Changing Epidemiology and Prevention of Clostridium difficile Infection

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Coordinator: Welcome and thank you for standing by.

At this time, all participants are in a listen-only mode. During the question and answer session, you may press star 1 on your touch tone phone.

Today's conference is being recorded. If you have any objections, you may disconnect at this time.

Now, I'll turn the meeting over to your host for today's conference, Ms. Alycia Downs. Ma'am, you may begin.

Alycia Downs: Thank you. Good afternoon and welcome to today's COCA Conference Call, entitled "Changing Epidemiology and Prevention of Clostridium difficile Infection."

We are very excited to have Dr. Carolyn Gould present on this call. Dr. Gould is currently a medical epidemiologist with the response team in the Prevention and Response Branch, Division of Health Care Quality Promotion, here at the Centers for Disease Control and Prevention in Atlanta, Georgia.

We'll be using a PowerPoint presentation for this call that you should be able to access from our Web site. If you have not already downloaded the

presentation, please go to www.emergency.cdc.gov/coca, click on Conference Call Information, Summaries & Slide Sets. You can find the PowerPoint there.

Objectives for today's call. After these activities, participants will be able to describe how the epidemiology of C. difficile infection is changing; two, discuss current recommendations for preventing C. difficile infection; and three, describe controversial areas in C. difficile infection control.

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CDC, our planners, and the presenter for this seminar do not have financial or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. This presentation does not involve the unlabeled use of a product or products under investigational use.

I will now turn the call over to Dr. Gould.

Carolyn Gould: Thank you, Alycia. Thanks everyone for joining and, as she mentioned, I'm going to be talking about the changing epidemiology and prevention of C. difficile infection.

This, on the first slide now, the second slide is just the continuing education disclaimer and onto the third slide.

C. difficile is an anaerobic spore-forming bacillus. C. difficile infection, which I will refer to throughout this presentation as CDI, previously known as C. difficile associated disease or CDAD, some of the slides still reflect the previous terminology, but I'll be using C. difficile infection for the most part.

And this can range from a mild diarrheal illness to more severe disease such as pseudomembranous colitis, toxic megacolon, sepsis, and death. In healthcare facilities, fecal-oral transmission, primarily through the environment or the hands of healthcare personnel is the main route of transmission.

Antimicrobial exposure is the major risk factor for C. difficile infection. And really, there are two prerequisites for C. difficile infection and these are the new acquisition of C. difficile and antibiotic suppression of the normal colonic flora.

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So this is an illustration of the pathogenesis of the C. difficile infection that was published by Sunenshine, et al. And C. difficile is initially acquired through the ingestion, oral ingestion of spores which resist the acidity of the stomach and germinate into the vegetative form in the small intestine.

And disruption of the commensal flora of the colon, which is typically - typically occurs through exposure to antimicrobials then allows C. difficile to proliferate and produce toxins that then lead to colitis.

And the primary toxins produced are Toxins A and B, which are two large exotoxins that cause inflammation and miposal damage. Both toxins appear to

have cell damaging effects through disruption of the (unintelligible) skeleton within themselves.

And although Toxin A is not to be the major toxin, there are Toxin A-negative, B-positive strain that has been found to cause disease, so they both seem to be important.

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So, as I mentioned before, there are prerequisites for C. difficile infection are primarily the receipt of antimicrobial therapy and acquisition of a new - a new acquisition of a toxigenic C. difficile strain, although the precise timing and order of these events is not very well understood.

It's believed that there may be a third factor which could be related to host susceptibility or virulent factors of the bacterial strain that then go on to determine whether the outcome with be asymptomatic colonization with C. difficile or actual C. difficile infection.

And the major host risk factors that affect susceptibility include advanced age and underlying co-morbidity.

The incubation period of C. difficile following acquisition has not been clearly defined. Although, one study suggest that an incubation period of less than seven days. There may be longer intervals between the onset of diarrhea and acquisition of C. difficile.

The timing of antimicrobial exposure in relation to the onset of the disease also can vary, although the two appear to be in close proximity.

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So, as many of you are aware, the epidemiology of C. difficile infection has gone through some very dramatic changes over recent years. C. difficile infection in the U.S. has been increasing in incidence over the last one to two decades.

According to analyses of surveillance data initially mostly from the National Nosocomial Infection Surveillance system, now NHSN, as well as hospital discharge data, for example, the National Hospital Discharge survey, and then by reports from individual healthcare systems, which have been repeating - have been reporting severe disease associated with complications, including colectomies, ICU admissions and deaths.

And a recently identified epidemic strain of C. difficile with increased virulence and antibiotic resistance has caused outbreaks associated with - has caused outbreaks both in North America and Europe.

And another recent development is the finding that C. difficile infection is occurring in people previously thought to be at low risk for the disease such as healthy persons with minimal or no exposure to healthcare settings and peripartum women, which I'll talk about a little bit more later

So, these are all the things that we've been seeing recently and have contributed to this changing epidemiology. So, in the United States...

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The number of hospital discharges where C. difficile infection was listed as any diagnosis, doubled between 2000 and 2003, with a disproportionate increase in persons over 64 years of age.

And, in this figure, additional data has been added through 2006, since this was originally published by McDonald, et al. And, although it suggests a leveling off of rates, there's actually more evidence that the trend is continuing upward based on some other data.

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From the Healthcare Cost Utilization Project, or HCUP, which is through ARC or the Agency for Healthcare Research and Quality, so this is also discharge data and these data show a more than doubling of hospital discharges where C. difficile infection was listed as a diagnosis between 2001 and 2005, where there were over 300,000 discharges with C. difficile listed as the diagnosis.

So, you can see that this - there's a much steeper trend between 2001 and 2005 compared to the previous four year and, actually, eight year period. These data also show that C. difficile infection is primarily affecting elderly patients over 65 and that C. difficile infection rates were highest in the Northeastern United States.

The death rate, also they looked at death rate, in this data and found that death rates in C. difficile infection patients were almost five times higher than the average death rates for hospitalized patients.

And, looking specifically, next slide, at mortality data, mortality rates from C. difficile infection in the U.S. are also increasing. These data are from national

- these are from national mortality records between 1999 and 2004. And C. difficile infection-related deaths were defined as all deaths for which the underlying cause of death or any contributing cause included the ICD9 code for enterocolitis due to C. difficile.

And, as you can see here, the reported mortality rate from C. difficile increased from 5.7 per million population in 1999 to 23.7 per million in 2004. So, we're not only seeing an increase in incidents, we're seeing increased mortality and we're seeing a disproportionate increase in both incidents and mortality in patients over 65 years old.

Now, we also have data from one state, in Ohio, where C. difficile was reportable in 2006. And this data also raises the awareness of the problem of C. difficile infection in the long-term care setting, which accounted for over half of all healthcare onset CDI cases.

So, of the over 14,000 cases reported, the long-term care facility onset cases made up approximately 7,900 or over half and that included about 4,800 initial cases and just over 3,000 recurrent cases, while the acute care hospital onset made up approximately 6,200 with 5,000 initial cases and 1,200 recurrent cases.

So this led to rates for initial cases of seven to eight per 10,000 patient days in acute care hospitals and two to three per 10,000 patient days in long-term care.

Now, this is the largest, most comprehensive surveillance data of healthcare onset C. difficile infection in the United States to date. And so, you can try to extrapolate this data to determine the burden in the U.S. population, which

suggests that there are, in 2006, were approximately 330,000 initial cases and 145,000 recurrent healthcare onset cases in the United States.

But, it's unclear whether Ohio's data is representative of other states and also the true over all burden is likely to be much greater because this data only includes hospital onset cases and doesn't include community onset cases, which may represent up to half of all CDI cases. And there's some data from North Carolina that I'll show you a little bit later with some data on community onset C. difficile.

So, looking at outcome of C. difficile infection, the excess costs attributable to CDI has been estimated at between $2,000 and $3,000 per index hospitalization and up to $7,000 for inpatient costs over six months of follow-up.

Other outcomes that have been shown have been increased length of stay of 2.8 days, a 19% attributable readmission rate over six months and a 5.7% six month attributable mortality, which has been reported to be higher in some outbreaks in that setting up to 15% or 16% in some settings with the epidemic strain. And there's also a greater likelihood of discharge to a long-term care facility when you have C. difficile infection.

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I'm sorry, I may not have been saying to advance slides. We're now on Slide 12.

In association with the increase in incidence in severity and the increased number of outbreaks that we've been hearing about, we've also discovered that there is a hyperviral and epidemic strain of C. difficile that's been

associated with many of these outbreaks in the U.S. and Canada and, subsequently, outbreaks in the United Kingdom and other parts of Europe.

And this epidemic strain has been characterized by different typing methods and is known as restriction enzyme analysis Type BI, and North American Pulse Scale type of NAP1. And PCR ribotype 027. So it really goes through three different typing identifications. But it's also known to be a toxinotype III strain and toxinotyping is done by restriction and time analysis of the region and the genome that contains the toxin and its associated regulatory gene.

And this toxinotype III is a previously uncommon toxinotype among hospital strains, but this strain existed before. It was not epidemic in the past, so it's not a completely new strain, but it has some new characteristics. One of those characteristics is that it produces an extra toxin called the binary toxin and it's not clear exactly what the role of that binary toxin is, but some studies suggest that it may increase virulence. And this strain is also universally resistant to fluoroquinolone and that is a new characteristic from previously.

The emergence of this strain is likely to be related to its having a selective advantage in the presence in increasing, wide-spread fluoroquinolone use. And there are polymorphisms in the toxins A and B regulatory gene tcdC, which there's a frameship mutation in this gene. And the product of this gene normally inhibits its toxin production, so this mutation appears to lead to increased concentrations of toxin A and B, at least seen in vitro.

There's also an 18-base (pardeletion) in this gene in the epidemic strain, but it doesn't alter the function of the protein, it's the characteristic that's been noted though.

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And this is just a demonstration of the in vitro increased toxin production by this epidemic strain, which produces about 16-fold higher concentration of toxin A and 23-fold higher concentration of toxin B in vitro, compared to control strain, which is a toxinotype 0.

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We're on Slide 14. And this map is an illustration of the, as of November 2007, the number of states where this NAP1 strain was described and there were 38 states as of November. But it is likely that more states have the strain, certainly more have it now, but since a strain type can only be determined by a culturing organism, which few clinical labs actually do, the epidemic strain does not - is not going to go recognized unless you're specifically looking for it.

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And this also shows during the same period, November 2007, the number of European countries where the NAP1 strain has been detected. You can see that it's fairly widespread throughout Western Europe.

So, moving on to the fluoroquinolone resistance issue, in some institutions such as this long-term care VA facility, it was noted that an increase in C. difficile infection rates coincided with the formulary change from levofloxacin to the newer, broader spectrum fluoroquinolone gatifloxacin and some of the other ones as well, moxiflaxcin, for example.

And, in fact, one of the control efforts that was made in this institution was to switch the formulary back to levofloxacin and, with this, it was found that the

C. difficile rates decreased. And this finding an added support to the idea that antimicrobial restriction may be a useful control measure during an outbreak.

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However, in another center, which also experienced an outbreak of C. difficile infection caused by this epidemic NAP1 strain after a formulary change from, in this case it was levofloxacin to moxiflaxcin, a formulary change back to levofloxacin did not reduce rates of disease. And as this graph shows, after the switch back, the rate of levofloxacin use was higher than the combined levofloxacin and moxiflaxcin use during the outbreak period.

So, it became clear that just by substituting use of one fluoroquinolone for another, without actually controlling the overall fluoroquinolone use, was unlikely to control outbreaks caused by fluoroquinolone-resistant strains of C. difficile.

So, you have to think about the resistance issue as being a classic fact that if it's resistant to one, it's going to be resistant to all of the fluoroquinolones. And the important control measure would be to reduce fluoroquinolone use overall.

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And this - that's exactly what this particular hospital did. That had tried - they were experiencing a C. difficile outbreak and they had tried multiple interventions and did not succeed in decreasing their rate. So, they ultimately resulted to complete fluoroquinolone restriction as you can see in the arrow.

At the same time or shortly thereafter, they also hired a new housekeeping company and, subsequently, the number of C. difficile infection cases declined. So, it's unclear what the specific effect of eliminating fluoroquinolone use was, but it likely did have some impact, because when you look at the strain types that were causing infection, the proportion of the fluoroquinolone-resistant epidemic strain isolates declined after the restriction.

What was really...

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...more interesting in this particular study was that the impact of restricting fluoroquinolone use reduced overall antimicrobial use substantially with no evidence of replacement - replacement phenomena. So, no other antimicrobials seemed to go up with restriction of the fluoroquinolone to substitute for their absence.

And, this really suggests that a large proportion of the fluoroquinolones that were being used were being inappropriately used or used unnecessarily, since they weren't necessarily replaced with other antimicrobials. And there also was no increase in mortality or any adverse events with restricting fluoroquinolone use. So, it did not seem to be detrimental to patients to do this.

So, control of the outbreak may have been due to the fluoroquinolone restriction itself or it also, more likely, due to the overall decrease in antimicrobial use that was observed.

And so, this is further evidence of the role of antimicrobial restriction and controlling outbreaks. And it's really a dramatic illustration of the inappropriate use of fluoroquinolones in this case.

And it suggests that there may be a lot of room for improvement in terms of reducing the amount of unnecessary antimicrobial use.

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So besides antimicrobial use, there have been another - a number of other risk factors for C. difficile infection that has been found. And this is one study that looked at some novel risk factors or specifically looked at C. difficile infection pressure, what they call CDAD pressure, which was defined as a modified form of colonization pressure, based on C. difficile infection cases. And this was found to be a significant risk factor for infection - independent risk factor.

So, the more patients you have with active C. difficile infection in an area, the greater risk of acquiring C. difficile.

And, going to the next slide, this is an illustration of this concept of the CDAD CDI pressure. So CDI pressure is calculated as the number of infectious patients per calendar day for each unit. And, each patient's exposure to infectious patients is the sum of the daily number of infectious patients in that unit during the same time that the patient is in the same unit.

So, here in Unit A, the CDI pressure is one patient with C. diff infection times the number of days in the unit. While, in Unit B, the CDAD pressure is five patients times the number of days in the unit. And the higher CDI pressure leads to a greater risk of acquiring C. difficile infection.

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But CDI pressure, CDAD pressure only accounts for patients with symptomatic C. difficile infection. So it's really not a true colonization pressure as we think about for other colonizing pathogens , like MRSA and CRE.

There is increasing evidence that asymptomatic C. difficile carriers may also contribute to the transmission. And this was a first study in CID that looked at skin and environmental contamination for patients with active C. difficile infection compared to asymptomatic patients with people with carriage of C. difficile and non-carriers. And this was in a long-term setting - long-term care setting.

And, in this facility, they actually had a very high rate of asymptomatically colonized patients. Over half of the asymptomatic patients were carriers of toxiogenic strains of C. difficile. And they found that frequency of contamination of skin and environmental surfaces among asymptomatic carriers was nearly as high as that among patients with active disease.

And they also found that spores on the skin of asymptomatic patients could easily be transferred to the investigators' hands and they did that by having the investigators wear sterile gloves and then inoculate plate.

So, this suggested a role for asymptomatic carriers in transmission, at least in the long-term care setting.

But detecting asymptomatic colonization through culture is not a feasible thing for clinical microlabs to do because it requires anaerobic culture. It's

pretty work-intensive and difficult. So, it's unclear how to go about using this data in terms of reducing the risk of transmission from asymptomatically colonized patients.

In this particular study, they developed a prediction rule. So they tried to determine what risk factors might predict patients who were likely to be asymptomatically colonized. And they found that having a history of previous C. difficile infection, as well as previous antibiotic use, both were risk factors for asymptomatic colonization. And when they combined these two risk factors, they found that that was pretty predictive of being colonized with a sensitivity of about 77% and a specificity of 58%.

If they added, fecal incontinence, they increased their sensitivity a little bit further without reducing specificity.

But further studies are really needed to validate the prediction rule but, it's intriguing to think that you might be able to predict, based on risk factors, who may be a C. difficile carrier, at least here in a long-term care setting. And it makes sense that patients with previous C. difficile patients who received antibiotics in the past would be at higher risk.

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So, the basic recommendation for hospitals for preventing C. difficile infection include, for one, conducting active surveillance for C. difficile infection by tracking positive laboratory results and then applying the surveillance definition for healthcare facility-associated C. difficile. And, at the minimum - I'm going to talk a little bit more about some of the community onset C. difficile surveillance.

Also, healthcare facilities should consider tracking severe outcome, given the severity reported with recent outbreaks. So, tracking things like colectomy, ICU admission and death.

And early diagnosis and treatment is also extremely important for reducing severe outcomes and reducing transmission. So that should be a key element. And applying strict infection control, including contact precautions, having an environmental cleaning and disinfection strategy, which I'll talk about a little bit more as well.

And, if you're having an outbreak situation with C. difficile, hand washing is recommended with soap and water rather than alcohol or hand gel.

And finally, an antimicrobial management program really should be incorporated into a hospital's general prevention strategy and maybe an effective control measure during outbreaks. And this is probably one of the most difficult interventions to do, but it really seems to be extremely important in both preventing C. difficile and controlling outbreaks.

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So just a word on hand washing. As many of you know, this is one of the more controversial areas in terms of recommendations for hand hygiene methods during non-epidemic periods. Experimental studies have shown that if you inoculate volunteer hands with C. difficile, that's the most effective means of removing the spores is through just hand washing with soap and water and plain soap works just as well and antibacterial soap. And alcohol hand rub does not - is not effective at removing spores.

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But the question is, outside of experimental conditions, has there been any evidence that increasing use of alcohol hand gel over the last decade has contributed to increasing rates of C. difficile infection and...

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And this is a study, that was done by John Boyce, show that probably not, but there has not been evidence and this is also true in other centers of an increase in C. difficile infection rate with increasing use of alcohol hand gel.

So, in a real world setting, it doesn't appear that this - the use of alcohol hand gel has contributed to the increasing incidences of C. difficile infection that we have been seeing. And, it's probably, you know, more important to insure that healthcare personnel are wearing gloves when they're caring for patients with C. difficile infection, because that's going to greatly reduce the amount of spore contamination of the hands.

And there are a number of reasons why we don't want to discourage people from using alcohol hand gel in general, because of it has greatly increased the compliance of hand hygiene, so. Currently, the recommendation is to - if your facility is having a problem or other evidence of transmission of C. difficile infection within the facility, then you should change the policy for caring for patients with C. difficile to hand washing with soap and water. But, otherwise, it's not recommended to do on a general basis.

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So, going onto other control methods, developing an environmental cleaning and disinfection strategy is very important and many facilities have switched

to using bleach solutions to control -for disinfection of patients' rooms who have C. difficile infection.

And this is a study by Mayfield; it's really one of the main studies that actually isolated this intervention from other infection control efforts, because many of the studies we've looked at in controlling outbreaks have looked at multiple interventions at once and it's hard to really separate out the effect of the environmental cleaning strategy.

But in this particular study, patients in three different units, it was before or after intervention study, and patients in three different units were evaluated to determine if a solution of one to ten hypochlorite would reduce the incidence of C. difficile infection. And, in fact, in one unit, which was a bone marrow transplant unit where C. difficile infection was pretty endemic, they did see a reduction in rates during the intervention. And then, when they switched back to their (progenarimmonium) the rates reverted back to their previous rate.

So, the use of bleach may be especially effective in reducing the burden where C. difficile infection is high endemic.

But, in the other two units that had lower rates, they did not see any effect of switching to bleach. So, obviously, there are downsides to using a bleach solution for cleaning for both the healthcare personnel and for sensitive equipment. It's caustic and it has to be mixed daily. There are downsides to using it and so the selective use of bleach, either during outbreak periods of in certain units, may be the best strategy.

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There are newer strategies on the horizon that have been evaluated. This is a study by Boyce, et al., that looked at hydrogen peroxide vapor, which can be injected into - with a generator - into a room and it creates a one micron film of hydrogen peroxide and the perimeter of the enclosure is monitored using these hand-held hydrogen peroxide vapor sensors. And then, the hydrogen peroxide is converted to oxygen and water vapor and the entire process is complete within about four hours.

So, in this paper just published in ICHE, it looked at the microbiological efficacy of the hydrogen peroxide vapor and the room decontamination process.

And they found that the hydrogen peroxide vapor was very successful in reducing the burden of spores in the environment by doing a sponge culture for C. difficile before hydrogen peroxide vapor treatment and afterward and found that about 25% of the surfaces were - of the sponge swabs were positive prior to hydrogen peroxide vapor treatment, whereas, none of them were - was positive after treatment.

And they also looked at the incidents of nosocomial C. diff infection on five wards that underwent hydrogen peroxide vapor decontamination and this is illustrated in the graph below where the gray bars are the pre-intervention period rate and the black bars are the intervention period rate.

So, you can see that there seems to be a reduction in rates when the hydrogen peroxide vapor was used, which is very promising.

There are downsides to hydrogen peroxide vapor use and limitations. Clearly, it’s not an effective strategy to be used on a daily basis because the room has to be vacated for several hours and has to be sealed off completely. And,

there’s also evidence that surfaces quickly become recontaminated with the introduction of a infected patient into the environment again.

So, the effect is not long lasting, there’s no residual sporacidal activity after the treatment, so. And, of course, it’s an expensive treatment. But, it may be useful in - for room decontamination when, again, when a facility is unable to reduce their rates by other means. It may be effective for terminal cleaning in some situations.

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But, we’ve clearly demonstrated that it requires a number of different strategies and intervention occurring simultaneously really to achieve the best control of C. difficile infection rates.

And this study by Muto, et al., that really looked at a succession of tiered interventions to control a C. difficile outbreak and they were successful by taking this tiered approach.

And that’s the similar approach that’s recommended in the NBRO guidelines, where if your rates are not increasing with the basic infection control measures, you can use expanded or enhanced infection control measures as you move up in the tier.

And, some of the things they did here, for example, is they expanded contact precautions for the whole hospitalization rather than just duration of illness and they used electronics to flag C. difficile positive patients to insure non-infected patients were not placed in the same room. And they monitored isolation compliance. They used daily bleach cleaning and hand hygiene with

soap and water. So, those were their enhanced infection control efforts that helped control this outbreak.

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And, in controlling antimicrobial use is also a key component of the program, as I mentioned earlier. And their antimicrobial use went down during this period with management program.

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And other studies have also shown successful reduction of C. difficile infection rates through the use of antimicrobial controls, in this case, audit and feedback targeting of broad spectrum antibiotics. So, they reduced cephalosporins, ampicillin (unintelligible) and increased the use of narrower spectrum antimicrobials and found that that was an effective strategy for reducing C. difficile infection rates.

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And I already alluded to earlier, there may be a rationale in some cases to consider extending isolation beyond the diarrhea and that is this role of asymptomatic C. difficile carriers in transmission. And, this study by Bobulsky, et al., found that skin contamination with C. difficile spores often persisted on patients' chests and abdomens after resolution of diarrhea.

And then this is similar to the study I showed you earlier in the long-term care facility where asymptomatic colonized patients were contaminated with spores on the skin and in the environment.

So this may be part of a tiered strategy if you're not having success controlling your C. difficile rate to extend the duration of isolation beyond the illness, because the current recommendation is to use contact precautions for the duration of diarrhea, because it is still believed that patients who actually have symptomatic infection are more likely to cause transmission that asymptomatic patients.

So, as I alluded to earlier, as well, with this recent changing epidemiology we've seen C. difficile infection occurring in previous low-risk populations and this is an MMWR that was published in 2005, describing pregnant women and some generally healthy persons in the community have developed severe C. difficile infection. And, some of these cases actually did not receive antimicrobial use.

And these peripartum or pregnancy-related cases were especially dramatic. There were ten cases that were described; only three had prior hospitalization. One did not have any antimicrobial exposure, six were prepartum, three of the four postpartum cases occurred within one week of delivery and six actually required intensive care unit admission for toxic megacolon.

We don't know the strain type in all of these patients, but two did have an affluent strain and five of the ten cases required colectomy and there were three deaths and three fetal losses.

So these were extremely severe cases. We're still monitoring these cases, CDC in collecting data, and it's unclear what the risk factors are in these pregnancy-associated cases.

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Rouphael who published this data also included a survey of - through the Emerging Infections Network of IDSA, where they queried infectious disease clinicians and 18 of the 400, 19 clinicians reported seeing 28 cases and 19 reported being aware of 27 cases. There were, overall, 55 cases of pregnancy-associated CDI; of these, 43% occurred prior to delivery, 29% occurred just over one week after delivery and there were ten or 18% relapses here.

So, we're just learning more about this but this is one of the emerging problems that's occurring with C. difficile now.

] So, I also wanted to mention the surveillance definitions that were recommended last year by the CDAD surveillance working group and this is an effort to standardize reporting and basically to, as you can see by this timeline, cases are classified as hospital onset, healthcare facility-associated, cases if they occur, here is says, after 48 hours of admission. We're using a calendar days so that it's - in order to have a more consistent reporting.

So, it really should be after two calendar - it's great - it's, you develop on symptoms greater than two calendar days after the day of admission. And then you're classified as a healthcare onset care facility-associated case.

And then, if they symptom onset was for patients who actually had community onset disease, if the symptom onset was less than four weeks after discharge from the facility, that the patient is categorized as having community onset healthcare-associated disease, as shown in the yellow.

And then, if you developed it four to 12 weeks of discharge, you're classified as indeterminate, in the light blue. And, if more than 12 weeks, then you're defined as having true community-associated disease and that's shown in the dark orange on the right.

The asterisk in the green indicates that if the symptom onset was within 48 hours of admission and depending on whether patient was discharged within previous four weeks, he or she would be categorized as community onset or community-associated disease.

Now, many of these community-associated disease may have other risk factors and we're currently evaluating some of the risk factors for community-associated disease and whether they've had other exposures to healthcare that don't include necessarily an overnight hospital stay or healthcare facility stay.

And, next slide.

This was a study done by Kutty, et al., in North Carolina, who looked at the C. difficile infection surveillance definitions in six hospitals in North Carolina and, the majority of cases, as you can see, were healthcare facility onset. But a substantial proportion, or 44%, were community onset and 20% were actually classified as true community-associated disease. So they did not have an overnight healthcare facility stay in this previous 12 weeks.

And, if you go to the next slide, they also analyzed these community onset cases to see what the relationship was to the previous discharge. And they found that, here in the graph, the X-axis represents the time in weeks and represents the whole year and the Y-axis shows the number of - the number of CDAD case patients.

And, you can see that there's clustering within the first five to six weeks after discharge, with the majority being in the first four weeks in yellow. And then there's an underlying baseline after that and then, it's interesting that 184, or

almost half of the community onset cases, actually occurred more than a year after discharge.

But, a substantial proportion occur within four weeks after discharge and these would be included as community onset healthcare-facility associated cases. And they found that if hospitals included these cases in their surveillance, that it does affect inter-hospital comparisons. And they also found a correlation between the monthly rates of healthcare onset cases and community onset healthcare facility-associated cases.

So, they actually recommend - this, these data really support the use of including community onset healthcare facility-associated cases in your surveillance because these really are cases that are most likely related to the previous hospitalization. But these numbers do affect inter-hospital comparisons and rankings, so it has to be done across the board in order to compare the facility rate.

And, next slide - and, there's also some data looking specifically at the community-associated cases in North Carolina with looking at population base rates. And VA hospital catchments, the rates were 24 per 100,000 population in this particular Durham County overall rate was 25 per 100,000 patients, with a higher rate among females than males.

And, next slide - and some of the predisposing factors that they found were for a community-associated disease was antimicrobial exposure and acid suppression, so proton pump inhibitors, specifically, as well as outpatient visits.

So, this is really new and emerging data on sort of what the risk factors are. We're looking at potential sources for community-associated disease as well.

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Some of the data from our FoodNet, this was done by (Brandy) Limbago, et al., where they did - they looked at the strain type causing C. difficile infection in community-associated cases and they looked at patients who had C. difficile, who met the definition for having community-associated CDI, meaning they had stool collected as an outpatient or within 72 hours of admission and with no hospitalization the preceding three months.

And they found 92 isolates from nine states that were submitted to CDC for typing.

Next slide.

These are the PFG patterns among the community-associated cases. Almost 50% were unnamed, but you have a substantial proportion of NAP1 or the epidemic strain and then a smattering of other PFG patterns. You can see the unnamed group actually is composed of 24 unique patterns, so there's a variety of different pulse scale types among the community strains.

And, next slide.

These are the toxinotypes I mentioned before. This is another typing method. The majority or 52% were toxinotypes 0, which is a common hospital-type strain and then 20% were the toxinotypes III, which is consistent with the epidemic strain. And then you have a substantial proportion, 10%, that were toxinotypes V, that I'll mention in a few minutes, and then other strains were represented.

Next slide.

And, this brings up the question of potential for food-borne transmission. And, I'm just going to talk to - a couple of minutes on this. C. difficile has recently been recognized as a pathogen in neonatal pigs and may cause enteritis in calves. And this really has been recognized around 2000. There's little evidence towards antimicrobic - to link antimicrobial use with disease in animals.

C. difficile has also been isolated from retail meat products in a couple of different studies.

Next slide.

And, when you compare epidemic animal strains with the human epidemic strain, there are several common characteristics, including the presence of binary toxin, this deletion that I mentioned in TcdC and the mutation in the TcdC protein.

So, there are similarities between the human epidemic strain and the animal epidemic strains as well. The animal, as you can see, animal strains are toxinotypes V, with the human epidemic strain is toxinotypes III.

Next slide.

And toxinotypes V strain in humans have been historically rare, but appear to be on the rise. This is data from Jhung, et al., that show prior to 2001, only 10 in 6,000 isolates were Tox V from humans, whereas, in - between 2001 and 2005, it was up to ten in 600. And then, just in 2006, five in 125. This seems to be an increasingly common strain among humans.

And, next slide.

This just shows the typing results of human C. difficile caused by strains similar to the animal epidemic strains between 2001 and 2006. And you can see these are toxinotypes V, they have the binary toxin and the 39 based para TcdC deletion.

So, there's some circumstantial evidence that animals may be a potential source for C. difficile in the community. Although, certainly, it's not the major source and the majority are 80% of C. difficile infection cases are actually occurring in healthcare.

So, this is not a major source of infection, but it's certainly something that we're looking into and it seems to be emerging.

So, in summary, the raised mortality and costs associated with C. difficile infection continue to increase and much of the increase is maybe due to the emergence of and spread of this epidemic strain.

And, as I showed you some data, hospital rates can be controlled through tiered implementation of both existing and enhanced recommendation.

Disease is also becoming more notable in previously low-risk populations and community-associated disease appears to be associated with variant toxinotypes, including toxinotypes V, where there's circumstantial evidence for animal to human transmission.

And, that's the end of my talk. Thank you very much.

Alycia Downs: Thank you very much, Dr. Gould. Your presentation was incredibly informative.

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

Coordinator: Thank you. If you would like to ask a question, you may press star 1. To withdraw your request, you may press star 2. And please record your first and last name clearly.

One moment please for the first question.

And our first question. Your line is open.

Questions: Could you please comment on the role of probiotics in C. difficile and recurrent disease.

Carolyn Gould: Sure. Though there are limited data on the benefit of probiotics, the probiotics and theory behind it is that, if you replenish some of the normal colonic flora, if you can help compete with the existing C. difficile and help both in patients who have recurrent disease and potentially in preventing disease from occurring, although the data are, as I mentioned, there aren't very good definitive data for the use of probiotics, some of the organisms that have been used include, (unintelligible) bacillus and sacchromyces yeast.

And there have been anecdotal reports and reports in literature that, especially sacchromyces, might be beneficial for recurrent infection. But, it really doesn't, it's unclear if there's a role in prevention, like putting patients on probiotics antimicrobials. There's really no hard data to support that.

For the most part, it appears to be safe, although some patients who have immuno-compromising conditions, have had reported bacteremias or fungemias with probiotics. So, I think you have to be careful with who you use it on.

But the whole idea is to replace or try to replenish some of the normal colonic flora. One of the issues is that we may not be replacing all of the flora that you need to compete with C. difficile by just giving one or two organisms. So, there are other strategies for replacing flora, such as using non-toxiogenic C. difficile strains and, in some cases of very refractory disease, patients have gone on to have stool transplants, which is done at a few centers, but it is not one of the conventional therapies, but it's the same idea.

But, overall, I don't think there's enough data to support the use of probiotics for treatment or prevention, although of people are using that strategy.

Coordinator: Our next question. Your line is open.

Question: Hello. I had a question about the toxin III and as far as our laboratory testing. How could we be sure that our lab, a lot of times we get patients that we assume have C. diff, but the toxin screen comes back negative, but we go ahead and treat these patients regardless?

Carolyn Gould: Yeah, the sensitivity of the toxin testing, I didn't really talk a lot about diagnostics, but it's thought to be fairly low. You actually should be testing Toxins A and B, which most (unintelligible) do now. But, even with that, the sensitivity may be quite low, even with multiple specimens.

And, so now there are some new strategies that have been proposed that aren't really in practice as of yet. Phototoxic assay testing is not really done very

often because it is more time-consuming and work-intensive and, certainly, cultures have downsides because of the work required and the time. And, plus, when you culture, you don't necessarily identify the toxiogenic strain.

So there are some proposals to combine toxin testing with cultures or to do antigen testing, which is not very specific, but can help rule out disease and, if it's positive, it can go on to be confirmed with additional testing.

So, there are some new testing methods that are on the horizon but, currently, as you mentioned, the EIA is the standard and because of the, in come cases, it doesn't seem to pick up disease, if you have a high suspicion of infection and you have multiple negative test, you probably need to go on to additional diagnostics like endoscopy to look for pseudomembranous colitis.

But, in many cases, if you have a very high suspicion, it's appropriate to treat empirically. But, you did mention a significant problem with testing and, hopefully, there'll be more sensitive diagnostic testing in the future.

Question cont'd: Thank you, thank you. Could I also ask another question?

Carolyn Gould: Sure.

Question cont'd: Actually, I had a couple of more. I don't know if I have that much time or not.

Use of oral vancomycin, should we be concerned about this as far as, you know, we don't want to try to increase any kind of resistance and less effectiveness of the vancomycin? So, I guess our question is, should we hold this or should we, you know, go ahead and advocate using it?

Carolyn Gould: Yeah, and, again, I apologize. I was mostly thinking about prevention and I really didn't address treatment.

But, there are - is increasing evidence that for severe cases, metronidazole may not be as effective as oral vancomycin and many are advocating the use of oral vancomycin if you have a severe case right off the bat, as first-line therapy.

And there are various definitions for what is considered severe. But, things like high white count and ICU admission or evidence of sepsis, other patient risk factors may push you to use oral vancomycin first. So that is the trend that's occurring.

We really haven't seen a lot of metronidazole-resistance as being the cause of the lower response rate with metronidazole, but that's something we're looking into. But, it does appear that metronidazole is becoming increasingly less effective for severe disease. So, it is reasonable to start with oral vancomycin for severe cases.

Question cont'd: What about, I've seen these light sterilizers, if you will, advocated? Is that effective against the spores?

Carolyn Gould: Light sterilizers, like UV light?

Question cont'd: Right.

Carolyn Gould: I'm not really familiar with those actually, to tell you the truth.

Question cont'd: Okay.

Carolyn Gould: I know there are no, you know, EPA-registered disinfectants with actually an indication for spore removal. But, that may be something that I think has been experimental thing - I think I actually did hear about that, but I don't know any data on it.

Question cont'd: Okay. Thank you very much.

Coordinator: Our next question. Your line is open.

Question: Hi. I enjoyed your program and I had a question.

You talked about community-acquired and the healthcare-acquired. I work in a unique situation. I work in an (ELPAC) and most of our patients come from acute care facilities. So, when I get a patient here and then the acquire C. diff, how do I know for sure if they acquired it here or if they might have acquired it at the other facility?

Carolyn Gould: Yeah, that's a great question.

So, for facilities like long-term acute care hospitals that get most of their admissions from acute care hospitals, you can't really call something community-associated or community onset so much. But you can apply the same definition to try to attribute it to your healthcare facility or not.

So, by using the two calendar day cutoff if the case occurs after two calendar days of - two calendar days after admission, then it should be classified as your healthcare facility onset.

There are, you know, as I mentioned, we don't know the incubation period. It could be that those cases are actually, you know, the patient actually acquired

C. difficile in the previous facility and, in fact, it's likely that, you know, patients who come into (ELPACs) have had a lot of antimicrobial exposure, a lot of ICU exposure.

It very well may be that those patients are bringing C. difficile into the facility. But, in order to standardize your surveillance, applying the same definition in terms of the two-day window, is really what we're recommending to do, even if we're not completely sure that those cases occurred, you know, because those cases were acquired in your facility.

Question cont'd: Right. And that's the issue I have. Is that really my infection rate or is it partially the other infections that they are bringing in with them? Like, you think after 48 hours, I should count it as...

Carolyn Gould: You should count it just for the sake of consistency. But, we're looking into that right now, actually...

Question cont'd: I hope you are.

Carolyn Gould: Because it does appear that a lot of patients are coming in with a previous history of C. diff who go on to recur. And, you know, we're looking at some of those issues, but, I think, for the sake of consistency it's important to use the same surveillance definition.

Question cont'd: Okay. Thank you.

Carolyn Gould: Sure.

Coordinator: Your line is open.

Question: Thank you. My question is regarding the disinfection of the environment.

We have been using a two-step process for disinfection some of our patient rooms and we're doing all patient rooms, not just the diff-identified patients. Our first step, we're using a quaternary ammonia compound and using the bleach wipe as our second step.

Are we overambitious in our efforts?

Carolyn Gould: It depends on sort of what's going on in your facility. You know, I think the environmental strategy you choose has to be specific to kind of what's going on with your rates and what other interventions you've been doing.

So, you know, it might be appropriate to limit that to C. diff patient rooms or if you're having more of a widespread problem and you suspect a lot of colonization, then it may be appropriate. So, it's hard for me to say, but...

Question cont'd: Is it appropriate to use a two-step? We were told that bleach was not as a successful cleaning tool as quaternary ammonia. True?

Carolyn Gould: I haven't heard that specifically, but it is obviously important to have both steps, the cleaning and the disinfection steps. The cleaning being kind of the physical removal of any debris and, if you want to use a different type of soap or disinfectant for that, and then use the bleach for disinfection, then it makes sense. But I don't know about the cleaning properties of bleach itself. That hasn't been advocated specifically.

Question cont'd: Correct. And then I have a second question. There's been some concern about the risk of transmission. I know that the Center for Disease Control has not recommended the use disposal meal trays, but in our institution it's being

investigated, even to the point of actually doing environmental cultures of those trays.

Carolyn Gould: Okay.

Question cont'd: What are your thoughts?

Carolyn Gould: Well, certainly, high-touch surfaces are frequently contaminated with C. difficile sports and that - we haven't looked specifically at meal trays, but it's a very good thought. And we haven't looked specifically at that issue so, but it certainly makes sense because it is a high-touch surface that goes from, you know, from patient to patient.

Question cont'd: Okay. Thank you.

Carolyn Gould: Sure.

Coordinator: Thank you. Your line is open.

Question: I was wondering if you could speak a little bit about the effect of fluoroquinolone use and the mechanism of action and how that increases the incidents of C. diff in the intestinal tract.

Carolyn Gould: Well, fluoroquinolones are typically pretty broad-spectrum gram negative - they offer gram negative coverage. Some fluoroquinolones have more gram positive coverage, some of the newer ones, also like moxiflaxcin, kill anaerobes as well.

And so, basically, the disruption of the colonic flora by an agent that is targeting gram negatives which make up the bulk of your intestinal flora as

well as, in some cases, anaerobes, that is really thought to be the pathogenesis of it.

So it seems that broader spectrum antimicrobials, in general, like cephalosporins, (clendomycin) also targets anaerobic flora in the colon and those are the antibiotics that seem to put people at higher risk. Although all the antibiotics are implicated.

Coordinator: Thank you. Your line is open.

Question: Could you address readmission? The C. diff patients is there any evidence that we should be putting them in contact precautions if they have stool symptoms or if they do not, as we are doing with MRSA?

Carolyn Gould: There aren't specific recommendations but, in general, if a patient comes in with diarrhea and they have a previous history of C. difficile, it does make sense to put patients on contact precautions, syndromically, until you rule it out. And that is a recommendation in the MGRO guidelines or the isolation guidelines.

So, syndromic isolation makes sense. So, if a patient comes in symptomatic and you have a previous history of C. diff, I would put them on contact precaution until you know that - whether they have C. difficile infection or not.

As far as asymptomatic patients coming in, there's no recommendation to isolate asymptomatic patients with a previous history of C. diff. As I showed you some of the data on colonization, there may be a role for asymptomatic colonizers in transmission but, right now, I don't think we have enough data

and there are enough downsides to put everybody on contact isolation off the bat.

It could be an enhanced infection control strategy if, you know, you're working on a tiered approach and you're trying to control your rate. So, that's something to consider, but I wouldn't recommend it off the bat.

Question cont'd: Okay. Thank you. Could you answer one more question? You mentioned something about protein pump inhibitors. I got interrupted and didn't hear that part.

Carolyn Gould: Oh, yeah, I mentioned briefly.

I didn't talk a lot about it but, proton pump inhibitors and histamine II receptor blockers are antacids that many studies have been shown to increase the risk of C. difficile infection and that may be because it makes the spores - are probably somewhat resistant to acids as they pass through the stomach, but if you reduce the acid in your stomach, you may be increasing the number of spores that get through and, although some studies have not shown them to be a risk factor, so it's a little bit unclear.

But I think the majority of studies do suggest that acid blockers do place patients at risk. So, it's important to, you know, only place patients on acid - gastric acid suppression if it's really indicated.

Question cont'd: And to maybe reduce it on purpose, if there's a...

((Crosstalk))

Question cont'd: ...going on.

Carolyn Gould: Yes, yes. I believe to reassess who was on them and to see if they really need them.

Question cont'd: Okay. Thank you.

Coordinator: Thank you. Your line is open.

Question: Thank you. Very good presentation. One of the previous callers was addressing the environmental cleaning concerns. My environmental director, besides the quaternary ammonia agent and the bleach solution, she's also stripping the was and then rewaxing as two other levels of preventing the return of bacteria and spores. Any comment on that process?

Carolyn Gould: I haven't heard specifically about the need to do that either in terms of - you know, if it's a porous surface, obviously, it's going to be difficult to clean. But, I haven't heard of that specifically.

Question cont'd: Okay. Thank you. And, any thoughts on some of these wipes with Clorox solution to the environmental surfaces, the horizontal surfaces in the rooms?

Carolyn Gould: Again, I don't have a lot of data for or against but, the important thing to remember is that with the wipes that contain Clorox, you have to make sure that there's adequate contact time with using the wipe for them to be effective. And so, the proper use of them is really critically important. I think there's going to be more to come on these wipes because they're - I've heard of more hospitals using them.

Question cont'd: Yes on the recommendations that say one minute soap time.

Carolyn Gould: Right, right. And that's not always done with this cleaning wipe in general.

Question cont'd: Okay. Thank you.

Coordinator: Your line is open.

Question: Thank you for taking my call. I have physicians who are interested in doing a process or procedure called recolonizing the colon. Now, you mentioned this earlier. I wonder if you have any direct information on it. How can I proceed to assist with this?

Carolyn Gould: Are you referring to the stool transplants or your...?

Question cont'd: Yes, I am.

Carolyn Gould: It's only done by, again, it's not a procedure that's done by many centers and there are a couple of specialists that are doing it. The only data I have seen really is the RK series and case reports of efficacy. People who tend to go to these as a last resort measure. People who have recurrent disease that can't be controlled otherwise and it seems to be an effective measure.

But, we don't have really established protocols for doing this. Again, it's done by individual investigators or centers in some cases. But, it seems to be an effective strategy for some people.

Question cont'd: Can you have any recommendations regarding this.

Carolyn Gould: I don't have specific recommendations for doing it or not doing it. I think, obviously, you have to, you know, there are infection control considerations

that have to be followed and otherwise we don't have specific recommendations.

Question cont'd: As we're building this policy, I think what I would say is it has to be for someone who has multiple relapses, something along that line, would you not agree?

Carolyn Gould: Yes. I mean that's only - those are the only cases where I've seen it used...

Question cont'd: Okay.

Carolyn Gould: ...someone who's had multiple relapses, have been on, you know, prolonged courses or antimicrobials for - with no improvement.

Question cont'd: And then I had another portion to this. I attended an annual conference and it was a suggestion that it might be a smart move to keep the antibiotic off, such as the vancomycin instead of just stopping it.

Carolyn Gould: Right.

Question cont'd: Anything?

Carolyn Gould: Yeah, again there are different strategies for recurrent disease and long, like six week courses oral vancomycin with tapering at the end has been used, sometimes in association with probiotics like sacchromyces and these are things that have been used, but not necessarily validated on a broad, you know, on a large scale, but have been reported to be successful in case reports.

Question cont'd: Thank you very much.

Alycia Downs: Dr. Gould, thank you very much for providing our listeners with this information.

And I would also like to thank our participants for joining us today.

In case you didn't get a chance to ask your question, we apologize, but please send an email to coca@cdc.gov and we will try to get that question answered.

The recording of this call and the transcript will be posted to the COCA Web site, www.emergency.cdc.gov/coca, within the next week.

You have a year to obtain continuing education credits for this call. All continuing education credits for COCA calls are issued online through the CDC Training and Continuing Education Online System, www.2a.cdc.gov/tceonline.

Thanks again, Dr. Gould, and I hope everyone has a great day.

Coordinator: Thank you. That concludes today's conference call. You may disconnect at this time.

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