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COVER STORY

ALLERGIC RHINITIS:

New and Established Treatment Options

pediatric forum

SUMMER 2016

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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.

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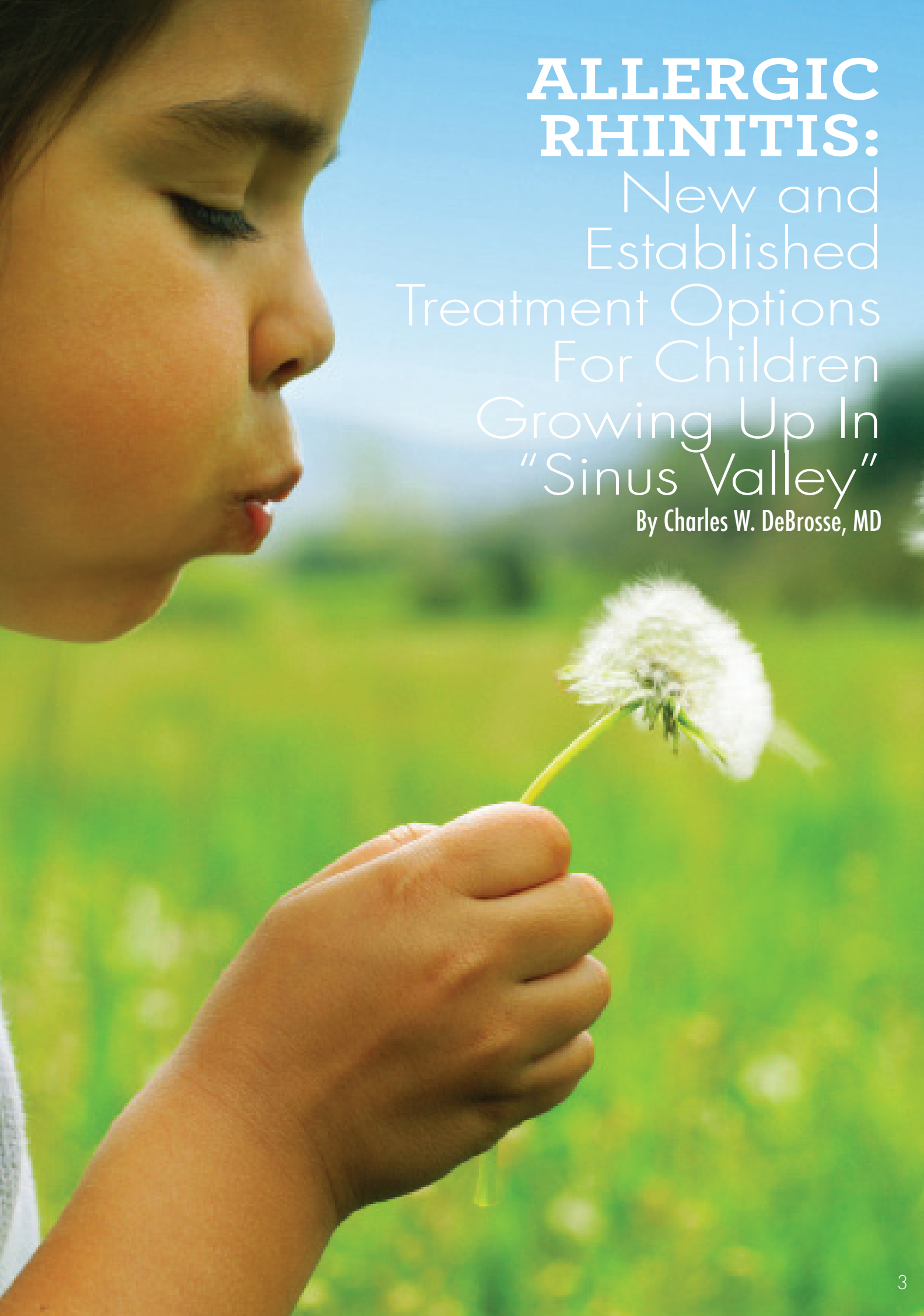

ALLERGIC RHINITIS: New and Established Treatment Options For Children Growing Up In "Sinus Valley"

By Charles W. DeBrosse, MD

Objectives

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

1. Review the benefits and use of subcutaneous and sublingual allergen immunotherapies.
2. Discuss emerging immunomodulatory therapies for allergic disease in children and adolescents.

Allergic rhinitis is a common pediatric problem that impacts the lives of 40 percent of children and adolescents each year. The symptoms associated with allergic rhinitis are many and the spectrum of disease severity is broad. Symptoms of nasal congestion, sneezing, rhinorrhea and itchy, watery eyes occur commonly and are the direct result of allergen binding to allergen-specific IgE present on mast cells.

When symptoms become severe, complications such as recurrent sinus infections and otitis media can arise. While second generation antihistamines and intranasal corticosteroids offer relief in many cases, there are many children who fail to respond to first line treatments. Additionally, undesirable side effects can occur with the use of antihistamines or intranasal corticosteroids. When faced with cases of refractory allergic rhinoconjunctivitis or patients who are unable to tolerate initial treatments, immunotherapy has the potential to provide sustained relief.

Immunotherapy: new and established approaches

Allergen immunotherapy has been a weapon in the fight against allergic disease for more than 100 years. Subcutaneous immunotherapy, commonly referred to as allergy shots, has been the primary method of immunotherapy used for pediatric and adult allergy sufferers. Subcutaneous immunotherapy uses the administration of progressively increasing doses of allergen in an effort to build tolerance to environmental allergens. Subcutaneous immunotherapy is highly effective and is often able to reduce allergy symptoms, the need for allergy medications and improve quality of life.[1]

The benefits of allergen immunotherapy can be seen at the cellular and molecular level. Patients who receive immunotherapy experience an increase in the activity of T regulatory cells. These cells are critical in establishing a healthy balance between the different arms of the immune system. Along with increased T regulatory activity, patients who receive immunotherapy also develop increased levels of IgG4.[2] IgG4 is a specific antibody that helps to inhibit the activity of IgE, the primary cause of symptoms in children with allergic rhinoconjunctivitis. Ultimately, as IgG4 levels rise, allergen specific IgE levels will fall. As a result, the symptoms of allergic rhinitis diminish. For the majority of patients who receive immunotherapy, the positive immunologic changes that occur during immunotherapy persist even after treatment is discontinued.

While subcutaneous immunotherapy is quite effective, not all patients are willing to consider treatment with subcutaneous injections. For children, two new options for allergen immunotherapy are FDA approved and can be given sublingually. Grastek and Oralair are new sublingual grass pollen tablets and both are approved for use in pediatric patients. Grastek is approved for children age 5 and up and Oralair is approved for children age 10 and up. Grastek is made from a timothy grass abstract, while Oralair is a mixture of five different grass pollens. When these tablets dissolve, small amounts of grass pollen are absorbed in the oral mucosa and presented to the immune system in local lymph nodes. In most cases, the repeated presentation of allergen to the immune system will lead to tolerance, and ultimately, decreased symptoms of allergic disease. Treatment is typically initiated 12 weeks prior to the onset of the grass pollen season and treatment is continued until the grass pollen season has ended. Patients do not have to wait long to see symptomatic relief; often, symptom reduction is noted within the first season. More marked reduction is seen in the next two years.[3]

While the benefits of sublingual treatment are noteworthy, there are important side effects and drawbacks of which pediatricians must be aware. Of these, oral itching represents the most common side effect of therapy, with almost 25 percent of patients reporting itching. Typically, oral itching is noted during the first two weeks of therapy, persists for 30 to 60 minutes and will often resolve over time. Anecdotally, the co-administration of a non-sedating antihistamine does seem to reduce this effect. In rare cases, significant angioedema has occurred with sublingual immunotherapy. There are also reports of anaphylaxis related to these products in the United States. For this reason, it is recommended that all patients receiving sublingual immunotherapy be prescribed an epinephrine autoinjector and be appropriately trained in its use. Finally, the first dose must be given in the office of a physician trained in the treatment of anaphylaxis and with the appropriate equipment present to treat an allergic reaction.

Which method of immunotherapy is best?

The emergence of sublingual immunotherapy has prompted an important question: Which mode of immunotherapy is most effective and most appropriate for children? The answer to this question hinges on a number of key factors, though most meta-analyses suggest that subcutaneous immunotherapy (allergy shots) provide the most relief (AHRQ.gov, August 2013). Most importantly, subcutaneous immunotherapy can be used to treat a number of critical environmental allergens. In Dayton, Ohio, at least 20 unique tree and grass pollens are present in the air we breathe each spring. While sublingual immunotherapy can address grass pollen allergy, subcutaneous immunotherapy can be used to address a broad range of allergens (dust mite, cockroach, cat dander, dog dander, outdoor molds, tree pollen, grass pollen and ragweed). Therefore, those sensitized only to grass pollen may see significant relief from sublingual treatment; however, those who are sensitized to tree and grass pollen would benefit most from subcutaneous immunotherapy. Finally, the use of sublingual immunotherapy in subjects with moderate to severe asthma has not been well studied. Therefore, for patients with asthma, the use of sublingual therapy should be used following careful consideration of the risks and benefits of treatment.

Emerging treatments for allergic disease beyond the nose

The past 12 months have also seen great progress in the treatment of allergic disease beyond immunotherapy and allergic rhinitis. A host of new immunomodulatory treatments are under investigation and showing promise for the treatment of allergic asthma and atopic dermatitis. These new modes of treatment are disease specific and block cytokines critical to the development of allergic disease (IL-4, IL-5, IL-13). Most notably, Mepolizumab was recently approved for use in children with refractory eosinophilic asthma. Available for use in children 12 and older, Mepolizumab inhibits the activity of IL-5, the cytokine responsible for eosinophil survival. Mepolizumab was shown to reduce the need for oral corticosteroid use in patients with severe eosinophilic asthma.[4] The approval of Mepolizumab is a substantial move forward for children with severe asthma and also offers hope for children with eosinophilic esophagitis (EoE). Studies of IL-5 inhibitors among children with EoE have shown decreases in eosinophil levels in the esophagus.[5] Surprisingly, these medications

did not lead to complete disease remission. Their use in EoE is very much under investigation, but optimism is strong that these medications may offer a new modality of treatment for these patients.

Additionally, the use of Omalizumab (an anti-IgE monocolonal antibody marketed under the brand name Xolair) was recently shown to reduce fall exacerbations in children with severe allergic asthma.[6] This study corroborated the findings of Busse et al., who published a landmark study in the *New England Journal of Medicine* demonstrating that the addition of Omalizumab to standard asthma treatment substantially reduced symptoms and exacerbations in children with asthma.[7]

In summary, allergists and pediatricians have new armamentarium in the battle against allergic rhinitis and allergic disease. The emergence of sublingual immunotherapy stands to expand the use of immunotherapy and improve quality of life for children with allergic rhinitis. The approval of Mepolizumab and the mounting data surrounding Omalizumab provide rationale for new treatment options in children with allergic asthma.

References

1. Assa'ad A, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology.* 2011;141(5):1593.
2. Busse WW, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med.* 2011 Mar 17;364(11):1005-15.
3. Durham SR, et al. Long-term clinical efficacy in grass pollen induced immunotherapy after treatment with SQ standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol.* 2010 Jan;125(1):131-8.e1-7.
4. Durham SR, et al. Long-term efficacy of grass pollen immunotherapy. *N Engl J Med.* 1999 Aug 12;341(7):468-75.
5. Hector G, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371:1198-1207.
6. Maggi E. T cell responses induced by allergen-specific immunotherapy. *Clin Exp Immunol.* 2010 Jul;16 1(1):10-18.
7. Teach SJ, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol.* 2015 Dec;136(6):1476-85.

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CME Questions

1. Sublingual immunotherapy has recently been approved for use in children allergic to which of the following pollens?

a. Birch tree pollen

b. Ragweed

c. Elm tree pollen

d. Grass pollen

2. Which newly approved therapy has been shown to reduce exacerbations in children age 12 and older with severe eosinophilic asthma?

a. Reslizumab

b. Infliximab

c. Mepolizumab

d. Montelukast

3. Which modality of immunotherapy is believed to generate the greatest symptom reduction for children with allergic rhinitis?

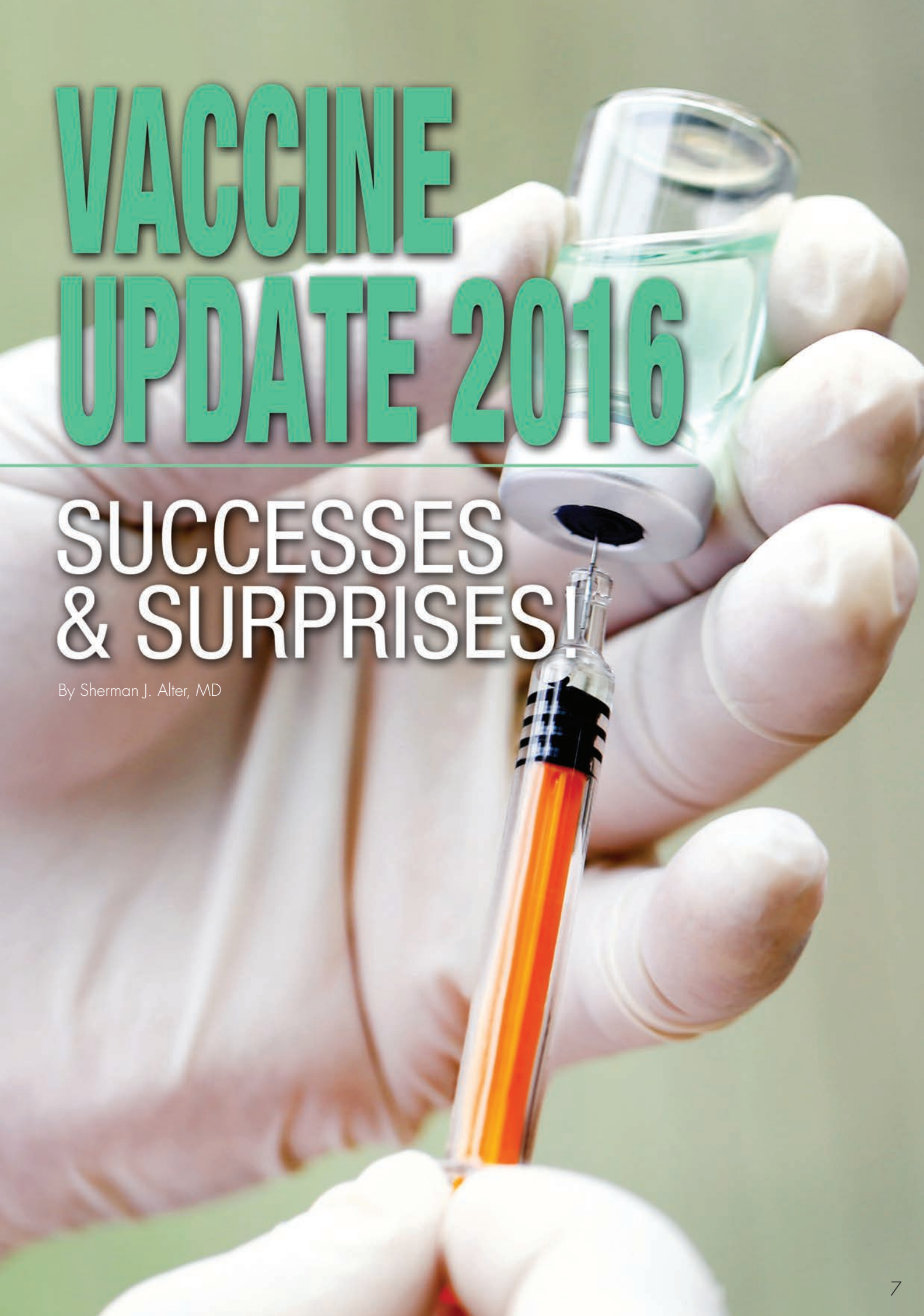
a. Sublingual immunotherapy

b. Subcutaneous immunotherapy

VACCINE UPDATE 2016

SUCCESSES & SURPRISES!

By Sherman J. Alter, MD



Objectives

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

1. Review recommendations for the use of serogroup B meningococcal vaccine.
2. List factors associated with the increasing incidence of pertussis across the nation.
3. Discuss appropriate utilization of human papillomavirus vaccine during adolescence.

Introduction

Vaccination is a fundamental tool in the prevention of infectious diseases of children and adolescents. New vaccine development and new or modified recommendations on vaccine use seem to have occurred regularly over the last few years. The following will provide an update on some recent key issues.

Meningococcus

A recommendation to expand vaccination against infection caused by serogroup B *Neisseria meningitidis* (MenB) to include adolescents and young adults was recently recommended by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC). Meningococcal disease is devastating and debilitating, with a 10 to 15 percent case fatality rate. Five major serogroups (A, B, C, Y and W-135) cause invasive disease worldwide. While rates of infection are highest in infancy, a second peak occurs in adolescents and young adults, and a third in adults greater than 65 years old. According to the CDC, 60 percent of invasive cases in children are caused by serogroup B meningococcus (MenB). Thirty percent of adolescent and adult infections are caused by MenB organisms. Fortunately, meningococcal disease caused by any serogroup is rare in the United States (0.18 cases/100,000). (http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-2015-06.pdf) From 2009-2013, MenB disease among those aged 11 to 24 years in the US ranged from 54 to 67 cases per year with roughly 80 percent occurring in those aged 16 to 24 years.

Almost all cases of meningococcal disease are sporadic. However, outbreaks of MenB disease have been reported from several college campuses. Data from recent college outbreaks (March 2013-May 2015) noted a 200 to 1,400-fold increased risk for meningococcal disease among students when compared with the general population in this age group. Significantly, college students not involved in an outbreak have a risk of MenB disease similar to that of the general population of a similar age.

Three meningococcal vaccines (Menomune, Menactra, Menveo) that protect against serogroups A, C, Y and W-135 are approved by the Food and Drug Administration

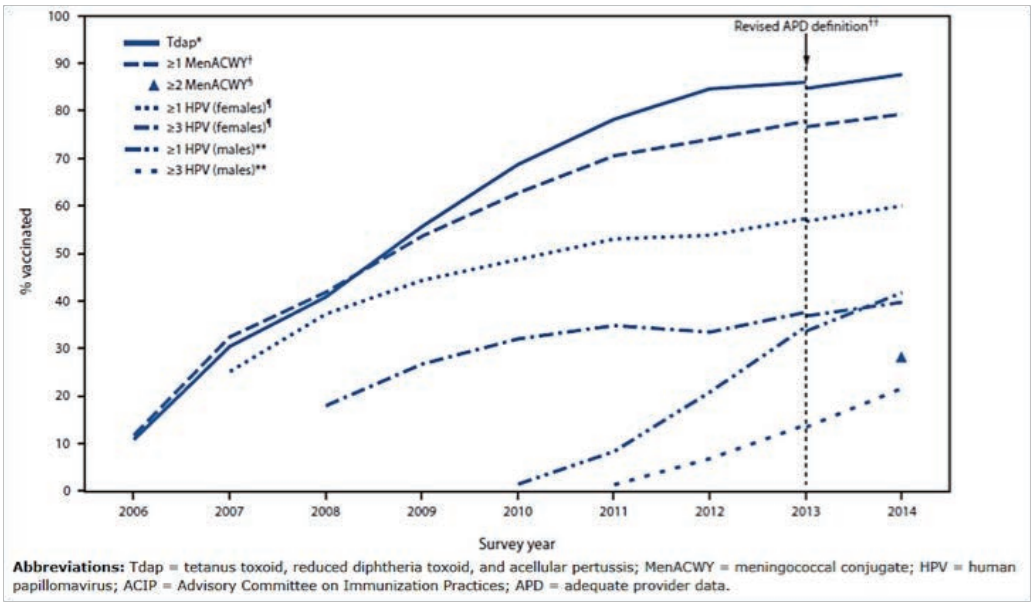


Figure 1. Estimated vaccination coverage with selected vaccines and doses among adolescents aged 13-17 years by survey year – National Immunization Survey, United States, 2006-2014 (CDC. National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 Years — United States, 2014. Morbid Mortal Wkly Rep 2015;64(29):784-92)

(FDA). A combination meningococcal/*Haemophilus influenzae* type b vaccine (MenHibrix) is approved for children 6 weeks to 18 months old, and protects against serogroups C and Y. In 2005, the CDC and the American Academy of Pediatrics published recommendations to routinely vaccinate all 11- to 12-year-olds with quadrivalent (A, C, Y, W-135) meningococcal-conjugate vaccines (MCV4) – Menactra and Menveo. In 2011, it was recommended that a second (booster) dose be given at 16 years in order to enhance protection during the age range of highest risk for meningococcal disease – ages 16 to 21 years. The second dose is delayed until age 16 to 18 years if the initial MCV4 was administered at age 13 to 15 years. No booster MCV4 dose is necessary if the first dose is delayed until 16 years or older.

Protein conjugation of polysaccharide antigens from serogroups A, C, Y and W-135 enhanced the immunogenicity of the MCV4 vaccines. Unfortunately, the polysaccharide capsule of MenB organisms is a poor immunogen due to its structural similarity to polysialic acid found on human neural tissue. Given this poor immunogenicity and the potential risk of adverse events with use of a MenB capsular antigen, a MenB vaccine had to be developed using other meningococcal antigens. Recently, two such vaccines have been developed. MenB-FHbp (Trumenba) is a bivalent vaccine consisting of subfamily A and subfamily B recombinant factor H binding protein (FHbp) antigens. MenB-4C (Bexsero) is a multicomponent vaccine consisting of recombinant meningococcal proteins (FHbp, Neisserial adhesin A, Neisserial heparin binding antigen and an outer membrane vesicle).[1]

Both vaccines were licensed by the FDA for the prevention of serious and life-threatening diseases. Because of the low incidence of MenB disease, vaccine effectiveness estimates have been based on demonstration of immunogenicity endpoints, as measured by serum bactericidal antibody activity using human serum complement, against MenB strains representative of prevalent strains in the US – reasonably likely to predict clinical benefit. In clinical trials, both vaccines were safe with few serious events.[2]

MenB vaccine should be administered intramuscularly either as a 3-dose series of MenB-FHbp (0-, 2- and 6-month schedule) or a 2-dose series of MenB-4C (0 and greater than one month later). The vaccines are not interchangeable and the same vaccine product should be used for all doses. On the basis of available data and expert opinion, either MenB vaccine may be administered concomitantly with other vaccines that are indicated for the patient's age, but at a different anatomic site, if feasible.

While FDA approved in persons aged 10 to 25 years, the ACIP recommended that persons aged 16 to 23 years may be vaccinated with a MenB vaccine to provide short-term protection against most strains of MenB disease. The preferred age for MenB vaccination is 16 to 18 years. It is recommended for those at increased risk for disease (Category A recommendation) including persons with persistent complement component deficiencies, individuals with anatomic or functional asplenia (including sickle cell disease), microbiologists routinely exposed to isolates of *N. meningitidis* and persons identified at increased risk because of a serogroup B meningococcal disease outbreak.

A permissive or Category B recommendation was made for low-risk adolescents and young adults. The treating clinician should determine which persons might benefit from receipt of one of the MenB vaccines. As such, in contrast to MCV4 recommendations, MenB vaccination is not routinely recommended for all college students or for international travelers. The safety and effectiveness of MenB vaccines have not been established in children less than 10 years of age.

Human Papillomavirus (HPV)

HPV is known to cause genital warts, as well as a number of cancers including cervical, vaginal, vulvar, penile, anal and oropharyngeal. Because HPV transmission occurs by contact, these infections are extremely common and easily spread. In North America and Europe, it is estimated that an individual's lifetime risk of a genital HPV infection is 75 percent.[7] The majority of HPV infections are unrecognized and individuals will clear the virus within a number of weeks. However, some mucous membrane-associated HPV types, classified as high-risk types, have an increased proclivity for causing malignant transformation of epithelial cells.

Both the bivalent vaccine (Cervarix – containing antigen against high-risk types HPV16 and HPV18) and quadrivalent vaccine (Gardasil – HPV6, HPV11, HPV16, HPV18), when given prior to acquisition of HPV infection, can prevent from 98 to 100 percent of cervical intraepithelial neoplasia grades 2/3 (CIN2/3). Protection against the development of HPV-associated malignant changes at other mucosal sites ranges from 75 to 100 percent.[8] The quadrivalent vaccine, because it contains HPV6 and HPV11 antigen, prevents 90 percent of genital warts. Recent analyses of data from the HPV vaccine era (2009-2012) demonstrated that among females aged 14 to 19 years and

20 to 24 years, prevalence of infection with the HPV types represented in the quadrivalent vaccine decreased 64 percent and 34 percent, respectively, compared to the prevaccine era.[9] In 2014, the FDA approved a 9-valent vaccine, formulated by the manufacturer of the quadrivalent vaccine, which contains antigens against an additional five oncogenic HPV types (HPV types 31, 33, 45, 52 and 58). This vaccine has an extremely high efficacy (96.7 percent) for prevention of the composite endpoint of all HPV-associated dysplasias and cancers.[10] Immunization is recommended for all females and males ages 11 to 12 years with a three-dose schedule. Females can receive either the bivalent, quadrivalent or 9-valent vaccine. Males should receive either the quadrivalent or 9-valent vaccine. HPV vaccination may be initiated in children as young as 9 years of age. Catch-up immunization recommendations have been developed for persons of either sex through age 26 years. The 9-valent vaccine may be used to continue or complete a series started with a different HPV vaccine product. It is not recommended, however, to administer 9-valent HPV vaccine to persons who have completed a three-dose series with either bivalent or quadrivalent HPV vaccines. Studies are ongoing evaluating the effectiveness of less than a complete three-dose series of HPV vaccination.

HPV immunization rates in the US remain quite low (Figure 1). A hefty proportion of the blame for such low uptake (in females and males, but worse among the latter) can be placed on the inability or reluctance of some health care providers to advocate effectively for the vaccine. One should simply declare to the patient and parent that the vaccine is due. The approach must be no different than that with other vaccines!

Rotavirus

Rotavirus (RV) was the leading cause of severe diarrhea among infants and young children in the US before RV vaccine was introduced over a decade ago. Prior to the vaccine, almost all US children were infected with this virus before their fifth birthday. Among children younger than 5 years of age, RV led to more than 400,000 doctor visits, more than 200,000 emergency room visits, 55,000 to 70,000 hospitalizations and 20 to 60 deaths annually. Globally, rotavirus is still the leading cause of severe diarrhea in infants and young children. In 2008, rotavirus caused an estimated 453,000 deaths worldwide in children younger than 5 years of age. (CDC Rotavirus, http://www.cdc.gov/rotavirus/surveillance.html)

Since vaccine introduction, RV disease among infants and young children has decreased considerably in the US. Each year, the vaccine prevents an estimated 40,000 to 50,000 hospitalizations. RV illness has also decreased among older children and adults that are not vaccinated; they are likely gaining indirect protection from rotavirus disease as vaccinated children are less likely to get the disease and spread it to others. Figure 2 displays rotavirus season duration and peak activity in the US from 2000-2014.

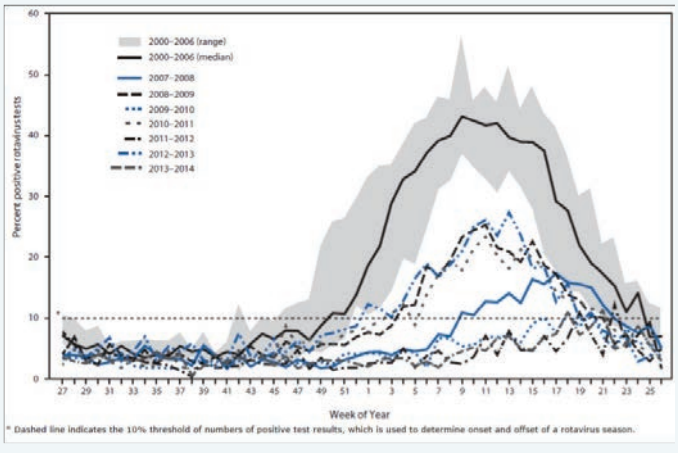


Figure 2. Rotavirus season duration and peak activity by reporting years (prevaccine 2000–2006 and postvaccine 2007–2011) — United States, 2000–2014 (CDC. Sustained Decrease in Laboratory Detection of Rotavirus after Implementation of Routine Vaccination — United States, 2000–2014. Morbid Mortal Wkly Rep 2015;64(13):337-342)

There are two licensed RV vaccines: RV5 (Rotateq), a live virus vaccine with a combination of five human/bovine reassortant rotaviruses, and RV1 (Rotarix), a live, attenuated rotavirus vaccine prepared from a single human strain. Both vaccines are safe and effective in preventing RV disease. A recent study investigated immune responses to the two licensed rotavirus vaccines when administered as a mixed schedule compared with administering a single vaccine formulation alone.[11] The children received either RV1 or RV5 for the first dose, followed by five distinct combinations of the two vaccines to complete the immunization series. Immune responses to all the sequential mixed vaccine schedules were shown to be noninferior when compared with the two single vaccine reference groups. The proportion of children seropositive to at least one vaccine antigen at one month after vaccination ranged from 77 to 96 percent, and was not significantly different among all the study groups. All schedules were well tolerated. This study demonstrates that should rotavirus vaccine administration not be possible using the same type of RV vaccine, a sequential mixed rotavirus formulation might offer a safe and an immunogenic alternative.

Pertussis

No new recommendations have been made as related to vaccination against pertussis. What is new, however, is the remarkable and persistent rise in the numbers of recognized cases over the last five to 10 years (Figure 3). No age group in the US is spared from pertussis infection. However, certain age groups seem to be more vulnerable. In the large California outbreak of 2014 (with the highest numbers in the state's history), infants had a remarkable 174.6/100,000 incidence.[3] This was approximately six times the rate for the overall population. Young infants are at risk of infection during the first six months of life due to incomplete immunization (although maternal immunization with an acellular pertussis-containing vaccine during pregnancy can decrease the infant's risk of acquiring infection during this vulnerable age). Young infants also bear a disproportionate burden of severe disease caused by the organism. Adolescents also have had increased rates of infection. These infections occur even among individuals who have received prior Tdap booster doses of the vaccine.

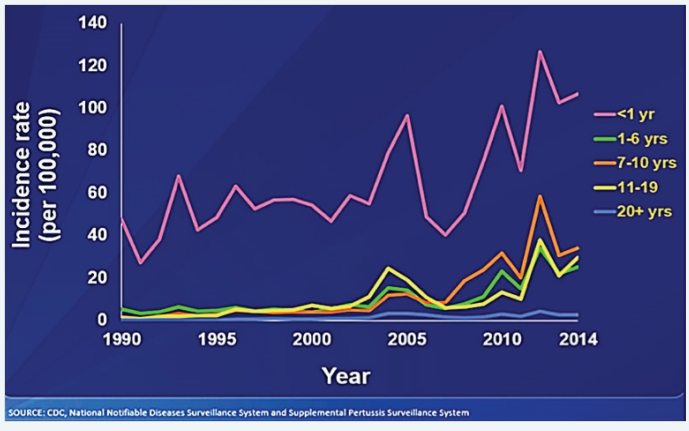


Figure 3. Reported pertussis incidence by age group - United States, 1990-2014 (Liang JL. Slide presentation before the Advisory Committee on Immunization Practices (ACIP) meeting, June 25, 2015)

A number of factors seem to potentially be related to the increased incidence of pertussis noted across the nation. Immunity to pertussis appears to wane three to four years after receiving an acellular pertussis-containing vaccine (aP).[4] This contrasts with an estimated 7—10-year protection afforded by whole cell pertussis-containing vaccines (DTP) from years past. Because of this declining vaccine efficacy, siblings of susceptible children (rather than mothers) now commonly are the primary index cases when pertussis is noted among infants. Furthermore, some *Bordetella pertussis* organisms have effectively altered their antigenic make up. These bacteria, for example, no longer possess the surface antigen, pertactin. Antibody to this antigen appears to be important in protection against clinical infection. Since currently available aP vaccines contain pertactin antigen, one can then question the efficacy of aP-containing vaccines against a pertactin-deficient B. pertussis strain. Finally, as demonstrated in studies among selected primate species, animals who have received aP-containing vaccines may have asymptomatic carriage of the organism and potentially transmit the pathogen to susceptible individuals.[5]

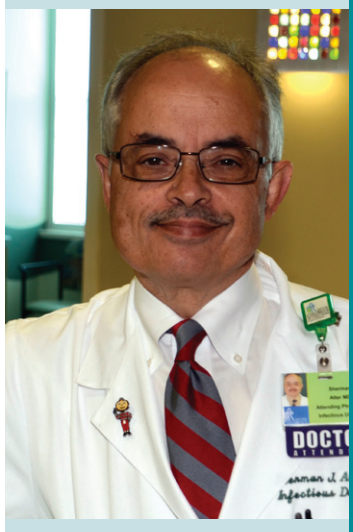
The childhood DTap and adolescent Tdap vaccines simply have not worked as well as predicted. As cases of pertussis continue to occur, clinicians must remain attentive to the signs and symptoms of pertussis. Still, despite their deficiencies, until more effective vaccines become available, use of aP vaccines remains the most formidable weapon to prevent pertussis disease.[6]

Conclusion

Vaccinology is a rapidly moving field. All clinicians must remain alert to both new vaccine developments and updated recommendations.

References

1. Bosch FX, de Sanjose S. The epidemiology of human papillomavirus infection and cervical cancer. *Dis Markers*. 2007;23(4):213-27.
2. CDC. Pertussis epidemic – California, 2014. *MMWR Morb Mortal Wkly Rep*. 2014;63(48):1129-32.
3. CDC. Use of serogroup B meningococcal vaccines in adolescents and young adults: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2015;64(22): 608-12.
4. Crum-Cianflone N, Sullivan E. Meningococcal vaccinations. *Infect Dis Ther*. 2016 Apr 16. [Epub ahead of print]
5. Libster R, McNeal M, Walter EB, et al. Safety and immunogenicity of sequential rotavirus vaccine schedules. *Pediatrics*. 2016;137(2):e20152603.
6. Markowitz LE, Liu G, Hariri S, et al. Prevalence of HPV after introduction of the vaccination program in the United States. *Pediatrics*. 2016;137(2):e20151968.
7. McGirr A, Fisman D. Duration of pertussis immunity after DTaP immunization: A meta-analysis. *Pediatrics*. 2015;135(2):331-43. doi: 10.1542/peds.2014-1729. Epub 2015 Jan 5.
8. Nash C, Harrison G, Alexander K. Human papillomaviruses. In: *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 7th ed. Elsevier; 2014:1871-87.
9. Pitisuttithum P, Velicer C, Luxembourg A. 9-Valent HPV vaccine for cancers, pre-cancers and genital warts related to HPV. *Expert Rev Vaccines*. 2015 Nov;14(11):1405-19.
10. Warfel J, Zimmerman L, Merkel T. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proc Natl Acad Sci U S A*. 2014;111(2):787-92. doi: 10.1073/pnas.1314688110. Epub 2013 Nov 25.
11. Zhang L, Prietsch SO, Axelsson I, Halperin SA. Acellular vaccines for preventing whooping cough in children. *Cochrane Database Syst Rev*. 2014 Sep 17;9:CD001478. doi: 10.1002/14651858.CD001478.pub6



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CME Questions

4. Individuals at increased risk for meningococcal disease include:

a. Persons with persistent complement deficiencies [C3, C5-9, properdin, factor D, factor H, or who are taking eculizumab (Soliris)]

b. Students living in a dormitory on a campus where a serogroup B meningococcal outbreak is occurring

c. Persons with anatomic or functional asplenia (including sickle cell disease)

d. a and c

e. All of the above

5. In an adolescent male who has received an initial dose of quadrivalent HPV vaccine, the recommended series MUST be completed with the same vaccine type (i.e., quadrivalent HPV vaccine).

a. True

b. False

6. After receiving the recommended, age-appropriate series of acellular pertussis-containing vaccines, the estimated duration of protection against acquiring whooping cough is:

a. Approximately 12 to 14 years

b. 7 to 10 years

c. 3 to 4 years

d. Less than 1 year

SUN EXPOSURE, SKIN CANCER & PREVENTION

By Melissa King, DO

Objectives

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

1. Understand the effects of sun exposure and the risks for developing skin cancer.
2. Describe the properties of sunscreen.
3. Identify the recommendations for prevention, screening and surveillance.

Introduction

In the past year have you had any episodes of sunburn? What about your family members? How many of your patients have had any degree of sunburn upon presentation to you? Did you take that opportunity to provide anticipatory guidance regarding sun exposure/protection?

Headlines about sunscreen and protection from the sun are everywhere in news, magazines and social media. There are benefits to sun exposure such as vitamin D production and mood elevation. There are also risks including premature aging, wrinkles and skin cancer. With the increasing prevalence in skin cancers in the United States linked to sun exposure, the risks appear to be far greater than any benefits. There are widely published recommendations to significantly reduce this risk of skin cancer, including the use of sunscreen. Unfortunately, there is a lot of public confusion surrounding the safety, efficacy and instructions for the use of sunscreen.

Sun exposure and the risk involved

The sun gives off solar energy that causes rays of light across the spectrum to strike the body. The effects from this energy on the skin range from minor, such as the sensation of heat caused by the visible and infrared rays, to major, such as breakdown of cellular DNA and cancer. Ultraviolet radiation A (UVA) and ultraviolet radiation B (UVB) are known carcinogens and have been linked to skin cancer. UVA rays are long wavelengths that penetrate the skin into the dermis causing breakdown of collagen and leading to premature aging and wrinkles. UVB rays are shorter and thus only penetrate to the epidermis but the effect is sunburn and cell damage.[5] While UVB radiation intensity varies with season and geography, UVA radiation is constant. The combination of these rays seems to have the most deleterious effects. Broad spectrum sunscreen allows for protection from both UVA and UVB rays.[2]

Sunburns

Sunburn is photochemical reaction which requires that light be absorbed into the skin at a sufficient dose to cause a reaction. Everyone is at risk for developing sunburn. The Environmental Protection Agency (EPA) developed a UV index that is published daily and hourly. This index provides a risk rating for overexposure to the sun that could cause sunburn, with low numbers correlating to lower risk.

In 2004, the Centers for Disease Control and Prevention (CDC) conducted a survey in which more than 40 percent of caucasian Ohio adult males and females self-reported having at least one episode of sunburn in the past year.[1] In 2002, Gellar published a study in Pediatrics where 10,000 children 12 to 18 years of age were surveyed; 83 percent self-reported at least one episode of sunburn during the previous summer and 30 percent reported having three or more sunburns.[6] One major concern from these surveys that are reporting a high incidence of sunburns is highlighted by a study out of the journal *Cancer Epidemiology Biomarkers and Prevention*. This study concluded that the largest risk factor for developing a skin cancer was experiencing blistering sunburns, especially five or more between 15 to 20 years of age.[1]

Skin cancer

According to the CDC, skin cancers including basal cell carcinoma, squamous cell carcinoma and melanoma are the most common types of cancer in the US. These cancers are linked to sun exposure and ultraviolet radiation (UVR). Melanoma, although the most common form of skin cancer in pediatric patients, is still rare in children. Approximately 400 new cases are diagnosed each year and this population has a high cure rate. Certain pediatric patient populations have increased risk, including patients with giant congenital melanocytic nevus, post chemotherapy or renal transplant patients, survivors of retinoblastoma and patients with genetic conditions such as xeroderma pigmentosum. The children who develop melanoma may also have a history of the common risk factors such as frequent sunburns, fair hair and freckles, and light complexion.[6]

The impact of skin cancer is widespread and devastating. Skin cancer can affect anyone, at any age. Of the five million skin cancer cases diagnosed each year, an estimated 9,000 lives are lost due to melanoma. Locally, 300 to 400 Ohioans lose their lives to melanoma every year. Although genetics and skin type play a role, we know that with skin cancer, prevention matters.

What is sunscreen?

Sunburn is a chemical reaction between the sun and your skin. Therefore, sunscreens seek to interrupt this reaction via different mechanisms such as formulation, spectrum coverage and sun protection factor ratings (SPF).[2] Sunscreen is a chemical placed on the skin that either chemically converts UV radiation received into nonharmful wavelengths or physically blocks the absorption of the UV radiation. Sunscreen was originally designed to prevent sunburn caused by UVB radiation, but has expanded to include protection from UVA radiation.

Formulation types

There are organic and inorganic types of sunscreens *(Table 1)*. The organic sunscreens, previously known as chemical absorbers, absorb UVR and convert it into heat energy. The older generations are strong UVB absorbers and strongly bind keratinocytes, allowing them to also be water resistant. This absorption of the sun's energy is protective, but can cause side effects including allergic reactions and skin staining. After about two hours the sunscreen breaks down and becomes less effective, necessitating frequent reapplication. The newer generations of organic sunscreens have less associated skin reactions and are broader spectrum with enhanced UVA protection; however, they are also less potent and less water-resistant. Often these agents are used in combination for improved efficacy to maximize spectrum protection and minimize side effects.

The inorganic sunscreens such as zinc oxide and titanium dioxide reflect or scatter UV radiation with little to no absorption into the body. Because these agents act as a barrier, they are applied to the skin in thick layers. For cosmetic reasons, these agents were not preferred until recently. Due to limited absorption into the skin, these agents are preferred for children. In addition, for parents, the opaque nature allows one to see where application has occurred which generates better coverage.

Vehicles

Various vehicles for applying the sunscreens include water-based gels, creams, lotions, sprays, sticks and cosmetics. Vehicle type can affect the efficacy of the agent, durability of the product and water resistance; however, the tolerability by the consumer affects use and frequency of application. The lotions and creams are well tolerated and the most common, often used in cosmetics. Gels are often preferred by those with oily skin or acne. People tend to use sticks on the lips and nose area. Sprays are well liked by the consumer, but are difficult to apply uniformly and consistently. Additionally, with wiggly children there is risk to getting into mucous membranes (eyes, mouth and nose). There are pros and cons to each type of vehicle; the key is recommending something that families will use regularly and apply frequently.

Spectrum of protection

As previously mentioned, UV radiation includes UVA and UVB radiation. Sunscreen agents typically provide the best coverage over a specified range of light wavelengths. Older agents targeted UVB rays whereas newer products target both UVA/UVB rays. Often different ingredients with different spectrum coverages are combined to optimize the effect. This is now labeled as broad spectrum.

Water-resistance

Water-resistant products maintain their photoprotective properties for two 20-minute exposures to water. Very water-resistant products provide protection for at least four 20-minute exposures to water. These terms have recently been standardized by the FDA in order to provide a more consistent experience for the consumer.

Sun protection factor (SPF)

One frequently misunderstood component of sunscreen labeling is the SPF rating. The SPF rating is a ratio comparing the amount of UVR that produces sunburn on protected skin versus unprotected skin. An SPF of 15 correlates to protection from 93 percent of UVB rays, whereas an SPF of 30 is NOT double the protection, but rather protection from 97 percent of UVB rays. This designation can be misleading to the undereducated consumer because it does not take into account protection from UVA. The protection from UVA is designated by a four-star rating system with four stars providing the most protection.

What are the recommendations?

In 2011, the US Preventive Services Task Force recommended all primary care physicians provide sun protection counseling for those children and adolescents at risk for sunburn. As a response to the increasing rate of skin cancer diagnosis in the US, the US Surgeon General gave a "Call to Action" in 2014 addressing skin cancer prevention. The Surgeon General's report highlights the importance of a multifaceted approach to increase public health awareness and reduce the burden of these diseases for our nation. Universal recommendations for the use of sun protection are noted in Table 1.

Table 1. Recommendations for sun protection

- Wear sun protective clothing: wide-brimmed hats, sunglasses, long-sleeved clothing.
- Apply one ounce of sunscreen with SPF 30, water-resistant, broad spectrum.
- Reapply every two to three hours, more frequently with water submersion/sweating.
- Seek shade from direct sunlight, use umbrellas.
- Limit exposure to sun during peak hours: 10:00 am to 4:00 pm.
- Avoid artificial sources of ultraviolet light such as indoor tanning.

Infants under 6 months of age

- No direct sun exposure
- Keep skin covered with clothing, hats, sunglasses
- No sunscreen recommended

Anticipatory guidance

All children should follow the recommended schedule for routine well child exams. This provides the opportunity for the clinician to see the child, assess their skin and provide the recommended anticipatory guidance for sun exposure protection.

Tips for providing anticipatory guidance:

- Review the patient's risk factors, personal history, family history, sun exposure and sun protection practices. Consider use of the risk screening questionnaire and, if positive, increase the amount of education you provide.
  - Have you ever had a sunburn? If yes, did it blister? How many times in your lifetime? Were you under 18 years of age?
- Review the universal recommendations for sun protection.
- Provide skin surveillance with appropriate referral to dermatology.

Community-based ideas/programs

- Use smartphone applications that send daily text reminders to apply sunscreen.
- Implement mandatory sunscreen distribution and education on appropriate use at high sun exposure locations: school/day cares, public pools, sports teams.
- Create single day or single use application packaging for improved convenience.
- Use novel packaging concepts such as Blue Lizards, a color changing bottle that alerts users to the need for sunscreen.
- Host skin cancer screening events and provide education regarding sun exposure.

Surveillance

Surveillance for skin cancer changes should be targeted to individuals with a family or personal history of melanoma, an individual with more than 50 moles and persons over the age of 65 years. In evaluating skin changes and moles, you are likely to remember the ABCDE criteria. There has been discussion regarding the applicability of these criteria to pediatric patients. As pediatricians we are all too aware that children are not just

little adults. One study published in the *Journal of American Academy of Dermatology* was a retrospective chart review looking at 70 patients, age 20 years or younger, diagnosed with skin cancer. The lesions in a large number of these patients presented with atypical criteria such as a loss of pigment, bleeding or itching. It is important to use the typical and the atypical criteria for detecting melanoma in children.

In conclusion, skin cancer and melanoma incidence are on the rise. Protection from sun exposure and prevention of skin cancer must be discussed frequently with every one of our patients. Patients should be encouraged to protect themselves by both avoidance and sunscreen. The ideal sunscreen would provide protection from both UVA and UVB radiation, not break down easily so that frequent application is not necessary, be water-resistant and be tolerated on the skin as to not create irritation, allergy or being uncomfortable, or unsightly to wear. We can make a difference!

References

1. Centers for Disease Control and Prevention (CDC). The Surgeon General's call to action to prevent skin cancer. http://www.surgeongeneral.gov/library/calls/prevent-skin-cancer/index.html
2. Cordoro KM, et al. Pediatric melanoma: Results of a large cohort study and proposal for modified ABCDE detection criteria for children. *J Am Acad Dermatol.* 2013:68(6):913-925.
3. Mallory SB, Watts JC. Sunburn, sun reactions, and sun protection. *Pediatric Annals.* 1987:16(1):77-84.
4. Sambandan DR, Ratner D. Sunscreens: *An overview and update. J Am Acad Dermatol.* 2011:64(4):748-758.
5. Wu S. Blistering sunburns in adolescence linked with 80% higher risk for melanoma. *Cancer Epidemiol Biomarkers Prev.* 2014. doi:10.1158/1055-9965. EPI-13-0821.
6. Jen M, et al. Childhood Melanoma. CID. 2009;27: 529-236.

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CME Questions

7. Which of the following statements is true regarding the effects of radiation on the skin?

a. A base suntan caused by UV radiation is protective against further damage from the sun.

b. UVB radiation penetrates deep into the skin causing wrinkles and early aging.

c. UVA radiation is primarily responsible for causing sunburn and cellular DNA damage.

d. Protection against UVA and UVB radiation is important to prevent premature aging and wrinkles, and to reduce the risk of skin cancer.

8. Sunscreens with SPF of 30 are twice as strong as sunscreens with SPF of 15.

a. True
b. False

9. All of the following statements regarding sun protection are true, EXCEPT:

a. Sunscreen should be applied thickly and evenly to all sun exposed areas.

b. Sunscreen should be applied every two hours or after being in the water for 40 minutes.

c. The average adult will use approximately one ounce of sunscreen with every application to cover sun exposed areas.

d. All sunscreens provide the same protection.

CASE REPORT:

MORE THAN JUST A CONSTIPATED BABY

By Angel Belgard, MD
Eric Shepard

A 2-month-old male presented to Dayton Children's Hospital. This baby was born at term after an uneventful pregnancy and was discharged at two days of age. The infant had been breastfed and gaining weight; however, beginning four weeks prior to admission, the patient began with constipation, frequently only having one bowel movement or less per day.

Objectives

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

1. Review the diagnostic approach to infants presenting with hypotonia and increasing weakness.
2. Describe management of an infant with suspected infant botulism.

Nine days prior to admission, he presented to the emergency department with decreased nursing, diminished urine output and dehydration. He had a two-week history of nasal congestion as well. He was admitted for intravenous fluids. A nasopharyngeal swab was submitted for viral studies and was positive for rhinovirus/enterovirus. Blood cultures remained sterile. An electrocardiogram and echocardiogram were normal. A lactation consultant believed that the child's less-than-vigorous suck was due to his nasal congestion.

For the two days after discharge, however, the patient continued to have poor feeding. His parents insisted that he had just two bowel movements in the last week. They observed the baby to be less active than usual and thought his cry was barely noticeable. The infant appeared to be very weak when held and had remained afebrile. There were no seizures noted. Since hospital discharge, the baby had been fed both formula and breast milk.

The patient's mother and father are healthy. There were no known ill contacts and no contact with animals. The baby's mother reported ingestion of honey over the last few weeks, but did not feed any to the baby.

The baby was admitted to the newborn intensive care unit. Repeat nasal swab for viral pathogens identified no viral targets. Cerebrospinal fluid (CSF) had three white blood cells. A CSF viral polymerase chain reaction assay (PCR) was negative for herpes simplex virus and enterovirus. Thyroid studies, creatinine kinase, electrolytes, ammonia, lactate and liver function tests were within normal limits. Organic and amino acid studies were collected. The white blood cell count was 4,400 with 75 percent lymphocytes. The hemoglobin was 10.9 g/dL and platelet count 454,000. A urinalysis was normal. A chest radiograph and computed tomography of the head were normal. Bacterial cultures of blood, CSF and urine remained sterile. Consultations were submitted to genetics, infectious disease and neurology.

Physical examination revealed a quiet but alert infant with a weak cry. His pulse was 158 beats per minute, respiratory rate 32 breaths per minute and temperature 36.9° C. Blood pressure was

normal. He was normocephalic with a soft, flat fontanel. Extraocular muscles appeared intact, pupils were equally round and reactive to light. No ptosis was observed. Ears, nose and oropharynx appeared normal. He was not drooling and had an intact gag reflex. There was no adenopathy. The chest was clear. Heart sounds were normal with no murmurs. Distal pulses were full and symmetrical. The abdomen was soft without hepatosplenomegaly or masses. Genitourinary examination was normal. His skin had neither rashes nor lesions and turgor was normal. He moved all extremities, had symmetrical facial appearance and cranial nerves appeared grossly intact. He had a poor suck with obvious truncal weakness and diminished head control.

Nerve conduction studies of upper extremities were normal. Electromyography of the upper and lower extremity muscles was normal. Repetitive nerve stimulation at 50 Hz demonstrated facilitation (potentiation) of the evoked muscle action potential, which can be seen in botulism.

A stool specimen was collected for *Clostridium botulinum* culture and for assay for botulinum toxin. Botulism immune globulin, human, was procured and the child was treated on the clinical suspicion of infant botulism. The Ohio Department of Health eventually alerted the hospital that the stool toxin assay was positive for botulinum toxin A. The infant was hospitalized for 16 days. He did not require ventilator support. The baby was seen in the clinic a week after discharge, and while still having some mild constipation, he was otherwise fine.

Epidemiology

There are three main types of botulism: foodborne, wound and infant botulism. Foodborne botulism occurs from the consumption of preformed botulinum toxin, often associated with canned foods. Wound botulism is rare and occurs when an open wound becomes inoculated with clostridial bacteria. Infant botulism is associated with the consumption of *C. botulinum* spores which germinate within the immature gut producing botulinum toxin in the large intestine. Infant botulism was first recognized in 1976 and has been identified as the most common form of botulism in the United States. Fewer than 100 cases are identified annually. The spores of the bacteria are found naturally occurring in soil and dust, most commonly in California, Washington, Utah and Oregon, but are found worldwide.[1] The risk of exposure increases in more rural areas or when parents of the child consistently work with soil. Historically, honey was identified as the culprit in infant botulism cases, but with increased public awareness, it is now associated with only 20 percent of the cases.[1]

Pathogenesis

The responsible bacteria causing disease are *Clostridium botulinum, Clostridium baratii* and *Clostridium butyricum*. All are anaerobic, gram positive, spore forming, toxin-producing organisms. The bacteria have the potential to produce one of eight distinct neurotoxins (A-G). The main types affecting humans are type A in the Western United States and type B in the Eastern US.[2] Botulinum toxin is carried by the bloodstream to peripheral cholinergic synapses, where it binds irreversibly, blocking acetylcholine release and causing impaired neuromuscular and autonomic function. The toxin can be deadly, 15,000 times more potent than Sarin nerve gas. A one microgram oral dose can result in death, rendering it the most lethal substance known.[1,2]

Clinical manifestations

Infant botulism typically occurs in children less than 12 months of age. Clinical manifestations result from cholinergic blockade of both autonomic and neuromuscular junctions. Presentations range from mild hypotonia to severe paralysis.[2,3] Parents may note that the baby feeds poorly. A breastfeeding mother may notice breast engorgement because the baby's suck is weak and not sustained. The infant becomes lethargic and listless. Oculomotor palsies, a blunted facial expression and poor head control may be seen. Respiratory effort may become shallow and rapid, and the cry is feeble. Drooling may become more noticeable. Autonomic dysfunction by way of constipation may be one of the earliest signs, occurring just a few days after toxin ingestion. The ensuing motor weakness is symmetrical and descending, starting with the cranial nerves, followed by the trunk, extremities and finally, the diaphragm. Cranial nerve deficits may initially manifest as ptosis (which may not be evident

until the infant's head is held erect) with sluggish pupillary light reflex. As the paralysis progresses, decreased truncal tone, loss of head control and decreased deep tendon reflexes are noted. The infant typically is afebrile and non-toxic appearing. Infant botulism is a self-limiting disease, generally lasting two to six weeks, or longer. A "catastrophic" presentation of infant botulism with a paucity of the usual clinical signs has been observed.[2,3]

Differential diagnosis

Infant botulism requires a high index of suspicion for early diagnosis. The differential diagnosis can be fairly broad and inclusive of conditions associated with infant hypotonia, polyneuropathy or diseases of the central nervous system (Table 1).

Diagnostic workup

The diagnostic workup is focused on ruling out other causes of hypotonia in an infant. Blood, urine and CSF cultures are generally normal, as well as metabolic and hepatic profiles. An edrophonium (Tensilon®) challenge can be carried out, but runs the risk of giving a false positive result. Electrophysiology may show incremental decrease in nerve conduction with repetitive stimulation, but this can be a nonspecific finding. In order to confirm a diagnosis of infant botulism, a stool sample must be obtained and analyzed for toxin and/or organism. In order to most effectively carry out this test, 25 mL of stool are needed and sterile water enema (due to constipation) is preferred to avoid disrupting the assay. Serum toxin analysis is not recommended due to its poor sensitivity.[3]

Table 1. Differential diagnosis of infant botulism

- Infections: sepsis, meningoencephalitis
- Systemic etiologies: electrolyte imbalances, dehydration
- Metabolic causes: organic acidemias, poisonings, hepatic encephalopathy
- Neuromuscular disorders:
- Congenital myasthenia gravis
    - Congenital myasthenic syndromes
    - Poliomyelitis
    - Spinal muscular atrophy
    - Guillain Barre syndrome
    - Tick paralysis
    - Congenital myopathy

Treatment

Infants with botulism should be managed in a newborn intensive care unit. Aggressive supportive care, especially respiratory and nutritional support through nasogastric tube feeding is vital.[3] Transcutaneous carbon dioxide (pCO_2) monitoring can be a very sensitive index of clinical deterioration early in the illness. A steadily rising pCO_2 signals that the patient may soon need intubation and mechanical ventilation because of waning respiratory muscle effort. About 50 percent of infants will require mechanical ventilatory support because of inability to protect their airway and/or respiratory insufficiency.[2] Some infants may require prolonged ventilator assistance.

The Infant Botulism Treatment and Prevention Program of the Division of Communicable Disease Control, California Department of Health, should be contacted immediately to review a suspected case and arrange for shipping of botulism immune globulin, human (BabyBIG®). The medication consists of human-derived, pooled antibodies to botulinum toxins A and B. Only a single infusion is required. However, it is expensive, costing approximately $45,000.[3] While costly, it has been estimated that administration of this immune globulin can decrease an expected hospital stay by three weeks and save approximately $88,000 in hospital costs. BabyBIG® has a half-life of approximately 28 days and neutralizes toxin for six months. Importantly, the decision to treat an infant with BabyBIG® should be based on clinical presentation and findings and not be delayed by waiting for results of botulism laboratory confirmatory testing.[4,5] The main, identified adverse effect of BabyBIG® is a temporary rash.

Patients with infant botulism excrete both C. *botulinum* toxin and organisms in their stools. Accordingly,

diapers from these infants should be placed in biohazard containers. Careful attention to hand washing should be observed by all who have contact with the infant. Excretion of organisms in feces may continue for as long as three months in infant botulism patients (and even longer in rare instances). Consequently, close contact between these babies and other infants (e.g., sharing crib and toys) should be avoided while such excretion may be continuing.[3]
The patient may be discharged from the hospital when the infant has shown steady recovery and is able to feed by mouth (or when the parents are comfortable with gavage feeding).

The healing process in botulism consists of sprouting of new terminal unmyelinated motor neurons. Movement resumes when these new twigs locate noncontracting muscle fibers and reinnervate them by inducing formation of a new motor end plate. A slow, long recovery is common. Autonomic function returns more slowly than does neuromuscular activity.[1]
Constipation may persist for months.
The mortality of recognized cases of infant botulism is estimated at approximately 2 to 5 percent.[4,5] With early identification and proper care, however, full recovery without residual weakness is normal.

Prognosis

References

1. Arnon SS, Schechter R, Maslanka SE, Jewell NP, Hatheway CL. Human botulism immune globulin for the treatment of infant botulism. *New Engl J Med.* 2006; 354(5): 462-71.
2. Fox CK, Keet CA, Strober JB. Recent advances in infant botulism. *Pediatr Neurol.* 2005; 32:149-54.
3. Ketcham EM, Gomez HF. Infant botulism: A diagnostic and management challenge. *Air Med J.* 2003;22(5):6-11.
4. Rosow LK, Strober JB. Infant botulism: Review and clinical update. *Pediatr Neurol.* 2015;52(5):487-92.
5. Underwood K, Rubin S, Deakers T, Newth C. Infant botulism: A 30-year experience spanning the introduction of botulism immune globulin intravenous in the intensive care unit at Children's Hospital Los Angeles. *Pediatrics.* 2007;120(6):e1380-5.

Useful resources

- Infant Botulism Treatment and Prevention Program of the Division of Communicable Disease Control, California Department of Health at ibtpp@infantbotulism.org, 510-231-7600
- Botulism – Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases http://www.cdc.gov/nczved/divisions/dfbmd/diseases/botulism/

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CME Questions

10. Infant botulism:

a. can occur following ingestion of *C. botulinum* toxin in prepared foods.

b. follows germination of spores of *C. botulinum* in the intestine.

c. is caused by ingestion of only a single *C. botulinum* type of neurotoxin.

d. is caused by a neurotoxin with the same molecular action as tetanus toxin.

11. The majority of botulism cases in the United States are:

a. foodborne.

b. in infants.

c. from infected wounds.

d. inhalational when aerosolized botulinum toxin is inhaled.

12. Based on clinical manifestations and initial diagnostic evaluations, a hypotonic 3-month-old girl is strongly suspected of having infant botulism. Botulism immune globulin, human (BabyBIG®) should be given:

a. due its expense, only after all other etiologies of hypotonia are ruled out.

b. following confirmation of botulinum toxin in a stool assay.

c. before the results of stool botulism confirmatory testing are final.

d. solely to children who necessitate mechanical ventilation.

UPDATE

Specialized MRI Helping Personalize Treatment

Dayton Children's joins the select league of children's hospitals offering advanced imaging of the upper airway, called a cine MRI. With the addition of special software, the 1.5 or 3.0 Telsa MRIs can visualize airway dynamics, identify the site of obstructions and precisely measure the severity of blockage. Specialists can then create a treatment plan personalized to the exact specifications the patient needs, improving outcomes.

Launched in March, 2016, a multidisciplinary team of specialists from otolaryngology, radiology, sleep medicine and anesthesia expect to do 25 procedures a year. It has been especially helpful so far in deciding treatment options with the greatest likelihood of success for obese sleep apnea patients and diagnosing airway abnormalities in children, especially those with genetic syndromes or craniofacial dysmorphism.

Expanded alliance will better serve urology patients

Dayton Children's and Nationwide Children's announce the addition of urology services to the existing joint venture between both hospitals called the Ohio Pediatric Care Alliance. This collaboration will allow families to get in to see a urology specialist sooner at Dayton Children's, improving access. Dayton-area patients will still see their favorite doctors, nurses and support staff, close to home, with additional staff to see new patients and those needing urgent appointments.

Dayton Children's and Nationwide Children's created the Ohio Pediatric Care Alliance in 2014 to provide a structure for the organizations to work together to improve access to specialty care services, collaborate on quality of care and patient safety initiatives, and avoid duplication of services. The first initiative was a joint operation serving the families of Springfield with pediatric specialty care.

Clinical-community linkage leading effort to help kids breathe easier

A doctor's reach can be limited in helping children cope with asthma. 60 percent of a child's health is determined by his or her environment and behavior. So Dayton Children's, Dayton Public Schools and Public Health Dayton & Montgomery County created the Dayton Asthma Alliance.

To have the greatest impact and to ensure all children with asthma have the opportunity of optimal health outcomes, the Alliance identified three strategic focus areas.

- Ensure asthma-friendly environments
- Enhance access to high quality healthcare and supportive social services through clinical-community linkages
- Educate and equip children, families and the community for asthma wellness

One of the first pilot programs is providing a home visit by a community health worker and air quality specialist to help identify and remediate environmental triggers for students with asthma.

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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Your answers to CME questions

(Please circle the BEST answer.)

1.	a	b	c	d	
2.	a	b	c	d	
3.	a	b			
4.	a	b	c	d	e
5.	True	False			
6.	a	b	c	d	
7.	a	b	c	d	
8.	True	False			
9.	a	b	c	d	
10.	a	b	c	d	
11.	a	b	c	d	
12.	a	b	c	d	

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