understanding of how to distinguish those that will have progression or late worsening and those that will not. Hence, until further study is accomplished to answer this question, it is imperative to provide postnatal follow-up. This does highlight the importance of collaboration and communication between the obstetrician and pediatrician to provide the details regarding the timing and results of prenatal US.

For those in UTD A2-3, it is recommended to have a repeat US during the prenatal period and follow-up postnatally. Regardless of whether the initial postnatal US is normal, it is imperative to perform a second US as an abnormal second US following normal initial US was found in 45% of children, and the risk of recurrence or worsening of HN was noted in 15% of children. It goes without saying that risk of uropathy is worse in those with persisting postnatal HN. The initial postnatal US should be performed after 48 hours, as the degree of UTD can be falsely reduced by neonatal oliguria and dehydration of infants. The second postnatal US should be completed within 1–6 months after the initial US.

Frequency of prenatal US surveillance has had limited study; however, it is generally appreciated that those with higher-severity HN, bilateral disease, or evidence of lower urinary tract obstruction (LUTO) should have more frequent US (every 4–6 weeks depending on the severity of the findings) as opposed to those without, who may be satisfactorily monitored with a second US in the third trimester.

There are several proposed exceptions to the delayed timeframe of postnatal surveillance, requiring earlier initial evaluation (<48 h) and more frequent follow-up for those with suspected obstructive uropathies or bilateral disease.

Concerns for those with the renal pathology that may progress and develop obstruction requiring surgery and renal dysplasia, as well as UTIs requiring antibiotic treatment, drive the need for surveillance and further examination. Considering that high-grade HN has a high likelihood of progression requiring surgical intervention, that childhood UPJO typically presents by 18 months, and that most low-grade HN will resolve by 2 years of age, follow-up may be reasonably provided until this age.

Deterioration past this age is estimated to be 2%; however, it is still not clear how to identify those that will progress to obstruction, hence the need to educate patient caregivers regarding obstruction and UTI presentation on discharge.

Treatment options for PHN depend on etiology, timing, and risk of postnatal pathology.

In utero interventions, such as vesicoamniotic shunting, can be considered in the mid–second trimester for fetuses with suspected LUTO. This intervention does not come without risk but does offer improvement of perinatal survival for those with severe obstruction. As such, involvement of tertiary centers and pediatric urologist counseling is necessary in these cases.

Alongside classification systems, the clinician must have a thorough understanding of risk factors for postnatal pathology. The main risk factors for postnatal pathology are those who are diagnosed in the second trimester and persist into the third trimester; demonstrate progression; present with bilateral disease and/or evidence of LUTO, such as oligohydramnios and thick-walled or dilated bladder. The presence of those risk factors should influence the frequency of prenatal and postnatal care and the need for involvement of a pediatric urologist.

The presence of antenatal abnormalities of any kind can cause significant anxiety for the families of these infants. Therefore, we must strive to provide them with an understanding of what signs they should look out for to seek urgent medical attention and to develop a plan for evaluation and treatment. This highlights the need for a widely adopted grading system as well as the ongoing analysis of grading systems to ensure appropriate application and to reduce clinical practice variation with respect to appropriate prenatal and postnatal care.

Comments: This "In Brief" article highlights the benefits and complexities that prenatal US brings in the variety of renal abnormalities that may be identified and the challenges in determining as soon as possible which abnormal findings may resolve and lead to eventual normal functioning and those that lead to long-term morbidity and renal dysfunction. I once cared for a patient in my practice who was diagnosed with PUVs postnatally, leading to renal dysfunction and his need to have 2 renal transplants during his first 20 years of life. I wish the US technology had been available then to help prevent the degree of renal dysfunction he experienced. Yet, future research is needed to better inform the predictive properties of these grading systems. Consider the importance of acknowledging the uncertainty of future diagnosis and balancing important factual information while supporting families through the inevitable anxiety that may result from identification of these abnormalities prenatally. While focusing on the continuum from the prenatal care, provided by the obstetrician, to the postnatal care, that is the responsibility of the pediatrician, the urologist, when involved, bridges the life continuum and is essential in the communication loop. I have always been an advocate of prenatal pediatric visits, and this is an example of when they can be beneficial. The opportunity for a pediatrician to meet with parents during their pregnancy can alert the pediatrician to potential issues that are relevant at the time of birth and the early postnatal period and allow the pediatrician and parents to establish an earlier trusting relationship and "hit the ground running" in collaboration with urologists should more urgent treatment be needed.

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IN BRIEF

Considerations for the Pre-Sports Evaluation in Primary Care

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INTRODUCTION

Athletes of all ages and levels may be required to undergo a preparticipation physical evaluation (PPE) before being allowed to participate fully in structured athletics. PPEs primarily function to ensure the health and wellness of athletes prior to sports participation, particularly to avoid exacerbation of a condition that could result in morbidity or mortality. PPEs can be a time to offer anticipatory guidance geared toward healthy living and athletics, provide a health check-in for those not otherwise required to have a yearly well visit, and meet jurisdictional and/or organizational requirements.

The conduct of the PPE has been detailed in a monograph, which reviews the purpose of the PPE, recommended location and frequency, notable historical and physical exam points, considerations for special populations, potential need for additional testing, and a clearance determination. The monograph was developed as a collaboration of the American Academy of Family Physicians, American Academy of Pediatrics, American College of Sports Medicine, American Medical Society for Sports Medicine, American Orthopaedic Society for Sports Medicine, and the American Osteopathic Academy of Sports Medicine. The fifth and most recent edition of the monograph was released in 2019 and includes updates to improve care for athlete mental health and gender identity. A supplement, with information about an athlete's COVID-19 history and vaccine status, was also released during the coronavirus disease 2019 pandemic.

The logistics of conducting PPEs has been well prescribed. It is recommended that the PPE occur at the primary care provider's office, providing continuity and, likely, a more complete evaluation. Station-based PPEs offer less privacy and a lower likelihood of an ongoing patient-provider relationship. PPEs should, thus, be conducted as part of routine wellness care whenever possible. Many jurisdictions and organizations also require a PPE on a regular timeframe, often, but not always, annually.

Providers completing a PPE should ensure appropriate documentation, including their clearance determination and any follow-up that might be needed. It can be helpful to utilize the standardized PPE documents for patient care (Table 1), although many providers use what is available in their electronic health record, in addition to the documents that meet jurisdictional and/or organization requirements. When considering documentation, providers should also consider their coding. If a PPE is performed at a well visit, it is recommended to include the sports

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TABLE 1. Important Considerations for PPEs in the Primary Care Office

	PEARL	PAUSE
General	Every visit with a pediatric athlete offers an opportunity to screen for and encourage healthy athletics participation	Avoid yearly PPEs in the absence of yearly well visits
History	Taking a history from both the guardian and the patient is crucial for a thorough and accurate assessment	Although abnormal cardiac history (in the athlete or family) is the greatest morbidity risk, it is important to elicit the athlete's overall medical history to assess for other risks
Special populations	Utilize the "Athletes with Disabilities Form" to document information for the health of special populations	Be sure to involve the entire care team for any additional testing, treatment, or sports restriction
Physical exam	Be sure to check range of motion for all joints, with particular attention to joints that would be affected by the sport being played	Pay special attention to previous injuries, as those are most likely to be reinjured
Additional testing	Consider consulting a specialist if you have a question and are not sure of whether to refer a patient or not	Do not ignore abnormalities—little issues and events can be harbingers of significant conditions
Assessment	For athletes who need yearly sports physicals, the same history of a remote or intermittent event or issue (eg, joint pain, exertional headaches) may be elicited each year. An initial investigation of the concern may allow it to be resolved early or to be appropriately monitored with routine follow-up	Being excluded from playing sports can have significant, negative mental health effects on young athletes. Carefully consider the ramifications before restricting or prohibiting sports participation
Online resources	The AAP Pediatric Care website includes helpful links for state-specific regulations for the PPE as well as forms that can be used to complete and document the different components of the PPE: www.aap.org/en/patient-care/preparticipation-physical-evaluation	

Abbreviation: PPE, preparticipation physical evaluation

physical diagnosis code, which could be helpful for future evaluation of the utility of the PPE and its components. As a complete sports physical is a separate service, it is acceptable to bill for this service at the same time as the well visit. Different insurances have different requirements for billing for this service. Be sure to check with the insurance carriers affiliated with your medical practice.

HISTORY

An accurate and thorough medical history has been shown to identify roughly 75% of issues that affect sports participation. The history should be obtained from both the patient and guardian, as studies have shown poor correlation between patient and guardian medical history reporting. Performing a separate history with the patient can also be an opportunity to discuss private psychosocial issues (eg, mood, safety, drug use) that are important to both sports participation and adolescent wellness care.

The medical history should review the patient's general health, current medical conditions, medications, supplements, allergies, and any past sports restrictions, medical and musculoskeletal (MSK). Other areas of import include mental health, menstrual health, sickle cell history, and weight/nutrition concerns. These questions can help uncover other potential concerns in male and female athletes, such as relative energy deficiency in sport.

Particular attention should be paid to personal and family cardiac health, as sudden cardiac death is the leading cause of death during sports participation for young athletes and results from underlying cardiac disease. Electrocardiograms (ECGs) are commonly used in European countries as part of evaluation; however, in the United States, given the current evidence, the cost, and issues with access to ECGs and cardiologists, the current recommendation is to test only those with abnormal cardiac screening (by history and exam).

PHYSICAL EXAMINATION

The physical examination includes vital signs, a general medical exam, a focused cardiac exam (including auscultation for murmurs in positions that decrease preload, like standing or performing the Valsalva maneuver, and that increase preload, like squatting, to evaluate for hypertrophic cardiomyopathy), and a comprehensive MSK exam. This MSK exam, which can be completed in under 2 minutes, checks overall range of motion, strength, and brief functional testing. Other recommended MSK functional

movement testing includes the double-leg squat test, single-leg squat test, and drop jump test. Based on the history, a focused exam of a previously injured joint may also be required. The most common abnormalities found during the physical examination are elevated blood pressure and visual acuity issues.

SPECIAL POPULATIONS

Athletes with certain medical conditions warrant particular consideration. For example, absence or nonfunction of one organ of a pair may affect clearance for sports that put the remaining organ of the pair at risk and may require additional protective equipment. Patients with glasses who are playing sports with a high risk of eye injury (eg, baseball, hockey) should wear polycarbonate lenses.

Sickle cell trait (SCT) can put athletes at risk for exertional sickling. Self-reporting by the athlete or guardian for SCT can be inconsistent; verifying the sickle cell test results from the newborn metabolic screen or obtaining a new sickle cell test may be required for collegiate sports participation.

Athletes with genetic disorders, like trisomy 21 and hemophilias, may require additional pre-sports testing and/or treatment. Similarly, athletes with physical and/or intellectual disabilities would benefit from a multidisciplinary approach with their specialists and other care team members to determine eligibility for their sport of choice. A supplemental form for athletes with disabilities is also available (Supplemental Material).

ADDITIONAL TESTING

Generally, additional diagnostic testing is ancillary to a PPE. The need for any additional tests should be based on history and exam findings. For example, an athlete with a fever, sore throat, cervical lymphadenopathy, and abdominal pain might have mononucleosis. In such cases, laboratory testing for mononucleosis would be helpful for diagnosis and subsequent counseling on temporary athletic avoidance if indicated. Radiographs are not typically necessary for PPEs without abnormal findings.

Referrals can also lead to additional testing. Common specialties and the reasons for referrals based on PPE findings include the following:

- Cardiology: loud murmur, syncope, hypertension
- Pulmonology: exercise-induced bronchospasm unresponsive to regular therapies
- Neurology: seizures, headaches with exercise
- Neurosurgery: bilateral burners/stingers (transient bilateral neurapraxia)
- Nephrology: hypertension
- Ophthalmology: monocular vision status

ASSESSMENT

Once the history and exam are complete, an assessment can be made. Occasionally, some questions may remain. What if there is a historical risk factor for sports participation that has not recurred? It can be helpful to determine how remote the risk-contributing event or issue was. Has the level of play stayed the same since that event or issue occurred without a recurrence? When in doubt, it is prudent to investigate further with testing and/or referral. The same approach is recommended in cases of intermittent or mildly abnormal findings on history or exam.

Clearance determinations are not always dichotomized into full participation or no participation. Some athletes may be cleared without restrictions, but others may be cleared with restrictions (to certain sports or activities) or cleared only after being evaluated by a specialist.

CONCLUSION

PPEs aim to ensure the safe and successful participation of all our young athletes. They should occur regularly and be conducted with a systematic and comprehensive method. Concerns should be addressed early. Clearance decisions may not be all or none. Consider limited participation to avoid complete restriction whenever possible.

Comment: During my high school swimming career, my PPEs were conducted assembly-line fashion by my health maintenance organization. On one evening each year, I could show up without an appointment and move through stations to have my sports physical form completed piecemeal. Times have changed, and the PPE monograph now stresses that exams should occur individually in a physician's office, in recognition of the fact that PPEs serve an important secondary function of bringing athletes in for preventive services that they might otherwise miss. This is particularly true for adolescents who, on average, play more organized sports and miss more recommended checkups than younger children. To make the most of this extra, mandated contact between athletes and health care providers, front office staff should be instructed to determine whether students are due or overdue for health maintenance exams and if so, convert requested PPE appointments into appointments for full checkups. Even when a checkup is not warranted, it is still advisable for health care providers to assess for and order recommended vaccinations at PPEs. Finally, given the high prevalence of mental health issues among all children, including athletes,

a thorough PPE would not be complete without screening for anxiety and depression. These days, children can get their PPE from pharmacy retail clinics. While this may be convenient for some families, retail clinics do not deliver the same level of continuous, coordinated, and comprehensive care to athletes that primary care providers are well prepared to deliver.

Linda Y. Fu, MD, MS
Associate Editor, In Brief

ANSWER KEY FOR MAY PEDIATRICS IN REVIEW:

Adolescent Sexual Health: A Focus on the Sexual Health Portion of HEADSS Examination:
1. A; 2. A; 3. A; 4. C; 5. E.

Balancing Digital Media Exposure: Enhancing Language and Social Development in Early Childhood:
1. C; 2. D; 3. C; 4. A; 5. B.

Diagnosis and Management of Acute Osteoarticular Infections: Summary of New Guidelines:
1. C; 2. B; 3. D; 4. C; 5. C.

VISUAL DIAGNOSIS

A White Reflex in a Previously Healthy 21-Month-Old Boy

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PRESENTATION

A 21-month-old boy presents to the ophthalmology clinic after an injury to the eye from a toy. His family describes that the patient's right eye has been developing a "shiny center" prominent under light starting around 12 months of age. The family noticed this spot continued to grow until around 18 months when they no longer noted any black part of the eye. The patient regularly follows with a pediatrician and has been healthy, meeting all developmental milestones. The family explains they forgot to mention the patient's eye at pediatrician appointments, and they do not recall any eye examination abnormalities mentioned at well-child visits. On examination, the patient favors keeping his right eye closed and is fussy when the left eye is covered. The left eye is central, is steady, and maintains fixation on objects during the examination, but the right eye is central, steady, and unmaintained. The right eye is deviated outward consistent with exotropia. Both pupils are round, but the right pupil does not constrict in response to light. Intraocular pressure measures 38 and 14 in the right and left eye, respectively (normal 10–21). The right eye appears injected with a white pupillary reflex (Figure 1). The lens is clear. The left eye is unremarkable (Figure 1). Dilated fundus examination of the right eye reveals a white mass with irregular, intrinsic vasculature occupying more than 50% of the globe with associated serous retinal detachment and no view of the optic disc (Figure 2). B-scan ultrasonography of the right eye confirms an intraocular mass with intrinsic calcifications (Figure 3). Ocular examination and ultrasonography results confirm the diagnosis.

DIAGNOSIS

Leukocoria is an altered pupillary reflex that appears white.[1] The differential diagnosis for leukocoria is wide, including Coats disease, persistent fetal vasculature, retinoblastoma, ocular toxocariasis, retinal detachment, and cataract.[1,2] This patient had leukocoria with a partially calcified mass present on ultrasound, pointing toward a diagnosis of retinoblastoma. Biopsy is not recommended or needed to diagnose retinoblastoma. Examination findings and imaging are sufficient to diagnose this cancer.

DISCUSSION

Retinoblastoma is the most common malignancy of the eye in children with an incidence of approximately 1 in 17 000 live births.[3] Most cases are identified by age 5, and

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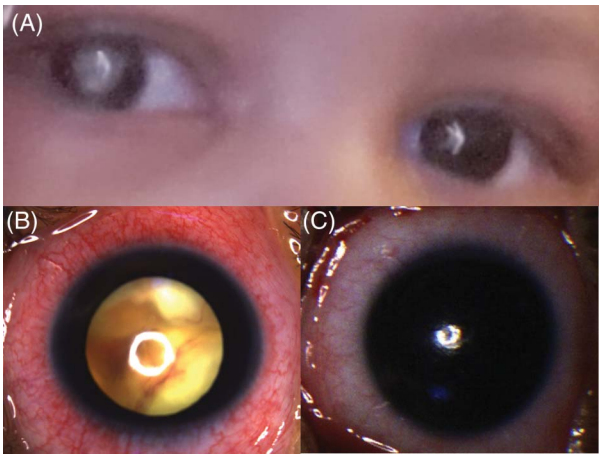

FIGURE 1. (A) A photograph provided by the family at the visit demonstrates a significant difference between the white pupil of the right eye compared with the normal pupil of the left eye. (B) The patient's right eye is injected with a white pupillary reflex present consistent with leukocoria. (C) The patient's left eye is unremarkable without leukocoria.

two-thirds are diagnosed by age 2.[4] Retinoblastoma occurs as the result of mutations in the retinoblastoma gene, RB1.[4] Retinoblastoma can occur in a bilateral, heritable form in about 25% of cases, or a unilateral, sporadic fashion in approximately 75% of cases.[4] The highly proliferative nature of retinoblastoma subsequently causes tissue damage and necrosis leading to calcification.[5] Therefore, calcifications are often more prominent in advanced tumors.[5] Although survival in patients with retinoblastoma is favorable in high-income countries, mortality is significantly higher in low- and middle-income countries where disease is often discovered in later stages.[6]

In more than half of retinoblastoma cases, the initial clinical manifestation is leukocoria.[7] In a review by Shields et al, the most common lesions mimicking retinoblastoma were persistent hyperplastic primary vitreous, Coats disease, and presumed ocular toxocariasis.[2] These conditions can present with leukocoria and disrupt visual development, potentially leading to vision loss. Coats disease, an idiopathic disease characterized by abnormal retinal vasculature, can be distinguished on examination by the presence of xanthocoria, a yellow/orange pupillary reflex, rather than the white reflex of a partially calcified tumor.[8] Parents are more likely to notice findings of leukocoria and strabismus rather than the pediatrician or ophthalmologist.[9] Therefore, asking parents about white or shiny pupils can help identify leukocoria early. Whether leukocoria is secondary to retinoblastoma or another diagnosis, a workup and ophthalmology evaluation are indicated.

The second most common presenting sign of retinoblastoma is strabismus, misalignment of the eyes.[7] When strabismus is a presenting sign of retinoblastoma, this often indicates the tumor has worsened visual acuity in one eye by growing near the fovea.[7] Therefore, the brain diverts attention toward the better seeing eye and away from the eye with retinoblastoma and poor vision, causing the eye to drift. If parents or patients mention drifting or lazy eyes, checking for leukocoria with an ophthalmoscope and a referral to ophthalmology are indicated.

Imaging studies such as ultrasound and magnetic resonance imaging (MRI) differentiate retinoblastoma from other causes of leukocoria by demonstrating a mass in the eye. Use of computed tomography imaging in suspected retinoblastoma is not preferred because radiation exposure can increase the risk of a second primary cancer in children with germline retinoblastoma.[6] Calcifications within the eye tumor can be detected by ultrasound, so computed

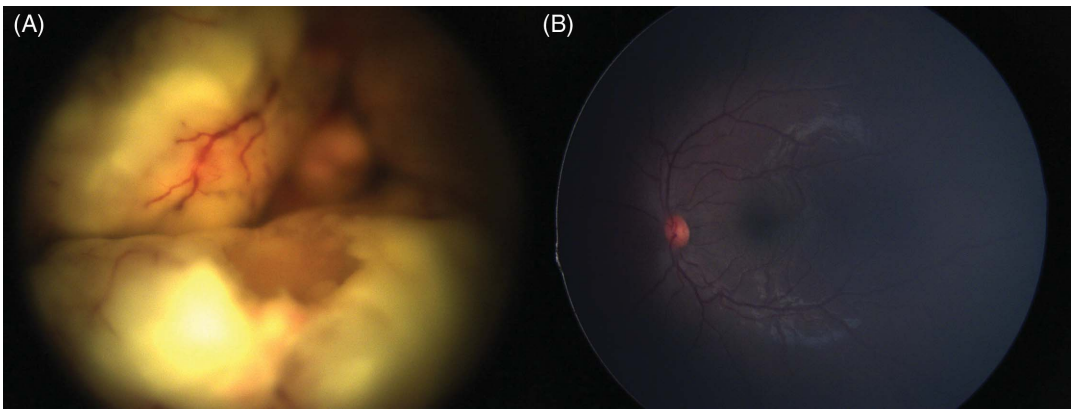

FIGURE 2. (A) A RetCam fundus photograph of the right eye demonstrates a large, partially calcified intraocular mass occupying more than 50% of the globe with no view of the optic nerve and no visible normal retina. (B) A RetCam fundus photograph of the left eye demonstrates a normal eye anatomy including a flat retina, a normal optic nerve, and no tumors.

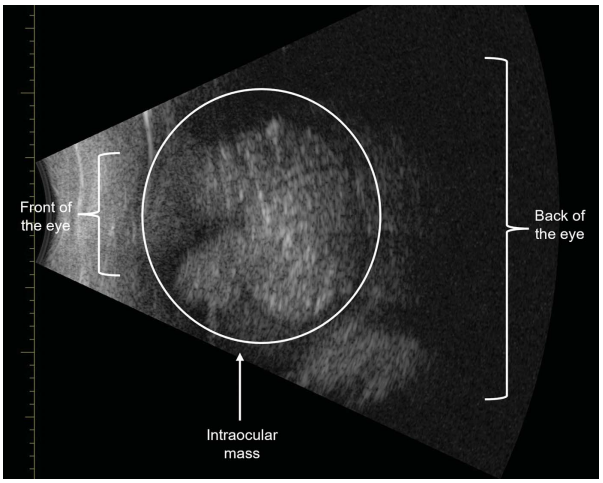

FIGURE 3. B-scan ultrasonography of the right eye demonstrates an intraocular mass with calcifications occupying more than 50% of the globe. The intraocular mass is circled with the front of the eye to the left of the figure and the back of the eye to the right.

tomography is not needed for diagnosis. Retinal detachment or vitreous hemorrhage can present concurrently with retinoblastoma.[7] After a diagnosis of retinoblastoma, an important initial step is evaluating for metastasis. This can include imaging of the brain, lumbar puncture for cerebrospinal fluid evaluation, bone scans, and bone marrow aspiration and biopsy. Extensive workup may not be required in clearly localized disease, but all children require an MRI to look for pinealoblastoma. Pinealoblastoma can occur concurrently with bilateral retinoblastoma in patients with germline mutations; this is often referred to as trilateral retinoblastoma and carries a poor prognosis.[10]

Retinoblastoma is a disease that can go unnoticed until late in its course. Examining every child for leukocoria with a direct ophthalmoscope is a simple, efficient way to help detect retinoblastoma earlier when there is a better prognosis. When discovered late such as in this patient, the likelihood of metastasis increases. Although leukocoria does not unequivocally mean a retinoblastoma diagnosis, detecting leukocoria on physical examination is an important step in the detection of retinoblastoma, as well as other vision threatening conditions.

Retinoblastoma classification and staging are important for developing a proper treatment plan. Classification and staging often require an eye examination under anesthesia to fully assess the extent of the tumor.[6] The American Joint Committee on Cancer cTNMH scheme is used for retinoblastoma. This system involves categorizing retinoblastoma based on characteristics of the primary tumor (T), regional lymph node involvement (N), metastasis (M), and presence of the heritable trait (H).[11] Classification of intraocular disease burden is often done with the International Classification of Retinoblastoma, which classifies tumors from A to E.[12] Genetic testing is also indicated in retinoblastoma cases to determine if a germline mutation is present, which influences management.[6] Although most germline mutations result in bilateral disease, 16% of patients with a unilateral retinoblastoma demonstrate a germline mutation, highlighting the importance of genetic testing in all cases.[10]

Treatment of retinoblastoma depends on the staging and classification. Treatment can involve intravenous chemotherapy, intra-arterial chemotherapy, which delivers medication specifically to the ophthalmic artery, intraocular chemotherapy, cryotherapy, transpupillary thermotherapy, and potentially enucleation.[6] Enucleation is typically reserved for more advanced or refractory disease.[6] Retinoblastoma treatment requires important care coordination among pediatricians, oncologists, and ophthalmologists, often with both an ocular oncologist and a pediatric ophthalmologist for cancer treatment and visual rehabilitation, respectively. A connected care team knowledgeable about retinoblastoma is important for quality care for these patients. Pediatricians are often the first and only contact for young, otherwise healthy patients. Their role to recognize potential signs of retinoblastoma and refer appropriately is essential.

The goal of retinoblastoma treatment is to first save the patient's life, ideally with therapies that avoid radiation. Although the eye can sometimes safely be saved, in cases of extensive disease such as our patient, vision and globe-sparing therapies may not be compatible with best practices for prevention of metastatic disease. Retinoblastoma can be a devastating diagnosis when caught late. When left untreated, retinoblastoma can extend to tissues beyond the eye. Thus, early detection is important not only to facilitate preserving eyesight but also to avoid life-threatening advanced disease.

PATIENT COURSE

An MRI was done urgently to determine if globe-sparing treatment options could be offered. The MRI confirmed an enhancing, calcified right intraocular mass with serous retinal detachment (Figure 4). The right optic nerve was involved extending to the prechiasmatic segment. There was no other intracranial disease. Because of extensive optic nerve involvement, globe-sparing treatment was not safe, and a surgically clean optic nerve margin would not be feasible. The eye was enucleated with partial removal of the optic nerve stump with positive margins (Figure 5), with a plan to follow with chemotherapy. Metastatic workup at the time of initial treatment

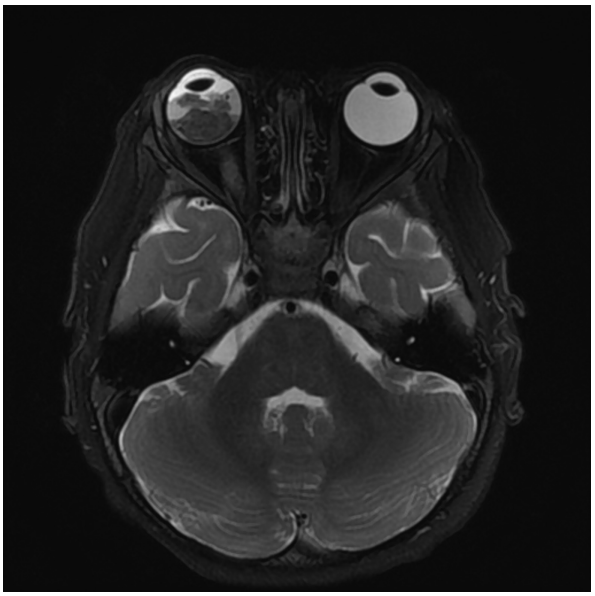

FIGURE 4. Magnetic resonance imaging orbits T2 FS demonstrates a heterogenous enhancing and calcified right intraocular mass with serous retinal detachment. The right optic nerve is involved extending to the prechiasmatic segment. There is evidence of choroidal invasion with scleral thinning and suspected involved of the right anterior chamber.

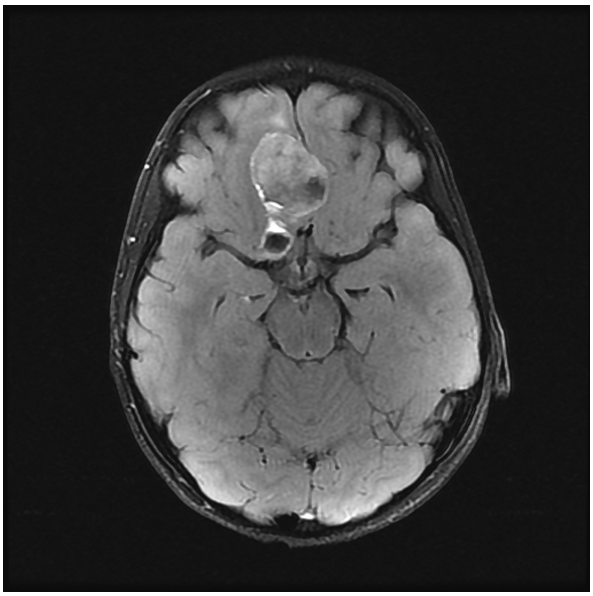

FIGURE 6. Magnetic resonance imaging brain T2 fluid-attenuated inversion recovery demonstrates a new 2.5 × 3.1cm enhancing mass along the floor of the anterior cranial fossa indicating metastasis of the patient's retinoblastoma to the brain.

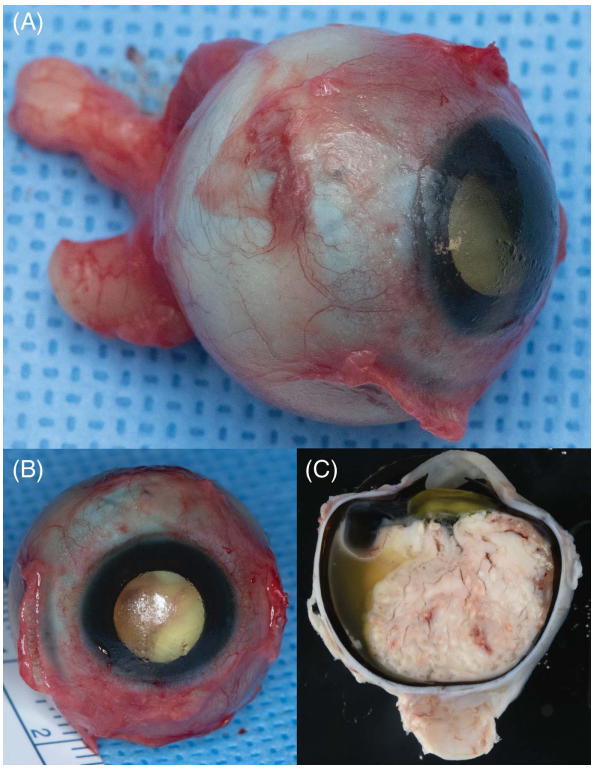

FIGURE 5. (A) A lateral view of the patient's enucleated right eye shows the resected portion of the optic nerve. (B) An anterior view of the patient's enucleated right eye reveals a visible white reflex. (C) An anterior-posterior section through the patient's enucleated right eye demonstrates retinoblastoma occupying a large portion of the globe and invading the optic nerve stump.

showed no metastasis. Under the direction of pediatric oncology, the patient received ARET 0321 chemotherapy consisting of 4 cycles with vincristine, cisplatin, cyclophosphamide, and etoposide followed by autologous stem cell transplant and proton beam irradiation to the unresectable involved optic nerve stump. Genetic testing revealed no germline retinoblastoma mutation. Unfortunately, about 1 year after his original diagnosis, an MRI demonstrated a new intracranial tumor suggestive of metastasis (Figure 6). The frontal lobe mass was successfully resected, but several months later, tumor growth was seen again in the anterior cranial fossa and right temporal lobe. The patient transitioned to hospice care and died a year and a half after his initial diagnosis.

Summary

- Retinoblastoma is the most common intraocular malignancy of childhood and comprises 3% of all pediatric cancers.[4]
- Prognosis and survival rates in retinoblastoma are dependent on the stage of disease when treatment is initiated. Later stage tumors are associated with poor prognosis.[12]
- The most common clinical sign of retinoblastoma is leukocoria, a white pupillary reflex, often

initially noticed by a family member.[7,9] Although leukocoria can be seen with direct ophthalmoscopy, subtle leukocoria may be difficult to detect in an undilated pupil, especially if the child is moving during examination. Any parental concerns including reflections or shine in the pupil should prompt ophthalmology referral.

- Strabismus is another possible presenting sign of retinoblastoma, which also warrants referral to an ophthalmologist.[7]
- Assessing the red reflex is a critical part of the well-child examination for infants. Recognizing the clinical signs of retinoblastoma at pediatric well visits can play a key role in discovering retinoblastoma as early as possible when prognosis is more favorable.
- Workup of retinoblastoma should always involve genetic testing and eye examination under anesthesia with fundus photography, B-scan ultrasonography, and MRI of the brain and orbits.
- Treatment of retinoblastoma involves coordination of care among multiple medical teams and can involve different modalities of chemotherapy, focal laser or cryotherapy, and potentially enucleation.[6]

References for this article can be found at
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