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cardiac magnetic resonance imaging

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learning objectives

Following the completion of this article, the reader should be able to:

1. Describe the physiology of late gadolinium enhancement in cardiac magnetic resonance imaging (CMR).
2. Review newer CMR modalities to assess the myocardium for inflammation, necrosis and fibrosis.
3. Discuss cardiac MRI in the evaluation of myocardial disease.

background

We have come a long way since the 1930s when Dr. Helen Taussig, founder of pediatric cardiology, was using palpation, EKG and fluoroscopy to diagnose and treat congenital heart disease. In those days, the life expectancy of patients with moderate to severe congenital heart disease was dismal. Only 20% of infants survived past 1 year of age.[1] Fortunately for us and our patients, medical, surgical and catheter-based treatments for congenital heart disease have advanced significantly, and the number of adults living with congenital heart disease outnumbers the number of children with congenital heart disease. Concurrent with advances in treatments are advances in imaging, which have afforded cardiologists the ability to evaluate anatomy and physiology in noninvasive ways. Whereas in the 1950s cardiac catheterization was the only way to truly understand a patient's anatomy and physiology, echocardiography, cardiac magnetic reasoning imaging (CMR), and cardiac CT and chest angiography are now the primary modalities, with cardiac catheterization serving the main function of complex physiology assessment, therapeutic intervention and biopsy. This article will discuss the benefits of CMR in the care of patients with congenital and acquired heart disease.

CMR is the technique by which a patient is placed into a strong static magnetic field. This extremely strong magnetic field results in the hydrogen protons of the body aligning "in phase." A varying weaker magnetic field and radiofrequency energy are then applied to selected portions of the patient's body resulting in "de-phasing" of those hydrogen protons. When the weaker magnetic field and the radiofrequency energy are removed, those affected protons once again align in phase but not before emitting radiofrequency energy. The radiofrequency image is then collected by the sensors in the MRI scanner. This information is collected as frequency and amplitude information. A mathematical procedure called the Fourier transform then produces a static image or picture of the heart.

a low-risk test

From what is now known, CMR poses no known hazards to human beings. Millions of patients have now undergone CMR without any ill effects noted. MRI has been used on pregnant women. Sometimes MRI is used to image certain structures in the fetal brain, chest and/or abdomen. CMR of the fetal heart is difficult and remains in the research realm.

Despite no direct harm to humans from the strong magnetic fields and radiofrequency energy, a patient must be properly screened before a CMR can occur. There is concern about any implanted metallic objects within the body that could move or heat during the procedure. This can include iron filings, shrapnel, implanted medical devices, jewelry, and even some types of tattoos. Obviously, intracranial, intraocular and intracochlear devices are usually considered a contraindication. Pacemakers and implanted defibrillation devices had previously been a contraindication. However, the technology on these devices is changing. More recent cardiac pacemakers are considered "MRI safe," and the patient with such a device can undergo CMR.

CMR is rarely used as a first or even sole diagnostic imaging test. It usually serves as a complement to other imaging modalities, especially echocardiography. It is also an alternative to CT scans and avoids the associated radiation. It is fair to say that CMR has

now replaced diagnostic cardiac catheterization as the gold standard for obtaining quality imaging of most cardiac structures and great vessels (figures 1-7).

advantages and disadvantages

CMR has many advantages when compared to other cardiac imaging modalities. For example, CMR is not affected by acoustic windows and the patient's body habitus. Patients with obesity or difficult acoustic windows due to bone and/or lung abnormalities can undergo CMR with excellent imaging results. CMR is noninvasive, does not involve exposure to ionizing radiation, and can be performed repeatedly without regard for radiation in growing children, pregnant women, and pre- and post-surgical patients.

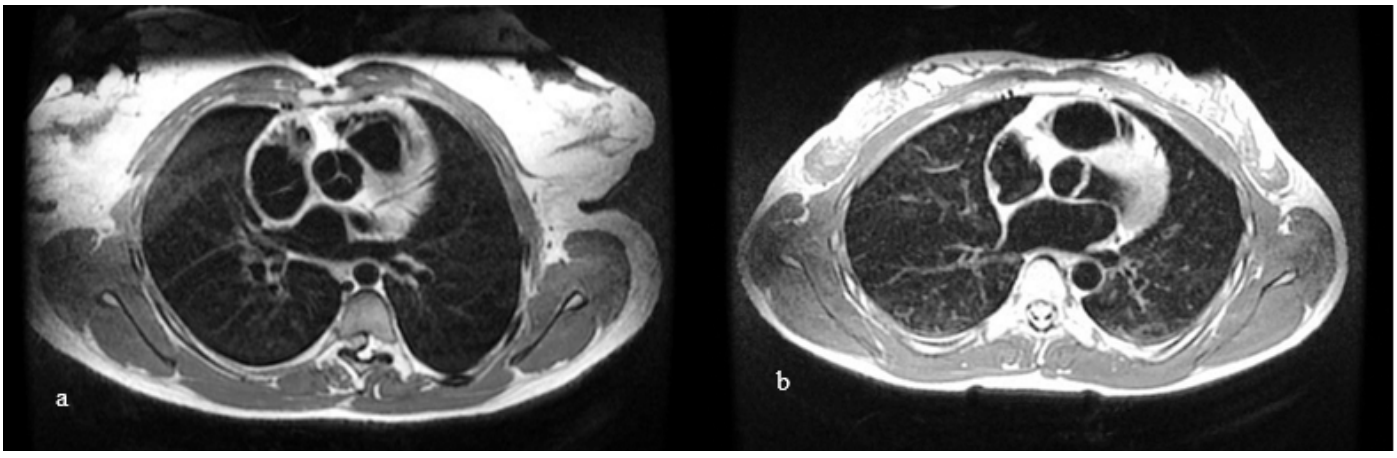

figure 1. Axial views of the heart demonstrating (a) normal tricuspid aortic valve, (b) bicuspid aortic valve.

figure 2. Axial view showing normal origins of the right (R) and left (L) coronary arteries.

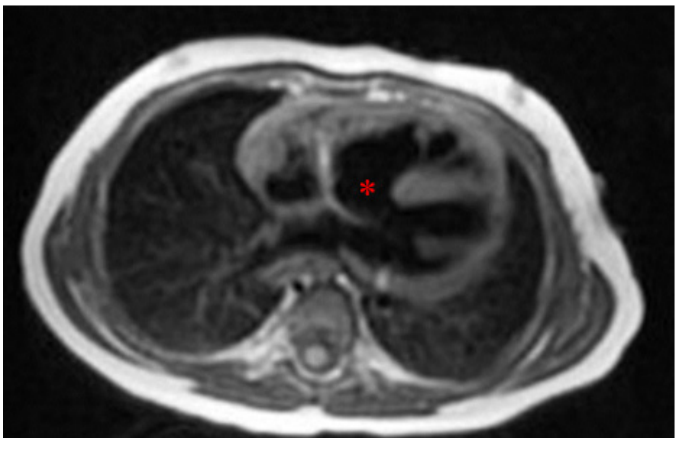

figure 4. Axial view; (*) denotes ventricular septal defect (VSD).

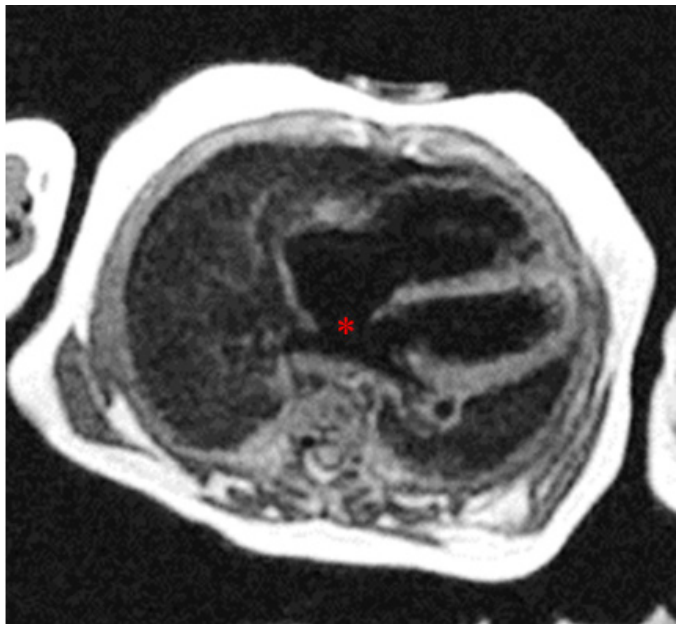

figure 3. Axial view; (*) denotes secundum atrial septal defect (ASD).

CMR disadvantages include the fact that it is not portable. The studies can sometimes take up to two or three hours to perform in complex anatomic or physiologic situations. Furthermore, children younger than approximately 12 years of age often are unable to lie still for the procedure and must be subjected to deep sedation or general anesthesia to accomplish the imaging study.

When one compares the advantages and disadvantages of CMR, it would seem that the advantages clearly outweigh the disadvantages. CMR results in excellent

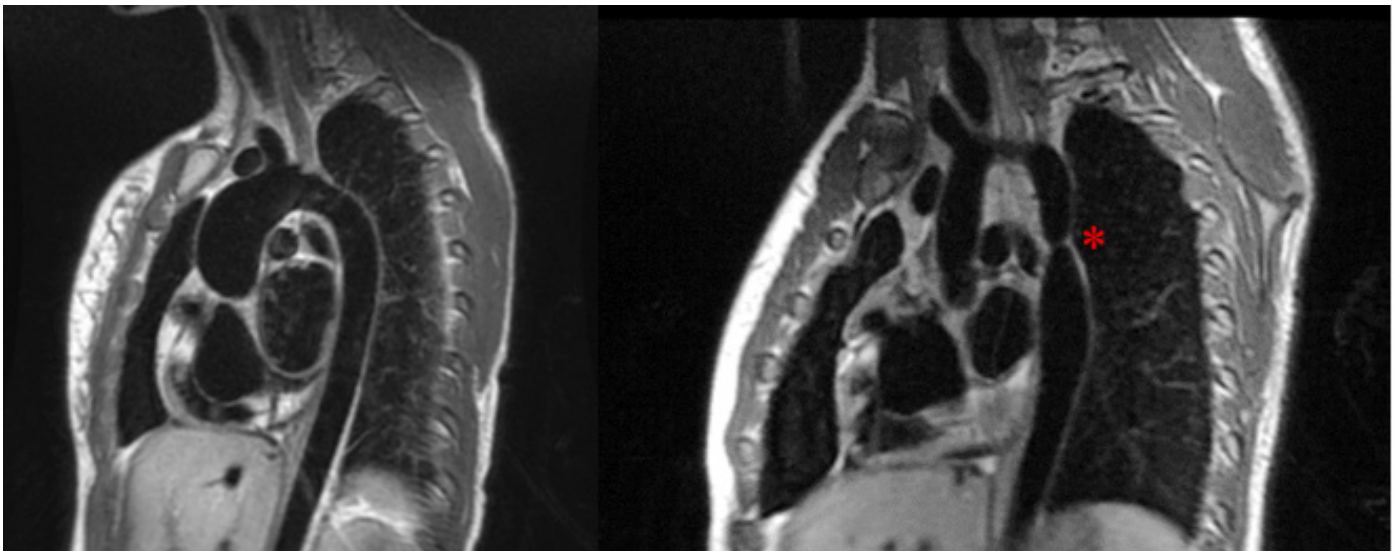

figure 5. Sagittal oblique views demonstrate (a) normal aortic arch and (b) aortic coarctation denoted by (*).

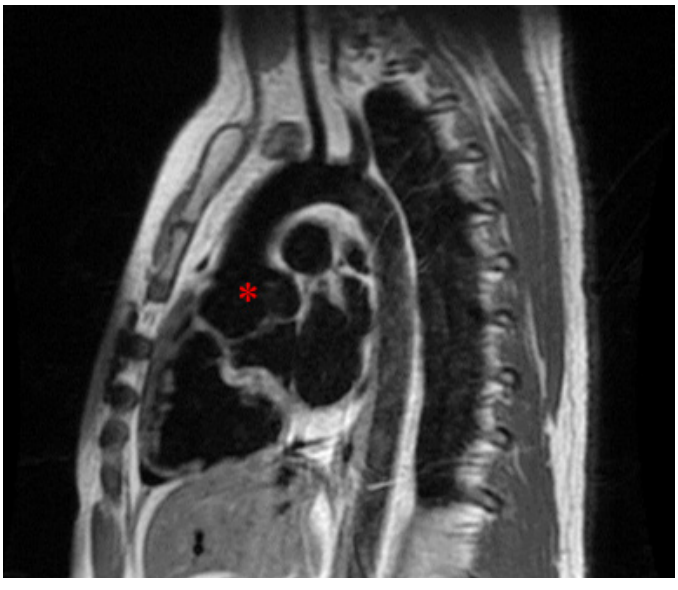

figure 6. Sagittal oblique view in a patient with Marfan syndrome. Note the dilated aortic root (*).

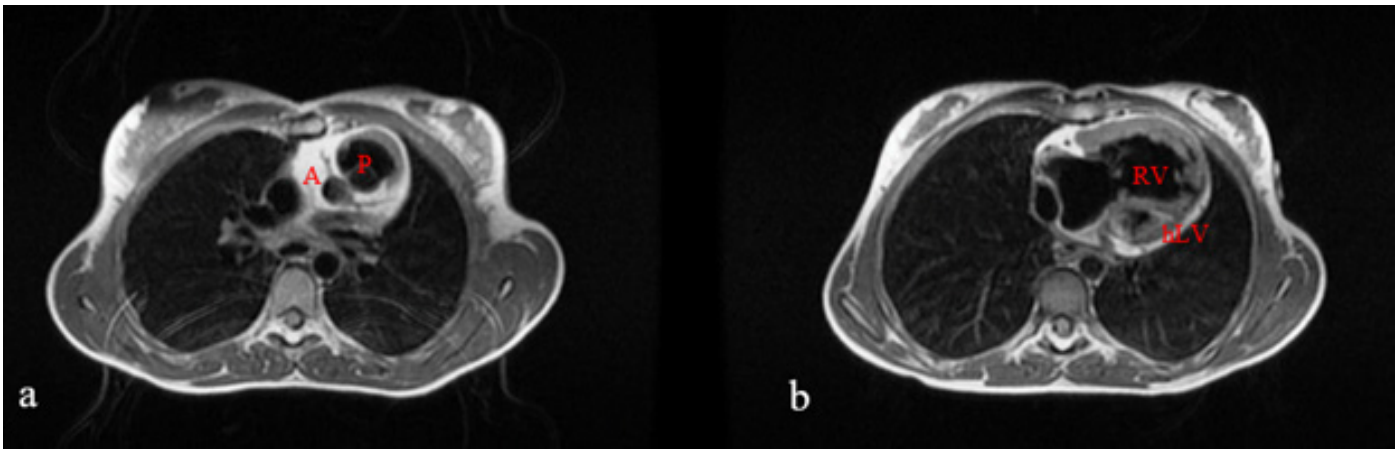

figure 7. Axial views of patient with hypoplastic left heart syndrome post palliative surgery. In (a), note the hypoplastic aorta (**A**) and larger dilated pulmonary root (**P**). In (b) the enlarged RV with hypertrophy (**RV**) is shown in contrast to the hypoplastic LV (**hLV**).

anatomic imaging, measurement of cardiac chamber volumes, determination of both systolic and diastolic function of the ventricles, shunt ratios, tissue characteristics of the myocardium, regional wall motion abnormalities, flow analysis, and myocardial perfusion and viability. This plethora of diagnostic data obtained with CMR explains the popularity of this imaging modality. Advancements in computer processing power and the creation of various imaging techniques have propelled CMR to the forefront of high-quality cardiac imaging and thus, resultant high-quality cardiac care.

The anatomic images that are obtained with CMR can be reviewed, analyzed, and reconstructed in a variety of body planes. These images can also be reconstructed in a three-dimensional format and then rotated in any direction to further enhance understanding of the anatomic features.

Using different methods of CMR imaging can result in obtaining cineangiographic pictures of the heart in motion. From this, ventricular systolic and diastolic function can be readily assessed. Again, using a different CMR technique, analysis of flow within the cardiac chambers, across cardiac valves, and within the great vessels of the heart can be visualized, measured and analyzed. This is particularly helpful for stenotic vessels, stenotic or insufficient cardiac valves, and in the analysis of shunt ratios. In previous years, this could only be achieved by invasive cardiac catheterization.

Finally, but not in the least, different imaging protocols can result in analysis of the tissue characteristics of the heart. CMR can determine whether or not there is myocardial edema, myocardial inflammation or myocardial scaring. This information can then be applied to patient diagnosis, treatment and prognostication.

myocardium assessment

CMR is the gold standard for noninvasive assessment of the myocardium. Two main types of imaging sequences, T1-weighted and T2-weighted scans, make this possible. Myocardium, like all tissues, has different T1 and T2 relaxation times after it is exposed to a radiofrequency impulse from the MRI scanner. Abnormal myocardium has abnormal T1 and T2 relaxation times. In most diseases of the myocardium, relaxation times are increased. T1 can be increased by many things including intracellular and extracellular edema, vasodilation, hyperemia, and the expansion of the extracellular space from necrosis and/or fibrosis. On the other hand, T2 is primarily increased by edema.

For many years, one of the most useful and well-studied T1-weighted imaging sequences has been late gadolinium enhancement (LGE), also known as delayed myocardial enhancement. It has been the reference standard for the noninvasive assessment of myocardial viability for the past 20 years. It has also been validated on several occasions against histologic studies.

What is gadolinium? Gadolinium is a biologically inert macromolecule that is unable to cross the intact cell membrane. Therefore, when injected intravenously, it distributes to the extracellular space in plasma and the interstitium. Due to gadolinium's effect of lowering relaxation times, tissue enhances, showing up as bright white on the image. Normally this enhancement occurs primarily in blood vessels that contain plasma. However, when the myocyte membrane is damaged, gadolinium enters the myocyte and enhances the myocardium (figure 8).

The basic protocol for LGE involves a bolus injection of gadolinium followed by image acquisition after a 10-minute delay. Healthy myocardium washes out the gadolinium, while injured myocardium retains it and shows up bright. LGE has utility in several pediatric diseases, but the most common examples are myocarditis and cardiomyopathy. In the acute phases of these diseases, LGE indicates necrosis, whereas in the chronic phase, it indicates irreversible injury in the form of myocardial fibrosis.

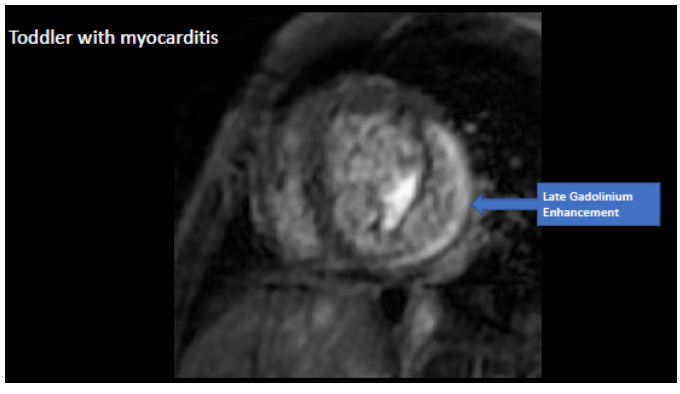

figure 8. Short axis slice of the left ventricle showing late gadolinium enhancement in a toddler with myocarditis.

T2-weighted imaging is a sensitive parameter for myocardial edema. Traditional use of T2-weighted imaging has relied on the comparison of the signal intensities of myocardium to skeletal muscle. This is semi-quantitative at best and can be unreliable in diseases that affect both the myocardium and skeletal muscle. An example of this is influenza, which can cause both a myositis and myocarditis.

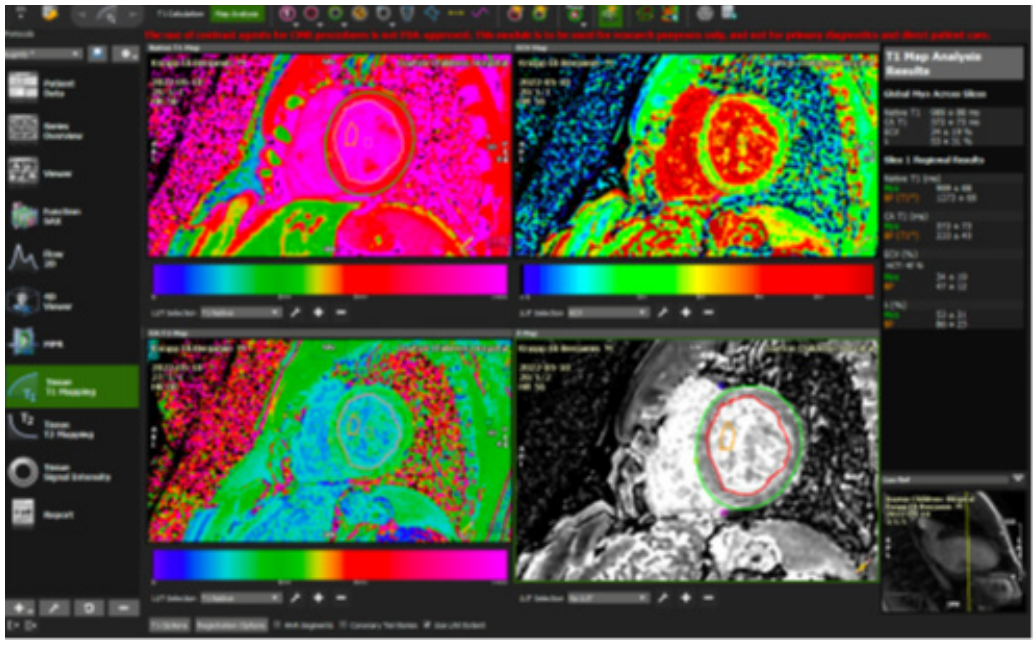

figure 9. Short axis slice demonstrating T1 and ECV in a healthy teenage patient.

T1- and T2-weighted imaging of myocardium is evidence-based in the diagnosis of myocarditis. The Lake Louise Criteria, which were published in 2009 to support the use of CMR in the diagnosis of myocarditis, target the three aspects of myocardial inflammation: edema, hyperemia and necrosis/fibrosis. They use both T1- and T2-weighted imaging modalities. The T1-weighted scans are early and late gadolinium enhancement, and the T2-weighted scan is signal intensity ratio of myocardium to skeletal muscle. In an adult study, if two out of three criteria were met, the sensitivity of diagnosing myocarditis was 72.5%, and the specificity was 96.2%. Since the original criteria were published, newer sequences were developed that have increased the sensitivity to 87.5% and the specificity to 96.2%.[2]

advances in software

Advances in MRI software have made precise quantification of T1 and T2 relaxation times possible. Extracellular volume (ECV) can also be calculated from pre- and post-contrast T1 values and hematocrit. ECV represents the percentage of the myocardium that is not myocytes. Like its derivative T1, ECV is nonspecific and can be altered by edema, necrosis and fibrosis. Parametric mapping, a post-processing technique, converts this data into a pixelated map of the myocardium where each pixel represents a different relaxation time (figure 9). The visual representation aids in the identification of segmental alterations in the myocardium.[3]

These advanced sequences have increased the sensitivity and specificity of diagnosing myocarditis, but have also shown promise in the early detection of other myocardial diseases. Duchenne muscular dystrophy (DMD), a genetic disease that results in dystrophin deficiency, inevitably leads to a dilated cardiomyopathy. All boys with the disease are treated with ACE inhibition by 10 years of age to slow the onset of cardiomyopathy.[4] LGE has been the primary mode of detecting myocardial fibrosis prior to the onset of frank systolic dysfunction and has guided heart failure medical management.[5,6,7] Studies have shown increases in T1 and ECV prior to the development of LGE in the DMD population.[8] How this will change the approach to early medical intervention is still to be determined, but the possibility of delaying this fatal cardiomyopathy is exciting.

In conclusion, cardiac MRI has been an invaluable tool in the armamentarium of the pediatric cardiologist. This relatively newer imaging modality provides anatomic, physiologic and prognostic data noninvasively. Recent advances in technology have tremendous implications for treating myocardial diseases in earlier stages. This is encouraging news for all Dayton Children's physicians and their patients.

references

1. Reid GJ, Webb GD, Barzel M, McCrindle BW, Irvine MJ, Siu SC. Estimates of life expectancy by adolescents and young adults with congenital heart disease. *J Am Coll Cardiol.* 2006;48(2): 349-355.

2. Luetkens JA, Faron A, Isaak A, et al. Comparison of original and 2018 Lake Louise criteria for diagnosis of acute myocarditis: Results of a validation cohort. *Radiol Cardiothorac Imaging*. 2019;1(3).

3. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc *Magn Reson*. 2017;19(1): 1-24.

4. Birnkrant DJ, Bushby K, Bann CM, et al; DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 2: Respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol*. 2018;17(4): 347-361.

5. Hor KN, Taylor MD, Al-Khalidi HR, et al. Prevalence and distribution of late gadolinium enhancement in a large population of patients with Duchenne muscular dystrophy: Effect of age and left ventricular systolic function. *J Cardiovasc Magn Reson*. 2013;15(1): 1-9.

6. Lamacie MM, Warman-Chardon J, Crean A, Florian A, Wahbi K. The added value of cardiac magnetic resonance in muscular dystrophies. *J Neuromuscul Dis*. 2019;6(4):389-399.

7. Tandon A, Villa CR, Hor KN, et al. Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in Duchenne muscular dystrophy. *J Am Heart Assoc.* 2015;4(4):e001338.

8. Soslow JH, Damon SM, Crum K, et al. Increased myocardial native T1 and extracellular volume in patients with Duchenne muscular dystrophy. *J Cardiovasc Magn Reson.* 2015;18(1):1-13.

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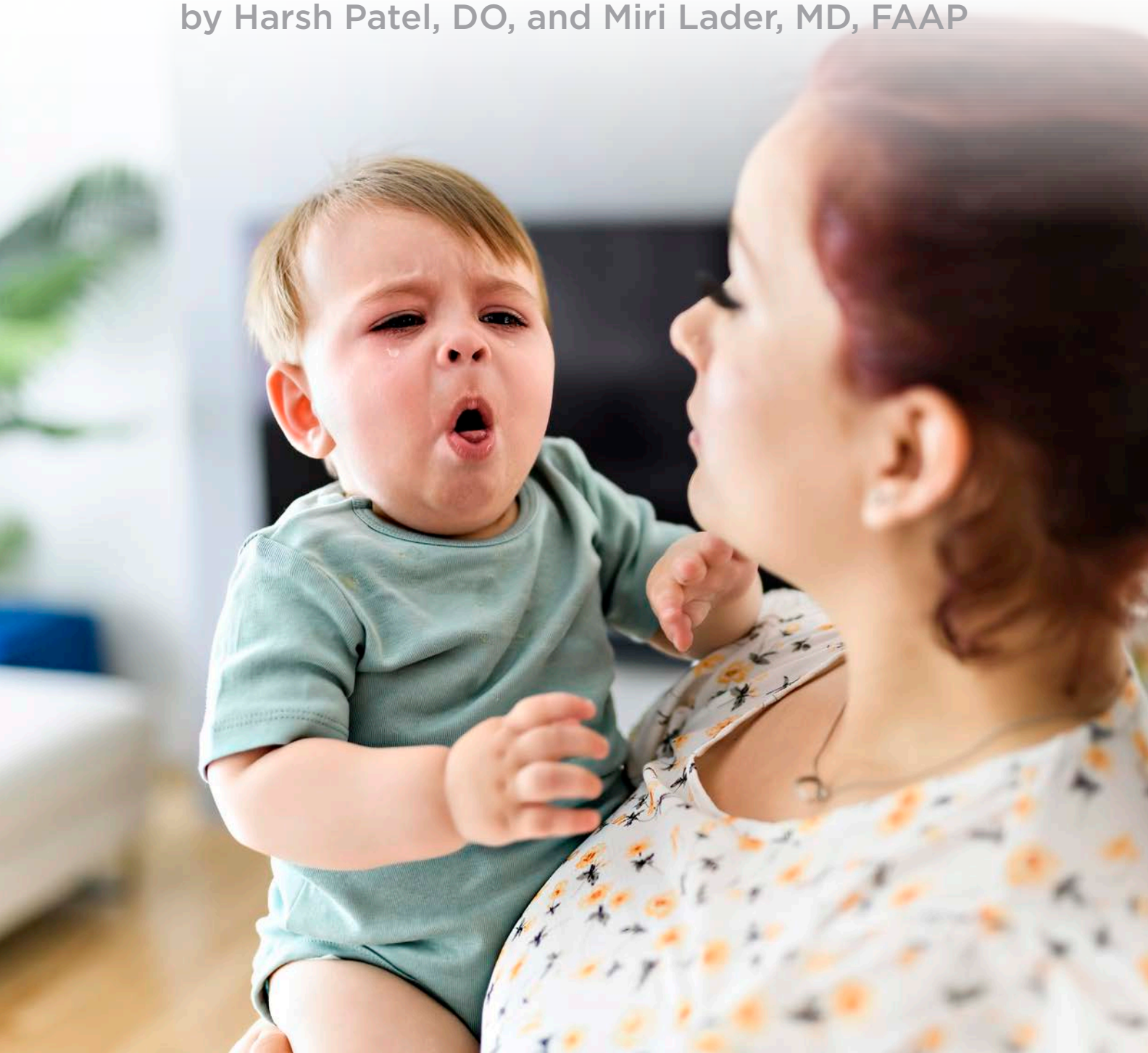
CME questions

1. **Pacemakers are an absolute contraindication for cardiac MRI.**
   - **a. True**
   - **b. False**
2. **The magnet in the MRI is turned off once daily to let the coil cool.**
   - **a. True**
   - **b. False**
3. **Gadolinium is a biologically active macromolecule that crosses an intact cell membrane.**
   - **a. True**
   - **b. False**

atypical teratoid rhabdoid tumor in an infant presenting as bronchiolitis, delayed diagnosis

by Harsh Patel, DO, and Miri Lader, MD, FAAP



learning objectives

Following the completion of this article, the reader should be able to:

1. List an appropriately broad differential diagnosis for viral bronchiolitis.
2. Identify subtle clinical findings that should prompt immediate broadening of the differential diagnosis beyond viral bronchiolitis.
3. Identify clinical indications for pursuit of imaging to rule out intracranial pathology in an infant.
4. Explain the importance of obtaining and trending head circumference, as an essential growth parameter in infants.

An atypical teratoid rhabdoid tumor (ATRT) is a very rare and aggressive central nervous system (CNS) tumor. This tumor is usually diagnosed in children under 3 years of age.[1] As a CNS tumor, it accounts for approximately 15% of embryonal tumors.[1] ATRT most commonly arises in the infratentorial region but can also arise in the supratentorial region or rarely in the spinal cord. These tumors are rapidly growing with a relatively short prodrome. Patients commonly present with symptomatic acute hydrocephalus caused by the tumor.[2] When the tumors are infratentorial, the patient presents clinically with increased intracranial pressure and cranial nerve deficits. When they are supratentorial, headaches and focal deficits are more common.[1] Sadly, up to 40% of the patients have metastatic disease at the time of their diagnosis.[1]

In the United States, ATRT accounts for 1.6% of all CNS tumors in children 19 years of age and younger from 2001 to 2010. Of those, 10.1% are diagnosed within the first year of life.[3] During this period, a billing code analysis revealed 586 cases of ATRT and an incidence rate of 0.07 per 100,000 children, with 1 year of age being the median age of diagnosis.[3,4] ATRT is diagnosed based on histological features along with the loss of SMARCB1/INI1 gene expression.[2] Given the aggressive nature of the tumor, management is very challenging. Multimodal therapy including surgery, multiagent chemotherapy, and focal radiation is usually used.[1,5] The estimated survival rate is merely 6 to 11 months after diagnosis.[5] Even when there is an initial response to the multimodal therapy, the tumors usually recur with metastasis.[5]

In this case report, we discuss a patient who initially presented with respiratory symptoms. However, when their clinical course diverged from the working diagnosis, further workup led to the identification of intracranial pathology as the underlying cause of their symptoms.

case presentation

A 4-month-old, previously healthy female presented to the emergency department (ED) with a 10-day history of increased irritability, decreased oral intake, and increased spitting up. The parents also reported six days of nasal congestion and a raspy cough. At the initial pediatrician's visit a few days prior, the patient had a negative respiratory infection disease panel (RIDP), negative COVID-19 and pertussis testing, and an unremarkable chest X-ray and urine analysis.

In the ED, the patient was in respiratory distress and had nasal congestion, rhinorrhea, vomiting, and intermittent coughing with choking episodes. Vital signs demonstrated a respiratory rate of 56 and an SpO2 of 94% on room air. The infant had increased work of breathing with subcostal retraction and accessory muscle use along with diffuse rhonchi and intermittent stridor. The patient was dehydrated with decreased energy level. She had age-appropriate alertness and a reassuring neurological examination. Laboratory testing was notable for a C-reactive protein (CRP) of 3.37 mg/dL, complete blood count (CBC) with platelets of 855 x10x3/mm3, negative RIDP and unremarkable chest X-ray. She was started

on supplemental oxygen and intravenous hydration before being admitted to the hospital with the clinical diagnosis of viral bronchiolitis.

Early during the inpatient admission, the patient had increasing oxygen requirements and required frequent suctioning and scheduled percussion/drainage treatments with respiratory therapy due to increased secretions. The child further developed recurrent apneic events associated with bradycardia, with heart rates dipping down to 70–90 beats per minute (bpm) for as long as 10–15 seconds before self-resolving. Since the clinical picture no longer fitted the expected bronchiolitis disease course, the differential diagnosis was expanded to include bacterial tracheitis and cardiac etiologies. Respiratory specimens collected via nasopharyngeal aspiration were positive for E. coli, Group B Streptococcus (GBS), and S. aureus, so the patient was started on a course of clindamycin and ceftriaxone due to concern that her escalating respiratory needs were caused by bacterial tracheitis. Echocardiography (ECHO) was said to be normal. On hospital day 2, the patient developed a new onset of brief, self-resolving horizontal eye movements that lasted approximately 2–5 seconds per episode. Following this, an electroencephalography (EEG) was obtained to rule out seizures, but despite capturing these eye movements, the study was assessed as normal.

On hospital day 3, the patient developed acute onset hypertension with a blood pressure of 164/110 mm Hg. The patient was noted to have decreased activity levels and a full fontanelle, leading to an immediate computed tomography (CT) scan and subsequent transfer to the pediatric intensive care unit (PICU). Imaging revealed a 4.3 x 4.0 x 2.9 cm right cerebellar mass and a 1.6 x 1.4 x 1.3 cm right insular cortex mass with obstructive hydrocephalus and compression/mass effect on adjacent brainstem tissue (figures 1a and 1b). The patient was electively intubated for magnetic resonance imaging (MRI) of the head, which showed a 4.1 x 3.1 x 3.5 cm tumor in the inferior aspect of the posterior fossa suspected to be arising from the medulla rather than the cerebellum and encasing the right vertebral artery (figure 1c). The second tumor, arising from the temporal lobe near the posterior aspect of the right sylvian fissure, was measured at 1.8 x 1.4 x 1.5 cm. Again, there was marked hydrocephalus with periventricular T2 prolongation compatible with transependymal flow. T2 MRI spine was also

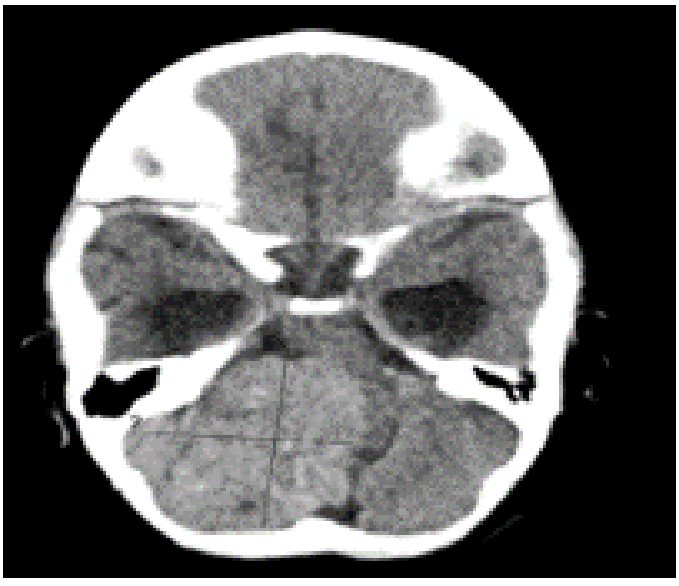


figure 1a. CT head without IV contrast; shows a 4.3 x 4 x 2.9 cm heterogeneous but hyperdense mass centered in the inferior aspect of the right cerebellar hemisphere. Along with the mass effect on the adjacent brainstem.

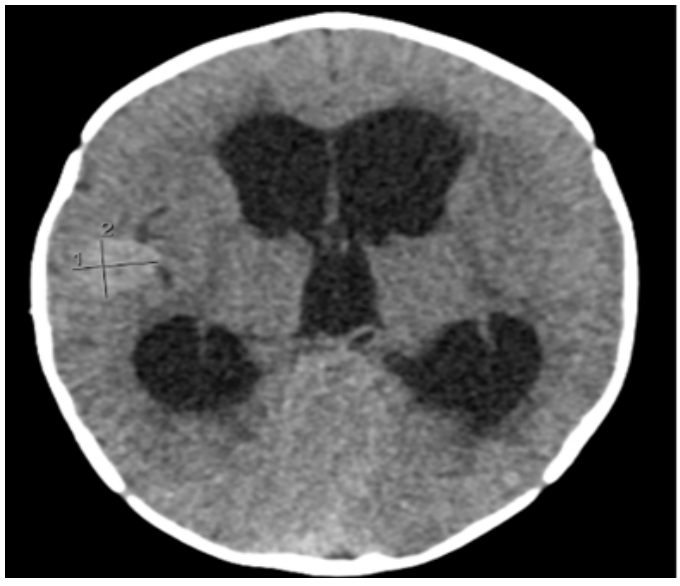


figure 1b. CT head without IV contrast; shows a hyperdense mass in the region of the right insular cortex measuring about 1.6 x 1.4 x 1.3 cm and ventricular system dilation.

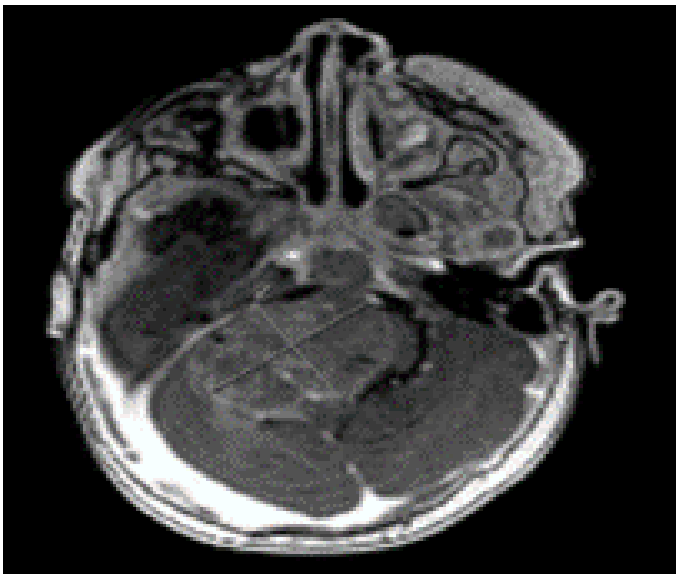


figure 1c. Initial MRI brain (Axial T1); shows a 4.1 x 3.1 x 3.5 cm posterior fossa tumor arising from the medulla rather, although difficult to be certain, encasing the right vertebral artery.

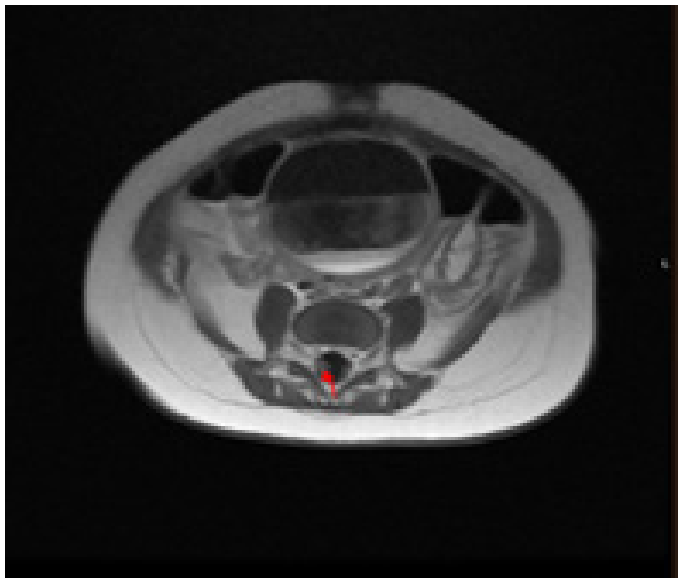


figure 1d. Initial MRI spine (Axial T1); arrow shows suspected leptomeningeal metastases.

obtained, which revealed irregular enhancement along the surface of the cord and cauda equina, along with small nodular foci in the distal end of the thecal sac suspicious for leptomeningeal metastases (figure 1d). A ventriculoperitoneal (VP) shunt was placed the next day to address the obstructive hydrocephalus.

figure 1a. CT head without IV contrast; shows a 4.3 x 4 x 2.9 cm heterogeneous but hyperdense mass centered in the inferior aspect of the right cerebellar hemisphere. Along with the mass effect on the adjacent brainstem.
figure 1b. CT head without IV contrast; shows a hyperdense mass in the region of the right insular cortex measuring about 1.6 x 1.4 x 1.3 cm and ventricular system dilation.

figure 1c. Initial MRI brain (Axial T1);

shows a 4.1 x 3.1 x 3.5 cm posterior fossa tumor arising from the medulla rather, although difficult to be certain, encasing the right vertebral artery.
figure 1d. Initial MRI spine (Axial T1); arrow shows suspected leptomeningeal metastases.

For surgical planning, a repeat brain MRI performed four days after the initial images demonstrated significant growth of the large tumor (figure 2a), now measuring 4.9 x 3.6 x 3.9 cm (compared to initial 4.1 x 3.1 x 3.5 cm [figure 2b]). There was also noted growth in smaller masses previously identified on imaging and new lesions suspicious for further metastasis.

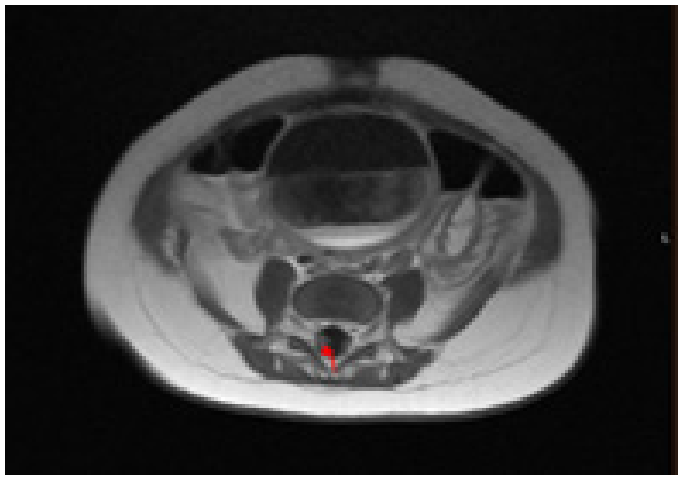


figure 2a. Repeat MRI brain (Sagittal Reformat) four days later, demonstrating growth in posterior fossa tumor.

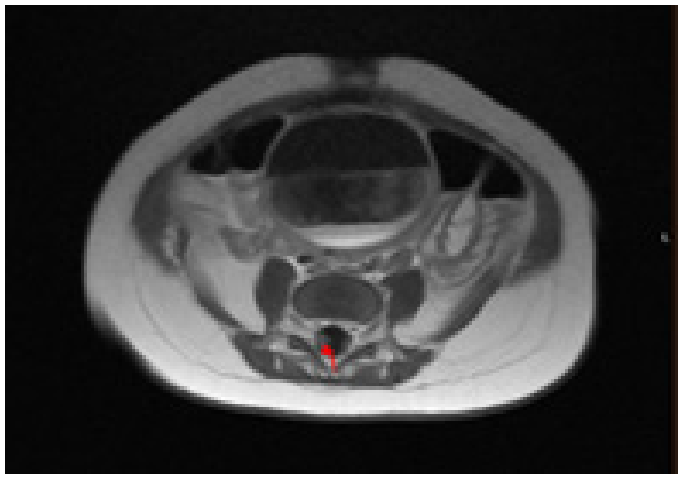


figure 2b. Initial MRI brain (Sagittal Reformat).

Following this second MRI, a biopsy of the right temporal lobe was obtained. Microscopic examination showed a highly cellular malignant neoplasm composed of sheets of medium-to-large-sized cells with round to oval vesicular nuclei and prominent nucleoli. Immunoreactivity for INI1 was lost in tumor cells, and the mass was characterized as atypical teratoid rhabdoid tumor, WHO grade IV.

Two days after the biopsy, the patient developed seizures that persisted despite treatment with lorazepam, phenobarbital, midazolam and fosphenytoin. After consultation with the oncology, neurosurgery, and palliative care teams, the patient's parents elected not to pursue chemotherapy due to the patient's poor prognosis and the side-effect profile of such therapy. Per the parents' request, all aggressive therapies were ceased, including mechanical ventilation and other life-sustaining support. The patient was continued on a midazolam IV drip to help control seizures. Subsequently, the patient was extubated on hospital day 14, and the time of death was declared 42 minutes later.

discussion

An ATRT is usually associated with biallelic inactivation of the SMARCB1 gene on chromosome 22, with up to a third of patients possessing a germline mutation.[5] The SMARCB1 protein is a subunit protein of the SWI/SNF ATP-dependent chromatin remodeling complex, which acts as a potent tumor suppressor.[6] The inactivation of this tumor suppressor gene can be detected with the loss of INI1 nuclear staining on histology. Rare cases (<5%) are associated with the SMARCB4 gene, which also plays a role in the SWI/SNF chromatin remodeling complex.[1,5,7] Our patient's tumor sample was nonreactive for INI1, and further workup showed that they were negative for a germline mutation, meaning she had a biallelic inactivation of the gene.

The presenting symptoms of intracranial pathology are specific to the tumor's location and any secondary insults caused by it, such as obstructive hydrocephalus. In infancy, those with posterior fossa tumors commonly present with lethargy, failure to thrive, and irritability.[5] You can also see clinical signs including an enlarging head circumference, bulging fontanelle, and cranial nerve dysfunction causing head tilt.[5] While our patient presented with poor feeding, increased irritability and poor oral intake, which could be attributed to an intracranial pathology, the patient also had respiratory findings including nasal congestion and a raspy cough that initially suggested bronchiolitis. The patient's head circumference obtained on admission was at the 49.^{3} percentile; between that normal measurement and their soft fontanelle, intracranial processes were considered lower on the initial differential diagnosis.

Further, their fontanelle was open and soft, therefore, ruling out papilledema was not indicated at the time of presentation and, thus that component of the eye exam was not performed. Strikingly, their neurological deterioration occurred rapidly, with the development of nystagmus starting on hospital day 2, subsequently followed by a newly bulging fontanelle on hospital day 3. The second MRI brain revealed an increase in tumor size in just four days, which is, in fact, consistent with the rapid progression of the ATRT tumor.

Our patient initially presented with signs and symptoms of viral bronchiolitis in the early winter months. Since bronchiolitis is a common diagnosis in this age group, especially during this season, we initially did not pursue additional testing. Pursuing an intracranial pathology was not indicated with a soft fontanelle and a head circumference on the same curve as their birth head circumference per electronic medical record (EMR). As the patient progressed through their hospital stay, the infant's symptoms did not follow the typical bronchiolitis disease pattern. We did not anchor on the bronchiolitis diagnosis when it no longer fitted the clinical picture, yet the intracranial process beyond seizures was not thoroughly ruled out. By slowly and methodically expanding our differential diagnosis, we were able to make the diagnosis of ATRT before the tumor grew large enough to cause herniation on the general medicine floor. The atypical presentation delayed our diagnosis by hours to days, but given the disease's poor prognosis and terminal nature, it likely would not have changed the patient's outcome.

Common mimickers of bronchiolitis which should be considered while composing differential diagnoses on these infants include gastroesophageal reflux (GER), congenital malformations of the airway or cardiovascular system, heart failure for any reason, asthma, aspiration of a foreign body.[8]

It is challenging to know if the patient's presenting respiratory symptoms were due to a viral process (a pathogen we were unable to identify with serial testing), or secondary to the tumor itself. It is questionable whether the patient's ability to control normal secretions was compromised at the time of presentation, despite an otherwise normal neurological exam. If indeed the clinically undetectable tumor was impairing the patient's ability to control secretions, this would potentially explain the respiratory symptoms. In addition, the patient would have been at elevated risk for aspiration, explaining the increasing need for oxygen support and required percussion/drainage intervention.

conclusion

Given our patient's presenting clinical picture and the time of year in which viral bronchiolitis is prevalent, intracranial pathology was not at the top of the differential diagnosis list. However, it is noteworthy that the patient did present with poor feeding, vomiting, and decreased energy level, which should have prompted concern for intracranial process sooner than it did. In addition, a fundoscopic eye exam on an infant is not easily accomplished in the ED, but it would likely have been normal on presentation due to the soft fontanelle. Nevertheless, as neurological symptoms developed, further workup specific to the intracranial space and not just limited to electroactivity, may have more quickly helped to make the diagnosis in this patient. Unfortunately, it is quite unlikely that this would have changed the outcome.

ethics statement

The patient's family gave explicit and informed consent to have their child's information published in this case report without using the patient's name and with every reasonable attempt made to ensure anonymity. The family was made aware that this information may be published in an online journal or in print, aimed mainly at education of health care professionals but may be seen by non-physicians.

references

1. Malbari F. Pediatric neuro-oncology. *Neurol Clin.* 2021;39(3):829-845. doi:10.1016/j.ncl.2021.04.005

2. Nesvick CL, Nageswara Rao AA, Raghunathan A, Biegel JA, Daniels DJ. Case-based review: Atypical teratoid/rhabdoid tumor. *Neuro-Oncol Pract.* 2019;6(3):163-178. doi:10.1093/nop/npy037

3. Ostrom QT, Chen Y, de Blank PM, et al. The descriptive epidemiology of atypical teratoid/rhabdoid tumors in the United States, 2001-2010. *Neuro-Oncol*. 2014; 16(10):1392-1399. doi:10.1093/neuonc/nou090

4. Lau CS, Mahendraraj K, Chamberlain RS. Atypical teratoid rhabdoid tumors: A population-based clinical outcomes study involving 174 patients from the Surveillance, Epidemiology, and End Results database (1973-2010). *Cancer Manag Res.* 2015;7:301-309. doi:10.2147/CMAR.S88561

5. Kieran MW, Chi SN, Manley PE, Green AL. Tumors of the brain and spinal cord. In: Orkin SH, Nathan DG, Ginsburg D, et al. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Elsevier Inc.; 2015:1779-1885. Accessed February 26, 2022. https://www-clinicalkey-com.proxy.library.ohio.edu/#!/content/book/3-s2.0-B9781455754144000577

6. Kohashi K, Oda Y. Oncogenic roles of SMARCB1/INI1 and its deficient tumors. *Cancer Sci*. 2017;108(4):547-552. https://doi.org/10.1111/cas.13173

7. Ho B, Johann PD, Grabovska Y, et al. Molecular subgrouping of atypical teratoid/rhabdoid tumors – A reinvestigation and current consensus. *Neuro-Oncol.* 2020;22(5):613-624. https://doi.org/10.1093/neuonc/noz235

8. Erickson EN, Bhakta RT, Mendez MD. Pediatric bronchiolitis. [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519506/

authors

Harsh Patel, DO

A well-established Ohioan, Harsh Patel, DO, grew up in Cincinnati. He graduated from Northern Kentucky University in Highland Heights, Kentucky, and attended medical school at Ohio University – Heritage College of Osteopathic Medicine in Athens. He is currently a first-year resident at Dayton Children's and has a career interest in intensive care.

Miri Lader, MD, FAAP

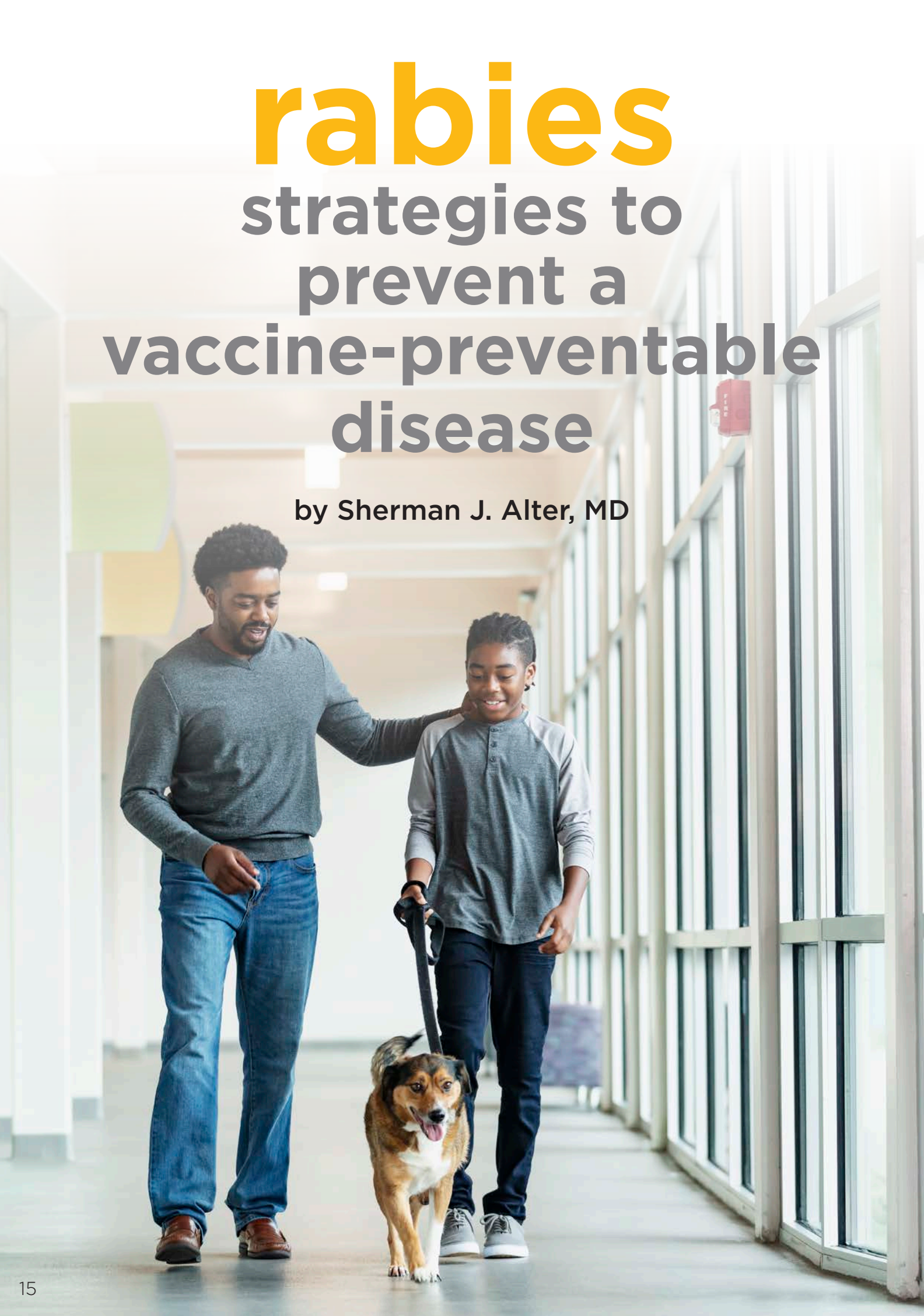
Native of New York City, Miri Lader, MD, FAAP, moved to Dayton in 2009 to attend Wright State University Boonshoft School of Medicine (WSU-BSOM). After graduation, she completed her pediatric residency at Dayton Children's. After serving as chief resident, Dr. Lader continued at Dayton Children's as a hospitalist. In 2021, she was named director of medical student education in the department of pediatrics, WSU-BSOM.

CME questions

4. Which of these diagnoses needs to be considered on the differential for viral bronchiolitis?
   a. Gastroesophageal reflux (GER)
   b. Congenital malformations of the airway
   c. Congenital heart disease
   d. Acute bronchospasm
   e. All of the above
5. A 6-month-old baby presents to the clinic in respiratory distress with increased use of accessory muscles and an SpO2 of 91%. She is afebrile and well-hydrated on exam. After nasal suctioning SpO2 is up to 98% while breastfeeding, and her breathing is noted to be calm and easy. What is the best next step in caring for this patient?
   a. Immediate referral to the emergency department for further workup.
   b. Observe in office for six hours as she may worsen in that time frame.
   c. Start supplemental oxygen, obtain a chest radiograph, and swab nose for respiratory viral panel.
   d. Reassure parents, review return precautions, and discuss symptoms that should prompt bringing baby to ED. Then discharge home with supportive care.
6. What are the three vital sign changes seen in the setting of increased interacranial pressure (Cushing's triad)?
   a. Elevated blood pressure, decreased heart rate, irregular respirations
   b. Low blood pressure, rapid heart rate, complete loss of respiratory drive
   c. Widening pulse pressure, rapid heart rate, irregular respirations
   d. No changes to vital signs associated with increased intracranial pressure in infants whose fontanelle is still patent

rabies
strategies to prevent a vaccine-preventable disease

by Sherman J. Alter, MD



learning objectives

Following the completion of this article, the reader should be able to:

1. List the primary reservoir animals responsible for maintaining rabies in the United States.
2. Discuss the approach to prevention of rabies infection using postexposure prophylaxis.
3. Review strategies to reduce both the risk of rabies in animals and the possibility of transmission to humans.

Rabies is a viral disease that occurs in more than 150 countries. It causes tens of thousands of deaths every year, mainly in Asia and Africa, 40% of which are to children under 15 years of age.[1] In the United States, the number of human rabies cases has been dramatically reduced through successful canine rabies control programs, vaccination of domestic animals and wildlife, timely administration of vaccine postexposure prophylaxis (PEP), and education both of the public and of health care professionals. Despite these advances, human rabies exposures remain relatively common because of interactions with wildlife and unvaccinated domestic animals. An estimated 60,000 people are treated for rabies exposure annually in the United States.[2] While rare, human rabies cases in the United States do occur primarily associated with bat exposures or exposure to rabid dogs in countries where canine rabies is still endemic.

pathophysiology

Rabies is an acute, fatal, progressive encephalitis caused by a zoonotic infection with rabies virus, an RNA virus that is part of the genus Lyssavirus.[3] The virus is typically transmitted through the saliva of a rabid animal, both domestic and wild. It may be transmitted through exposure to nervous tissue. Other uncommon routes of infection include inhalation of the virus in aerosolized form, ingestion, transplacental transmission, and rarely through organ transplantation. Following a bite from a rabid animal, the virus travels from the bite wound into the peripheral nervous system. The virus then traverses to the brain where it replicates and further disseminates to various tissues, including salivary glands, where the transmission cycle repeats itself. The incubation period averages one to three months but may extend up to one year.

clinical presentation

Once clinical symptoms appear, rabies is virtually 100% fatal. Persons infected with the rabies virus typically present with a prodromal illness consisting of nonspecific or flu-like symptoms—myalgias, gastrointestinal symptoms and fever. Infected individuals then develop increasing anxiety, radicular pain, dysesthesia or pruritus, agitation, change in mentation, and dysautonomia. Patients may exhibit hydrophobia or aerophobia, where spasms occur following stimuli such as swallowing liquids. Paralysis may also develop. Apnea, coma and cardiopulmonary failure occur prior to death.[3]

epidemiology

There is great diversity in the global epidemiology of rabies and distribution of rabies virus reservoir species.[4,5] Rabies is present on all continents except Antarctica, with over 95% of human deaths occurring in Asia and Africa. Unfortunately, global rabies cases are rarely reported, and registered numbers differ greatly from the estimated burden. Children between the age of 5 and 14 years are frequent victims. Worldwide, canine rabies presents the greatest health risk with >99% of human rabies deaths

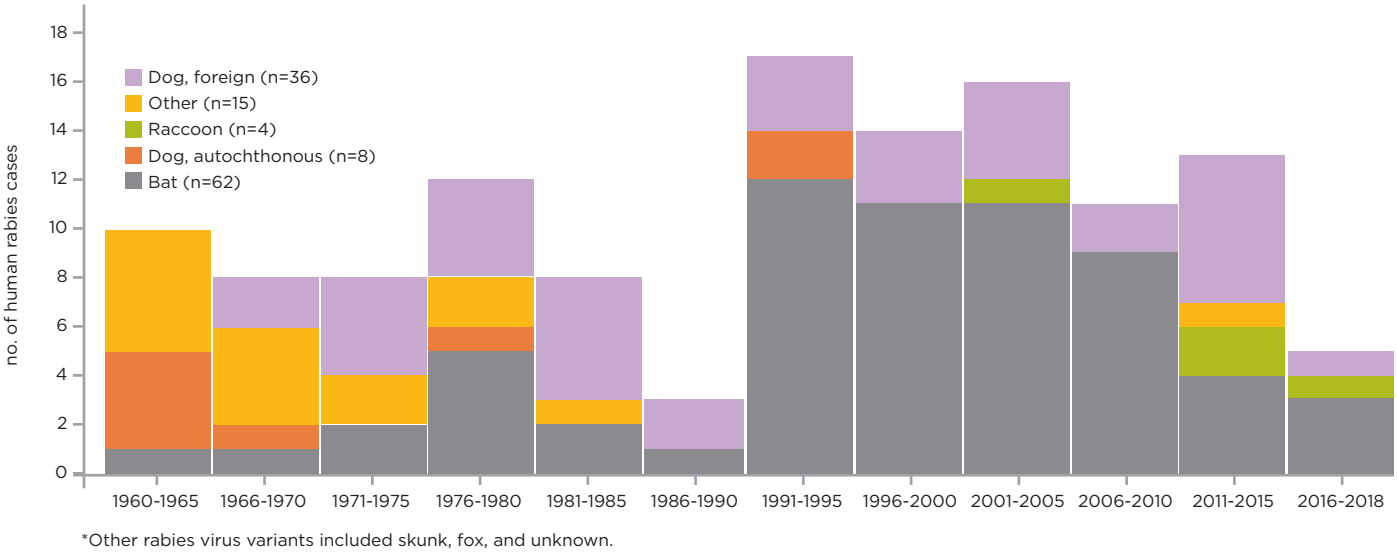


figure 1. Rabies virus variants* associated with human rabies cases (N=125) – United States, 1960-2018.[2]

acquired from the bite of an infected dog. In the United States, however, national canine rabies control efforts that began in the early 1940s resulted in the elimination of canine rabies by the late 1970s (figure 1).

Though at least 30 reservoir species have been identified, wildlife account for >90% of all rabid animals in the United States. Infected animals are seen in all states except Hawaii. While any mammal may be susceptible to rabies, certain primary reservoir species are responsible for maintaining rabies. These include bats (multiple species), raccoons, skunks, gray and arctic foxes, coyotes, bobcats, and mongooses (in Puerto Rico). Wild animals accounted for 92.7% of reported cases of rabies in 2018.

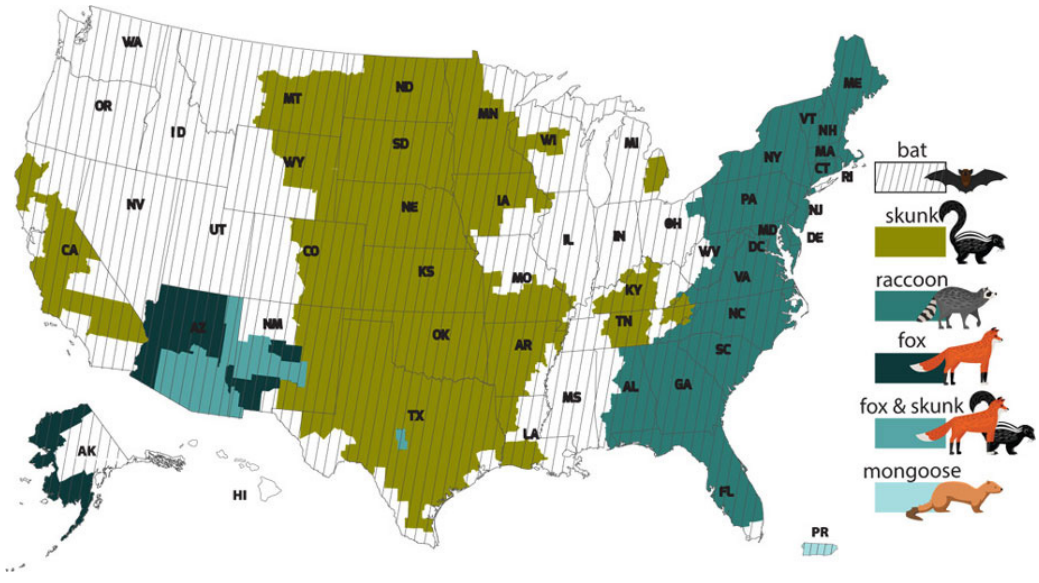


figure 2. Wildlife rabies variants across the United States. CDC.

Bats were the most frequently reported rabid wildlife species (33% of all animal cases during 2018), followed by raccoons (30.3%), skunks (20.3%), and foxes (7.2%). Viral circulation occurs in these reservoir species and spreads within geographically distinct regions where interspecies transmission readily ensues (figure 2).

Conversely, bats have a quite broad geographic distribution with frequent transmission of the virus among closely related bat species. Cattle, dogs, cats, ferrets and other animals can on occasion be infected (typically after contact with rabid wildlife). Small rodents (squirrels, hamsters, guinea pigs, gerbils, chipmunks, mice and rats) and lagomorphs (rabbits, hares and pikas) almost never are found to be infected with rabies and have not been known to transmit rabies to humans.[4]

management of persons following bite wounds

The initial and perhaps most difficult task in preventing rabies is identifying an at-risk exposure. Delivery of passive immune protection (rabies immune globulin) and active inducement of the immune response (rabies vaccine) are critical to defend against rabies viral infection following animal bites. Postexposure prophylaxis (PEP) for rabies initiated as soon as possible is recommended for all persons bitten by domestic animals that are suspected to be rabid, or by bats or wild animals unless laboratory tests prove that the animal does not have rabies.[3] PEP is not necessary if an animal has already been tested and determined not to be rabid. If PEP has been initiated and subsequent testing shows that the exposing animal was not rabid, PEP may be discontinued. Many times, additional factors need consideration when determining if PEP is warranted. An unprovoked attack by an animal (typically a dog or cat in the United States) is more suggestive of a rabid animal than a bite that occurs during attempts to feed or handle an animal. Properly immunized animals have only a minimal

chance of developing rabies. However, in rare instances, rabies has developed in properly immunized animals.

Postexposure prophylaxis must be initiated immediately following exposure to either wild animals or to any animal displaying clinical signs of rabies. Local and state health departments should be consulted for guidance. Dogs, cats and ferrets may be observed for 10 days if healthy and are available to observe. If an animal shows clinical signs of rabies, an exposed person should immediately begin PEP. If the animal does not die or exhibit abnormal behavior during the 10-day observation period after the bite, do not administer PEP. If treatment has already been started, it can be discontinued. An available wild animal should be euthanized at once and tissue forwarded for postmortem rabies testing (consult local and state health departments for guidance). In this this situation, the exposed person need not receive PEP if the result of rapid examination of the animal's brain by immunofluorescent testing is negative for rabies virus infection.

PEP is recommended for people who report an open wound, scratch or mucous membrane that has been contaminated with saliva or other potentially infectious material (e.g., brain tissue) from a rabid animal. Contact with a rabid animal, such as petting, or contact with blood, urine or feces of a rabid animal does not constitute an exposure. While contact with bats, including bites, is typically recognized by the recipient because of the bite force impact, many species of bats in the United States have small teeth and might not leave observable puncture marks.[6] Given the high risk for rabies transmission from bats, rabies PEP is recommended after any bat contact when a bite or scratch cannot be ruled out. Certain circumstances of contact with a bat may hinder accurate recall (e.g., a bat in a room of a deeply sleeping or medicated person or a previously unattended child, such as an infant or toddler who cannot reliably communicate about a potential bite). PEP is indicated, following proper risk assessment, for such situations in which a bat physically is present in the same room if a bite or mucous membrane exposure cannot reliably be ruled out, unless prompt testing of the bat has excluded rabies virus infection.

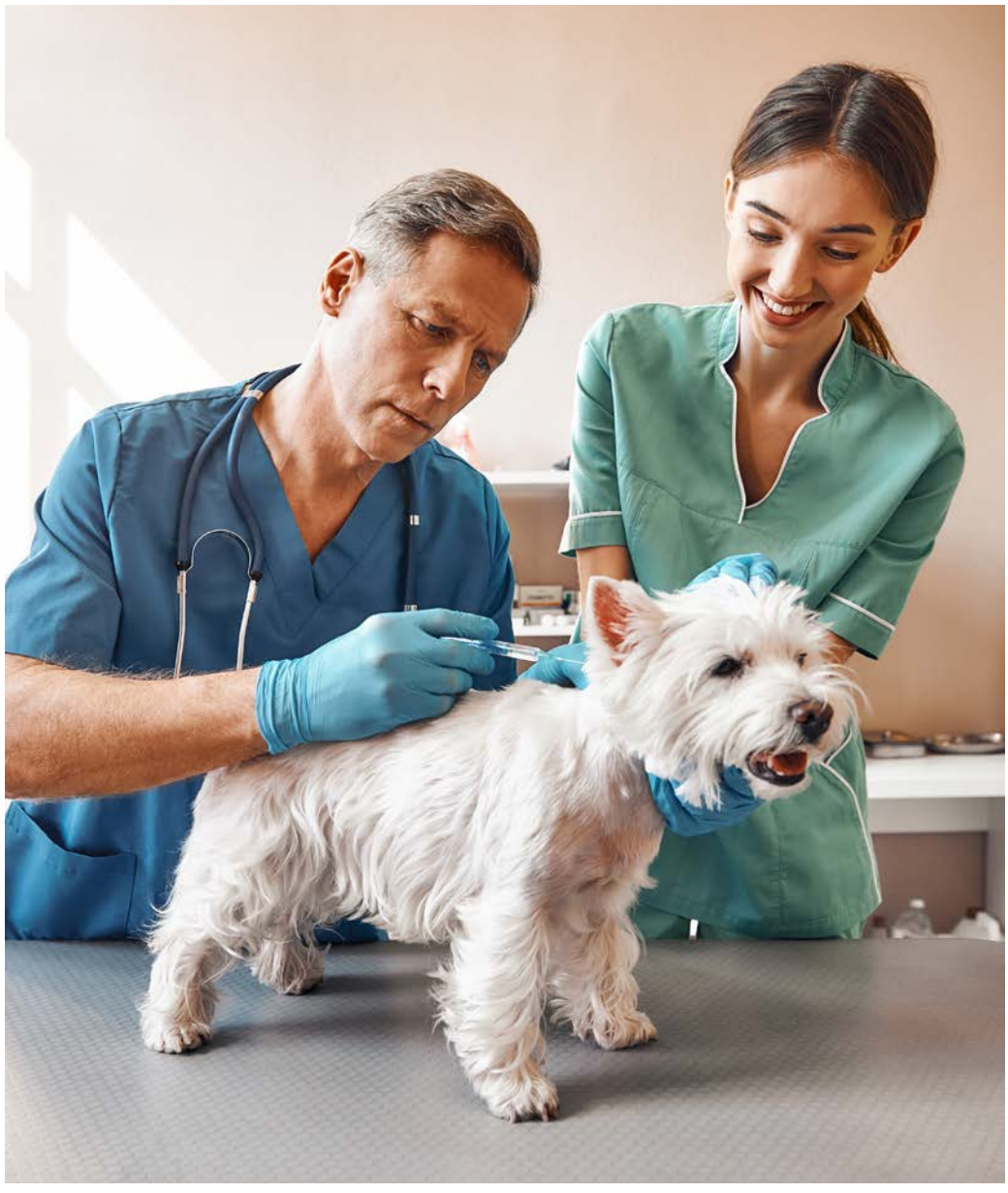
follow these guidelines[3,4]

- The immediate objective of PEP is to prevent virus from entering neural tissue. Because virus may remain localized to the area of the bite for a variable time, prompt and thorough washing of all bite wounds with soap and water is perhaps the most effective measure for preventing rabies. Quaternary ammonium compounds (such as benzalkonium chloride) are not considered superior to soap.
- Assess need for tetanus prophylaxis and consider measures to control bacterial infection.
- A bite wound can be loosely sutured but only after human rabies immune globulin (RIG) is administered. For severe facial wounds, which often also are infected with bacteria, improved cosmesis results from single sutures, widely placed, several hours after local instillation of RIG (see below), followed by plastic surgery days later.
- After wound care is completed, concurrent use of RIG and rabies vaccine is optimal. Persons who previously completed a rabies vaccination regimen (pre- or postexposure) with a cell culture vaccine or people who have been vaccinated with other types of rabies vaccines and have previously had a documented rabies virus-neutralizing antibody titer need only receive vaccine.
- Prophylaxis should begin as soon as possible after exposure, ideally within 24 hours. A delay of several days or more, however, may not compromise effectiveness. Prophylaxis should be initiated if reasonably indicated, regardless of the interval between exposure and initiation of therapy. Physicians should obtain expert counsel from their state or local health departments when uncertain about administering these products.
- Human diploid cell vaccine (HDCV) and purified chicken embryo cell vaccine (PCECV) are licensed in the United States.7 In a previously unvaccinated person, a 1.0-mL dose of vaccine is injected intramuscularly (IM) in the deltoid area on the first day of PEP (day 0), and repeated on days 3, 7 and 14 after the first dose (4-dose regimen). Since virus-neutralizing antibody responses in adults who received vaccine in the gluteal area sometimes have been less than in those who received vaccine in the deltoid muscle, the deltoid site always should be used for rabies vaccine. The anterolateral thigh is the appropriate site for infants and young children. Vaccines licensed in the United States are not approved for intradermal administration in the postexposure setting. Every attempt should be made to adhere to the recommended vaccination schedule (to this end, a home care program developed to facilitate timely, scheduled administration of follow-up vaccines has recently been implemented at Dayton Children's with the assistance of Children's Home Care of Dayton). Doses should not be given sooner than the minimum time interval, as lower neutralizing antibody titers may result. While delays between doses mean delayed increases in titers, with minor delays the final titers would not be lower provided the subsequent doses have the same minimum intervals between doses as in the original schedule. Adverse reactions to HDCV and PCEVC are uncommon in children.[3]
- Human rabies immune globulin (20 IU/kg of body weight) should be infiltrated around the wound(s) on day 0.3 As much as possible of the calculated dose of RIG should be injected close around and deep into the wound, taking care that it does not escape from the wound. Any remaining volume of the immune globulin should be injected intramuscularly at a site distant from the vaccine administration site. When more than one wound exists, each area should be locally infiltrated with a portion of the RIG using a separate needle and syringe. If the original calculated amount provides an insufficient volume for all the wounds, the RIG should be diluted two- to three-fold in a solution of 0.9% sodium chloride. If the site of the wound is unknown (e.g., suspected tiny bat bite wound), the entire dose should be administered intramuscularly. Do not exceed the recommended dose; too much RIG can interfere with the active production of antibody from the rabies vaccine.
- PEP in an immunocompromised person requires a 5-dose vaccination regimen (vaccine on days 0, 3, 7, 14 and 28), with one dose of RIG on day 0.
- Serologic testing to document seroconversion after administration of a rabies vaccine series usually is unnecessary except for recipients who may be immunocompromised or for people with deviations from the recommended vaccination schedule. Immune response should be assessed by performing neutralizing antibody testing seven to 14 days after administration of the final dose in the series.

prevention

Human rabies is entirely avoidable. It is a vaccine-preventable disease. Rabies vaccination of dogs and cats stands as the most important strategy to reduce both the risk of rabies in these animals and the possibility of transmission to humans. Moreover, dog vaccination reduces the need for PEP. Education on dog behavior and bite prevention for both children and adults is essential. Children must be instructed to avoid contact with stray or wild animals. Efforts should be implemented to prevent and/or remove at-risk wildlife from living near human residences (e.g., inform animal control or local public health authorities when bats build roosts within or around dwellings, securing garbage and pet food containers to decrease attraction of wild and domestic animals).

In some individuals, pre-exposure prophylaxis (PrEP) with rabies vaccine may be indicated: certain high-risk occupations (laboratory workers handling live rabies and rabies-related viruses) and those whose activities might lead to direct contact with bats (frequent exposures while spelunking) or other mammals that may be infected with rabies (animal disease control staff and wildlife rangers).[8] PrEP may be also indicated for outdoor travelers to and people living in remote, highly rabies-endemic areas with limited local access to rabies biologics. Importantly, wildlife vaccination programs have had impact in reducing human rabies in some countries.



Lastly, novel vaccines that are more immunogenic (e.g., ability to produce protective immunity after a single vaccine dose) and less costly are in late-stage pre-clinical testing or have already undergone clinical testing.[9] These newer vaccines have the potential for replacing current vaccines.

references

1. Hampson K, Coudeville L, Lembo T, et al. Estimating the global burden of endemic canine rabies. *PloS Negl Trp\op Dis.* 2015;(9):e0003709.

2. Pieracci EG, Pearson CM, Wallace RM, et al; Centers for Disease Control and Prevention (CDC). Vital signs: Trends in human rabies deaths and exposures — United States, 1938–2018. *MMWR Morb Mortal Wkly Rep.* 2019;68(23):524-528.

3. American Academy of Pediatrics. Rabies. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases.* American Academy of Pediatrics; 2021:619-627.

4. Fooks AR, Cliquet F, Finke F, et al. Rabies. *Nat Rev Dis Primers.* 2017; 3(17091). https://doi.org/10.1038/nrdp.2017.91

5. Xiaoyue M, Monroe BP, Cleaton JM, et al. Rabies surveillance in the United States during 2018. *J Am Vet Med Assoc.* 2020;256:195–208.

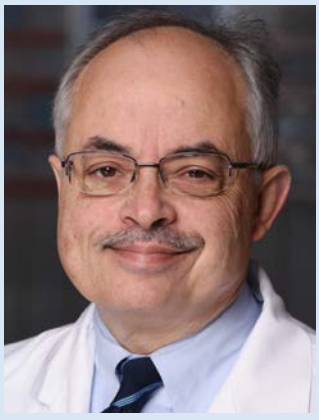
6. Blackburn D, Minhaj FS, Hammoud RA, et al; CDC. Human rabies – Texas, 2021. *MMWR Morb Mortal Wkly Rep.* 2022;71(49):1547-1549.

7. Rupprecht CE, Briggs D, Brown CM, et al; CDC. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies. *MMWR Morb Mortal Wkly Rep.* 2010;59(RR-2):1-9.

8. Rao AK, Briggs D, Moore SM, et al. Use of a modified preexposure prophylaxis vaccination schedule to prevent human rabies: Recommendations of the Advisory Committee on Immunization Practices – United States, 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71:619-627. http://dx.doi.org/10.15585/mmwr.mm7118a2

9. Fooks AR, Banyard AC, Ertl HCJ. New human rabies vaccines in the pipeline. *Vaccine.* 2019;37(Suppl 1):A140-A145.

author



Sherman Alter, MD

Formerly the division chief of infectious disease at Dayton Children's, Sherman Alter, MD, has been a member of the division of infectious disease for almost 38 years. He is professor of pediatrics at Wright State University Boonshoft School of Medicine. He continues to work in medical education interacting with learners at all levels. Dr. Alter is also the medical director of Children's Home Care of Dayton.

CME questions

7. **Worldwide, what is the most common source of human rabies?**
   a. **Bat bites**
   b. **Tiger bites**
   c. **Racoon bites**
   d. **Dog bites**
8. **What is the most effective treatment to prevent rabies after a bite?**
   a. **Human diploid cell vaccine (HCDV) 20 IU/kg in the gluteal muscle**
   b. **Three doses of chick embryo vaccine**
   c. **One dose of RIG and one dose of HDCV**
   d. **Immediate and thorough washing of a dog bite with soap and water**
9. **Two-year-old twin sisters are sleeping the same room. One cries out in the early morning that she sees something flying in their bedroom—a small bat! The father uses a broom to guide the bat out of a window. No bite wounds are seen on either child. What should be done now?**
   a. **Rabies postexposure prophylaxis is not warranted in that neither child appears to have been bitten.**
   b. **The parents should be given rabies vaccine because of the high-risk situation.**
   c. **RIG and rabies vaccine should be administered to both children.**
   d. **One dose of RIG alone should be administered to the sisters.**
10. **Rabies PEP should be considered after bites from all of the following except:**
    a. **Field mouse**
    b. **Young racoon**
    c. **Fox**
    d. **Skunk**

impact of indoor air quality on respiratory disease

by Daniel A. Evans, MD, CPE

Air quality has been a general health concern for decades. The World Health Organization published their report on the impact of environmental health on the quality of life and health outcomes in 2006, declaring that 23% of all deaths and 24% of the global disease burden are related to environmental factors.[1] Over 50 years ago, the Environmental Protection Agency (EPA) was established for the purpose of reducing air and water pollution to protect the health of the American people. The charter of this organization followed several publicized environmental disasters and the publication of Silent Spring by Rachel Carson. Her book brought to light the dangers of the widespread use of pesticides. The two specific disasters fueling the American outcry for better regulation included the oil spill onto California beaches from a Pacific oil rig, and the spontaneous ignition of the Cuyahoga River due to the chemical contaminants having been dumped into the river. When these were combined with the public concerns of the industrial smokestack and automobile exhaust output, President Richard Nixon led the establishment of the EPA.[2]

The deleterious effects of air pollution have been previously described.[3,4,5] Though Jonathan Samet and John Spengler began calling awareness to the problem of indoor air pollution in the early 1990s,[6] indoor air quality has just recently been capturing a greater attention over the past decade. Momentum has increased because of studies that estimated children spend 90% of their time indoors.[7] Indoor air quality is now understood not to simply reflect the external environment. Key to the establishment of the notable difference between outdoor and indoor air quality was the energy crisis of the 1970s that motivated housing manufacturing to develop domicile constructions that were much "tighter," decreasing air exchange rates within the homes.[8] Studies indicated that an air exchange rate of >1 exchange/hour equilibrated the indoor air quality to more closely reflect the outdoor air quality and significantly reduced the impact that indoor air quality has on health.[9] Therefore, what is experienced inside may be quite different from what is going on outside. When it is considered that children on the average take over 20,000 breaths a day, then it is not surprising that the indoor environment is important in maintaining the health of patients, especially those with asthma.

Many sources contribute to indoor air pollution within homes. Outside air pollutants can make their way into the home, but often the indoor environment contains higher concentrations of allergens, endotoxins, nitrogen dioxide, products of combustion, volatile organic compounds, ozone and particulate matter.[10,11] Humidity, dampness and temperature within the home environment have also been determined to be important to the health of patients with asthma.[12] Other activities that directly impact the development of poor indoor air quality have been described. Simple everyday activities such as cooking, smoking, fireplace/wood-burning stove use, candle

learning objectives

Following the completion of this article, the reader should be able to:

1. Discuss the history of the concerns for air quality.
2. Determine why indoor air quality differs from outdoor air quality and why that matters for respiratory health.
3. Cite specific contributors to poor indoor air quality.

burning and vacuum cleaners have all been implicated.[13,14,15,16,17]

Particulate matter (PM) is a primary contributor to poor indoor air quality. PM is a mixture of inorganic and organic chemicals that vary in size. Sources of PM within the home include cigarette smoking, cooking, wood stoves and wood-burning fireplaces, burning incense or candles, pets, cleaning the home and the movement of people.[11] PM has been analyzed by size of particle, specifically categorizing particles as either <2.5 micrometers or <10 micrometers in diameter with standard concentrations having been established.[18] Higher concentrations of PM have been associated with increased asthma symptoms.[18,19]

Nitrogen dioxide (NO2) is produced primarily by the combustion of gas appliances and kerosene heaters.[20,21] A review of 141 studies from 29 countries by Vardoulakis and associates described the association between elevated NO2 concentrations with increased asthma symptoms in children.11 A recent study published by Gruenwald and associates calculated the population attributable fraction (PAF) from 27 manuscripts. The PAF indicates the proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario. From their calculations, the exposure to gas cooktops within the homes may account for 12.7% of the current asthma in the United States. The authors caution that mitigation studies would be necessary to validate their assessment.[22]

Ozone, according to the Environmental Protection Agency, is a known respiratory irritant that can cause damage to the lungs.[23] Gent and associates have shown that even low levels of ozone contributed to the exacerbation of persistent asthma symptoms.[24] Weschler has suggested that indoor ozone concentrations, mainly reflecting outdoor concentrations, may exert their deleterious health effects by the interaction with certain indoor chemicals.[25] Volatile organic compounds (VOCs) such as benzene and toluene have also been shown to have some correlation with respiratory symptoms.[26] Data of formaldehyde's role in the development or exacerbation of asthma has been mixed. Rumchev and associates described an increased risk for the development of asthma in children exposed to formaldehyde[27] while Ezratty and colleagues reported a protective effect against asthma responsiveness to allergens in exposure to even higher concentrations of formaldehyde.[28] Polycyclic aromatic hydrocarbons (PAHs) have been credited as contributors to asthma symptoms and are primarily derived from cigarette smoking.[29] Likewise, carbon monoxide and sulfur dioxide exposures have been correlated with a decline in pulmonary function in adults with asthma.[30] The above summary indicates that there are a number of components contributing to poor indoor air quality that have been associated with respiratory symptoms possibly complicating the control of asthma.

There are multiple variables beyond the composition of the air contributing to poor indoor air quality that can complicate the health of children with asthma. Though the indoor air quality does not always reflect the outdoor air quality, still the location of the home within an urban or rural setting can play a significant role in PM, NO2 and VOC concentrations.[31,32,33,34,35,36] Dampness has been shown to potentiate the development of mold allergens, dust mite allergens and endotoxins[12] aggravating the chronic inflammation of the airways of children with asthma. Other factors include the tightness of the construction limiting the air exchange rate, the quality of ventilation, the opening of windows, the source of heat and the presence of attached garages.[11] This says nothing of secondhand smoking within the home. Seasonal variations have been described in indoor air quality in homes[37] especially since air pollutants are frequently increased during the hot summer months.[20] Ventilation rates within the homes, ambient/ room air temperatures, emissions from indoor materials, and activities such as window opening and the use of heating and air conditioning systems also contributed significantly to the seasonal variability that has been described.[34,38]

This summary suggests that there is much work to be done in the treatment of asthma. Though quality treatment plans—including emphasis of controller medication use along with written asthma action plans according to national guidelines and the recent development of biologic injectables—have contributed greatly to improved asthma outcomes, it is apparent that optimum control of asthma requires an upstream approach. That

is one of the reasons the pulmonary division at Dayton Children's includes a community health worker as part of the asthma treatment team. A community health worker provides assessments within the homes of the patients with asthma, often identifying stressors and triggers that the family fails to mention with the clinic visit. The pulmonary division is also launching a pilot study in collaboration with two heating, ventilation, and air conditioning technology companies in the Dayton area, investigating the effects of mitigating poor indoor air quality on asthma control. Care of asthma, like many chronic illnesses, mandates a holistic approach that extends beyond episodic care and begins where the patients live.

references

1. Pruss-Ustun A, Corvalan C; for World Health Organization. Preventing disease through healthy environments: Towards an estimate of the environmental burden of disease (2006). Accessed July 9, 2021. https://www.who.int/publications/i/item/9241593822?ua=1

2. United States Environmental Protection Agency. The origins of EPA. Accessed July 9, 2021. https://www.epa.gov/history/origins-epa

3. Pope CA, Dockery DW. Health effects of fine particulate air pollution: Lines that connect. *J Air Waste Manag Assoc.* 2006;56:709–742.

4. Pope CA, Ezzati M, Dockery DW. Fine-particulate air pollution and life expectancy in the United States. *NEJM.* 2009;360(4):376–386.

5. American Academy of Pediatrics, Committee on Environmental Health. Ambient air pollution: Health hazards to children. *Pediatrics.* 2004;114(6):1699-1707.

6. Samet J, Spengler J. *Indoor Air Pollution: A Health Perspective – The Johns Hopkins Series in Environmental Toxicology.* Johns Hopkins University Press, 1991.

7. Klepeis NE, Nelson WC, Ott WR, et al. The National Human Activity Pattern Survey (NHAPS): A resource for assessing exposure to environmental pollutants. *J Expo Anal Environ Epidemiol.* 2001;11,(3):231–252.

8. Jones AP. Asthma and domestic air quality. *Soc Sci Med.* 1998;47(6):755–764.

9. Abt E, Suh HH, Allen G, Koutrakis P. Characterization of indoor particle sources: A study conducted in the metropolitan Boston area. *Environ Health Perspect.* 2000;108(1):35–44.

10. Bryesse PN, Diette GB, Matsui EC, Butz AM, Hansel NN, MaCormack MC. Indoor air pollution and asthma in children. *Proc Am Thorac Soc.* 2010;7:102–106.

11. Vardoulakis S, Giagloglou E, Steinle S, et al. Indoor exposure to selected air pollutants in the home environment: A systematic review. *Int J Environ Res.* 2020;17(23):8972-8995.

12. Richardson G, Eick S, Jones R. How is the indoor environment related to asthma?: Literature review. *J Adv Nurs.* 2005;52(3):328–339.

13. Coombs KC, Che GL, Schaffer C, et al. Indoor air quality in green-renovated vs. non-green low-income homes of children living in temperate region of US (Ohio). *Sci Total Environ.* 2016; June 1:178–185.

14. Cortez-Lugo M, Moreno-Macias H, Holguin-Molina F, et al. Relationship between indoor, outdoor, and personal fine particle concentrations for individuals with COPD and predictors of indoor-outdoor ratio in Mexico City. *J Expo Sci Environ Epidemiol.* 2008;18:109–115.

15. Lung SCC, Mao IF, Liu LJS. Resident's particle exposures in six different communities in Taiwan. *Sci Total Environ.* 2007;377:81–92.

16. McCormack MC, Breysse PN, Hansel NN, et al. Common household activities are associated with elevated particulate matter concentrations in bedrooms of inner-city Baltimore pre-school children. *Environ Res.* 2008;106(2):148–155.

17. Romagnoli, P, Balducci C, Perilli M, Vichi F, Imperialli A, Cecinato A. Indoor air quality at life and work environments in Rome, Italy. *Environ Sci Pollut Res.* 2016;23:3503–3516.

18. McCormack MC, Breysse PN, Matsui EC, et al. In-home particle concentrations and childhood asthma morbidity. *Environ Health Perspect.* 2009;117(2):294–298.

19. McCormack MC, Breysse PN, Matsui EC, et al. Indoor particulate matter increase asthma morbidity in children with non-atopic and atopic asthma. *Ann Allergy Asthma.* 2011;106:308–315.

20. Uchiyama S, Tomizawa T, Tokoro A, et al. Gaseous chemical compounds in indoor and outdoor air of 602 houses throughout Japan in winter and summer. *Environ Res.* 2015;137:364–372.

21. Hansel NN, McCormack MC, Belli AJ, et al. In-home air pollution is linked to respiratory morbidity in former smokers with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2013;187:1085–1090.

22. Gruenwald T, Seals BA, Knibbs LD, Hosgood III DH. Population attributable fraction of gas stoves and childhood asthma in the United States. *Int J Environ Res Public Health.* 2023;20:75–78.

23. United States Environmental Protection Agency. Ozone generators that are sold as air cleaners. Accessed July 9, 2021. www.epa.gov

24. Gent JF, Triche EW, Holford TR, et al. Association of low-level ozone and fine particles with respiratory wymptoms in children with asthma. *JAMA.* 2003;290(14):1859–1867.

25. Weschler C J. New directions: Ozone-initiated reaction products indoors may be more harmful than ozone itself. *Atmos Environ.* 2004;38(33):5715–5716.

26. Rumchev K, Spickett J, Bulsara M, Phillips M, Stick S. Association of domestic exposure to volatile organic compounds with asthma in young children. *Thorax.* 2004;59:746–751.

27. Rumchev KB, Spickett JT, Bulsara MK, Phillips MR, Stick SM. Domestic exposure to formaldehyde significantly increases the risk of asthma in young children. *Eur Respir J.* 2002;20:403–408.

28. Ezratty V, Bonay M, Neukirch C, et al. Effect of Formaldehyde on Asthmatic Response to Inhaled Allergen Challenge. *Environ Health Perspect.* 2007;115(2):210–214.

29. Karimi P, Peters KO, Bidad K, Strickland PT. Polycyclic aromatic hydrocarbons and childhood asthma. *Eur J Epidemiol.* 2015;30:91–101.

30. Canova C, Torresan S, Simanto L, et al. Carbon monoxide pollution is associated with decreased lung function in asthmatic adults. *Eur Respir J.* 2010;35:266–272.

31. Brauer M, Hruba F, Mihalikova E, et al. Personal exposure to particles in Banska Bystrica, Slovakia. *J Expo Anal Environ Epidemiol.* 2000;10:478–487.

32. Chatzis C, Alexopoulos EC, Linos A. Indoor and outdoor personal exposure to benzene in Athens, Greece. *Sci Total Environ.* 2005;349:72–80.

33. Hulin M, Caillaud D, Annesi-Maesano I. Indoor air pollution and childhood asthma: Variations between urban and rural areas. *Indoor Air.* 2010;20:502–514.

34. Nazariah SS, Juliana J, Abdah MA. Interleukin-6 via sputum induction as biomarker of inflammation for indoor particulate matter among primary school children in Klang Valley, Malaysia. *Glob J Health Sci.* 2013;5(4): 93–105.

35. Simoni M, Scognamiglio A, Carrozi L, et al. Indoor exposures and acute respiratory effects in two general population samples from a rural and an urban area in Italy. *J Expo Anal Environ Epidemiol.* 2004;14:S144–S152.

36. Simons E, Curtin-Brosnan J, Buckley T, Breysse P, Eggleston PA. Indoor environmental differences between inner city and suburban homes of children with asthma. *J Urban Health.* 2007:84(4):577–590.

37. Stamp S, Burman E, Shrubsole C, Chatzidiakou L, Mumovic D, Davies M. Seasonal variations and the influence of ventilation rates on IAQ: A case study of five low-energy London apartments. *Indoor Built Environ.* 2021;0:1–17.

38. Clarisse B, Laurent AM, Seta N, Moullec YL, Hasnaoui AE, Momas I. Indoor aldehydes: Measurement of contamination levels and identification of their determinants in Paris dwellings. *Environ Res.* 2003;92:245–253.

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Daniel Evans, MD, CPE, is a pediatric pulmonologist and division chief of pulmonology at Dayton Children's. Dr. Evans treats children with all varieties of respiratory diseases and is the medical director of the department of respiratory therapy and the pulmonary diagnostics laboratory. Dr. Evans was born and raised in the greater Dayton area. He completed his medical school education at Wright State University Boonshoft School of Medicine in Dayton, Ohio. Following college, he spent his internship and residency at Dayton Children's. He completed his fellowship at Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio. Dr. Evans is board certified in both pediatric pulmonology and general pediatrics.

CME questions

11. 1. Why was the EPA established?
    a. To reduce air and water pollution
    b. To protect the health of the American people
    c. In response to very public environmental disasters
    d. All of the above
12. Why is indoor air quality particularly important for people with respiratory illnesses?
    a. Indoor air quality can be different from the outdoor air quality.
    b. Children spend approximately 90% of their time indoors.
    c. Many of the contributors to poor indoor air quality have been associated with increased symptoms or decline in pulmonary function in individuals with asthma.
    d. All of the above
13. What contributor to poor indoor air quality has recently been proposed as a cause of as much as 12.7% of the asthma in the United States?
    a. Cigarette smoke
    b. Endotoxins
    c. Nitrogen dioxide
    d. Ozone

Dayton Children's updates

brand new specialty care center opens — built from families' wish lists

In March, Dayton Children's unveiled a new five-story, 150,000-square-foot specialty care center, offering more than 30 specialties where the entire experience is built around the conveniences and care the families of our region want.

"We've talked in depth to our families about what would make it easier on them to take care of their child," says Cindy Burger, vice president and chief experience officer for Dayton Children's. "We combined that with what our physicians, nurses and care teams need to provide the outstanding level of care our families expect from us. These new spaces allow for that exceptional care and experience."

easy and efficient

- Surface parking. Top of the wish list for families was surface parking so we added 150 spaces for their convenience, in addition to the existing parking garage.
- Efficient registration. Families can register for all their appointments that day at once with assistance at the registration desk or on their own at a kiosk.
- Co-located diagnostic testing. Any tests that a child may need are mostly located right in the clinic, just a few steps away from the exam room.
- Multi-appointment flexibility. The exam rooms have built-in flexibility that allow for multiple specialists to come to the child, reducing the family's need to go from room to room.
- Easy pivot to virtual visits. If a family can't make it to an appointment, every exam room is designed to easily pivot to a virtual visit, if medically appropriate.

advanced technology

- Water therapy tank in Orthopedics The Hydroworx water therapy tank allows kids to safely perform exercises with less pain or they couldn't do without the water's support.
- Bio-simulation lab. Clinicians can train on the latest treatments and procedures to provide the most advanced care to children of the region.

above and beyond touches

- Whimsical artwork and visual delights.
- Distraction devices include a Rube Goldberg-type ball machine in the lobby, a sensory wall, touch-and-play games in the waiting rooms and an outdoor garden with a unique sculpture play area.
- Sensory features inside exam rooms as well as features such as marble walls and touch-sensitive lights throughout the space and for those in need of a quieter experience, there are nooks in the waiting rooms to provide a calm-down space and distraction-free exam rooms.

CareSource donates $2 million to support Dayton Children's behavioral health expansion

Dayton Children's received a $2 million donation by CareSource to support its new behavioral health building. The building, announced in May 2022, will nearly double the number of inpatient beds available for children in a behavioral health crisis.

The $2 million donation from CareSource was made in honor of Jayda Grant, daughter of Anthony Grant, University of Dayton men's basketball coach, and his wife, Christina. Jayda passed away in May 2022. The donation was announced last night at an event held at the home of CareSource president and CEO, Erhardt Preitauer, to an audience of corporate leaders from the Dayton community.

While children's mental health concerns were growing rapidly prior to the pandemic, COVID-19 only exacerbated the already untenable situation. Even though Dayton Children's opened a behavioral health inpatient unit in July 2019, those 24 beds are not enough to care for the growing need. The new behavioral health building, breaking ground next year, will:

- Double the number of behavioral health inpatient beds currently available at Dayton Children's
- Allow expansion for specialized program development
- Allow for strengthened and smoother continuity of care by bringing behavioral health inpatient, outpatient and crisis services all under one roof
- Provide customized outdoor space that is critical to healing
- Create operational efficiencies and improved communication through cross-trained staff, proximity and access

"We are so grateful to CareSource for its support and for shining a light on this critically important issue," said Debbie Feldman, president and CEO of Dayton Children's Hospital. "This donation will go a long way toward helping us meet the growing need for behavioral health services. As always, it is the gracious support of a generous community that helps us take every project from good to great."

Last year, more than 200,000 of CareSource's youth members had an identified behavioral health diagnosis.

Regarding CareSource's donation, Anthony and Christina Grant provided the following on behalf of their family:

"We are very grateful to CareSource for their generous donation to support the expansion of the Dayton Children's behavioral health facility and their compassion towards our family by honoring the memory of our beloved daughter and sister, Jayda Danielle Grant. Jay was diagnosed with anxiety and depression and was in therapy and treatment at the time of her passing. Our hope is that this expansion will help provide more resources and increased synergy to what Debbie Feldman has appropriately identified as 'the health care crisis of this generation.' We are grateful for the love, prayers, and support we've received and for the commitment of the doctors, therapist, corporate & individual partners, and everyone in between that are working to make a difference in the lives of those impacted by mental and behavioral health challenges. Thank you and God Bless."

Dayton Children's behavioral health building is expected to be complete in 2025.

program evaluation

1. The material presented in this publication met the mission to enhance health care delivery in our region through education based on the essentials and policies of the Accreditation Council for Continuing Medical Education.
   ☐ Strongly agree ☐ Agree ☐ Neutral
   ☐ Disagree ☐ Strongly disagree

2. Did the material presented in this publication meet the educational objectives stated?
   ☐ Yes ☐ No

3. Did the material presented in this publication have a commercial bias?
   ☐ Yes ☐ No

4. Please rate the contents of this issue using the following scale:
   1 = Poor, 2 = Fair, 3 = Good, 4 = Very good, 5 = Excellent *(Circle one response for each.)*

	Poor				Excellent
Timely, up-to-date?	1	2	3	4	5
Practical?	1	2	3	4	5
Relevant to your practice?	1	2	3	4	5

5. Please describe any changes you plan to make in your clinical practice based on the information presented in this program.

   _____

6. Are there any other topics you would like to have addressed in this publication or future educational programs for health care providers?
   ☐ Yes ☐ No If yes, please describe:

   _____

7. Please describe how you will incorporate information obtained from this publication into your practice.

   _____

8. Letter to the editor — Letter to the editor may be emailed to alters@childrensdayton.org or attached to this evaluation and may be published in the next issue.

physician accreditation statement and credit designation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Wright State University (WSU) and Dayton Children's Hospital.

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program test

to obtain CME credit you must:

Read and reflect on each article.

Answer the questions from each article and complete this test — cmequiz.childrensdayton.org/SummerPediatricForum2023. 70 percent correct answers are needed to obtain the full 2.0 AMA PRA Category 1 Credits™.

Complete the program evaluation.

Return your completed test and program evaluation by email, mail or fax to: Sue Strader, coordinator
Department of Continuing Medical Education
Dayton Children's Hospital, One Children's Plaza,
Dayton, Ohio 45404-1815
Fax: 937-641-5931

E-mail: straders@childrensdayton.org

Take test online: cmequiz.childrensdayton.org/SummerPediatricForum2023

This test must be received by August 31, 2025 for the credit to be awarded

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your answers to CME questions
(Please circle the BEST answer.)

1.	true	false			
2.	true	false			
3.	true	false			
4.	a	b	c	d	e
5.	a	b	c	d	
6.	a	b	c	d	
7.	a	b	c	d	
8.	a	b	c	d	
9.	a	b	c	d	
10.	a	b	c	d	
11.	a	b	c	d	
12.	a	b	c	d	
13.	a	b	c	d	

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pediatric forum

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The purpose of Pediatric Forum is to provide information and news about pediatric health care issues and to provide information about clinical services and management issues of Dayton Children's.

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target audience

This education activity is designed for pediatricians, family physicians and related child health care providers.

educational objectives

- Identify the four pediatric issues covered in this journal and develop appropriate intervention.
- Appropriately use the resources of Dayton Children's Hospital to improve patient care.

dayton children's

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