COCA Call: Shiga Toxin-Producing Escherichia Coli Infections: What Clinicians Need to Know.

Date/Time: September 16, 2010 (1:00 PM- 2:00 PM ET)

Speakers:

Dr. Rajal Mody, Medical Epidemiologist, Enteric Diseases, Epidemiology Branch in the National Center for Emerging and Zoonotic Infectious Diseases – CDC

Dr. Phillip Tarr. Director, Division of Gastroenterology and Nutrition, and Melvin E. Carnahan Professor of Pediatrics, Washington University School of Medicine, St. Louis, Missouri.

Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode. After the presentation, we will conduct a question and answer session. To ask a question at that time, please press star then 1. Today's conference is being recorded, if you have any objections you may disconnect at this time.

Now I would like to turn the call over to your speaker, Ms. Loretta Jackson-Brown. You may begin.

Loretta Jackson-Brown: Thank you, (Tonya). Good afternoon. I'm Loretta Jackson-Brown and I am representing the Clinician Outreach and Communication Activity, COCA, with the Emergency Communication System at the Centers for Disease Control and Prevention. I am delighted to welcome you to today's COCA's conference call, Shiga Toxin-Producing Escherichia Coli (STEC) Infections: What Clinicians Need to Know.

We are pleased to have with us today Dr. Rajal Mody, from the Centers for Disease Control and Prevention, and Dr. Phillip Tarr, from the Washington

University School of Medicine here to discuss epidemiology of STEC and appropriate clinical guidance.

During today's call, you will hear the presenters referring to slides in their PowerPoint presentations. The PowerPoint slide set is available from our COCA Web site at emergency.cdc.gov/coca. Click on conference calls. The slide set can be found under the call-in number and call passcode.

The objectives for today's call are that participants will be able to discuss the epidemiology of STEC infections in the United States, discuss the clinical description of diseases caused by STEC, discuss clinical management of patients with STEC infections with post-diarrheal hemolytic-uremic syndrome (HUS), and identify laboratory tests used to diagnose STEC infections.

Following the presentation, you will have an opportunity to ask our presenters questions. Dialing star 1 will put you into the queue for questions.

In compliance with continuing education requirements, all presenters must disclose any financial or other relationship with the manufacturers of commercial products, suppliers of commercial services or commercial supporters as well as any of use of an unlabeled product or products under investigational use.

This presentation will not include the discussion of the unlabeled use of a product or products under investigational use. CDC, our planners, and our presenters wish to disclose that they have no financial interests or other relationship with the manufacturers of commercial products, suppliers of commercial services or commercial supporters. There is no commercial support for this presentation.

Our first presenter, Dr. Rajal Mody, is a Lieutenant Commander in the US Public Health Service and a Medical Epidemiologist, Enteric Diseases, Epidemiology Branch in the National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention. He provides expert consultation to state health departments and foreign ministries of health during outbreaks of STEC infections and HUS and oversees surveillance for STEC infections and HUS cases throughout the ten-site FoodNet System.

Dr. Mody serves as the lead for several projects related to STEC infections and (SUS) including an ongoing ten site cohort study to determine the risk factors for the development of HUS in patients with E. coli O157:H7 infections and he has been working on a new study to identify risk factors for non-O157 STEC infections.

Our second presenter is Dr. Phillip Tarr. He is the Melvin E. Carnahan Professor of Pediatrics, Professor of Molecular Microbiology, Director, Division of Gastroenterology and Nutrition, and Co-Leader, Pathobiology Research Unit, Department of Pediatrics at the Washington University School of Medicine, St. Louis, Missouri.

He has a longstanding interest in gastrointestinal infections of children with a particular focus on diarrheagenic E. coli. His research interests has included collaboration with veterinarians, diagnostic microbiologists, public health officers, molecular microbiologists, and clinicians in which the collaboration has led to numerous publications. Dr. Tarr is board certified in pediatrics and pediatric gastroenterology.

If you are following along on the slides, you should be on Slide 6. Again, the PowerPoint slide set is available from our COCA Web site at emergency.cdc.gov/coca.

At this time please welcome today's presenter, Dr. Mody.

Dr. Rajal Mody: Good afternoon or morning everyone, wherever you may be dialing in from. I'll start today's presentation on Shiga Toxin-Producing Escherichia coli or STEC by describing what they are, why they matter, and how to look for them.

I'm going to structure the presentation around a simple clinical scenario. Suppose an otherwise healthy person presents with acute community-acquired bloody diarrhea. You decide to order a routine stool culture and the result comes back negative for Salmonella, Campylobacter, and Shigella. What additional testing ideally should have been done?

We propose the following as a best practice for detecting the cause of this patient's illness, which happened to be an STEC infection. All stools submitted for testing from patients with acute community-acquired diarrhea should be cultured on receipt for E. coli O157 on selective and differential media and tested simultaneously for non-O157 STEC with an assay that detects Shiga toxin or the genes encoding these toxins. Additionally, all suspected E. coli O157 isolates and Shiga toxin positive stools should be reported to the physician and public health department promptly.

I'll cover some attributes of STEC that form the framework for why we consider this a best practice. Here is the outline. What are STEC and what do they cause? How are they monitored? How are they transmitted? And how are

they diagnosed? I'll then finish up by hopefully tying things together by explaining the benefits of proposed best practice.

So what are Shiga toxin producing E. coli or STEC? Well, they're E. coli that have acquired genes that encode Shiga toxins. And Shiga toxins are also known as verocytotoxins meaning, among other things, they can kill vero cells from the kidneys of Green Monkeys. I mention this because you may be more familiar with the term VTEC. STEC is equivalent to VTEC.

STEC can cause illness ranging from non-bloody diarrhea, to bloody diarrhea, to post-diarrheal hemolytic uremic syndrome or HUS, a potentially fatal condition. However, not all STEC have been associated with human disease. The term EHEC or Enterohemorrhagic E. coli was developed as a definition intended to define a subset of pathogenic STEC, but the simplest term is STEC and that's what I'll stick with.

So now I'm on Slide 12 and I want to discuss a little bit more terminology before moving on. STEC have been categorized into two groups by surface antigens they display, STEC O157 and non-O157 STEC. In the STEC O157 group there is E. coli O157:H7, a pathogen I'm sure most of you have heard of. In the other group there are many other E. coli that you may not have heard of. I listed three here, but there are many more. The O's in all of these names refer to the somatic O antigen and the H's refer to the flagellar H antigen. O antigen by itself defines the E. coli serogroup and the combination of the O antigen and H antigen define the E. coli serotype.

E. coli O157:H7 is the most frequently detected STEC serotype in the US and the most strongly associated with severe disease. But there's actually another serotype of STEC O157, one that doesn’t have any flagellar, but that serotype

is not as common in the United States. And there are over 50 non-O157 STEC serogroups.

Next - go on the next slide, Shiga toxins act locally and systemically. Receptors are found on the intestinal epithelium and kidney endothelium. Once internalized into these cells, the toxins inhibit protein synthesis, in addition, binding of the toxin to vascular tissues is thought to trigger a coagulation cascade. There are two subgroups of Shiga toxins, Shiga toxin 1 and Shiga toxin 2, and strains that produce Shiga toxin 2 are believed to be more virulent.

Shiga toxins are necessary but not sufficient to cause disease. Other virulence factors are involved. But one key point to remember when we get back to the proposed best practice guidelines is that virtually all E. coli O157:H7 contain a full complement of factors necessary for severe disease. It's a known bad actor.

So next I'll walk through the sequence of events following ingestion of STEC O157. In about three to four days after ingestion, a person typically will develop non-bloody diarrhea and abdominal cramps, which are often severe, and during this phase some people may experience a short lived fever. One to two days later, the diarrhea will become bloody for most patients. And within five to six additional days most people will experience a self-limited resolution, but 6% will develop HUS, almost always within the first week of the initial diarrhea onset, but rarely it could be as delayed as two and even more rarely three weeks after diarrhea onset.

This 6% is for all ages. Fifteen-percent or more of young children may develop HUS and less than 2% of person's age 18 to 59 years old develop

HUS. And just as a reminder, HUS is defined as - by the triad of acute renal failure, thrombocytopenia, and non-immune hemolytic anemia with microangiopathy, meaning there's evidence of intravascular erythrocyte destruction such as presence of schistocytes.

Another key point is that prompt diagnosis facilitates management and may decrease risk of progression and spread to others and Dr. Tarr is going to talk more about this. Also it becomes much more difficult to diagnosis STEC infection later in the clinical course because of the number of organisms and Shiga toxin in the stool can decline quickly.

So now I'm on Slide 15. On the right is a generic sequence of events for non-O157 STEC infections. I say generic because although non-O157 STEC strains are often discussed together as one big group, strains can often marked - differ markedly with respect to virulence, and the general timing of events is the same as seen in STEC O157 infections. Although as a whole non-O157 STECs cause less severe infections with a lower frequency of bloody diarrhea and HUS, some strains do cause illness just as severe as STEC O157. So a key point here are non-O157 STEC are a diverse group that vary in virulence and STEC are isolated from persons with both bloody and non-bloody diarrhea.

The table on Slide 16 shows Shiga toxin profiles of O157 and non-O157 STEC infections reported to FoodNet in 2007. On the left are the different possible combinations of Shiga toxins, the middle column is the number and percent of O157 infections, and the right column is the number and percent of non-O157 STEC.

You can see that the O157 isolates had a much lower frequency of expressing only Shiga toxin 1 as compared to - or compared with the non-O157 STEC,

5% versus 60%, and strains that produce only Shiga toxin 1 are rarely isolated from persons with HUS. However, if we were to look more closely at the non-O157 STECs, we would see that those isolated from patients with HUS have Shiga toxin profiles very similar to those of - seen in O157 STEC.

So moving on, how are STEC infections and HUS monitored in the United States? There are three national surveillance systems which capture STEC and HUS cases in a passive manner, meaning they only detect what's reported to them.

The National Notifiable Disease Surveillance System monitors both STEC infections and HUS cases. This usually involves the healthcare provider reporting to the state or local health departments and then - who then report on to CDC. The Public Health Laboratory Information System reports all isolates of STEC, both O157 and non-O157, confirmed at the state public health laboratories to CDC. The CDC National E. coli Reference Laboratory is not a surveillance system per se, but serves as an important role in fully characterizing STEC isolates sent in from states.

And to supplement these passive national systems, a smaller network of sentinel sites was formed in 1996 that perform surveillance for HUS and nine pathogens commonly transmitted through food. The Foodborne Disease Active Surveillance Network, or FoodNet, actively audits all clinical laboratories that could potentially serve residents in the system’s catchment area to make sure that all laboratory-confirmed infections are captured.

The next - on Slide 19, the map shows the current FoodNet sites in green. There are ten sites, including seven entire states and selected counties within

three additional states. Forty-six million persons reside in the ten sites, making up 15% of the US population.

So now we know STEC can cause bad disease and we know how they're monitored, so now how common are STEC infections and post-diarrheal HUS? So now I'm on Slide 21. Piecing together results from several studies suggests that STEC might be detected as often as other pathogens in persons with diarrhea. STEC has been isolated from 0 to 4% of clinical samples and this compares with 1.9 to 4.8% for Salmonella, 0.2 to 3.1% for Shigella, 0.9 to 9.3% for Campylobacter. So STEC are not extremely common, but they're not zebras either and depending on what you do, you could likely expect on seeing some during your career.

The next slide shows the incidence of reported laboratory confirmed STEC O157 cases in FoodNet from 2000 to 2009. The Y axis is the number of cases per 100,000 persons and the green line represents the Healthy People 2010 objective of one lab confirmed case per 100,000 persons. After a decline in incidents from the late 1990s, the objective was met in 2004 and again in 2009.

On the next graph, I've added in the incidents of non-O157 STEC infections. The red line suggests a gradual increase in incidence during the past decade. However, shown on the next slide, this increase is likely explained in large part by changes in diagnostic testing practices. So Slide 24 shows that the number of non-O157 STEC infections reported to FoodNet, indicated by the bars, has increased as the number of labs testing for them has increased, indicated by the line.

On the next slide is a list of the six most common non-O157 STEC serogroups reported to FoodNet in 2009 by rank. They are O26, O103, O111, O121, O45, and O145 and collectively these six serogroups accounted for 66% of all non-O157 STEC infections reported.

Slide 26 shows the number of STEC infections by month of isolation. The blue is for O157 infections and yellow for non-O157 infections. A commonly-held belief is that STEC infections pretty much only occur in the summer. While it's true that about half of cases occur in summer months, the other half do not. So testing for them only in the summer would miss a lot of cases.

The next graph shows the average annual incidence of STEC O157 isolations by age group. Another perception people may have is that these infections only affect children. You can see here that while the highest rates occur in - among children, illnesses do occur in all age groups.

On Slide 28 is shown the percent of STEC O157 cases that develop HUS by age group. The same group with the highest rates of STEC O157 infections, children aged 1 to 5 years old, also are most likely to develop HUS, roughly 12 to 18% depending on the specific year of age. And notice as well a smaller peak in the oldest age group, persons over 60. Although they account for a smaller number of HUS cases, older patients are the ones most likely to die from HUS.

The next slide we're going to start talking about how STEC are transmitted. So here are a list of key factors in STEC transmission. First, the reservoir for these pathogens is the intestinal tract of animals, especially cattle. Second, the infectious dose is very low, less than 100 organisms. And these first two attributes account for multiple modes of transmission.

Foodborne transmission can occur through foods contaminated with animal feces and this is not just limited to foods like meats or foods of other animal origin. Animal contact is a well-established mode of transmission. Nearly every year we hear of illness acquired from children touching animals at petting zoos or farm visits or fairs. And if animal waste gets in the water, infections can be spread through recreational water activities or untreated drinking water.

Finally, given its low infected dose, STEC are easily spread from person to person. One way in which this can manifest is spread among children in daycare settings.

And although we hear a lot about E. coli outbreaks in the news, it's important to note that most infections are not outbreak related. Only 19% of E. coli O157 infections and 9% of non-O157 STEC infections are part of recognized outbreaks. However, early detection of outbreaks is very important because the investigations may identify a source of infections that could be removed from commerce and thereby preventing additional illness.

I'm on Slide 31 now. In addition, outbreaks offer a unique opportunity to identify new sources of infections and possibly gaps in prevention regulations pertaining to already known sources of infections. Outbreak detection is greatly improved by subtyping infections.

Here is a schematic of PulseNet, the National Molecular Subtyping Network for Foodborne Disease Surveillance. Public health laboratories in all 50 states receive isolates of bacterial enteric pathogens from clinical laboratories. The public health lab subtypes the isolates by pulsed-field gel electrophoresis, or

PFGE, which produces DNA fingerprints of the strains and the fingerprints are sent electronically to the national database at CDC.

People here are daily looking for spikes in any given fingerprint to detect outbreaks and this is especially helpful for detecting widely disbursed outbreaks in which contaminated products may have been distributed widely. And all of this requires that an STEC be isolated in culture.

So on the next slide is a breakdown of food commodities causing illness in outbreaks of STEC O157 infections due to simple foods. And we define simple foods as those in which all ingredients fall under a single food commodity. For example, a fruit salad or juice would fall under the fruit and nut category.

Two time periods are shown, '98 to '03 and 2004 to '08. You can see beef is on top in both time periods, but in more recent years, we've seen an increase in the percentage of outbreak illnesses caused by contaminated leafy greens and a large decrease in illness caused by fruits or nuts, likely as a result of pasteurization of juices. But recall the majority of infections are not part of recognized outbreaks.

So what causes these sporadic infections? And now I'm on Slide 33. FoodNet serves as a platform to conduct case-control studies of sporadic enteric diseases and there are many more risk exposures than what are - than what I have shown on this table, but this is just what two studies were able to detect. Sporadic cases share some risk exposures as those identified in outbreaks, such as hamburgers, yet non-food related exposures are also important risk factors for sporadic illness, such as drinking untreated water and animal exposures on the farm.

Shown on the next slide are modes of transmission of non-O157 STEC outbreaks reported in the US from 1990 through 2008. And you can see only about 1/3 of outbreaks were believed to be caused by contaminated food and this contrasts to about 50% for STEC O157 outbreaks. And you'll also notice the number of non-O157 STEC outbreaks is relatively low, 27 reported over 28 years. Twenty-seven would be a typical number of O157 STEC outbreaks seen in a single year.

On our next slide, an outbreak of STEC O145 infections occurred in April of this year. There were 33 cases in five states making it the first recognized multistate outbreak of non-O157 STEC. Forty-percent of cases were hospitalized and 10% developed HUS. So this is an example showing that non-O157 STEC can cause illness as severe as E. coli O157:H7. The outbreak was caused by contaminated romaine lettuce.

So now we're making our way back to those proposed best practices by looking at how STEC infections are diagnosed. Detection of E. coli O157:H7 infections is relatively straightforward because the organisms do not rapidly ferment sorbitol. So they can be readily identified if selective and differential agar is used. Usually Sorbitol MacConkey plates with or without cefixime and tellurite, referred to as SMAC or CT-SMAC plates. In the photo, the circled O157:H7 colony has a pale appearance, whereas the background growth has a stronger pink color.

It would be great if the same was true for detecting non-O157 STEC. However, as shown on Slide 38, the typical non-O157 STEC colony on a SMAC plate looks just like all of the other background growth. And this is because most non-O157 STECs do ferment sorbitol rapidly, just like most

commensal E. coli of our normal flora, making them indistinguishable in culture. But all hope is not lost, looking for Shiga toxins or the genes that encode them help detect STEC.

The most common way to detect Shiga toxins in a clinical lab is through enzyme immunoassay, or EIA, on an enrichment broth depicted here on Slide 39. This might seem like a great way to detect all STEC infections because you get results back usually within 24 hours, however, what happens if this is all that is done?

If only Shiga toxin EIA is performed, the serogroup will not be determined, so the labs can only report Shiga toxin positive back to the doctor. But it's important to know quickly if it's an O157 infection and the quickest way to know if it's an O157 is to culture for it. Also the subtype will not be determined by DNA fingerprinting, but subtype is important for outbreak detection.

Third, it could lead to false positives. Norovirus outbreaks have been incorrectly attributed to STEC because of false positive Shiga toxin EIA tests. And finally, you could miss about 5% of E. coli O157:H7 infections.

So this brings us back to the proposed best practice for the diagnosis of STEC infections. These best practices, outlined on Slide 42, were published as a clinical laboratory recommendation in 2009. And the recommendations, again, are to simultaneously culture all stools submitted from patients with acute community-acquired diarrhea or suspected HUS for E. coli O157 and assay for non-O157 STEC with a test that detects Shiga toxin. And then to report and send E. coli O157 isolates and Shiga toxin positive broth to a public health laboratory as soon as possible.

So on Slide 43, we see what's involved in culturing for E. coli O157. Suspicious colonies on a SMAC plate should be tested for the O157 antigen through an agglutination test and physicians should be notified before the isolate is then biochemically identified as an E. coli. Once it is identified as an E. coli, the isolates should be sent to a public health lab to confirm and to characterize Shiga toxin profiles, other virulence factors, and to test for the H7 antigen, as well as to perform PFGE for outbreak detection.

Slide 44 shows what's involved in detecting non-O157 STEC. Once a clinical lab finds an enrichment broth positive for Shiga toxins, the physician should be notified and the lab should send the broth to the public health lab if no E. coli O157 was detected simultaneously by culture. The public health lab will confirm the presence of Shiga toxins often with a PCR based test and then plate the broth on culture media and test for - test representative colonies for Shiga toxin. Those Shiga toxin positive colonies can then be serogrouped and further characterized.

So you might ask, why do both tests simultaneously, why not just start with the Shiga toxin EIA test and proceed to culture if positive? Well, the combined testing approach is the most sensitive approach to detect all STEC infections and testing simultaneously most rapidly distinguishes O157 from non-O157 STEC infections, which is important for clinical decision making, and isolates are obtained in a timely manner, decreasing the time it takes to detect outbreaks.

So the next slide essentially reiterates what I just said and Dr. Tarr will talk in more detail about how early diagnosis benefits patient care. With regards to public health, in addition to improving detection and hopefully control of

outbreaks, the best practices should lead to an isolate being obtained for most STEC infections and these isolates are needed to monitor epidemiological trends in the types of STEC infections affecting the population.

So how are we doing? On the following slide here is a look at what percent of clinical labs in FoodNet were using a method to detect Shiga toxins during a few snapshots in time. It increased from 3% in 2000 to 11% in 2007. And if we were to survey labs today, it'd likely still be higher. So that's good progress. But what we were really interested in knowing is how many of the labs are following the proposed best practice recommendations and back in 2007 only 2% of labs were doing this. Hopefully it's starting to increase following the publication of the recommendations.

So on the last slide here, what can you do? The most important thing you could do is just to get these recommendations to take hold and to improve individual patient care is to talk to your clinical labs and ask them if they are following the best practice guidelines outlined here one last time. And if they're not, you can request that these tests be done when ordering cultures on patients with acute community-acquired diarrhea. And you can also give them a copy of the recommendations published in the MMWR.

And on Slide 50 is the Web site where you can find a copy of the recommendations. That's all I have and thanks for listening.

Loretta Jackson-Brown: Thank you, Dr. Mody. Please welcome our next presenter, Dr. Tarr.

Dr. Phillip Tarr: Thank you for inviting me to talk to this group today. This is a multidimensional problem and I - I'm going to bring in the various aspects that

need to be considered when a physician is trying to identify and treat these infections. I'm going to present from the perspective of a physician, but with the many interactions with diagnostic microbiologists and health departments that these illnesses obligate.

I'm going to first start on Slide 53. This is a rare infection. There is really only about 4000 diagnosed E. coli O157:H7 infections in the United States per annum, probably a similar number in total of non-O157 STEC infections. There's about 500 to 750 cases, by my estimation, of hemolytic-uremic syndrome, the most dread and potentially fatal complication of E. coli infections, per annum in this country. About half of these complications occur in children under age ten.

Now these rare infections need very good systems and I'm delighted by the emphasis on good microbiology protocols and vigilance by the initially evaluating medical provider.

Slide 54. In this talk I'd like to try to improve our abilities to diagnose this infection at points of presentation, put into play a few ways to potentially reduce the severity of an illness in infected patients, and finally I'll discuss a couple ways to prevent outbreaks and sporadic infections and this, too, relies a lot on microbiology.

Slide 55. This is an illness that was really first introduced in the medical community in the early 1980s by nearly simultaneous publications from Toronto describing the presence of E. coli O157:H7 in the stools of children with HUS and by Lee Riley and colleagues from the Centers for Disease Control described two outbreaks among adults in Oregon and Michigan and

this rare E. coli serotype was isolated in the stool. Before that this had not been known to be a pathogen.

We've learned a fair bit in the past generation. On slide 56, this is the timeline of the stereotypical case of a patient, a child infected with the E. coli O157:H7, and this pattern occurs about 80% of the time. Briefly, there's about a three day incubation period and then there's two to three days of non-bloody, usually rather painful diarrhea and about 80% of the time that diarrhea becomes bloody. About 15% of infected patients overall, infected being defined as those identified with a positive stool culture, will develop this complication called hemolytic-uremic syndrome.

Now the white arrow at the top points to a thrombus in the middle of an afferent arteriole of the glomerulus. This is a clotting disorder. The model is that of a heart attack and time is not on your side. This is not an illness where you can say let's see how you look tomorrow. You - when you suspect an E. coli infection, to the providers on this call, you really got to start a bunch of actions in motion.

Slide 57. You are very unlikely to identify a patient or to meet a patient with E. coli O157:H7 until the diarrhea turns bloody. That will occur between day two and four of illness in most cases. A very careful history focusing on what happened first, what happened next can often trigger in your mind the thought that this could be a patient infected with E. coli O157:H7.

Now these patients do not have mild illnesses. Slide 58 shows the colon, the serosal side of the colon of a patient who underwent a laparotomy during the acute infectious interval - during the acute diarrhea interval and you can see

how severely this organ is affected. And these patients generally look rather ill.

So what one could do, in Slide 59, to profile such a patient has been delineated in a review article written by Dr. Lori Holtz. The reference is at the bottom. This is what should trigger a light bulb going off in a provider's mind.

Now these patients frequently present first to emergency rooms, at least in North America. They have one to three days of non-bloody diarrhea and then suddenly it turns bloody. There's a lot of abdominal pain and it seems to be worse around the act of defecation. There's about seven bowel movements in the 24 hours prior to presentation. That's another clue.

Don't try to dig out too much in the way of contact history because Dr. Mody just discussed many different vehicles, many different foods and environmental exposures can transmit this pathogen, so absence of exposure does not prove absence of risk.

Patients by the time they come into medical attention are usually afebrile. This is a clue that a patient is infected with an O157 and not, for example, with a Shigella. Now about half of the time the families will report that there was a fever prior to the visit, but it's very rare to find a demonstrated fever in an emergency facility or a doctor's office with this infection.

Finally, the abdomen is frequently tender. If your patient fits this profile, strongly consider E. coli O157:H7 or other Shiga toxin-producing E. coli.

Now to Slide 60. You are only as good as your microbiologist and certainly bloody diarrhea, acute bloody diarrhea in North America is going to obligate a

stool culture. I have trouble stating that C. difficile is that helpful in most cases, but I don't object to obtaining it at the same time. But I would not act on a C. difficile test unless and until I had the culture back in this situation. Parasite and viral studies are not helpful in North America and they could potentially be confusing. I recommend against getting them.

If a patient does not produce a stool for you on site or immediately, I encourage getting a rectal swab, the laboratory can start the bacterial culture with a specimen submitted in that format. Don't wait for the next bowel movement. Again, time is not on your side.

Then in Slide 61 I talk about the additional laboratory tests you do ideally - should get a few additional tests. But I prefer to focus. Don't get too many tests because the likelihood of being misled increases with every additional test you get.

I think a situation like this could be well managed with a blood count, a BUN, a creatinine, and a set of electrolytes at the time of presentation. I discourage getting urinalysis because the likelihood of getting a contaminated specimen that then causes you to go down some diagnostic misadventures is much higher than any useful data. If a patient is going to run into trouble with the kidneys, you'll know with the rise in creatinine.

I personally don't like to get too many imaging studies but that often does not stop emergency facilities from getting CT scans and/or ultrasounds. And in this situation, one often finds a thickened colon and a thickened terminal ileum suggesting edema.

Slide 62. You'd better hope and if you have - and if you don't know, be sure to request that your microbiology laboratory as doc - as Ra - as Rajal - as Raj just said, screens for E. coli O157:H7, that colorless colony is what you need to know about as soon as possible. You need to do this, you need Sorbitol MacConkey agar. Again, make sure that they plate that stool in Sorbitol MacConkey agar and not use any exclusion criteria such as month of year, age of patients, visible blood or not visible blood. This is a microbiologic safety surveillance measure.

Many labs are increasingly using enzyme immunoassays to detect toxin. I think that that is an outstanding idea. It's part of the best practices. But again, do not forsake the Sorbitol MacConkey agar, shown on the left side of Slide 63, for the toxin assay detection protocol shown on the right.

Slide 64, why are Sorbitol MacConkey agar screenings so critical? It is absolutely the quickest way to getting an O157 identified, isolated, and sent on to the state. An O157:H7 remains the nearly exclusive cause of post-diarrheal HUS in much of the northern hemisphere. So it should be your highest priority. You've got to do everything you can to get to that diagnosis as quickly as you can.

Slide 65 also shows some disturbing data, which are also described in the MMWR. For reasons that are entirely unclear, the Sorbitol MacConkey agar screening at the time of presentation appears to be more sensitive than the toxin assay for detecting - for the detection of O157:H7. About 70% of O157:H7s are missed by the toxin assay screen for unclear reasons.

Slide 66. Why rapidly diagnose O157? There's no medication to treat it. Well, O157:H7 is head and shoulders above any other pathogen in North America,

at least any other enteric pathogen, at causing a fatal outcome from a gastrointestinal illness. It's clearly the leader in terms of causing epidemics and getting into widely disseminated food products. And a syndromic profile is helpful and these patients should be admitted, but the culture is really what sets the gears in motion. The health department needs the isolate. They don't need a signal, they need an organism.

And now some data suggest that an intervention is possible. Page - Slide 67. What we have done at St. Louis Children's Hospital, with the assistance of Pat Sellenriek, is adopted two policies. Fist, all stools are plated on receipt. They are not kept until the morning shift to plate. And second, practitioners are advised of presumptive positives, not pending E. coli testing or H7 testing.

This is critical because in Slide 68 and Slide 69, these are two pathophysiologic studies that demonstrate that while children come in on or before day four of illness, they have massive prothrombotic abnormalities, even those who don't go on to develop HUS. They have activated vessels.

And you can't tell them by the laboratory test you get on Slide 70. They have normal hematocrits, normal platelet counts, and normal creatinine.

Slide 71, when you study these children, and the reference is at the bottom, they actually have, even though they still have plenty of E. coli O157 in their stool, diminishing amounts of free fecal toxin. The toxin is about to - is on the way down, as is the organism count. So the toxic bomb has probably gone off prior to presentation.

Slide 72, a little toxin in the stool, coagulation system is activated, the kidneys are threated, the pathogen is still present, what should the provider in the

emergency room do? Well, page - Slide 73. Admit to hospital. This is a medical emergency.

Slide 74, chief reason for admission to hospital of anyone with bloody diarrhea is that this is the most sensible way, like it or not, of infection control in 2010. Inpatient precautions are fairly stringent, dedicated equipment, gowns and gloves. Outpatient advice is the rather weak admonition, well, wash your hands well when you go home. Remember you're dealing frequently with children, there's other children in the house, the family is stressed, and the biohazardous stool is entering that domestic environment beyond any ability of a non-professional to control. In a UK study, isolation of the first child by admission dramatically decreased secondary spread in the community and HUS.

Slide 75, withhold antibiotics. This is from a study published a decade ago. However, no subsequent study has ever shown that antibiotics help and several data suggest that antibiotics, again, are a risk for the development of kidney failure when given to children with first presentation with E. coli O157:H7.

Slide 76. In addition to admission, we are now strongly encouraging volume expansion by intravenous fluid. The overall strategy is to protect the kidneys, keep blood flowing to it to that organ, and wait for the platelet count to rise.

Slide 77 shows a fairly typical course in the six out of seven patients who would never go on to develop HUS. It's quite common from the day of admission to the next day for the platelet count to fall, the hematocrit remains stable or falls a little bit, and ideally the creatinine will remain stable. The patient gets better and can go home.

However, about 25% of patients who present with E. coli O157 in first four days of illness will go on to develop HUS. And on Slide 78, there's really two kinds of HUS that they might develop. There's a non-anuric and then there's the anuric form. Anuric, they stop urinating, if they stop urinating for about a week, they require dialysis. Non-anuric, they continue to urinate, go home much sooner. Slide 79 lists about a dozen references that suggest that if you stop urinating during HUS, you have a much worse long-term prognosis.

Slide 80 demonstrates a study structure formed by Dr. Julie Ake that compared children with good outcomes, non-anuric, from those who developed anuria during HUS.

And I'm going to slip - skip - I'm going to go to Slide 81 and briefly point out one item here. And the reference is given for those who want to dig further. The first culture was obtained and then reported back 2-1/2 days earlier in the children who had good outcomes compared to those who had bad outcomes. So adroit and rapid and accurate microbiology put - clicks a light bulb in the provider's - in the requesting physician's mind. They know now that they're dealing with something other than gastroenteritis and they get that child back and get them hydrated.

Slide 82 demonstrates the benefit, children who had good outcomes, meaning they continued to urinate during HUS, had about ten times as much intravenous sodium and volume administered compared to those who had bad outcomes.

I'm going to slip over Slide 83 and go to Slide 84 and briefly review the strategy. For people in the setting of first - the first person to evaluate these

patients, these patients are ill, they have abdominal pain, they have multiple bowel movements in the previous 24 hours. Send stool from them, make sure your micro lab screens for Sorbitol MacConkey agar 24/7. Don't rely entirely on toxin tests. Volume expand while you wait for your culture to come back. Don't give antibiotics. And get daily platelet counts, you probably should also get a complete blood count and a set of chemistries, and wait for the platelet count to rise and then you can send the child home.

Slide 85 is a table - is from a table or actually refers to a table in Dr. Holtz's review. And briefly, if you know the day of illness, with day one being the first day of diarrhea, the trend in the platelet count is going up, going down, or stable, the clinical condition of your patient better, worse, or about the same, and the culture result, if you know all of these variables when you go to this paper, you can plug it in and try to figure out if the patient is at high, medium, or low risk of developing hemolytic-uremic syndrome.

Thank you.

Loretta Jackson-Brown: Thank you, Dr. Mody and Dr. Tarr, for providing our COCA audience with such a wealth of information. Joining us for the question and answer session is Dr. Patricia Griffin, Enteric Disease Epidemiology Branch Chief in the National Center for Emerging and Zoonotic Infectious Diseases, CDC, and Dr. Nancy Strockbine, Chief of the Escherichia and Shigella Reference Laboratory Unit, National Center for Emerging and Zoonotic Infectious Diseases, CDC.

We will now open up the lines for the question and answer session.

Coordinator: Thank you. We will now begin the question and answer session. If you would like to ask a question, please press star then 1. Please unmute your phone and record your name clearly when prompted. Your name is required to introduce your question. To withdraw your question, press star then 2. Once again, to ask a question, please press star then 1. One moment please for the first question.

Once again, to ask a question, please press star then 1. At this time we have no questions.

Loretta Jackson-Brown: I would ask that if any of our presenters or those who have joined us on to answer questions have any additional comments for our audience.

Dr. Rajal Mody: This is Raj Mody. I don't really have any additional comments. That's it.

Dr. Phillip Tarr: Same here. I - we hope we were clear.

Coordinator: I do have a couple of questions that just came in the queue. I have a question from Dr. Richard Duma. Your line is open. Dr. Duma? Please check your mute button. I'm going to go to the next question. (Lauren), your line is open.

(Lauren): Yes, recently we had a case of a child who died of HUS and two - one sibling and one close relative was also tested. The one close relative was positive for E. coli O157 and the HUS case and sibling were both negative at the local hospital laboratory. However, when those three specimens were sent on to our state laboratory, all three tested positive for the E. coli.

And in speaking with the state laboratory, they said that that was fairly typical that the lower level labs don't always have the ability to have the E. coli labs

come out positive, whereas the upper - the higher level state laboratory has that capacity. So we were a little concerned that we might be missing cases. Do you have any comments?

Dr. Rajal Mody: This is Raj Mody and maybe Nancy Strockbine will follow up with me. But it is - we hear of that happening from time to time and the state public health labs often will have a little bit more culturing technology that can enhance isolation of an STEC out of a stool sample. There's something called immunomagnetic separation where there are actually little magnetic beads impregnated with antigens against various STECs and that can help enrich the stool specimen and increase your yield of finding an O157 or a few other non-O157 STECs.

Nancy...

Dr. Nancy Strockbine: Pardon me.

Dr. Patricia Griffin: This is Patricia Griffin. We did a study early on in the 80s when we were trying to get labs to look for O157 and we had ten hospital labs who were very interested in looking for E. coli O157 in all stool specimens. And they got specific instruction from CDC. And despite that, some of them had trouble identifying O157 that we later showed was present in the sample. And I think that illustrates what every microbiologist knows, that microbiology is an art as well as a science and that experience helps.

Sometimes those clear colonies aren't as easy to find as you'd like them to be. When a person comes in with acute bloody diarrhea, often those - the clear O157 colonies make up a large portion of the - of what you see on the plate, but later on in the illness, they're harder to find on the plate and harder to pick

out. So sometimes a microbiologist that's more used to looking for these and more used to successfully finding them will find the needle in the haystack and find that O157 even in using conventional methods.

Dr. Phillip Tarr: Yes, Phil Tarr here. I quite agree with the previous comments. I - it - this tragic situation does emphasis the value of profiling and you - while you do need to rely on your lab, if a patient seems to have an illness that looks like an O157, remember by the time of presentation, and I have seen this on several occasions and they tend to be very ill children, the organism's titer is on the way down and may not be easily distinguishable without, for example, immunomagnetic bead separation.

It also demonstrates, tragically, that the microbial injury probably occurs, in large part, before presentation. Or much earlier in the illness. You got to be vigilant and it's a tough infection.

Dr. Patricia Griffin: It - and just one comment on the profiling. I think Phil's description of the classic case of O157 is very helpful in increasing suspicion, but when we've looked at clinical profiles of patients with various enteric illnesses, we haven't been able to clearly distinguish who has O157 with any degree of specificity. So and that's the reason why rather than using a clinical profile and saying just test for O157 on those patients who fit the profile, we recognize that accuracy in predicting is not that high and so you really need to test all stools.

Dr. Phillip Tarr: Right.

Dr. Patricia Griffin: And especially have a high index of suspicion for those with bloody diarrhea because those have the most severe illness.

Dr. Phillip Tarr: And admit while the micro lab is working through it.

Coordinator: Our next question comes from Dr. Richard Duma. Your line is open.

Dr. Richard Duma: Yes, I was going to ask about antibiotic usage. Is there - in those individuals who have received antibiotics, have they been separated at all in terms of their class or the way they act in terms of for those that might be a protein-inhibitor versus those non-protein inhibitors? Is there any data to look at the - has examined whether any inhibition of toxin synthesis occurs with any sort of protein inhibiting antibiotics?

Dr. Phillip Tarr: Well, I can address the first question better than the second part. The antibiotics that inhibit protein synthesis were not well-represented in the first and largest study. The - so they were predominantly beta-lactams and trimethoprim sulfamethoxazole. In vitro, the antibiotic that appears to be quite promoting of toxin release is ciprofloxacin or fluoroquinolones, which are often prescribed somewhat empirically for these illnesses.

So the answer is not - I don't think that the protein synthesize inhibitors have been fully explored. But, again, it appears that by the time these patients come to light, the organ and host injury has occurred and we're seeing a thrombotic play out.

Dr. Richard Duma: Thank you.

Coordinator: Our next question comes from (Mandy). Your line is open.

(Mandy): Hi, my question was why is it called a Shiga toxin? Do any other bacterial generally produce this toxin or is it just E. coli?

Dr. Rajal Mody: Hi, this is Raj Mody. The name Shiga came from Dr. Shiga who discovered Shiga toxin and Shigella a long time ago I think around the turn of the century.

Dr. Nancy Strockbine: 1898.

Dr. Rajal Mody: 1898. And in the 80s, 1980s when they were discovering these E. coli's from children with HUS, they found that they were producing these toxins that were killing vero cells and so they were initially given the name verocytotoxins. But then additional work found that those initial verocytotoxins were essentially or nearly identical to the Shiga toxin identified by Dr. Shiga.

So there is one Shigella out there, Shigella dysenteriae Type 1 that produces Shiga Toxin Type 1 and that can occasionally cause HUS, typically in developing countries. And we don't really see that here in the US.

Coordinator: Our next question comes from Brent Barrett. Your line is open.

Brent Barrett: Thank you very much. Is the presence of Shiga toxin 2 a good predictor that the patient will develop HUS? And the second part is there any new treatment options or studies going on using monoclonal antibodies to neutralize the toxins?

Dr. Phillip Tarr: I can take a stab at some of this and then encourage colleagues at CDC to add on. If you get an O157 almost all of them have Shiga toxin 2. So whether or not that is the determinant of the worse outcome, most - many or most of the non-O157s have only Shi - the ability to produce Shiga toxin 1, is an open

question and many of us believe that it is - that the Shiga toxin 2 is the culprit. The best way to diagnose Shiga toxin 2 is to diagnose O157 and they're pretty much synonymous.

With respect to antibodies, there is nothing active, at least at clinicaltrials.gov, as of a month or so ago. But I - and nothing else that I am aware of in North America. Remember though that when patients come to light, there's not much toxin left in the stool. So the likelihood of finding neutralizable toxin in the body, when there is not toxin where there is stool and bugs, might be on the theoretical basis rather low.

I don't know if my colleagues at CDC want to add on.

Dr. Rajal Mody: I guess addressing the first part of your question whether or not all isolates or most isolates with Shiga toxin 2 lead to HUS, when we look at patients who have HUS, the majority of them will have infections that produce Shiga toxin 2, but that's only, you know, looking at that - those with HUS. There's a lot of people with similar infections, the same Shiga toxin profiles that do not go on to develop HUS. So it - I think the answer would be no, not everyone - most people with Shiga toxin 2 do not go on to develop HUS. But it - what we think, it's possibly a virulence factor associated with bad disease.

Brent Barrett: Good, thank you. That's what I've been telling folks.

Coordinator: The next question comes from (Eric Sage). Your line is open.

(Eric Sage): Yes, I had a two-part question. The first is in what percentage of pediatric patients with HUS today due to E. coli 157:H7 go on to develop brain or permanent neurological damage? And then the second part of the question is if

in fact a pediatric patient had a E. coli 157:H7 infection, could they go on to develop the brain or neurological sequelae without evidence of the HUS footprint either renally or in the creatinine?

Dr. Phillip Tarr: I don't that the data could entirely - I don't know that the data are really available to answer those questions with complete certainly, but in recent years it's been all of our impression that with the ability to identify a child at risk for HUS by finding an O157 or profiling a child with acute bloody diarrhea and monitoring their electrolytes closely as they go into the HUS phase and admitting them to hospital and controlling BUN with dialysis when appropriate, they had - the frequency of major bona fide neurologic events are diminished - is diminishing, seizures, comas, and stroke.

My estimate is it's under 10% now, probably closer to 3 to 5% of all cases with HUS associated with E. coli will have those serious in-hospital complications. That's still too high, but it's lower than it was 20 or 30 years ago.

With respect to neurologic injury without full-blown HUS, I am not aware of any data.

(Eric Sage): You're not aware of any cases either anecdotally or empirically?

Dr. Phillip Tarr: The only one I'm aware of anecdotally was a patient who had a seizure prior to the development of HUS and then developed HUS, but not - I'm not aware of any bona fide neurologic or severe neurologic injury without HUS.

(Eric Sage): Thank you.

Coordinator: Our next question Mr. (Sochise). Your line is open.

Loretta Jackson-Brown: And operator, we have time for one more question. Yes.

Coordinator: So this is the last question. Sir, please check your mute button. Mr. (Sochise), your line is open. At this time, we have no further questions.

Loretta Jackson-Brown: On behalf of COCA, I would like to thank everyone for joining us today with a spank - special thank you to our presenters, Dr. Mody and Dr. Tarr as well as Dr. Griffin and Dr. Strockbine, for joining us today.

If you have additional questions for today's presenters, please email us at coca@cdc.gov. Put Dr. Mody or Dr. Tarr in the subject line of your email and we will ensure that your email is forwarded to them for a response. Again, that email is C-O-C-A @cdc.gov. The recording of this call and the transcript will be posted to the COCA Web site at emergency.cdc.gov/coca within the next few days.

Continuing education credits are available for this call. Those who participated in today's COCA's conference call and would like to receive continuing education credit, just complete the online evaluation by October 23, 2010 using course code EC1648. That is E as in echo, C as in Charlie, and the number is 1648. For those who will complete the online evaluation between October 23 - 24, 2010 and October 23, 2011, use course code WD1648. That is W as in Walter, D as in delta, and the number is 1648.

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Thank you again for being a part of today's COCA conference call. Have a great day.

Coordinator: Thank you for joining today's conference. You may disconnect at this time.

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