



# VIRGINIA • PEDIATRICS

## American Academy of Pediatrics • Virginia Chapter

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American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Virginia Chapter

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## 2015 Legislative Preview

AIMEE SEIBERT,

VIRGINIA CHAPTER LOBBYIST



The 2015 legislative session began on January 14, 2015. It will be a short session this year, ending on February 28. Here are our priorities and the bills we will be actively supporting this year:

### Prior Authorization

One of MSV's biggest priorities this session will be introducing a bill to alleviate the current administrative burden on physicians as they navigate the maze of prior authorization processes for pharmaceuticals. This is a huge area of frustration with pediatricians, especially when their patients change health plans and then the process to prescribe certain drugs changes dramatically. Senator Newman and Delegate Habeeb will be patroning these bills.

### Liquid Nicotine/E-Cigarettes

In 2014, we supported legislation to ban the sale of e-cigarettes for minors. Vapor products are now included in the definition of tobacco and minors are prohibited from purchasing them. Throughout Virginia and the country, there has been a rapid increase in poisonings from liquid nicotine, which is used to refill e-cigarettes. Liquid nicotine can be harmful or even deadly in certain amounts, if ingested or absorbed by the skin. Children are especially susceptible to this and sometimes mistake the flavored liquid for something they can ingest. We will be introducing legislation for 2015 that would require child-resistant packaging on liquid nicotine containers. Other states have passed similar legislation. Delegate DeSteph and Senator Stuart will be carrying this legislation for us.

### Smoking in Cars

We will continue to work on legislation to prohibit smoking in cars with children under the age of eight. We made significant progress last year when this bill successfully passed out of the House subcommittee for the first time. We have been able to garner more support for this bill every year and we will continue to work with fellow stakeholders on this important legislation. Delegate Pillion, who was recently elected and represents parts of Southwest Virginia, will be carrying the legislation this year.

### Epinephrine in Schools

As you know, we passed legislation a few years ago to require public schools to have auto-injectable epinephrine under standing orders. Legislation will be filed this year to amend the language, to account for private schools that educate public school children. This will guarantee that the law will protect all public school students in Virginia. Delegate Greason is carrying this bill.

### Maternal Mental Health Month

Delegate Robinson will be carrying a resolution designating May of every year as "Maternal Mental Health Month." This is a great way to raise awareness every year to this important issue and educate people on the risk factors and symptoms of postpartum depression.

### Stay Tuned!

As always, we know there will be additional bills filed that we will support or oppose and as your legislative team, we will be ready to alert you and education the legislature on VA AAP's position on bills.





## President's • MESSAGE

Barbara M. Kahler, M.D. | *President Virginia Chapter | American Academy of Pediatrics*

There has been some discussion on the Chapter list serve about several issues concerning Medicaid in Virginia.

We are currently being presented with two issues. The first is the loss of the Medicaid reimbursement “bump” that Congress did not extend. Those of us who take Medicaid, depending on the percentage, will lose the increase in revenue. Concern has been expressed about practices declining to continue to see patients with Medicaid and/or those patients being shifted back to more expensive ER care. This could also be enough of an economic burden that practices may be forced to close their doors.

In an effort to find out what National is doing, I called The Federal Affairs Office in Washington, DC to see what their current strategy is. I spoke with Bob Hall who is working on this. He and the staff in DC are working with Sen. Brown from Ohio to reintroduce a bill to restore the Medicaid “bump,” hopefully by March. He is asking anyone with stories of how patients and practices have been adversely affected by the decrease in reimbursement to send them to him at [rhall@aap.org](mailto:rhall@aap.org). Also speak with your Federal Legislators about how this decrease has affected you and your patients.

The second is the refunding of CHIP (the Federal program). National is again working with Sen. Brown to submit legislation to refund this program by September. Again, we all need to contact our Congressional leaders to help them understand the impact these programs have on some of their most vulnerable constituents.

If we want to continue to have a majority of the children of the Commonwealth covered by health insurance, in light of Virginia’s choice not to expand Medicaid we must do all we can to make sure those who represent us, understand the implications these issues have.



## Dates to Remember ...



### 2015 Pediatric Conferences

#### Clinical Challenges in Pediatric Primary Care 2015

March 7, 2015 - 8 a.m. - 3 p.m.

“Population Health: From the Bedside to the Community”  
Speaker: Colleen Kraft, MD, FAAP

#### Lewis Ginter Botanical Garden

1800 Lakeside Avenue  
Richmond, VA.

Contact: Sherry Black 804/228-5971 or  
visit [www.virginiapediatrics.org](http://www.virginiapediatrics.org).

#### 35th McLemore Birdsong Pediatric Conference

April 17 - 19, 2015

Wintergreen Resort, Virginia

For more information and registration go to [www.cmevillage.com](http://www.cmevillage.com)

#### VA-AAP 1st Annual Art & Business Conference

May 15 & 16, 2015

The Westin Richmond

6631 W. Broad Street | Richmond, VA

The conference format will be a morning General Session, the Breakout Sessions will be a School Health, Business of Pediatrics and Breastfeeding. Sessions specifically designed to meet today’s needs for all participants!

Contact Jane Chappell [jchappell@ramdocs.org](mailto:jchappell@ramdocs.org)  
for more information.

#### 2015 Peds at the Beach Conference

July 17-19, 2015

Wyndham Virginia Beach Oceanfront Hotel  
Virginia Beach, VA

Register Online at [www.vcuhealth.org/cme/register](http://www.vcuhealth.org/cme/register)



Present

# VIRGINIA•PEDIATRICS NEWSLETTER

American Academy of Pediatrics – Virginia Chapter

## Continuing Medical Education

This activity has been planned and implemented in accordance with the Essential Areas and policies of Medical Society of Virginia through the joint sponsorship of Children's Hospital of The King's Daughters and the American Academy of Pediatrics – Virginia Chapter.

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For providers, significant relationships include large research grants, institutional agreements for joint initiatives, substantial gifts or other relationships that benefit the institution. For speakers, significant relationships include receiving from a commercial company research grants, consultancies honoraria and travel, other benefits, or having a self-managed equity interest in a company.

### Disclosures:

The following faculty have disclosed that they do not have an affiliation with any organization that may or may not have an interest in the subject matter of this CME activity and/or will not discuss off-label uses of any FDA approved pharmaceutical products or medical devices.

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Otto Louis-Jacques, MD

Robert D. Fildes, MD  
Benjamin Solomon, MD

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None.

## Genomic Sequencing in Clinical Genetics

Benjamin D. Solomon, MD<sup>1</sup>

<sup>1</sup>Chief, Division of Medical Genomics,  
Inova Translational Medicine Institute,  
Inova Children's Hospital

**Objective:** Participants will be able to describe how current Genomic Sequencing technologies are changing the practice of clinical pediatric genetics.

**ACGME Competencies:** Patient Care and Medical Knowledge



In many fields of medical practice, the standard approach to diagnose a condition follows the “House” method (in reference to the popular television show). That is, based on a patient’s signs and symptoms, the most likely disorders are tested for first. If no answer is found, more testing may be done, and on and on until either an answer is achieved or the differential diagnosis is exhausted. Sometimes, patients with especially challenging or confusing presentations may also participate in research studies in an effort to find explanations. In the case of “House,” the answer is neatly wrapped-up, albeit with a great deal of sound and fury, in a little under an hour. In real life, things usually play out over the course of months or years, and the chance of success depends on a number of factors, including the knowledge and experience of involved clinicians, the availability of a diagnostic test, and how aggressively patients and families work to find specialists and have testing performed.

The field of pediatric genetics has long followed this classical tiered approach. However, new genomic technologies are challenging the way things have traditionally been done. These technologies include whole-exome sequencing (sequencing all known genes, which make up about 1% of a person’s genetic information) and whole-genome sequencing (sequencing the genes as well as the rest of the genetic information).<sup>1</sup>

More specifically, there is growing evidence that conducting genomic sequencing at the

first sign of a disorder of potential genetic etiology is a more efficient, cost-effective, and accurate way to provide answers for patients and families affected by certain types of Mendelian disorders.<sup>2</sup> In other words, instead of testing condition-by-condition, it may be better to apply genomic sequencing as the initial test. This allows many genes and genetic regions to be examined at once – both those that are in the differential diagnosis, as well as novel targets that may not be initially suspected.<sup>3</sup> Further efforts are underway to study whether this approach may have benefits for wider groups of patients potentially affected by genetic conditions.

One of the ways that the Inova Translational Medicine Institute (ITMI) is capitalizing on new genomic technologies is by using these genomic tools to diagnose infants in the Inova Children’s Hospital NICU. Through one of its research studies, ITMI uses trio-based (infant + both parents) whole-genome sequencing to provide molecular diagnoses for those neonates who have disorders that may have a genetic cause. This study has provided answers for neonates with biochemical disorders/inborn errors of metabolism, single or multiple congenital anomalies (“birth defects”), dysmorphic features, and other neonatal presentations that suggest a genetic cause.<sup>4-6</sup> While many of these disorders often fall into the practice of pediatric genetics, virtually all types of inpatient and outpatient pediatricians will encounter such patients. In addition to providing answers for patients and families, and therefore ending the diagnostic odyssey, identifying the precise molecular etiology of a patient’s presentation often directly impacts patient care. In other words, in the field of genetics (and beyond), there are some generally accepted benefits of finding the cause of a condition. These include a better understanding of the condition and its prognosis, which translates to the ability to make more informed medical decisions. Additionally, finding the cause allows counseling

related to the chance of another current or future family member being affected.

However, equally importantly, knowing the cause of an infant’s condition frequently helps provide more tailored medical care, which can directly benefit outcomes. In a recent survey, finding the genetic cause has been shown to alter patient care related to mutations in 49.8% of the 2,873 currently known (as of June 2014 – approximately 12 new such genes are reported each month<sup>7</sup>) individual genes involved in Mendelian disease. Perhaps unsurprisingly, the vast majority (95.6%) of these interventions would take place during the pediatric time frame.<sup>8,9</sup> The fact that precisely identifying the underlying cause of an infant’s disorder can be directly beneficial, coupled with the increasing availability and affordability of genomic sequencing technologies, may hopefully help surmount issues that often heavily affect clinical practice, such as insurance reimbursement policies.<sup>10</sup>

### References

1. Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. *The New England journal of medicine* 2014;370:2418-25.
2. Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med* 2014;6:265ra168.
3. Hennekam RC, Biesecker LG. Next-generation sequencing demands next-generation phenotyping. *Human mutation* 2012;33:884-6.
4. Stittrich AB, Lehman A, Bodian DL, et al. Mutations in NOTCH1 cause Adams-Oliver syndrome. *American journal of human genetics* 2014;95:275-84.
5. Solomon BD, Bodian DL, Khromykh A, et al. Expanding the Phenotypic Spectrum in EP300-Related Rubinstein-Taybi Syndrome. *American journal of medical genetics Part A* 2014; [Accepted; In Press].
6. Bodian DL, Solomon BD, Khromykh A, et al. Diagnosis of an imprinted gene syndrome by a novel bioinformatics analysis of whole genome sequences from a family trio. *Molec Genet Genom Med* 2014; [Epub ahead of print].
7. Solomon BD. Obstacles and opportunities for the future of genomic medicine. *Molec Genet Genom Med* 2014;2:205-9.
8. Solomon BD, Nguyen AD, Bear KA, Wolfsberg TG. Clinical genomic database. *Proceedings of the National Academy of Sciences of the United States of America* 2013;110:9851-5.
9. Solomon BD. Genomic sequencing and the impact of molecular diagnosis on patient care. *Molec Syndromol* 2014; [Accepted; In Press].
10. Steenhuisen J. As sequencing moves into clinical use, insurers balk. *Reuters* June 19, 2014.

## Eosinophilic Esophagitis - An Update

Otto Louis-Jacques, MD

Pediatrician

Pediatric Specialists of Virginia

**Objective:** Participants will be able to explain that eosinophilic esophagitis is a chronic disorder and requires long term follow-up. Recall that symptoms can be subtle or intermittent, leading to delay in diagnosis or lapse in follow-up. Be aware that uncontrolled inflammation appears to lead to fibrosis, structure formation. Discuss the different treatments and their relative effectiveness.

**ACGME Competencies:** Patient Care, Medical Knowledge

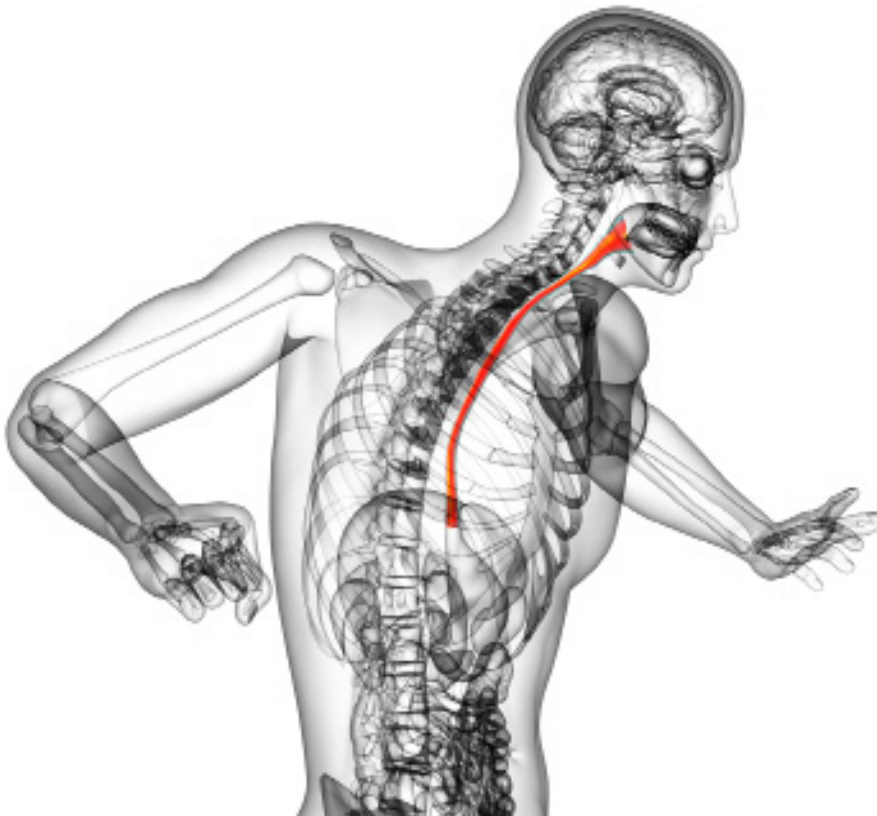
Over the past two decades, eosinophilic esophagitis (EoE) has become widely recognized and most pediatricians have one or several patients with EoE in their practice. While many questions remain about this disorder, our knowledge of its pathophysiology and natural history has progressed. Here, we will review major aspects of EoE, with an emphasis on recent developments.

**Epidemiology:** EoE has been reported in all age groups, with a higher frequency in children and adults <50. EoE is strongly associated with atopic disease; there is also a significant predominance in males (4 to 1) and in Whites. Several studies have confirmed our impression that the number of cases of EoE has been increasing. Recent prevalence

estimates of 0.5-1/1000 people are close to those for inflammatory bowel disease. An increase in incidence (new cases) to approximately 1/10,000 population has been documented in several population based studies. Several factors for this increase in EoE have been identified or hypothesized: an increase in awareness and in the number of endoscopies performed does not fully account for this increase in number of cases. A recent analysis of a national U.S. database found that the prevalence of EoE increases with age, peaks between 35-45 years, then decreases. This suggests a cohort effect, pointing possibly to an environmental factor that appeared in the past 40-50 years and has not affected older individuals. Varying degrees of evidence support a role for a

decrease in tolerance to allergens as a result of improved sanitary conditions (the hygiene hypothesis), environmental factors, including aeroallergens and climatic factors, the decrease in the incidence of *H pylori*, which may have a protective effect on EoE, early life exposures (increased use of antibiotics, cesarean section), a possible role of proton pump inhibitors among others. The strongest evidence points to foods as a trigger for EoE; the reasons for the apparent change in tolerance of foods have yet to be determined. The increased association of EoE with male gender and race, as well as familial cases, suggest a genetic predisposition to EoE. The gene *TSLP* (thymic stromal lymphopoietin), which has been previously linked to asthma and atopic dermatitis, was found to confer an increased risk for EoE. More recently, four novel loci were found to be associated with EoE.

**Clinical presentation and diagnosis:** In children, the clinical presentation of EoE changes with age and symptoms and can fluctuate in an individual. Infants and toddlers generally present with symptoms suggestive of gastroesophageal reflux, feeding difficulties, failure to thrive, whereas older children have nonspecific symptoms such as abdominal pain or vomiting. With increasing age, symptoms more typical of esophageal pathology, such as chest pain, sensation of foreign body in throat, dysphagia become more frequent. As there is no biomarker for EoE and the symptoms and histologic findings are not specific, the 2011 consensus guidelines define EoE as a "chronic, immune/antigen mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation (> 15 eosinophils/hpf)". Therefore, establishing a diagnosis of EoE requires that other causes of esophageal eosinophilia, in particular acid reflux be excluded, either by performing a 24-hour esophageal pH probe/impedance study or



## ... (cont.) Eosinophilic Esophagitis - An Update

by documenting the absence of response to treatment with a proton pump inhibitor (PPI). Even in the absence of excessive acid reflux however, some patients will respond clinically and histologically to PPIs and are classified as having PPI-responsive eosinophilia. The mechanism underlying this response is not established and may not involve an immune process. A small study and our own experience indicate that response to PPI therapy may be temporary.

A recently developed molecular diagnostic test called EoE diagnostic panel (EDP), which is performed on esophageal biopsies, identified patients with EoE with 96% sensitivity and 98% specificity, distinguished patients with EoE in remission from controls, and identified patients treated with topical steroids. In addition, patients with inconclusive biopsies (6 to 14 eosinophils/hpf) who had a positive EDP had a 4.4 fold increased risk of developing active EoE. The major applications of this test, which was recently commercialized, appear to be in predicting if patients with intermediate levels of esophageal eosinophilia or patients previously treated with topical steroids (presumably because of more severe symptoms) are likely to have chronic EoE.

Active search for non-invasive markers is ongoing: serum and stool measurements of proteins derived from eosinophils suggest a possible role for eosinophilic derived neurotoxin, but will require confirmation. The esophageal string test, a modification of the Enterotest whereby the patient swallows a string, to which a capsule is attached and samples of luminal secretions are obtained, showed good correlation between degree of inflammation noted on biopsies and various proteins derived from eosinophils retrieved by the string. This test holds promise for reducing the need for repeated endoscopies and biopsies.

**Treatment:** The two main forms of therapy for EoE include diet changes and topical steroids. Esophageal dilatation is used for treatment of strictures but this does not treat the underlying inflammation. Dietary treatment of EoE includes use of an elemental diet,

removal of foods based on allergy testing and empiric removal of most commonly implicated foods (6 or 8 food elimination diet). A recent meta-analysis of 33 reports (including a total of 1317 patients) of dietary intervention for EoE confirmed that an elemental diet was the most effective (90.8%) in inducing resolution of esophageal eosinophilia. Six-food elimination diet (72.1%) was more effective than food elimination based on allergy testing (45.5%). Topical steroids (fluticasone dipropionate and oral viscous budesonide, OVB) are effective in the treatment of EoE, with studies showing 50-75% resolution of symptoms and inflammation.

Each of these treatments has its own set of challenges: while it is the most effective treatment, an elemental diet is expensive and difficult to maintain over time because of poor palatability, effect on quality of life. Other forms of dietary therapy can also be restrictive and difficult to comply with and, as symptoms do not reliably predict recurrence of inflammation, repeated endoscopies are required to identify the causative foods. Working with a registered dietitian is crucial in helping families navigate dietary therapy and avoiding nutritional deficiencies. The long term use of medications can be a source of concern. Topical steroids have very low bioavailability, so that systemic effects are expected to be negligible. The main side effect of topical steroids is the increased risk of esophageal candidiasis found in up to 15% of patients. Adrenal suppression has not been found in a pediatric clinical trial of OVB, however long term monitoring of growth is advised. On the other hand, a recently validated quality of life module specific to EoE was used to assess the effect of different treatments on patient reported outcomes: researchers found that children with EoE who were treated with topical steroids (and their parents) reported higher quality of life scores than those on elimination diets. These facts highlight the need for an individualized approach to treatment of EoE.

**Natural history and outcome:** EoE is a chronic disorder and esophageal inflammation recurs with discontinuation of treatment (as many as 45% within 12 weeks of discontinuation of prednisone or topical fluticasone

according to one study). Animal studies and in vitro human studies have provided evidence that, over time, tissue remodeling (defined as tissue changes in target organs that result in organ dysfunction) occurs in EoE. It is presumed that ongoing inflammation leads to histologic alterations such as fibrosis and angiogenesis which result in formation of esophageal rings and strictures. This change from an inflammatory to a fibrostenotic phenotype, is similar to the progression seen in Crohn's disease and is the main reason for treating patients with EoE. A recent retrospective study found that the risk of strictures correlated with the duration of untreated disease. In a group of 200 adult patients with symptomatic EoE identified through the Swiss EoE database, the presence of strictures (inability to pass endoscope) increased from 17.2 % (diagnostic delay 0-2 years) to 70.8% (diagnostic delay >20 years). In another study of adults with EoE from a single center, the risk of fibrostenotic features more than doubled with every 10 year increase in age. Notably, there have been no reports of progression of EoE to malignancy. These studies are important as they allow us to quantify the risk of disease progression in EoE. An important question to elucidate is whether our current interventions affect these outcomes.

In summary, EoE is a chronic inflammatory disorder of the esophagus that is being recognized with increased frequency in the U.S. Uncontrolled inflammation appears to lead to fibrosis and stricture formation as a result of tissue remodeling. Effective interventions aimed toward controlling inflammation include removal of dietary antigens and topical steroids. As researchers continue to uncover the reasons for the increase in incidence of EoE and understand its pathophysiology, this will lead to new strategies for treatment and possibly prevention. Currently, studies to confirm the effectiveness of current interventions on progression of disease, assess the effectiveness of less restrictive diets, study non-invasive biomarkers of disease, and of medications specifically formulated for EoE, are areas of ongoing investigation.

## Hemolytic Uremic Syndrome

Robert D. Fildes, MD  
Medical Director  
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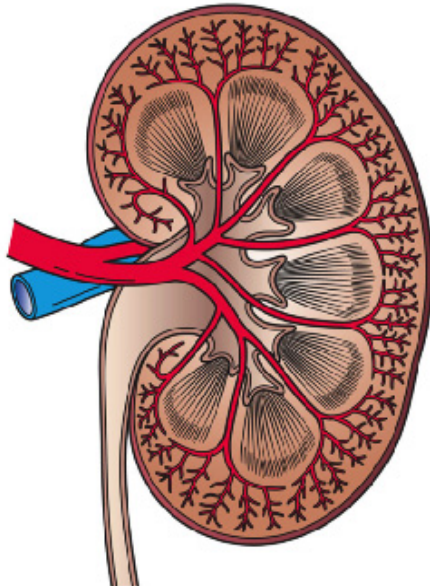
**Objective:** Participants will be able to review HUS in children and new information regarding atypical HUS and its management.

**ACGME Competencies:** Patient Care, Medical Knowledge,

### Background and Etiology.

The hemolytic-uremic syndrome (HUS), initially described by Gasser in 1955, is characterized by the interrelated triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.

Recently, the etiologies of HUS have been differentiated as either **primary** involving



complement dysregulation, or **secondary** including infectious etiologies (eg, Shiga toxin-producing *Escherichia coli* [STEC] and *Pneumococcus*). Other rare causes include inborn error of cobalamin metabolism; drug toxicity in pediatric solid organ recipients and children with cancer; adverse effect of antiplatelet agents, quinine ([http://www.uptodate.com/contents/quinine-pediatric-drug-information?source=see\\_link](http://www.uptodate.com/contents/quinine-pediatric-drug-information?source=see_link)), and oral contraceptives; and complications seen in patients with systemic lupus erythematosus and antiphospholipid syndrome, or pregnancy. Diarrhea positive (D+), shiga toxin (STEC) associated HUS (or “typical” HUS) accounts for 90 % of cases of HUS, and diarrhea negative (D-), non shiga toxin (NSTEC) associated

HUS, or atypical HUS (aHUS) around 5-10 %.

D+ HUS primarily occurs after a prodromal episode of entero-hemorrhagic diarrhea following an infection with Shiga toxin producing strains of *Escherichia coli*. The most common serotype in the United States is O157:H7, which is found in 70 percent of cases, but other serotypes have been reported (O111:H8, O103:H2, O121, O145, O26, O113 and O104:H4 ). The infectious dose of *E. coli* O157:H7 for humans is only 10 to 100 organisms, which is low compared to that of most other enteric pathogens. It principally affects children under the age of five years, but as we have recently witnessed this summer, children of all ages may acquire the illness. The annual incidence of the disease in North America and Western Europe is 2 to 3 per 100,000 children less than five years of age. This disorder is commonly observed during the summer (50% of all cases occur from June to September) and is more frequently seen in rural versus urban populations. Most cases of typical HUS are sporadic, but outbreaks have been reported

*Shigella dysenteriae* type 1 associated HUS occurs in India, Bangladesh, and southern Africa. Although the pathogenesis of disease is similar to that of HUS induced by O157 *E. coli* infection, the disease is usually more severe with an acute mortality rate of 15 percent and over 40 percent of patients develop chronic renal failure

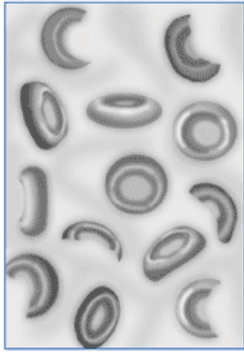
Although found in other animals, cattle appear to be the main vectors of *E. coli* O157:H7, with the bacteria being present in the cattle intestines and feces. Infection in humans occurs following ingestion of contaminated undercooked meat, unpasteurized milk or milk products, water, fruits or vegetables. STEC-associated HUS may also occur in siblings within a few days or weeks of the index family case.

Unlike many other fecal isolates, *E. coli* O157:H7 ferments sorbitol slowly and can be screened for on sorbitol-MacConkey (SMAC) agar. Sorbitol-negative (translucent) colonies can be confirmed as *E. coli* biochemically and, subsequently tested for reaction with antisera to the O157 antigen. Ninety-five percent of cultures positive for *E. coli* O157:H7 come from patients with visibly bloody stools or a history of bloody diarrhea. The rate of stool isolation is substantially higher in the first week after onset of diarrhea.

**Pneumococcal-associated hemolytic uremic syndrome (HUS)** is the second most common infectious cause of HUS. It occurs mainly in young children and infants who usually present with pneumonia. Most patients undergo dialysis treatment, and extra-renal complications are common. There is about a 10 percent mortality rate and another 10 percent of patients with pneumococcal-associated HUS progress to end-stage renal disease (ESRD. After the introduction of the seven-valent pneumococcal vaccine, the incidence of cases due to serotypes 3, 6A, 12F, and 19A, which were not covered in the vaccine, has increased <sup>[4,8]</sup>. The effect of newer vaccines, such as the 13-valent pneumococcal vaccine introduced in 2010 and the 23-valent vaccine (which is only recommended for children below two years of age who are at risk for pneumococcal infection,) on the underlying causative serotype is yet to be determined

Although the pathogenesis of pneumococcal-associated HUS is uncertain, it has been proposed that N-acetyl neuraminidase (sialidase) released during pneumococcal infection might play an important role. Neuraminidase cleaves sialic acid on the cell glycocalyx, resulting in the exposure of the Thomsen-Friedenreich antigen (T antigen) on red blood cells, platelets, and glomeruli. The T antigen is recognized by a natural IgM

... continued from page 7



antibody, a normal plasma constituent, which leads to polyagglutination of patients' red cells and hemolysis. However, two observations argue against a pathogenetic role for the T antigen. First, the IgM is a

cold antibody and

is therefore unlikely to cause agglutination in vivo. Second, T antigen can be detected in approximately half of children with invasive pneumococcal disease without HUS and is not found in children with pneumococcal-associated HUS.

An alternative proposal is based on the finding that desialylation by neuraminidase disrupts complement factor H (complement regulatory protein) binding sites, which would result in the inability of complement factor B to bind with C3 convertase. This would lead to unregulated complement activation and cell injury similar to the mechanism observed in patients with complement-mediated HUS due to identified mutations resulting in complement dysregulation.

**Primary, aHUS** occurs year round and is now considered a genetic disease of complement dysregulation with an underlying TMA as the histologic lesion. Complement-mediated HUS accounts for 5 to 10 percent of HUS pediatric cases and is primarily due to mutations in the genes for complement proteins C3, CD46 (previously known as membrane cofactor protein [MCP]), and complement factors H, I, and B. Acquired complement dysregulation due to antibodies to complement proteins has also been implicated in the etiology of complement-mediated HUS. A heterogeneous disorder, it is usually distinguished clinically by the absence of diarrhea or Shiga toxin-producing *E. coli* infection, but with the same key features of microangiopathic hemolytic anemia, elevated lactate dehydrogenase (LDH) level, thrombocytopenia, and some degree of acute kidney injury.

## Pathophysiology.

All types of HUS are glomerular thrombotic

microangiopathies (TMA). TMA refers to the characteristic pathological features of endothelial cell injury and damage. The endothelial cells develop endotheliosis, become swollen, and detach from their basement membranes. Debris becomes visible in the sub-endothelial space. This allows for the expression of a pro-coagulation phenotype, expression of von Willebrand factor, attraction of platelets and the formation of microthrombi with fibrin deposition.

Multiple factors may contribute to the development of HUS, depending on the underlying etiology. In D+/STEC HUS, endothelial injury appears to be primary, and has been attributed to multiple factors, including direct toxin damage, neutrophil accumulation, and increased release of endothelins and other cytokines and chemokines. Neutrophil accumulation may be induced by one or more of the following mechanisms: toxin-induced activation of leukocyte adhesion molecules (such as E-selectin), toxin-induced secretion of proinflammatory substances (including interleukin-8 and platelet activating factor), or inhibition of apoptosis. Leukocytosis is common in diarrhea-induced HUS and the clinical course and prognosis appear to be related to the degree of elevation in the white cell count. Some have suggested that these observations may be compatible with a pathogenetic role for neutrophil activation.

Shiga toxin may also have a variety of other effects including colonic vascular injury, allowing endotoxin and other inflammatory mediators to gain access to the systemic circulation (the amount and rate of endotoxin absorbed may also affect disease activity); promoting platelet aggregation, which is characteristic of TTP-HUS, up-regulation of tissue factor activity in proximal tubular cells (which may initiate activation of the coagulation pathway), and indirect sensitization of renal epithelial cells to increased heme toxicity.

The central involvement of the kidney in D+ HUS suggests that Shiga toxins have a particular affinity for the renal circulation. Two different observations provide evidence in support of this hypothesis: First, the glycolipid receptors (Gb3) in the endothelial cell membrane that bind toxin appear to be

preferentially expressed in the kidney and glomeruli. As an example, expression in renal endothelial cells is 50 times greater than in umbilical vein endothelial cells. Differential localization of this receptor in infant versus adult kidneys may be partly responsible for the enhanced risk of the disease among children. Second, the bacterial toxin appears to selectively stimulate the release of tumor necrosis factor within the kidney. How this occurs is not clear, but TNF may promote vascular injury in part by increasing expression of the glycolipid receptors. Shiga toxin can also cause apoptosis of and/or significant damage to renal tubular epithelial cells; however, the degree to which direct tubular injury contributes to renal failure in D+ HUS is unknown.

**In primary aHUS**, the complement proteins associated with complement-mediated hemolytic uremic syndrome (HUS) are components of the alternative complement pathway. HUS results from a loss-of-function mutation in a regulatory gene (CFH, CFI, or CD46) or a gain-of-function mutation in an effector gene (CFB or C3). The development of HUS is initiated by a trigger event like an infection or pregnancy, in a genetically predisposed individual with a gene mutation(s) or by the development of antibodies to complement proteins, which leads to uninhibited continuous activation of the alternative pathway resulting in the formation of the membrane attack complex (MAC). This causes results in the endothelium damage leading to activation of the coagulations cascade and thrombotic microangiopathy. A growing number of observational studies suggest that C5 activation is important in the pathogenesis of HUS, thus supporting the use of eculizumab ([http://www.uptodate.com/contents/eculizumab-drug-information?source=see\\_link](http://www.uptodate.com/contents/eculizumab-drug-information?source=see_link)), a humanized monoclonal antibody that binds to complement protein C5, which blocks its cleavage, thereby preventing the production of the terminal complement components C5a and the membrane attack complex C5b-9

## Clinical Presentation.

Children with STEC HUS have a prodromal illness characterized by abdominal pain, vomiting, and diarrhea that immediately precedes the development of HUS. As noted above, the prodromal illness is followed

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within 5-10 days by the sudden onset of the triad:

## 1. Microangiopathic hemolytic anemia.

Hemoglobin levels are usually less than 8 g/dL. The peripheral blood smear is characterized by the large number of schistocytes and helmet cells, serum LDH levels are characteristically very high, haptoglobin levels low, bilirubin may be elevated, and the Coomb's test is negative. The severity of the anemia does not correlate well with the severity of the renal disease. A brisk leucocytosis and reticulocytosis are often observed early in the course.

2. **Thrombocytopenia.** Platelet counts often drop to  $\leq 40,000/\text{mm}^3$ , and do not correlate well with the severity of the renal disease.

3. **Acute kidney injury.** The severity of renal involvement ranges from hematuria and proteinuria to severe renal failure and oligoanuria (which occurs in one-half of cases). Hypertension is also frequently observed. Although as many as 50 percent of those with HUS require dialysis during the acute phase, the prognosis for recovery of renal function is generally favorable.

STEC HUS often affects multiple other organ systems including the central nervous system (up to 1/3 of hospitalized children with HUS), gastrointestinal tract (severe colitis with possible bowel perforation), pancreas, liver, lungs and heart. When present, severe CNS involvement (seizures, coma, and stroke) is associated with significant mortality. In addition to local thrombus formation, some neurologic abnormalities may reflect other factors such as cerebral edema, uremic encephalopathy, or excess drug accumulation due to the impaired renal function.

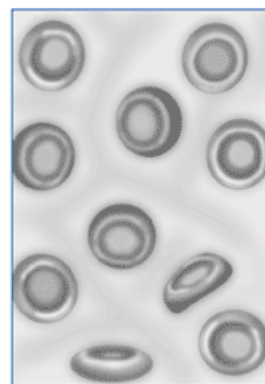
**Primary aHUS** is really a multisystem disease. It occurs commonly in children, often less than two years of age. Several studies suggest that patients younger than six months who present with HUS are more likely to have complement-mediated disease than Shiga toxin-producing *E. coli* (STEC) HUS. The presenting findings include concurrent microangiopathic hemolytic anemia, thrombocytopenia, and some degree of acute kidney injury. A family history can

be found in 20 – 30%, and an antecedent trigger event that is thought to play a role in complement activation. In most patients, the trigger is an upper respiratory infection, however, a diarrheal prodrome has been observed in about one-quarter of patients. Pregnancy has also been reported as a trigger event in adolescents and adult women. Patients may have already presented with a prior episode of HUS. Severe HTN is not uncommon. Stroke, prolonged seizures, severe cardiomyopathy, may ensue. Patients with C3 and factor B mutations and those with antibodies to factor H typically have low plasma C3 levels but normal C4 levels. In patients with other mutations (eg, mutations to factor H, CD46, and thrombomodulin), levels of plasma C3 levels may be decreased or remain normal<sup>[2]</sup>. As a result, normal plasma levels of C3, C4, CFB, CFH, and CFI do not exclude the diagnosis of complement-mediated HUS

## Diagnosis.

The diagnosis of a TMA is suggested by the characteristic symptoms and signs. STEC HUS in children is generally made on clinical grounds from the characteristic clinical and laboratory findings of the clinical triad following a diarrheal prodrome. Many of the individual clinical and laboratory findings of HUS in children may be associated with other disorders. These include other enteric infections, Henoch-Schönlein purpura, systemic vasculitis, sepsis, and disseminated intravascular coagulation; however, the presentation of the HUS triad following enterohemorrhagic enterocolitis is quite recognizable.

**aHUS** should be part of the differential diagnosis when faced with TMA. Multiorgan system involvement is suggestive. The diagnosis of complement-mediated hemolytic uremic syndrome (HUS) is based on the clinical presentation of the classical triad findings of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury, and demonstration of complement dysregulation, either due to gene mutations of complement proteins or antibodies to complement factors. Although more than 100 different mutations within complement regulators have been detected as associated with aHUS, 30-50% of all aHUS cases do not have detectable genetic mutations of anti-



bodies to CFH.

**Thrombotic Thrombocytopenia Purpura (TTP)** in children is due to deficient activity of the Von Willebrand factor cleaving protease. Pediatric TTP is rare and is usually due to

mutations of the ADAMTS13 gene. Affected children usually present at birth with hemolytic anemia and thrombocytopenia. Renal involvement usually occurs later in life and has a progressive course. TTP and may be differentiated from HUS by abnormally low ADAMTS13 activity. The mainstay of initial treatment for TTP is plasma exchange, as untreated patients progress to renal failure and further neurologic deterioration, and are at risk for cardiac ischemia and death.

## Management

Therapy for children with STEC HUS is supportive with special attention to correct and prevent fluid and electrolyte disorders in the face of declining renal function, diagnose and treat CNS, GI, hematologic, other comorbid illness, and provide adequate nutritional support for recovery.

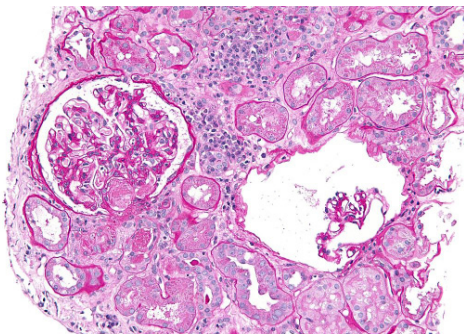
1. For every child, the fluid status is frequently assessed and management is directed toward restoring and maintaining the patient in a euvolemic state. Fluids are then administered as insensible losses (skin, respiration), ongoing abnormal losses (GI), plus urine output until renal function returns to normal. Frequent monitoring of fluid balance, weight, and vital signs are required to detect early signs of fluid overload. If this occurs, prompt fluid restriction is begun.
2. Initial assessment and monitoring are required to detect hyperkalemia, hyperphosphatemia, and metabolic acidosis. Management of these disorders is the same as in patients with other causes of acute renal failure.
3. Diuretic therapy may be beneficial if

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urine output can be restored/preserved.

4. Dialysis therapy is initiated as indicated for acute renal failure. Parenteral nutrition may require dialytic support in the face of oligoanuria and azotemia.

5. Hypertension, when present, is managed by fluid restriction, antihypertensive agents,



and dialysis as required. Calcium channel blockers (nifedipine or nicardipine) are often an effective initial choice for antihypertensive agents.

6. Parenteral antiepileptic agents (diazepam, phenytoin, and fos-phenytoin) are useful in the control of seizures in patients with HUS. Based upon data demonstrating successful treatment outcome in adults with thrombotic thrombocytopenic purpura, we recommend plasmapheresis be used in children with significant neurologic symptoms, such as seizures or strokes.

7. Pending additional studies, the use of antithrombotic agents or oral Shiga toxin-binding agent cannot be currently recommended.

8. Children with HUS may require red blood cell transfusions when they become symptomatic (hypotension, tachycardia, malaise, etc) and/or the hemoglobin level falls below 6 g/dL.

9. Platelet transfusions should be reserved for active bleeding or prior to a required invasive procedure.

10. The management of aHUS relies on the prevention of uncontrolled activation of the complement system. Plasma exchange and/or infusion, and the use of Eculizumab are

currently recommended. Early recognition and prompt therapy is imperative as the extent of functional renal recovery is inversely related to the time interval between presentation of HUS and treatment.

## Prognosis

In general, the prognosis for D+ HUS is excellent with mortality rates < 5 percent; however, some studies have reported that another 5-10 percent of patients will have significant long-term sequelae from either stroke or end-stage renal failure. In the rare patient who requires renal transplantation, recurrence of HUS is very uncommon. We recommend that the follow-up of patients with HUS include blood pressure measurement, urinalysis, and serum creatinine, and renal imaging (ultrasound, nuclear scans).

Some children will have persistent proteinuria, and subtle signs of chronic kidney disease. In this context, we recommend that antihypertensive therapy be changed to ACE inhibitors or angiotensin peptide blockers for children with persistent hypertension, persistent proteinuria, or chronic kidney disease (reduced GFR).

Pancreatitis occurs in approximately 20 percent of children with HUS, and although pancreatic involvement is often subclinical, permanent insulin-dependent diabetes mellitus can occur.

The clinical course for aHUS and outcome appear to vary based on the underlying genetic complement disorder: Patients with CFH mutations generally have a poor prognosis with most patients progressing to end-stage renal disease (ESRD) or death within the first year of presentation. In contrast, patients with mutations of CD46 do not usually progress to ESRD, although relapse is common. Patients with CFI mutations have an intermediate course between those with CFH and CD46 mutations, with one-half of patients progressing to ESRD or death within two years of presentation

## Prevention

The prevention of STEC HUS depends upon the application of measures that decrease the risk of infection. Prevention of EHEC

infection requires a reduction in fecal soilage of meat during slaughter and processing. In addition to public health inspections of meat and produce processing and handling facilities, individuals can decrease the risk of infection by properly cooking meat (core temperature  $\geq 155$  OF) and properly washing produce prior to consumption.

There is no known effective therapy to prevent progression from the bloody diarrheal phase to the postdiarrheal phase of HUS. In children with confirmed or suspected *E. coli* O157:H7, **it is currently recommended not to use antibiotics or antimotility agents.**

Although clinical evidence remains elusive, early antibiotic administration for diarrhea caused by *E. coli* O157:H7 may increase the risk of developing HUS, perhaps due to enhanced toxin release as the bacteria are killed. Likewise, antimotility agents given to minimize the diarrhea may also potentially exacerbate HUS by decreasing fecal excretion of *E. coli*, thereby increasing exposure to the toxin.

Because of the clinical significance of this strain of *E. coli*, efforts to develop an effective vaccine against this organism would be well received.

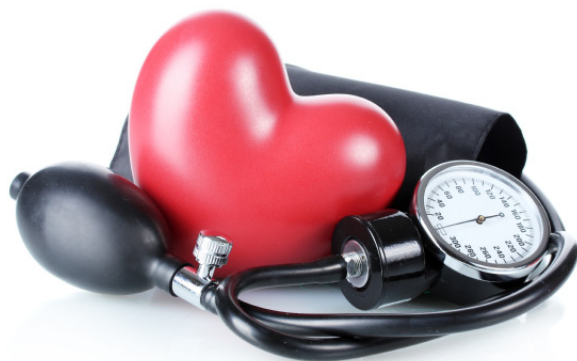
## References

1. Noris, M, Remuzzi, G. Hemolytic uremic syndrome. *J Am Soc Nephrol* 2005; 16:1035.
2. Werber, D, Mason, BW, Evans, MR, Salmon, RL. Preventing Household Transmission of Shiga Toxin-Producing *Escherichia coli* O157 Infection: Promptly Separating Siblings Might Be the Key. *Clin Infect Dis* 2008; 46:1189.
3. Trachtman, H, Cnaan, A, Christen, E, et al. Effect of an oral Shiga toxin-binding agent on diarrhea-associated hemolytic uremic syndrome in children. A randomized controlled trial. *JAMA* 2003; 290:1337.
4. Safdar, N, Said, A, Gangnon, RE, Maki, DG. Risk of hemolytic uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 enteritis. *JAMA* 2002; 288:996.
5. Garg, AX, Clark, WF, Salvadori, M, et al. Absence of renal sequelae after childhood *Escherichia coli* O157:H7 gastroenteritis. *Kidney Int* 2006; 70:807.
6. Keir, L.S., Saleem, M.A. Current evidence for the role of complement in the pathogenesis of Shiga toxin haemolytic uraemic syndrome. *Pediatr. Nephrol.* 2014; 29:1895.
7. Sinha, A, Gulati, A, Saini, S, et al. Prompt plasma exchanges and immunosuppressive treatment improves the outcomes of anti-factor H autoantibody-associated hemolytic uremic syndrome in children. *Kidney Int* 2014; 85:1151.

## Pediatric Ambulatory Blood Pressure Monitoring (ABPM)

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**Objective:** Participants will be able to discuss the newer, improved, guidelines for ABPM in children, from the consensus recommendations for the performance and interpretation of ABPM in pediatrics.  
**ACGME Competencies:** Patient Care, Medical Knowledge,



Following the first set of consensus recommendations for the performance and interpretation of ABPM in pediatrics, published in 2008, ABPM has found increasing use in children and adolescents. This is, in part, related to the well-documented increase in the prevalence of hypertension (HTN) in children reported by the U.S. National Health and Nutrition Examination Study (NHANES) and recognition that hypertension is the leading risk factor-related cause for mortality in the world. Furthermore, a number of studies have linked onset of hypertension in childhood with future target organ damage (CV/Heart, CNS, Kidney).

On the other hand, BP variability, even reaching > 95th %ile for age, sex, and height, related to anxiety, “stress” in the office setting affects both children and adults often referred to as “White Coat Hypertension (WCH)”, may contribute to untoward clinical concern and misclassification of hypertension. ABPM is a well-established clinical tool to help differentiate WCH from true HTN. Even WCH may be significant as an intermediate step in the

progression from normal BP to genuine HTN. In fact, a wide range of WCH has been reported over the past few years.

Additional clinical circumstances, shown to be amenable to study and clarification using ABPM, include: Masked HTN, Prehypertension and Progression to Sustained HTN, to evaluate the effectiveness or potential side effects of drug therapy for HTN, and in high risk patients (CKD, IDDM, Solid Organ Transplant patients, severe obesity with or without sleep apnea, etc).

Only devices validated according to the Association for the Advancement of Medical Instrumentation or British HTN Society standards are recommended. Both Oscillometric or Auscultatory techniques are valid, and the appropriate cuff sizes as recommended in the “Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents” must be used. A standard approach to obtaining ABPM readings by trained physician and nursing personnel is required. Finally, appropriate pediatric normative data must be used to interpret the studies for individual patients. The current lack of pediatric cardiovascular outcome data based on ABPM has resulted in consensus-based schemes for staging ABPM as opposed to evidence-based recommendations.

### References:

1. Flynn, J.T, Daniels, S.R., Hayman, L.L., et al. Hypertension. 2014;63:1116-1135
2. Samuels J, Ng D, Flynn JT, Mitsnefes M, Poffenbarger T, Warady BA, Furth S. Ambulatory blood pressure patterns in children with chronic kidney disease. Hypertension. 2012;60:43-50.
3. Flynn JT, Urbina EM. Pediatric ambulatory blood pressure monitoring: indications and interpretations. J Clin Hypertens (Greenwich). 2012;14:372-382.

## The Gluten Story: Celiac Disease vs. Gluten Sensitivity

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Pediatrician  
Pediatric Specialists of Virginia

**Objective:** Participant will be able to distinguish celiac disease from gluten sensitivity.  
**ACGME Competencies:** Patient Care, Medical Knowledge



Over the last decade a great deal of interest has been generated in gluten associated digestive problems. The classic condition is Celiac Disease (CD), an auto-immune disease triggered by the sustained exposure of the intestinal mucosa to gluten which is found in wheat, rye and barley. More

recently, gluten sensitivity, a symptomatic response to gluten containing products, without an allergic or autoimmune mechanism has been described. Distinguishing between these conditions is essential due to long term consequences which can occur in CD.

CD is the most common genetically-induced food intolerance in the world. The prevalence is about 1 in 150- 300 depending on the population studied. As described above it is an immune reaction to gluten which occurs in the genetically predisposed patient (HLA DQ2 and/or DQ8 positive). In

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these patients, CD 4+ T cells are activated by gluten exposure causing tissue damage. CD manifests clinically in many different ways including the classic pediatric presentation of abdominal pain, diarrhea, and failure to thrive or weight loss. Some children will present with short stature, delayed pubertal development, or constipation as their only symptoms. Less common presentations include rash (dermatitis herpetiformis), iron deficiency anemia unresponsive to oral iron, behavioral changes and psychiatric disorders. Some patients are completely asymptomatic and are only diagnosed after screening due to a family history. CD is more common in patients with other autoimmune diseases such as Type I diabetes or Hashimoto's thyroiditis, as well as genetic conditions such as Down Syndrome and Turner's Syndrome.

Diagnosing CD has become easier and more precise with the evolution of newer serologic testing. Diagnosis usually begins with positive serum IgA antibodies to tissue transglutaminase (TTG) and/or endomesium (EMA) in patients with a genetic predisposition (positive HLA typing). Definitive diagnosis requires a small bowel biopsy demonstrating mucosal damage. The mucosal changes are graded ranging from inflammation of the epithelial lining with lymphocytes without villous blunting (mild) to total villous atrophy (severe). Most important to remember is that positive results will only occur if the patient is still consuming a gluten containing diet while being tested.

There is a small subgroup of patients

who are labeled as potential CD as they may have positive serum biomarkers with a negative small bowel biopsy. Natural history studies of these patients will define the proper approach to this group.

Some gastroen-

terologists believe in starting a gluten-free diet with possible gluten challenge at a future time versus the approach of continuing a gluten-containing diet, monitoring the serum biomarkers, and repeating the biopsy at a later date. Despite this aberration, the small bowel biopsy continues to be the gold standard for confirming the diagnosis of CD.

After confirmation of the diagnosis, a gluten-free diet (GFD) is begun. Once patients begin the diet resolution of symptoms usually occurs within 4-6 weeks. The serum antibodies will become negative in most patients, but this can take 6-12 months or longer to. Follow up measurement of the antibodies is used to assess patient adherence to the diet and has replaced follow up biopsies as a guide to mucosal healing. Dietician support is extremely valuable for the newly-diagnosed patient due to pitfalls in recognizing gluten-containing products.

Long-term consequences of non-compliance with a GFD in CD, even if asymptomatic, can be significant. They include chronic anemia, osteoporosis, infertility, and an increased risk of small bowel lymphoma. This is why a definitive diagnosis is so important, especially in the asymptomatic patient. It is also important in the adolescent population where compliance with the diet may be more of an issue.

Screening for CD should be performed in all first degree relatives of a proband. Younger family members should not be tested until after age 2 unless they are exhibiting

symptoms. When testing family members, in addition to measuring TTG and EMA antibodies, HLA typing for DQ2 and DQ8 could be done. Absence of HLA markers makes it extremely unlikely that someone will ever develop celiac disease. Presence of the HLA DQ2 and/or DQ 8 does not by itself confirm a diagnosis of CD, as thirty percent of the general population carries either one or both of these genes and only 1-3% will develop CD.

Gluten sensitivity (GS), different from CD, is being more commonly diagnosed in children and adults. Unlike CD, this condition is defined as a symptomatic reaction to gluten in patients without the presence of IgA antibodies to TTG and EMA, negative immune-allergy testing to wheat, and either positive or negative HLA typing. These patients may have positive biomarkers, such as the anti-gliadin IgG antibody, which is sensitive for gluten reaction but not specific for CD. Patients with GS describe symptoms when ingesting gluten containing products which are similar to those seen in CD. They include abdominal pain, bloating, diarrhea, and weight loss. There is not, however, the same incidence of the extra-intestinal manifestations seen in CD and the risk of small bowel lymphoma in GS is similar to the general population.

In GS, symptom improvement occurs with a GFD. This has been demonstrated in several double blind studies in adults. Unlike CD, total gluten elimination is not essential in GS, except for symptom relief. This has led to some questions about the specificity of the response as many changes in diet occur when initiating a GFD.

In conclusion, when assessing patients with symptoms that may be associated with gluten consumption, perform all tests while the patient is on a gluten-containing diet. If serum biomarkers and allergy testing for wheat is negative, then a trial of a GFD is reasonable. If, however, the biomarkers (TTG, EMA) are positive then a small bowel biopsy should be performed before starting the diet. CD carries with it a significant risk of long term complications if gluten elimination is not complete; whereas, the end point for treating GS is symptom resolution.

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## *Pediatric Practice 2020*

**Russell Libby, MD**

*Pediatrician*

*Virginia Pediatric Group*

It was 11 a.m. and I had already seen 10 of my prescheduled appointments. I had decided to come into the office to see a seven-year-old boy who had been complaining of abdominal pain overnight. He had vomited once, but then had kept down some fluids and was febrile to 102. He had been healthy and was complaining of intermittent periumbilical pain over the last several days and had seemed to just be over a URI that started last week.

I put on my glasses and slipped the earmike

those days.

The way I see it, a process that had started as a way to improve care and demonstrate outcomes ended up being a tool to subordinate and control physicians. Initially it was that they could generate the orders that would generate the most margin and volume; but as the payment models changed, it was physicians as leaders of the health care team who could create cost efficiencies that would result in profit from population health insurance plans that the hospitals and health

systems created around themselves. Still, the hard costs of these entities and the evolution of portable technology and ambulatory surgical care started to drive revenue away from the bricks and mortar. Only the systems that could truly partner with physicians thrived, and the others found themselves looking for a nation-

(trademarked by PCC) over my ear and tapped the sensor on the front of the right stem to activate the EMR. Google glass was where the real HIT progress started, but it was the need to free up the physician after all those years of EMR creep where it just was about capturing charges for an RVU based care and payment system. It turned into decades of building platform on top of dysfunctional platform adding unsustainable expense; impossible regulatory impositions, and technical impediments that made the patient exam an incidental part of the office visit. It was amazing that trillions of dollars invested in that rudimentary technology was initially thought to be able to create a meaningful database on patients and the population, but it turned out to be a manipulative tool that was used by local and regional entities to control data and in that way capture whatever portion of the \$3-plus trillion of health care dollars spent in our country in

al partner like Mayo, Cleveland, or Hopkins. As the cost and experience of turnover of employed clinicians began to take its toll on the profession and the patient-physician relationship, there began a migration back into physician-led integrated medical groups.

So, just before entering the exam room, I looked into the lens where the EMR display screens are displayed. There was a time when I had to use a remote scribe who was on the other end of the earmike and who would either load the screens that had the patient's recent history as well as any pertinent information related to the chief complaint for this visit. The software has become much more intuitive and is very sensitive to my voice commands much like Dragon had become before it became was acquired by PCC. I tapped the mid-shaft of my glasses and the relevant screens became visible. I asked the system to read me the

assessment on his last IPA-at-Night visit which was 2 weeks prior and was attributed to constipation. He had been given a care regimen with reminders on his and his parents' cell phone IPA app. Our care coordinator follow up the next day reported success and that he was back at school that morning. I double tapped and the template for abdominal pain, prompted by the CC, was loaded.

I had started my office day at home sipping coffee and answering a few email follow-ups and directing the appropriate staff person to activate the home-based routines we package for all new patients. We deal with the fairly straight-forward things like possible strep with a home kit that requires a swab of the tongue and uses a PCR type of technology that is read by a box that contains weight-based antibiotic dosing. If the test is positive, the box opens and the antibiotic, with instructions, is conveniently there so treatment can begin immediately. Although it is a 5 day once daily course, reminders are part of the IPA app that is activated by the positive test and noted in the patient chart. It has become a relatively standardized approach to treat more common typically uncomplicated problems like strep, asthma, and UTI's. It certainly saves the family a trip to the neighborhood CVS which ends up taking a lot of time and has lost its credibility as a place for care as IPAcare and other competitive-merged groups with better clinicians and easier access have taken over. CVS, Walmart, and Walgreens are now the owners of most of the small local hospitals which have taken a beating as technology has evolved and most of the available insurance options have very limited benefits for care outside of the competing provider groups like IPAcare.

It was my day to be at the office and it started off with the telemedical visits that I usually schedule before 9 AM and after 4 PM. I will have 5 visits an hour, mostly for psychopharm follow-ups and monitoring chronic care conditions like asthma and diabetes where I can review medication use and look at a week's worth of data from the related wrist watch apps that monitor vitals, O2 saturation, blood sugars and other parameters. Using care

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pathways and providing families with easy to follow care plans, we have really been able to cut down on emergency room use and hospital-based care. Our hospitalists have pretty much been reduced down to intensivists at the hospital and most have either gone to primary care or become “extensivists,” taking care of observation level admissions in the IPA’s 23-hour care center or performing home visits with bedside lab, imaging, and

I am examining and note the positive and negative findings as I go by stating them out loud. I find the patients and their parents like that because it lets them know what I am thinking and it gives the record a more accurate representation unlike the checklists we used to use and not necessarily validate that qualified us for E&M payments. I did use the video to observe his response to palpating his abdomen and with his winces and rebound

response, it was clear to me that he had a peritoneal process that would likely be appendicitis.

The IPA had joined a regional collective that negotiated incredible deals for all kinds of supplies, DME, and office equipment. We leased a hand-held high resolution ultra-

it was not yet perforated, we were able to arrange transport to the pediatric surgical center where the surgeon was located and he could perform a laparoscopic procedure, observe him over night and send him home with follow up home care for 24 hours. I think back to the archaic ways in which we handled these cases not so long ago with ER intervention, then CAT scans, OR scheduling, and often several days in the hospital where it was so easy to catch something even more catastrophic.

It was fortunate that I was able to get this taken care of so efficiently. To be able to avoid complications and cost-related to exposure to different care settings and interventions is just what our population health contracts strive for. Using our contracted physicians and facility, decreasing recovery time so the family could get back to its routines, and getting the Press-Ganey approval ratings will improve my health scores and help the IPA in its contracting and marketing. Although we used to rely on capturing the gain share from a standardized case cost, we now have that built into the total health insurance premium which we manage through the IPA. The evolution of private insurance exchanges that were developed in response to the ACA gave us an opportunity to develop the credentials for narrow networks that were so contentious when they started. That experience evolved into direct contracting with employers and other groups. IT has worked out pretty well for us.

I was in practice for more than 30 years when I realized my pediatric office needed to focus on where things were going, not just trying to cope with the moment. We were lucky to join up with a primary care IPA and invested in the infrastructure that worked because health care was looking for better solutions than having insurance companies and mega health systems be the source of health care evolutions. It needed to be physician-directed and the allocation of resources needed better stewardship. Technology has facilitated the process, giving virtual linkage between regions and physician practice setting. It has also given us tools to work with our patients in ways we never contemplated. It is amazing what impact it has had on medical education and the evolution of ancillary health professionals, but that will be the subject of another report.



respiratory and infusion equipment.

So as I started to get a more detailed history from my patient’s parent, I tapped the front left of the glass stem which recorded the questions and answers, putting them into the template as I went through its prompts. It is amazing how the combination of spoken word to text has evolved, especially with its key word phrasing and how the medical record software has embedded current guidelines to make sure I ask all of the relevant questions as key historical and physical findings prompt it. I was able to get a picture of my patient’s pale and uncomfortable appearance by using the squint shutter. There is also a video feature, but I rarely use it unless I feel there is something it will contribute for comparative viewing or when there is a unique event like a seizure right there in front of me.

He told me he had never felt sick like this and he could not lie down on his back. I grinned to myself that a seven year old could put it in a lifetime perspective. I started my physical exam in the ritualistic fashion I always do so I do not forget any body part. I identify what

sound device that can be used in a variety of ways. At first it was marketed as a way to diagnose pneumonia although it was not so easy for those of us who only did the 2 hour CME program. They improved the resolution and we developed a direct telemedical connection with the radiology group who our IPA has contracted with and it added an incredible dimension to auscultation. As the medically dedicated connections improved, we were able to develop other supportive and consultative ways to provide better, more efficient, timely, and cost effective care. We now routinely echo children during the first and fifth year of life to identify any cardiac anomalies that were not severe enough to be identified earlier. We do three-way consults with our pediatric cardiologists who are there for hands-on consults or home visits in their “cardio-van.”

I had used the U/S several times for abdominal pain, but, surprisingly, never looking for a peritoneal process. I got the radiologist and pediatric surgeon on the telemedical connection and actually conducted a four-way consult. It did not take long for the diagnosis I suspected to be made and because

## *Congenital Bilateral Mandibular Alveolar Cysts in a Newborn*

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### **Case Report:**

While most congenital oral soft tissue lesions in the newborn are benign, some can present with complications requiring intervention. One such complication was observed in a case of congenital bilateral alveolar cysts in the mandible of a newborn, who presented with difficulty feeding fol-

lowing birth. The newborn was a term (40 week, 5 day) healthy black male born to a healthy 23 year old black female. Two Apgar scores of 9/10 and 10/10 were recorded following an uncomplicated vaginal delivery.

The newborn's mother reported difficulty with breast feeding, presumably due to the

and the clinical appearance. Pre-operative photographs (Figure 1, Figure 2) were obtained with consent.

After the clinical findings were presented to the mother and all available treatment options were discussed, including observation, a plan for draining of the cysts was decided



lowing a normal vaginal delivery. A description of the hospital course with photographs, a diagnosis of lymphangioma with a discussion of the differential diagnosis, and a conclusion of the case are provided.

### **Hospital Course**

The pediatric dental service received a request for consultation at a hospital in Richmond, Virginia regarding two intraoral cysts that were impeding a one-day-old newborn's ability to effectively latch and feed

cysts impeding proper glossal function in the newborn. Upon examining the infant, two alveolar cysts were observed on the lingual aspects of the patient's right and left posterior mandibular alveolar ridges. The firm to fluctuant bilateral cysts each measured 6 x 6 mm, and encroached on the infant's tongue space. A differential diagnosis of dental lamina cyst, eruption cyst, or lymphangioma was established. A working diagnosis of lymphangioma was formulated due to the patient's ethnicity, the location of the cysts,

upon. The cysts subsequently underwent needle aspiration to drain their contents. Approximately one-half milliliter of fluid was aspirated from each cyst, and hemostasis was achieved with light digital pressure and cotton gauze. Following aspiration, small voids in the alveolar ridges beneath the drained cysts could be palpated. Instructions were given to the mother to notify the dental service if the cysts recur or if there are were issues with swelling, fever,

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pain, or feeding. The mother and child were discharged from the hospital uneventfully. A follow-up phone call was placed by the dental service to the mother one week after the cysts were drained; the mother reported that the child continued to feed without

### Discussion

Congenital soft tissue pathologies in the newborn are common developmental anomalies, the majority of which are benign and regress within a few weeks to months of life. Such soft tissue anomalies include

fetal development.<sup>1,2</sup>

Lymphangiomas are defined as benign, hamartomatous tumors of lymphatic vessels that likely result from the miscommunication of lymphatic tissue with the lymphatic system during development. The head and neck account for 50-75% of all cases. Intraoral lymphangiomas in neonates have been described by Levin, Jorgensen et al, and Wilson. While Neville et al<sup>3</sup> report that the most common intraoral site of lymphangiomas is on the anterior two thirds of the tongue, they may also be found on the mucosa of the posterior alveolar ridge of the maxilla and the mandible. Lymphangiomas show a marked predilection for blacks, with an incidence of 4% in black neonates, and a 2:1 male-to-female distribution.<sup>3</sup> Teenage mothers are also at greater risk of giving birth to affected offspring.<sup>7</sup> Lesions can present as either single or multiple, with the majority presenting as bilateral on the mandibular alveolar ridges.<sup>3,4</sup> Histologically, the cysts are filled with protein rich fluid and few blood cells. It is believed that lymphangiomas resolve spontaneously, as lesions are not observed in older individuals.<sup>3</sup>

Eruption cysts, also referred to as eruption hematomas, are defined as the soft tissue analogue to the dentigerous cyst. They result from the separation of the dental follicle from around the crown of the erupting tooth. As a primary tooth erupts, the separated dental follicle is trapped between the soft tissue above and the erupting tooth below. Fluid accumulates between the reduced enamel epithelium and the tooth crown, resulting in the formation of the eruption cyst. Trauma may result in extravasation of red blood cells into the fluid-filled cyst. Degraded hemoglobin will result in a cyst with a red-blue-black color, hence the alternate name eruption hematoma. Aguiló et al reported that in a study of 36 cases, the most common sites for eruption cysts are in the incisor and molar regions for the maxilla and the molar region for the mandible. Alternatively, Bodner reported in a study of 24 cases that the mandibular central incisors and first molar sites were most affected, and cyst formation showed a male predilection with a 2:1 male-to-female ratio. Few cases of eruption cysts in neonates have been documented.



complication.

Six months following the initial consultation, the child was seen at the dental service office for a follow up visit. At this appointment, the mother reported no problems with feeding, swelling, or drainage related to the lesions. Furthermore, the child was well, and his growth and development were appropriate for his age. Upon performing and intraoral exam, it was found that the lesions were still present bilaterally, though each significantly smaller in size measuring 2 x 3 mm. The cysts were fluctuant and their color was confluent with that of the surrounding gingiva (Figure 3, Figure 4). Since the child presented without complication, a second draining of the cysts was deemed unnecessary. Further reevaluation in another six months was decided upon.

Epstein pearls, Bohn nodules, dental lamina cysts, lymphangiomas, and eruption cysts. Fromm classified Epstein pearls, Bohn nodules, and dental lamina cysts under the umbrella of oral inclusion cysts. While inclusion cysts are all similar in appearance, each is clinically and histologically distinct. Epstein pearls result from the entrapment of epithelial tissue during the formation of the palate, and are typically found approximating the midpalatine raphe. Bohn nodules, on the other hand, result from the entrapment of mucous glands during development. Furthermore, Bohn nodules are typically located on the alveolar ridges of both the maxilla and the mandible, as well as on the palate away from the midpalatine raphe. Dental lamina cysts can be found on the crest of the maxillary and/or mandibular alveolar ridges, and are theorized to be remnants of the dental lamina trapped during

... continued from page 17

### Conclusion:

Multiple case reports of lymphangiomas have been reported in the literature.<sup>6, 7</sup> Available literature concerning congenital oral lymphangiomas of the alveolar ridge suggests that in most cases, treatment is unnecessary and the lesions typically resolve within a few months of life. In this somewhat atypical case, though, the size of the cysts upon initial presentation were such that they were impeding the child's glossal functioning. Maternal concern regarding feeding resulted in draining of the cysts.

Six months following the initial consultation, the child was seen at the dental office for a follow up visit, at which time the mother reported no complications. Of available case reports, nearly all have cited spontaneous resolution by six months of age. <sup>6, 7, 11</sup> Since these lesions had not resolved at six months, they will be reevaluated at the child's age one dental visit to ensure no change in clinical appearance or transformation into pathology.

### References:

- Fromm A. Epstein pearls, Bohn's nodules and inclusion cyst of the oral cavity. *J Dent Child* 1967;34:275-87.  
 McDonald, R.E. and Avery, D.R.: *Dentistry for the child and adolescent*. Ninth Ed. St. Louis: The C.V. Mosby Co, 2011, pp 158-159.  
 Neville, B.W.; Damm, D.D.; Allen, CM. et al. *Oral and Maxillofacial Pathology*. Third Ed. Philadelphia: W.B. Saunders Co., 2009. pp 547-548.  
 Levin SC, Jorgenson RJ, Jarvey BA: Lymphangiomas of the alveolar ridge in neonates. *J Pediatr* 58:881-84, 1976.  
 Jorgenson R, Shapiro S, Salinas C, Stefan L: Intraoral findings and anomalies in neonates. *Pediatrics* 69(5):577-82, 1982.  
 Wilson, S., Gould, A.R., Wolff, C. Multiple lymphangiomas of the alveolar ridge in a neonate: case study. *Pediatr Dent* 1986; 8 (3): 231-234.  
 Friend GW, Harris EF, Mincer HH, Fong TL, Carruth KR: Oral anomalies in the neonate, by race and gender, in an setting. *Pediatr Dent* 1990; 12: 157-161.  
 Neville, B.W.; Damm, D.D.; Allen, CM. et al. *Oral and Maxillofacial Pathology*. Third Ed. Philadelphia: W.B. Saunders Co., 2009. P 682  
 Aguilo L, Cibrian R, Bagan, JV, Gandia JL. Eruption cysts: retrospective clinical study of 36 cases. *ASDC J Dent Child* 1998;65: 102-106.  
 Bodner L, Goldstein J, Sarnat H. Eruption cysts: a clinical report of 24 new cases. *J Clin Pediatr Dent* 2004;28: 183-186.  
 FitzGerald K, Barry S, Fleming P: Alveolar lymphangioma in infants: report of two cases. *J Ir Dent Assoc* 2009; 55:144-145.

Figure 1: 6mm x 6mm cyst located in the newborn's left mandibular alveolar ridge

Figure 2: 6mm x 6mm cyst located in the newborn's right mandibula Fromm A. Epstein pearls, Bohn's nodules and inclusion



Figure 1



Figure 2



Figure 3

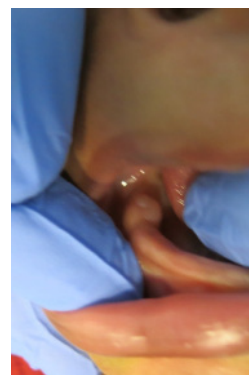


Figure 4

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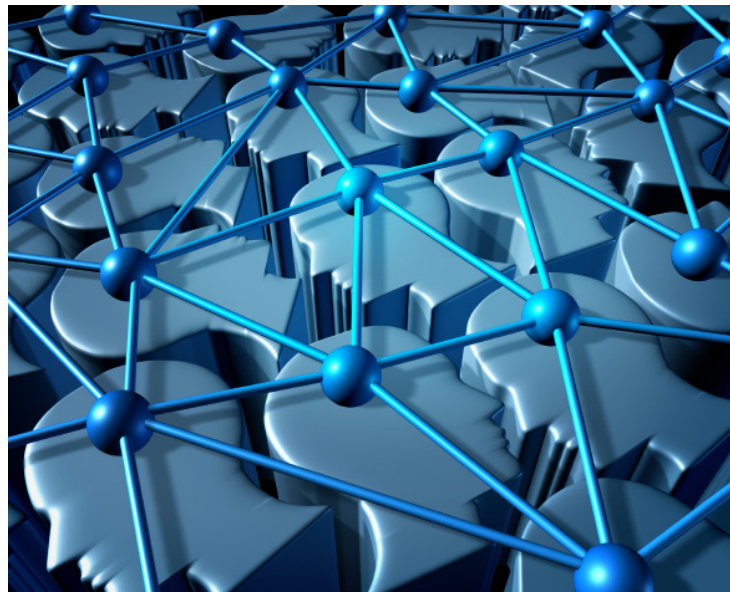
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|                                                                        | <u>2 Days / 1 day</u> |
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