Carbapenem-Resistant Enterobacteriaceae: Detection and Control

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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 please press star 1 on your touchtone phone.

Today's conference is being recorded. If you have any objections you may disconnect at this time. Now I will turn the meeting over to Alycia Downs. Thank you Alycia. You may begin.

Alycia Downs: Good afternoon and welcome to today's COCA conference call entitled Carbapenem-Resistant Enterobacteriaceae: Detection and Control.

We are very excited to have Doctor Arjun Srinivasan and Doctor Jean Patel present on this call. Dr. Srinivasan and Dr. Patel both work for the Division of Healthcare Quality Promotion within the National Center for Preparedness, Detection and Control of Infectious Diseases here at the Centers for Disease Control and Prevention in Atlanta Georgia.

Dr. Patel is a Microbiologist in the Clinical and Environmental Microbiology Branch. And Dr. Srinivasan is the team leader for the response team.

We are 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 emergency.cdc.gov/coca.

Click on the conference call information summaries and slide sets. The PowerPoint can be found under the call in info - call in number and pass code. To save it to your desktop just right click it, save and hit Save As.

The objectives for today's call, after this activity the participants will be able to: describe the mechanisms and epidemiology of carbapenem-resistant enterobacteriaceae, identify laboratory methods for the detection of carbapenem producing enterobacteriaceae, discuss infection control measures for limiting transmission of carbapenem-resistant enterobacteriaceae in the healthcare setting.

In compliance with continuing education requirements, all presenters must disclose any financial or other relationships with manufacturers of commercial products, suppliers of commercial service or commercial supporters.

As well as any use of unlabeled products or under investigation leave. CDC, our planners and our presenters wish to disclose that they have no financial interest or other relationships with the manufacturers of commercial products, suppliers of commercial services or commercial supporters.

Presentations will not include any discussion of the unlabeled use of a product or product under investigational use, with the exception of Dr. Srinivasan and Patel's discussion on use of CHROMagar and PCR for CRE detection from rectal specimens. These are non-FDA-approved tests. There's no commercial support.

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

Jean Patel: Thank you very much. Dr. Srinivasan and I appreciate this opportunity to talk to you about this important emerging antimicrobial resistance in enterobacteriaceae.

We're going to begin on Slide 4. And this describes an outline of the topics we'll discuss today.

So first I'm going to begin by giving you some background. I'm going to discuss the mechanisms molecular epidemiology and laboratory detection of carbapenem resistance in enterobacteriaceae.

Then Dr. Srinivasan will discuss the epidemiology of carbapenem-resistant Klebsiella pneumoniae, describing specific outbreaks. And he will discuss recently approved CDC HICPAC recommendations for controlling carbapenem-resistant enterobacteriaceae in acute care settings.

Let's move to the next slide. So first I'll begin by giving you a little bit of background on enterobacteriaceae. These are important pathogens, both in the community setting and in the healthcare setting.

E Coli is the most common cause of outpatient urinary tract infections. In both E Coli and Klebsiella species, two species of enterobacteriaceae, are important causes of infection in the healthcare setting.

If we look at data from the National Health Safety Network, NHSN, these two species of bacteria account for 15% of all HAIs reported to NHSN in 2007.

The next slide. Beta-lactam antibiotics are important treatment for infections caused by enterobacteriaceae. However, we have seen resistance to beta-lactams emerge in enterobacteriaceae.

And we've heard about extended spectrum beta-lactamases, these are called ESBLs, as well as plasma mediated AmpC-type enzymes.

These are broad-spectrum beta-lactamases that confer resistance to the extended spectrum cephalosporins.

Treatment of infections with these beta-lactamases usually relies upon use of carbapenem antimicrobial agents.

The next slide. So fortunately our most potent beta-lactam drugs, the carbapenem, have remained active against isolates that produce ESBLs and AmpC-type enzymes.

There are four carbapenems that are on the market. These are doripenem, ertapenem, imipenem, and meropenem.

Unfortunately, recently we have seen resistance emerge to the carbapenem and it’s that resistance that we’re going to discuss today.

The next slide. The most common mechanism of carbapenem resistance in enterobacteriaceae is acquiring the enzymes called the Klebsiella pneumoniae carbapenem or KPC for short.

KPC is a Class A beta-lactamase. And it’s a beta-lactamase that confers resistance to all beta-lactams, including extended spectrum cephalosporins and carbapenem.

The KPC enzyme was first identified in an isolate of Klebsiella pneumoniae. And that's where it got its name.

It is still most commonly found in the Klebsiella pneumoniae, but it has also been identified in other species of enterobacteriaceae. And these include Klebsiella oxytoca, Citrobacter freundii, Enterobacter species, E Coli, Salmonella and Serratia.

The KPC enzyme has also been reported in pseudomonas aeruginosa, and these reports have primarily come from South America.

To my knowledge there's only one report of a pseudomonas isolate in the United States containing the KPC enzyme. And that's an isolate from Texas.

The next slide. Isolates that are producing the KPC enzyme are resistant to multiple classes of antimicrobial agents. And on this slide we show you the typical susceptibility profile of a KPC producing Klebsiella pneumoniae isolate.

This is an isolate that's resistant to all of the beta-lactam agents that are tested. It's also resistant to most of the aminoglycosides. There is an intermediate result to amikacin.

We do see some isolates that are susceptible to gentamicin. The isolate is only susceptible to tigecycline. There are some concerns about using tigecycline to treat bacteremic infections.

And reports in the literature suggests that there are some - this might not be effective treatment in all cases.

This isolate is also non-susceptible to callistin, which is an older antimicrobial agent that has been used more frequently to treat varied drug resistant infections.

Not all isolates of KPC producing Klebsiella pneumoniae are resistant to callistin. But there have been reports of emerging resistance.

So as you can see, there are very limited treatment options when a patient is infected with one of these isolates.

The next slide. There are several types of carbapenemases that are occurring in bacteria in the United States. And this slide summarizes some of those carbapenemases.

In enterobacteriaceae, the most common enzyme is the KPC enzyme. In pseudomonas aeruginosa there have been reports of metallo-beta-lactamases. Metallo-beta-lactamases are enzymes that also confer resistance to nearly all betalactin agents.

Reports of metallo-beta-lactamases are pretty uncommon in the United States. They’re a much bigger problem in other parts of the world. We do anticipate that at some point metallo-beta-lactamases will be a problem in the US. But so far that just hasn't happened.

In Acinetobacter species that are resistant to carbapenems, these isolates most likely produce the OXA carbapenemases. These are relatively weak carbapenemases and usually have to be combined with some other (unintelligible) changes such as porin loss to see high-level carbapenem resistance.

Then finally we also see carbapenemases in Serratia marcesens. And these are called SME enzymes. SME is unusual for two reasons. One is that it’s typically chromosomally encoded.

The other is that it has a very unusual resistance pattern. SME confers resistance to the carbapenem. But an isolate that produces SME enzymes would test susceptible to all of the extended spectrum cephalosporins.

So if you have a Serratia marcesen that tested susceptible to cefotaxime, but resistance to imipenem or meropenem, you would expect that this isolate was producing the SME carbapenemases.

The next slide. In enterobacteriaceae, there are multiple mechanisms of resistance to carbapenems. There is carbapenemases production, which I just described.

An isolate can also become resistance to carbapenems if it is producing a cephalosporinase, and this would include extended spectrum beta-lactamases or AmpC-type enzymes.

And these enzymes are combined with a porin loss. So when you have this combination, an ESBL or an AmpC enzyme, combined with the porin loss, the isolate can test resistant to carbapenem.

Now both mechanisms of carbapenem resistance are treatment and infection control concerns. Now for those of you looking at the slide, I'll ask you to just advance to see the animation.

And we're highlighting carbapenemase production. And we're going to focus on that for the rest of this talk. And that's because carbapenemase production seems to be a particularly mobile mechanism of resistance.

The next slide. The KPC enzyme is located on a plasmid. Sometimes these plasmids are conjugative, sometimes they're not. But we do see evidence of plasma transfer between isolates.

The gene encoding KPC, blaKPC is usu - is flanked by transposon sequences. In fact, this transposon has been named. It's called TN 4401.

And this transposon can move. And that movement has been demonstrated in vitro.

The KPC gene occurs on plasmids with other mechanisms of resistance. So this includes normal spectrum beta-lactamases, extended spectrum beta-lactamases, aminoglycoside resistance and fluoroquinolone resistance.

So acquiring resistance to a carbapenem might include acquiring resistance to multiple other antimicrobial agents.

Next slide. We have evidence of the emerging of carbapenem resistant enterobacteriaceae by looking at NHSN data. And these are data from January 2006 to September 2007.

So we know that these isolates are causing infection. And the types of infection include catheter associated blood stream infection, catheter associated urinary tract infections, ventilator associated pneumonia.

And all together, 8% of the Klebsiella pneumoniae reported to NHSN were resistant to carbapenem.

Next slide. So based upon isolates that have incented the CDC for reference susceptibility testing. We've drawn a map of where we've identified KPC producing enterobacteriaceae in the United States.

Most of these isolates are focused in the northeastern United States. And in some hospitals isolation of a KPC producing enterobacteriaceae is a common occurrence.

The isolate mult - they have multiple isolates in a month. In other parts of the country it's still more sporadic. But what you should notice is that KPC producers are occurring in all geographical areas of the United States.

We're adding new states to this map everyday. And in fact since we've sent out this talk, we can now add South Dakota to the map. They've identified their first KPC producing isolate.

And we think that with new guidelines for detection of KPC producing isolates, we'll see a lot more states light up on the map.

The next slide. Our laboratory at the CDC has received hundreds of KPC producing Klebsiella pneumoniae isolates for confirmation. And we type these isolates by pulsed field gel electrophoresis.

This is a dendogram of the PFGE data that we've collected. And it's a condensed dendogram.

So anywhere you see a black dot, that’s a point where you would have additional branching to the right side of that dendogram.

And you see that some of these branches contain a lot of isolates. So the very top branch represents 172 isolates that have been sent to our laboratory. And these isolates came from all different geographical locations within the United States - Arizona, Colorado, New Mexico, New York, Virginia, etc.

These have very similar pulsed field gel electrophoresis patterns. The patterns demonstrated greater than 80% similarity.

There are other branches that also represent multiple isolates within a geographical region that are related. So for example, there are isolates, the third bar from the bottom are isolates from Illinois, Michigan and Missouri.

There are six isolates here and these are all highly related as well. Go to the next slide.

So here is a dendogram again. And once again I'd like you to click, and we'll highlight that first bar.

We've asked whether those isolates are related to each other. And we did that by employing a second typing mechanism that’s called multilocus sequence type, and that’s sequencing of housekeeping genes.

All of the isolates that we tested in this group, which were 12 isolates had the same sequence type. That’s sequence type 258.

And that suggests that these patterns that have greater then 80% similarity represent a common lineage of Klebsiella pneumoniae.

That other branch that I mentioned, the one from the Midwest, if you click again you'll see this highlighted.

These are isolates from Illinois, Michigan and Missouri. And these are all sequence type 14. Once again these represent a common lineage of Klebsiella pneumoniae.

So what we see evidence of are these lineages that seem to be spread over a diverse geographical region and carry the KPC enzyme.

We're not sure what this means. It could represent transmission of a KPC producing Klebsiella isolate across a broad geographical region.

Or it could mean that there is a lineage of Klebsiella pneumoniae that's just more competent at carrying this resistance mechanism.

Next slide. We do see evidence of plasma transfer between species of enterobacteriaceae. This - these are data from two enterobacteriaceae isolates that were recovered in the same institution.

So one was a Citrobacter freundii and the other one was a Klebsiella oxytoca. And we compared the plasmas from these two isolates to each other.

And the first gel is a restriction profile of these plasmas. And the second gel is the southern blot analysis using the KPC gene as a probe.

So you'll see that the plasmas are identical in these two isolates. And that the KPC gene is in the same place.

And we suggest that this may be transfer of a plasmid from the Citrobacter freundii to the Klebsiella oxytoca that's occurred within patients in this healthcare facility.

There have been other reports of similar plasmas found in diverse isolates from China and from other institutions in the United States. So this is a mechanism for transfer as well.

The next slide. There are some problems with laboratory detection of KPC producing isolates. One problem is that isolates producing the carbapenemase may test susceptible to carbapenems but demonstrate elevated carbapenem MIC.

In this case they may not be identified as a treatment or an infection control concern.

The second problem is that there are some automated systems that fail to detect this low level carbapenem resistance.

So strategies have been developed to identi - more accurately identify these in the laboratory.

Next slide. The strategy is to first identify screening criteria to - in order to identify carbapenemase-producing or carbapenem susceptible isolates.

Then employee a phenotypic test to confirm carbapenemase activity in these isolates.

Finally there are recommendations for how to follow up when carbapenemase activity is detected.

And these are guidelines that have been published in the clinical and laboratory standards institute guidelines in their M100 document.

Next slide. This is an example of susceptibility data that were used to identify screening criteria for detection of KPC producing or carbapenemase-producing isolates.

These are a group of enterobacteriaceae that have been testing for meropenem susceptibility by the reference broth microdilution method. That’s the BMD MIC that you see on the y-axis. And by disk diffusion testing, and those are the zone diameters on the x-axis.

All of the numbers highlighted in red represent isolates that are producing a carbapenemase. The lines that you see drawn on this graph are the current CLSI breakpoints for meropenem.

So you see a number of isolates that would test - that are producing a carbapenemase, but would test susceptible to meropenem.

Now if you click for the animation you'll see the new MIC screening breakpoint for detection of carbapenemases. And if you click again you'll see the disk diffusion screening criteria for identification of carbapenemase producers.

And now there are many more isolates highlighted in red that would be identified as potential carbapenemase-producing isolates. These isolates would be candidates for the phenotypic test.

The next slide. The phenotypic test that’s recommended by CLSI is the Modified Hodge test. This has also been referred to as the carbapenem inactivation assay.

This assay was chosen because it’s an assay that could be used to detect all carbapenemases. And it’s a simple assay so it could be employed in multiple laboratories.

This assay is performed by inoculating Mueller-Hinton agar with a susceptible E Coli. So I'd like you to click for the first bit of animation.

This susceptible E Coli is inoculated just as you would inoculate a plate for disk diffusing testing.

Then if you click again, the next step is to add a carbapenem disk to the agar. And click again. Now you take your test isolate and you just pick a few loopholes, and you streak from the carbapenem disk toward the edge of the plate.

This is incubated overnight. And you read the test by looking at the intersection of the test isolate with the zone of hidden vision around the carbapenem disk.

If you see growth of a susceptible E Coli toward the carbapenem disk, right around that test isolate streak, you would score that as positive.

So the test isolate that occurs at 12 o'clock is a positive. That isolate is producing a carbapenemase. The isolate at 4 o'clock is negative. That isolate is not producing a carbapenemase.

And finally the isolate that’s at 8 o'clock, that isolate is positive for carbapenemase production.

One problem with this test is that it’s very subjective. And that makes it a little challenging for clinical laboratories. But right now I think this is the best test that we have on hand.

Next slide. The Modified Hodge test, or the carbapenem inactivation assay was studied in a multi center study with different carbapenem disks, ertapenem disk, mero - imipenem disk and meropenem disk.

And it was the meropenem disk that demonstrated the great (said back) performance characteristic.

Next slide. So how would laboratories use these recommendations? CLSI is recommending that for carbapenems that have intermediate or resistant, to report the susceptibility without additional testing.

The idea here is just the intermediate or resistant results alone is sufficient to signal a treatment and an infection control alert.

Laboratories may consider performing the carbapenem inactivation test for epidemiological or infection control reasons.

Next slide. When would a laboratory test for carbapenemases? This is recommended when an isolate tests susceptible to the carbapenem, but meets the screening criteria.

And here I list the MIC screening criteria for ertapenem, imipenem and meropenem. There are also disk diffusion screening criteria. And these are published in the CLSI document.

Next slide. It is recommended that if the isolate tests positive by the Modified Hodge test, that you would report that carbapenem MIC without an interpretation. That was an unusual recommendation by CLSI.

Also it's recommended that you would add this comment. The comment is "This isolate demonstrates carbapenemase production. The clinical efficacy of the carbapenem has not been established for treating infections caused by enterobacteriaceae that test carbapenem susceptible, but demonstrate carbapenemase activity in vitro."

I'd like you to go to the next slide. And this explains the rational behind this reporting mechanism. There is a lack of data on clinical outcomes. And these isolates are resistant to almost all antimicrobial agents.

So if carbapenems could be effective for treatment, the idea of reporting an MIC without an interpretation is to preseer - preserve that possibility.

There are unpublished reports from institutions that see a lot of carbapenemase producing isolates. That treatment with high dose carbapenems administered by continuous infusion may be an effective therapeutic option.

And until more data become available, we won't know whether these isolates that test susceptible to carbapenems really are going to fail therapy and therefore should be reported as resistant.

Next slide. So this is a fairly complex detection and reporting scheme that laboratories are being asked to incorporate.

I think CLSI recommends that. And they are considering changing carbapenem breakpoints. The implementation of these lower break points would decrease the need for additional testing.

Next slide. The new challenge for clinical microbiology laboratories will also be detection of carbapenemase-producing enterobacteriaceae from a surveillance specimen.

So detection of these isolates are - controlling these isolates is an infection control concern. And one of the ways to limit transmission is to identify patients who are colonized with carbapenemase-producing enterobacteriaceae.

Colonization occurs in the GI tract. And right now there are no FDA approved methods for identifying carbapenem -resistant isolates from a GI specimen.

Next slide. There is a method that's been published by Landman et al. This is the method that uses reagents in the microbiology laboratory.

And incorporation of this method in the laboratory would not be regulated by FDA. So this is something laboratories could incorporate without this need for FDA approval.

This is an assay that's performed where the specimen is either a rectal swab or a perirectal swab. That's inoculated into tryptic soy broth that contains carbapenem disk.

The tryptic soy broth is incubated overnight. And then plated onto (Miconti) agar. And on the (Miconti) agar, that's incubated overnight as well.

And laboratories would look for lactose fermenting isolates. And then analyze the lactose fermenting isolates for resistance to carbapenems or carbapenemase production.

The procedure describing this method will be posted on the CDC Web site as a reference for laboratories who may need to incorporate this method.

In addition to this method described here, there are non-FDA-approved methods. One of those is a KPC Chrome agar. That's an agar that's available in a dehydrated form from a company called CHROMagar in Paris, France.

The Chrome agar allows for differentiation of enterobacteriaceae species. And it contains a low-level concentration of carbapenem for selection of carbapenemase-producing isolates.

And finally, there are reports of real time PCR assays for detection of the blaKPC gene from rectal specimens. And that's been reported from Israel laboratories.

This is also a significant problem - KPC producing isolates are a significant problem in Israel. They've attempted to control these isolates, and one of the methods is this real time PCR assay. And references for those will be available on our Web site as well.

With that, I'm going to turn the talk over to Dr. Srinivasan.

Arjun Srinivasan: Thanks Dr. Patel. This is Arjun Srinivasan and I'm going to turn now and cover some of the epidemiology of these KPC producing organisms with information on how the epidemiology that we've - epidemiologic information that we've acquired is now informing our new infection control recommendations for the control of these pathogens.

So I'll begin with what I think is the most comprehensive study of risk factors and outcomes of carbapenem-resistant Klebsiella pneumoniae infections, which were KPC producing organisms done in New York City and published in Infection Control in Hospital Epidemiology in 2008.

That's the slide immediately following the lab detection slide. So on the next slide I've listed the comorbidities that were recovered or determined from the study.

They did a case control study comparing patients who had carbapenem-resistant Klebsiella pneumoniae infections to those who had carbapenem-susceptible Klebsiella pneumoniae infections.

And as you can see comorbidities were common in both groups of patients. The one statistically significant difference was in transplant status where more of the patients who had a KPC producing Kleb pneumonia infection had undergone a transplant.

But both of these groups of patients had a number of underlying comorbidities.

On the next slide I summarize the information on the pre-infection length of stay between the resistant and susceptible Kleb pneumonia infection.

And here is where you begin to see some important differences. The patients who had the carbapenem resistance Klebsiella pneumoniae infections had very long pre-infection lengths of stay compared to the patients who had the susceptible organisms recovered.

A mean of 25 days compared to 6 days for the patients who had the susceptible infections. So these are organisms that we see in patients who have a lot of healthcare risk factors, underlying diseases and have been in the hospital for a very long period of time.

And that of course will come as no surprise when you look at all of the information available on infections with multi drug resistant pathogens. As this pre-infection length of stay has certainly been reported for other pathogens as well.

On the next slide I show the analysis of the healthcare associated factors. And again we do see some differences between the patients who had the KPC or carbapenem resistance to Klebsiella pneumoniae infections and those who have the susceptible infections.

And what we see here is that the patients who had the infections caused by the resistant pathogens were more likely to have central lines, be in intensive care units, be on the mechanical ventilators or have prior exposure to antibiotics.

Again, none of these risk factors will come as surprises to those of you who are familiar with risk factors for multi drug resistant organisms.

But it’s important to note that the patients who get these carbapenem -resistant infections also have these same exposures.

The next slide summarizes information on the prior antibiotic exposures among the patients who have the carbapenem-resistant and susceptible Klebsiella pneumoniae infections.

And as you can see there were statistically significant differences in all the classes of antibiotics that were looked at - cephalosporins, fluoroquinolones, beta-lactam, beta-lactamase inhibitor combination, aminoglycosides and carbapenems.

Of interest, the carbapenem exposure, 54 or 48%, I'm sorry, of the patients who had a resistant Klebsiella pneumoniae infection were on a carbapenem at the time that the resistant organism was recovered.

And nearly 70% had been on a carbapenem within the two weeks prior to these organisms being recovered.

So certainly in this setting where these organisms are now endemic, carbapenem exposure is an important driving factor it appears in the development of these infections.

The investigators also looked at mortality of these infections. And you might have to click through a couple of times to show the animations where the P values appear.

They looked at both overall mortality and attributable mortality for these infections. The overall mortality of the carbapenem-resistant infections shown in the dark blue was 48% compared to 20% overall mortality in the patients who have the carbapenem susceptible Kleb pneumonia infections.

And this difference was statistically significant. And the odds ratio was a nearly four-fold increase in overall mortality between the KPC producing Kleb pneumo infections and the non-KPC producing infections.

The investigators also then looked at attributable mortality. And they define this as patients who died with evidence of an active infection caused by a KPC producing organism.

And here you can - KPC producing or non-KPC producing organism. And as you can see here the mortality remains very, very high in the KPC group with 38% of the patients dying or having a mortality that was attributable to the KPC infection compared to 12% for the carbapenem susceptible Klebsiella pneumoniae.

And here the odds ratio of mortality increased to 4 1/2 fold. So think this study makes the point quite dramatically that these are infections that are associated with significant mortality.

On the next slide I'd like to turn now and talk about a couple of recent outbreaks that we've investigated here at CDC in collaboration with public health and hospital partners on KPC producing Klebsiella. Because I think some of the findings from these outbreaks also inform our infection control approaches.

I'll say a few words about outbreaks at an acute care hospital in Ponce, Puerto Rico in September of 2008 and from a long-term care facility in Illinois that was investigated in November of 2008.

The methodologies for these investigations were fairly standard in healthcare associated infection investigations.

We did a review of microbiology data for case finding, a review in infection control practices and also did surveillance cultures of patients who were epidemiologically associated with cases.

The goal of which was to look for possible transmission, to look for patients who might be colonized with the organisms but not clinically infected who might be serving as a reservoir for more transmission.

The next slide summarizes the epidemic curve of carbapenem-resistant Klebsiella species recovered from the hospital in Puerto Rico.

And I show this slide to make the point that in some instances these organisms are circulating in healthcare facilities. But infection control and healthcare epidemiology staff may not be aware of their occurrence.

When the hospital called us about this outbreak to seek input and assistance with investigation, it was in the summer of 2008. And their impression was that these - the outbreak had been going on for several months.

However, when we went back and took a more detailed look at the antibiogram at the hospital. We found that carbapenem -resistant Klebsiella pneumoniae had actually been present in that facility for quite some time, perhaps as long as about a year before the summer that they thought this outbreak began.

So it makes the point that these results had not been communicated to the healthcare epidemiology and infection control staff, even though these organisms were present in the hospital.

The next slide summarizes the infection control observations both in Puerto Rico and in Illinois. And again it would come as no surprise to those of you familiar with healthcare outbreaks that there were frequent issues with infection control procedures that were noted.

Staff were entering rooms without (stauning) gowns or gloves in compliance with the contact precautions that the patients had been placed on.

There was incomplete hand hygiene, reuse of gloves between rooms without hand hygiene, exiting rooms without removing gowns, touching patients and equipment without putting on personal protective equipment as recommended by the guidelines and by contact precautions.

And inconsistent use of personal protective equipment during activities that might result in high risk to the splatter of infectious material, including wound care and respiratory care.

The next slide summarizes some information on the infection control assessments in Puerto Rico. And you can see from this summary that hand hygiene compliance was suboptimal both among nurses and physicians, where it was about 50% on room entry and 60% on room exit.

And contact precautions compliance which was observed on room exit to note whether or not the patient came out or had (dawned) the appropriate PPE and then took it off appropriately was 76% among nurses, but quite a bit lower at 33% among physicians.

We also in these investigations performed active surveillance testing. Active surveillance testing refers to the practice of culturing asymptomatic patients for the presence of an organism.

This is a strategy that’s been used repeatedly as part of successful control strategies in healthcare outbreaks of a variety of different pathogens.

Where we’re looking for unrecognized, both looking for unrecognized transmission of the pathogen, but also looking for patients who might be harboring the pathogens who are serving as reservoir for ongoing transmission.

As many of you are now probably aware, the use of active surveillance testing has now also been applied to endemics control efforts for multi drug resistant pathogens line vancomycin-resistant enterococci, and more notably from methicillin-resistant Staphylococcus aureus.

As Dr. Patel alluded to in her comments, this active surveillance testing has been an important part of KPC control efforts in Israel.

And on the next slide I'll just say a few words about the experience with KPC producing organisms in Israel because I think it is illustrative.

Carbapenem-resistant enterobacteriaceae, predominantly KPC producing organisms and mostly Klebsiella pneumoniae were first encountered in Israel in 2005 but were very rarely seen. The occurrence was highly sporadic.

However in 2006, for reasons which we don't well understand, there was a nationwide clonal epidemic of a KPC producing strain of Klebsiella pneumoniae.

The emergence of this strain and this outbreak was really fairly startling in it's rapidity where they went from occasional cases to literally hundreds of cases within a very short timeframe, a matter of weeks to months.

The associated mortality with these infections was very high. It was about 44%, which was highly consistent with the experience reported from the investigators in New York.

Next slide. The investigators in Israel did turn to an active surveillance strategy as part of their control efforts. When their efforts at controlling the outbreak by simply reinforcing compliance with infection control recommendations was unsuccessful.

What they did in their strategy was target contacts of carbapenem-resisting Klebsiella pneumoniae cases. And they defined these epidemiologic contacts as patients who had been treated by the same nurse or treating team or who were in the same high risk unit as a case patient.

In their experience they screened roughly 4 to 14 patients per case that was detected. And they found about 15% of all screened contact patients were positive.

So there was a fair bit of unrecognized transmission. In this strategy they repeated these screening cultures until at least one cycle of culturing of all of the epidemiologic contacts was negative, suggesting that there was no further transmission.

Now they did look at non-epidemiologically linked patients in what they call non-contact wards. And did find there that there was very little evidence of KPC producing organisms.

Which suggested that the vast majority of the KPC producing organisms that they were seeing and detecting were representing transmission within the facility and not importation of cases from the community.

Now it's difficult to know exactly what role this active surveillance strategy played in controlling the outbreak because obviously they did a number of interventions at the same time.

However the investigators do point out that they added this strategy after their reinforcement of the infection control precaution had not successfully controlled the outbreak. And it was this addition of the active surveillance strategy that seems to coincide with control of the outbreak.

So the next slide - the next two slides I summarize our point prevalence experience in both Puerto Rico and Illinois beginning with Puerto Rico on this slide.

In this investigation rectal swabs were obtained from all of the patients who were currently hospitalized on the two wards where the KPC cases had been hospitalized and that was the surgical intensive care unit in a diabetic ward and about 20 to 30 patients were cultured. Two of those patients had unrecognized colonization with a carbapenem-resistant Klebsiella pneumoniae.

So the point prevalence of unrecognized cases was between 6.6% and 10%.

On the next slide the findings at the long-term care facility in Illinois were even more dramatic. In this situation we performed perirectal swabs on other patients who were on the same floor as the initial cases. And in that

investigation 20 out of the 41 patients who were cultured were found to be colonized with these carbapenem-resistant Klebsiella pneumoniae.

So we had unrecognized colonization in almost half of the patients on the unit.

We did culture a number of epidemiologically-related patients including patients who had previously been on that floor who had previously been roommates of the cases or had undergone dialysis with some of the case patients had undergone and found that 1 out of 14 of these patients were - also had unrecognized colonization with a carbapenem-resistant Klebsiella pneumoniae.

We cultured epidemiologically unrelated patients as well. And here we picked eight patients who had not been exposed to the floor where the case patients had been and didn't have any other epidemiologic links to the case patients but had been in the facility for a very long period of time. And there none of the eight patients that we cultured were colonized.

So this again was encouraging because it suggested that, in this setting at least, the findings represented a transmission of the organism among patients with epidemiologic contact rather than importation of cases into the facility and that the transmission was limited to patients who had epidemiologic links to a case patient.

So on the next slide I summarize a couple of the important lessons learned from these outbreaks. And I think there are two major take-home points.

First of all that healthcare epidemiology and infection control staff at some facilities might not be aware that these carbapenem-resistant Klebsiella

pneumoniae are actually circulating in their facilities or have previously been recovered in their facility.

The second major point I think is that the etiology of outbreaks of these organisms are multi-factorial but are likely due in part to both non-compliance with infection control procedures and unrecognized carriers who are serving as reservoirs for transmission of these pathogens.

So on the next slide I summarize what I think is the - are the concerning features or the bad news with these carbapenem-resistant enterobacteriaceae.

First of all these pathogens, especially carbapenem-resistant Klebsiella pneumoniae, are being encountered more commonly in healthcare settings.

Second, infections caused by these pathogens are associated with high mortality.

Third, there is ample evidence now I think both from Israel and other published reports that these pathogens are readily transmitted in healthcare settings.

Fourth, we don’t have any new treatment options for these pathogens. There are not new agents that are near approval that will treat these carbapenem-resistant Klebsiella pneumoniae that are resistant to our other antimicrobial agents.

And finally these are pathogens that are also important causes, enterobacteriaceae that is, of community associated infections.

Next slide please.

There are however some opportunities that are presented here. And so there is some good news in this picture.

First of all carbapenem-resistant enterobacteriaceae as Dr. Patel noted are not endemic in the vast majority of the United States. The occurrence in most of the country is sporadic.

Second, simple infection control intervention have been very successful in controlling the transmission of carbapenem-resistant Klebsiella pneumoniae, including hand hygiene, contact precautions, and identification of unrecognized carriers.

In December of 2008 a couple of the investigators in Israel published a commentary in the Journal of the American Medical Association on carbapenem-resistant enterobacteriaceae based on their serious experience with this nationwide outbreak that they had.

In this editorial the authors state, and I quote, “An effective intervention at containing the spread of carbapenem-resistant enterobacteriaceae, or CRE, should ideally be implemented before CRE has entered a region or at the very least immediately after its recognition. Policy makers and public health authorities must ensure the early recognition and coordinated control of CRE.”

Next slide.

We could not agree more with that statement. And CDC fully agrees that the time to act to control CRE is now before these organisms become endemic in more places.

This fall CDC began working on infection control recommendations for carbapenem-resistant enterobacteriaceae and in December these recommendations were approved by the Healthcare Infection Control Practices Advisory Committee.

Over the next several slides I'll summarize these infection control recommendations. But before I do I'll provide a couple of caveats.

Number one is to explain that the procedures that are being recommendation are being drawn from the current guidelines that exist from the CDC and HICPAC on controlling multi-drug resistant organisms in healthcare settings.

So as you'll see there's really nothing new about what's being recommended. The recommendations simply call them out specially to applications for carbapenem-resistant Klebsiella pneumoniae.

And second I'll also mention that the full details of these recommendations and the supporting rationale and some literature will be published in an upcoming edition of the Morbidity and Mortality Weekly Report that we expect to be published this week.

Next slide.

The infection control recommendation is that all acute care facilities should implement contact precautions for patients colonized or infected with carbapenem-resistant Klebsiella pneumoniae or carbapenemase-producing enterobacteriaceae as detected by the modified Hodge test or carbapenem inactivation assay as Dr. Patel mentioned.

Currently no recommendation can be made regarding when to discontinue these precautions.

Next slide.

The rationale of course is that contact precaution has been useful in controlling outbreaks of resistant enterobacteriaceae including carbapenem-resistant Klebsiella pneumoniae.

Next slide.

Clinical microbiology laboratories should follow Clinical and Laboratory Standards Institute, or CLSI, guidelines for susceptibility testing and establish a protocol for the detection of carbapenemase production.

Next slide.

The rationale here is given the presence of the KPC enzyme in isolates that had elevated but susceptible MICs to carbapenems ensuring that labs can detect this enzyme is going to be critical in our early control efforts for CRE.

Next slide.

Clinical microbiology laboratories should establish systems to ensure prompt notification of infection prevention staff of all enterobacteriaceae isolates that are non-susceptible to carbapenems or that test positive for a carbapenemase.

The next slide provides the rationale of course. The laboratory identification must of course be paired with rapid implementation of infection control

interventions and hence assuring optimal communication between the laboratory and infection prevention staff will be critical.

Next slide.

We recommend that all acute care facilities review clinical culture results for the past 6 to 12 months to determine if previously unrecognized carbapenem-resistant enterobacteriaceae have been present in the facility.

Next slide.

The rationale for this recommendation is that we have seen some instances where cases of carbapenem-resistant enterobacteriaceae do occur but are not reported to healthcare epidemiology and infection control staff.

And knowing whether CRE are already being encountered in your facility will help establish optimal control plans and help direct detection and control efforts.

Next slide.

If the review does not identify any previously unrecognized CRE continue to monitor for clinical infections.

Next slide.

However if this review does identify previously unrecognized carbapenem-resistant enterobacteriaceae we recommend the performance of a single round of active surveillance testing or a point prevalence survey to look for CRE in

high-risk units. That is, units where the cases were hospitalized intensive care units or other wards where there is high antibiotic use.

And follow the screening recommendations if cases of CRE are found.

Next slide.

If a single clinical case of hospital-onset CRE, or carbapenemase-producing enterobacteriaceae is detected, or if the point prevalence survey mentioned on the previous slide reveals unrecognized colonizations the facility should investigate for possible transmission by--next slide--conducting active surveillance testing of patients with epidemiologic links to the CRE case patients, for example those in the same unit, continuing active surveillance periodically, for example weekly, until no new cases of colonization or infection suggesting transmission are identified.

Now if transmission of CRE is not identified following repeated active surveillance testing in response to clinical cases this would suggest that your infection control procedures are controlling transmission of CRE in your facility.

In that instance you could consider altering your surveillance strategy to the performance of periodic point prevalence surveys in high-risk units just to continue to make sure that unrecognized cases are not present.

Next slide.

In areas where CRE are endemic in the community there is an increased likelihood of importation of CRE. And we recognize that this means the

approach described above with contact tracing may not be sufficient to prevent transmission.

Facilities in these endemic regions should monitor clinical cases and consider additional strategies to reduce the rates of CRE as described in Tier 2 interventions of the MDRO guidelines.

A couple of concluding comments on the next slide.

CRE, and for now predominantly KPC-producing Klebsiella pneumoniae in the United States, do pose a major clinical and infection control challenge in healthcare facilities.

However the good news is that we appear to be early in the emergence of this problem.

Hence CDC and HICPAC do believe that an aggressive infection control strategy implemented now may help curtail the emergence of these pathogens.

Next slide.

The work that Dr. Patel and I present obviously represent not just our efforts but the efforts of a huge number of people here at CDC and other places and we do want to acknowledge and thank all of the people who have contributed to our efforts to develop with a laboratory and epidemiologic understanding of KPC-producing organisms and the infection control recommendations.

And with that I'll conclude our remarks and turn it back over to you Ashley to begin the question and answer session.

Ashley. Ashley are you on the line for the question and answer session?

Coordinator: We will now begin the question and answer session. If you would like to ask a question please press star 1. Please un-mute your phone and record your name clearly when prompted. Your name is required to introduce your question.

To withdraw your question press star 2. One moment please for your first question.

Alycia Downs: And yes I'd also like to remind everyone if we are unable to answer their question or if they have to go at the moment they can also email coca, that's c-o-c-a, @cdc.gov and we will try to get a response to your question. Thank you.

Coordinator: Your first question. Your line is open.

Question: Hi. I'd like to ask in areas where you seen transmission from a long-term care facility is there any recommendation to screen patients coming to that facility to an acute care facility?

Arjun Srinivasan: Thank you. That's an excellent question. I think this is something that facilities will need to work in partnership with transferring long-term care facilities.

I think the simple answer is, yes, that if you are seeing evidence of importation of the organisms from residence of along-term care facility it may make sense to do some admission screening and to then work in partnership with public health and that long-term care facility to try and investigate what's going on there.

Question cont'd: Thank you.

Coordinator: Your next question. Your line is open.

Question: Yes. I understand there's no recommendation for the length of contact precaution but I'm concerned if - I know the mortality's higher as well but if you have patients who have been in your hospital and are readmitted, and we're talking a year or so later, what is the potential for them to still be carrying and - I mean are we going to keep these people in nursing homes and in hospitals in contact precautions for the rest of their lives if they're still carrying?

Arjun Srinivasan: That's an excellent question. I'll comment and see if Dr. Patel has any other comments.

You know, I think the recommendation for contact precautions obviously these are currently limited to acute care settings. In our MDRO guideline we do recommend that long-term care facilities have to really take a case-by-case basis to the application of contact precautions because as you point out, those are residential facilities.

With respect to the readmission issue unfortunately we simply don't have enough information to know what the length of carriage would be to be able to give guidance as to whether or not those patients would need to be placed back in contact precautions.

So we'd recommend that you follow your facility's policy for what you do with other multi-drug resistant organisms like MRSA or VRE.

Jean do you have any other comments or thoughts on that?

Jean Patel: No. Dr. Srinivasan I think your comments were appropriate.

Laboratories are just now collecting data on how long patients are colonized with these isolates.

We're supporting some studies from an outbreak at a long-term healthcare facility in Illinois and we have seen patients who are colonized with these isolates for several months. But that's as long as the study's been. We still need more data to really understand how long it can go.

Coordinator: Your next question. Your line is open.

Question: Hi. I have a question. Having noticed the information about the physicians and nurses' poor hand hygiene and the association of the close proximity of patients who are seemingly infected or colonized by these organisms why don't we start checking for the healthcare workers colonization of this organism as well as many others that are problems to find out who are those contaminating the patients and carrying it from room to room?

Arjun Srinivasan: So in the outbreaks that have been investigated the primary mode of transmission appears to be transient carriage of the organism on the hands of healthcare workers, so not long-term carriage of healthcare workers.

So in reality what we're looking at is perhaps transient contamination primarily of the hands that would be an important vector for transmission.

In investigations that have been done of other enterobacteriaceae if you look in the literature both for KPA-producing Klebsiella and also for ESBL-producing Klebsiella cultures of healthcare workers have not identified

healthcare worker carriage as in important vector for transmission in those outbreaks.

And perhaps more importantly the outbreaks have come under control through reinforcement of infection control precautions rather than a search for a colonized healthcare worker.

Question cont'd: Actually there's not - there aren't very many studies that look - have checked the healthcare workers around the country in the US, some in the - mostly in Europe. But you can probably count them on one hand that have been done unless there are some that are being kept secret and not being disseminated (unintelligible).

Arjun Srinivasan: No I agree. And I think the reason that people have not looked at healthcare workers as - again as being colonized say in the gastrointestinal tract is this issue that the reinforcement of infection control precautions, adherence to hand hygiene, have all been successful in controlling these outbreaks and have not had to prompt a more detailed look for a colonized healthcare workers.

So that's I think the rationale that the healthcare workers do serve as an important intermediate vector for transmission but the carriage is likely to be transient on the hands.

Question cont'd: Well interesting - here's the thought. I was concerned that if they start checking the nares of the healthcare workers studies have been shown 15 years ago that through thoracic - cardiothoracic surgical results (unintelligible) the same phenotype existed in the nares of the nurse and physicians on the cases in a handful have never seen those repeated since - I think it was 1989.

So I would strongly recommend not just checking patients but we really should involve the healthcare workers similar to what we do for TB annually as a surveillance in the hospital.

Arjun Srinivasan: Yeah. I think we'll need to move on to other questions. But I will point out here that there's an important difference here in the ecological niche of the enterobacteriaceae compared to the studies that you're citing which I believe were staph aureus studies.

Question cont'd: Correct.

Arjun Srinivasan: So the ecological niche here of course is the gastrointestinal tract.

Next question.

Coordinator: Your next question. Your line is open. Your line is open. Your line is open.

Question: Yes this is Linda from Microbiology Lab. We have a question regarding Proteus mirabilis.

Jean Patel: Yes, this is Jean Patel. Is your question whether Proteus mirabilis could be tested using the CLSI recommendations?

Question cont'd: Yes. We noticed - we see a frequent occurrence of Proteus mirabilis that's imipenem-resistant but ertapenem-sensitive. And our question is, is that a false positive for KPC or is that an organism that should be subjected to the modified Hodge test?

Jean Patel: That's an excellent question. Proteus mirabilis is one of the species of enterobacteriaceae that don't fit well with these CLSI recommendations. And

in the CLSI document it warns you that Proteus mirabilis is an isolate that probably can not be applied to these recommendations.

There are two reasons. One is Proteus mirabilis naturally have very high carbapenem MIC. It's very close to the breakpoint. So I'm not surprised to hear that you have some isolates that will test resistance to one carbapenem but susceptible to another.

And I think that might just reflect natural variability in carbapenem MICs from laboratory susceptible testing methods.

It's likely that those isolates do not possess an acquired resistance mechanism.

Also Proteus mirabilis can not be tested in the modified Hodge test and that's because of it's ability to swarm. We just tried an isolate the other day this last week just to see what it would look like and the isolates swarm all over the place. The test was uninterpretable.

So these recommendations would not apply to that species.

Question cont'd: Very good. Thank you.

Coordinator: Your next question. Your line is open.

Question: Hi. We're calling from Connecticut and we were wondering where should we send suspicious isolates to?

Jean Patel: This is Jean again. So isolates - we're asking for laboratories to try to incorporate phenotypic methods in their laboratory to confirm carbapenemase producers.

Now the modified Hodge test is not 100% specific so we do recommend when laboratories identify their first positive carbapenemase-producing isolate that they do have those confirmed.

There are commercial laboratories that are confirming that. Usually in the United States that will be confirmed with PCR for the block APC gene.

In addition you can send that to your state public health laboratory to the CDC and we will do the (unintelligible) testing for you as well.

Question cont'd: Thank you.

Jean Patel: Sure.

Coordinator: Your next question. Your line is open.

Question: Yes. I'm calling from New Jersey and actually my question on Proteus was answered. But while I have you on the line: on your culture methods for isolation, the scheme described on Slide 29: is there a proportion of TSB to the carbapenem disc? Is that an imipenem disc in that? Is there any more information on how you do that?

Jean Patel: Right, sure. That would be - I believe it's a 2 ml TSB broth. So those - that's a volume that well come in most commercial forms of TSB broth.

And it is in a imipenem disc.

We don't think there is much reason not to use a different carbapenem so it could be a meropenem or an ertapenem disc. But the original procedure was described with imipenem.

And specific details regarding that procedure will be available on our Web site. And I believe those materials are going to be made available in conjunction with the slides for this call.

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

Jean Patel: Sure.

Alycia Downs: Can I ask people if we can take one more question?

Coordinator: Your next question. Your line is open.

Question: Yes. We're calling from Texas. And when you're starting your risk assessment where do you recommend we start? Should we start with a specific organism?

Should we start with specific site like sterile sites, blood, urine, (unintelligible)? Where would you recommend we start?

Arjun Srinivasan: This is Arjun. This is the microbiology review you're referring to?

Question cont'd: Yes.

Arjun Srinivasan: Yeah I think I would start with Klebsiella pneumoniae. I mean that's been the species where this has been recovered most commonly.

And it should be fairly simple of your lab to look for carbapenem-resistant Klebsiella pneumoniae. It should be something that - you know, that they have none of.

So you can work with your lab folks to see - you know, if you need to limit it to a site you could look at a couple of different sites.

But my suspicion is if you work with your lab they'd be able to help you review the susceptibility profiles for - at least for Klebsiella pneumoniae to see if you have any carbapenem-resistant isolates.

But Dr. Patel do you have any other tips for how that review might happen in the lab?

Jean Patel: No I think that's appropriate.

Alycia Downs: Well Dr. Srinivasan, Dr. Patel thank you again for providing our listeners with this information.I'd also really like to thank our participants for joining us today.

If you were not able to ask your question please send an email to coca@cdc.gov: c-o-c-a@cdc.gov and we'll work with Dr. Srinivasan and Dr. Patel to get a response back to you.

The recording of this call and the transcript will be posted to the coca Web site at 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 conference calls are issued online through the CDC training and continuing education online system: www2a.cdc.gov/tceonline.

Thank you again and have a wonderful day.

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

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