Carbapenem-Resistant Enterobacteriaceae (CRE) & Multi-drug Resistant Acinetobacter (MDR-A)
Enterobacteriaceae are a large family of bacteria that are a normal part of a person’s digestive system (2). Examples include Escherichia coli and species of the genera Klebsiella, Enterobacter, Serratia, Salmonella and Shigella. Since Enterobacteriaceae live in the gut, they are potentially spread through fecal-oral and contact (13).

Once intestinal carriage is established, individuals are at risk of infection under the right conditions (13). These organisms can cause serious infections when they spread outside of the digestive system and are a common cause of community-acquired and health care-associated infections (2).

Infections caused by Enterobacteriaceae may include pneumonia, kidney and bladder infections, and bloodstream infections (4).
What is *Acinetobacter*?

- Common in soil & water
- *A. baumannii* – 80% of reported infections
- Can cause variety of illnesses
  - Little risk to the healthy

From CDC website
• CRE is not the first organism we’ve had that has become resistant to antibiotics, so why is it so important? CRE resistance is complex because it can occur in different Enterobacteriacea and is mediated by several mechanisms as discussed previously.
• Currently, CRE has developed and spread only within health-care settings, but has the potential to move into the community much like MRSA did. LTACHs have been shown to have a high colonization rate (7).
• CRE infections are currently resistant to most all the antibiotics available. New antimicrobial treatment for multidrug-resistant gram-negative bacilli are being developed, however they are in the early stages and will likely not be available in the immediate future (2).
• When a patient develops an invasive CRE infection, studies have shown that mortality rates are as high as 40-50%. (6); Carbapenem-resistant Klebsiella pneumoniae (CRKP) is independently associated with an increased mortality rate compared to patients with CSKP (7).
So what is CRE and how do we think it occurred? Enterobacteriaceae infections were originally treated with beta-lactam antibiotics such as penicillin and cephalosporins. Over the past few decades Enterobacteriaceae started to develop resistance to this standard antimicrobial treatment with the production of beta-lactamases.

Beta-lactamases are enzymes that provide bacteria with resistance to certain beta-lactam antibiotics. With time, the bacteria also started to develop extended-spectrum beta-lactamases. We commonly call these ESBLs. ESBLs are enzymes that furthered the bacteria’s resistance to beta-lactam antibiotics by providing additional resistance to monobactams like Aztreonam, and 3rd generation of cephalosporins (5)(9). It’s these 3rd generation of cephalosporin's that are known as ‘extended spectrum’ antibiotics. There are currently over 200 different kind of ESBLs or enzymes identified. ESBLs do not effect 2nd gen cephalosporin's and carbapenems are not effected. An ESBL is not a CRE.

Carbapenems are a class of beta-lactam antibiotics with broad-spectrum activity they were developed as a last-resort treatment for hard to treat infections, such as Enterobacteriaceae that had become resistant to most other beta-lactam antibiotics. This class of antibiotics includes imipenem, meropenem, doripenem, and ertapenem (12). As usage of carbapenems for the treatment of Enterobacteriaceae increased, resistance started to develop. Carbapenem-
resistant Enterobacteriaceae (CRE) was uncommon in the United States before 1992, though it had been seen in other parts of the world (8)(11).

- Carbapenemase-producing Enterobacteriaceae often carry genes that are resistant to many other antimicrobials, in addition to beta-lactam antibiotics. For this reason, CRE are becoming increasingly multidrug resistance and pandrug-resistant strains have been identified, this means some strains are resistant to all antibiotics (9).
So we know how CRE developed and the enzymes that cause a bacteria to be labeled as CRE but exactly do these enzymes work? There are several ways Enterobacteriaceae may develop resistance to carbapenems, unlike other multi-drug resistant organisms, such as MRSA, which are mediated by a single mechanism.

- One mechanism of resistance is due to the active expulsion of carbapenem antibiotics out of the cell with the use of bacterial efflux systems. These systems pump out unwanted substances, like antibiotics, from the cell which contribute to bacterial antibiotic resistance.

- The two main mechanisms of CRE resistance are 1) structural mutations with beta-lactamase production and 2) production of carbapenemases.

- Carbapenem antibiotics are structured to be highly resistant to most beta-lactamases. However, Enterobacteriaceae infections caused by beta-lactamase enzymes (ESBLs or AmpC cephalosprinases) combined with the loss of proteins on the outer membrane of the gram negative bacteria causes a structural change of the cell and prevents antibiotic entry. The combination of an overproduction of beta-lactamases and the structural mutation allow for the resistance to develop.
• The production of carbapenemases, which are enzymes that inactivate carbapenems, can lead to carbapenem resistance. Carbapenemase-producing Enterobacteriacea can quickly spread from patient to patient and is associated with the increase of CRE in the U.S.

• As we stated in the previous slide, CRE often carry more than one type of gene that make them resistant to many types of antibiotics. They are also capable of transferring their beta-lactam and carbapenem resistance to other bacteria within the Enterobacteriaceae family, making additional bacteria resistant to antimicrobial treatments. An example would be a gene spread from Klebsiella pneumoniae to E.coli since these are both Enterobacteriaceae (7).
Now that we know how carbapenemases came to be, here are some of their names.

- **Klebsiella pneumoniae** carbapenemase (KPC)
- Metallo-beta-lactamases (MBL)
  - New Delhi (NDM)
  - Verona integron-encoded (VIM)
  - Imipenemase (IMP)

**All of these are enzymes that make a bacteria be labeled as “CRE”**

Now that we know how carbapenemases came to be, here are some of their names.

- **Klebsiella pneumoniae** carbapenemase is an enzyme that has spread widely throughout the United States since first being discovered in the United States in 2001. KPC is most often found in *Klebsiella* spp. and *Escherichia coli*. Even though the name of the enzyme has a specific bacteria in it, it can appear in any Enterobacteriaceae bacteria. KPC has been found in almost every state according to the CDC - EXCEPT for Maine, Indiana and Alaska.

- In addition to KPC, new enzymes have emerged in the U.S. since 2009 but are less common within North America. They are called NDM, VIM, and IMP and are usually associated with patients who had exposure to health care in countries where these enzymes are more common (2).

- KPC and the MBL carbapenemases are in two different structural classifications. KPC is in the class A carbapenemases and the MBLs are in Class B. The difference in the classes is dependent on their active site of the hydrolytic mechanism, KPC requires serine at the active site and the MBL carbapenemases require zinc (9).
The comment period for the proposed MDRO reporting rules closed on January 5th and no comments were received from anyone across the state.

What does the Texas Administrative Code (TAC) say?

- Reporting of CRE-\textit{E. coli} or CRE-\textit{Klebsiella} as defined in the Centers for Disease Control and Prevention, National Healthcare Safety Network (NHSN) Manual, Patient Safety Component, Protocol for Multidrug-Resistant Organism and \textit{Clostridium difficile} Infection (MDRO/CDI) Module, or its successor.

- Multi-drug resistant (MDR) \textit{Acinetobacter}--MDR-\textit{Acinetobacter} as defined by ...
There are varying definitions of what a CRE or Resistant Enterobacteriaceae is. For the purposes of Texas DSHS we are using the NHSN Definition.

The toolkit bases this definition on the 2012 Clinical and Laboratory Standards Institute (CLSI) criteria (4).

Often people will think you can call any gram negative rod “CRE” – you can only call bacteria that fall under the family Enterobacteriaceae’s CRE. This means Acinetobacter and Pseudomonas are NOT considered CRE.

NOTICE: Ertapenem is not part of the definition.
**MDR-Acinetobacter**

Nonsusceptible to at least 1 antibiotic in at least 3 antimicrobial classes of the following 6 antimicrobial classes:

<table>
<thead>
<tr>
<th>Beta-Lactam</th>
<th>Aminoglycosides</th>
<th>Carbapenems</th>
<th>Fluoroquinolones</th>
<th>Cephalosporins</th>
<th>Sulbactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin</td>
<td>Amikacin</td>
<td>Imipenem</td>
<td>Ciprofloxacin</td>
<td>Cefepime</td>
<td>Ampicillin/sulbactam</td>
</tr>
<tr>
<td>Piperacillin/Gentamicin</td>
<td>Gentamicin</td>
<td>Meropenem</td>
<td>Levofloxacin</td>
<td>Ceftazidime</td>
<td></td>
</tr>
<tr>
<td>Pipacillin/Tobramycin</td>
<td>Tobramycin</td>
<td>Doripenem</td>
<td></td>
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</tbody>
</table>

If you have an Acinetobacter that meets this criteria – report it.

Nonsusceptible means Intermediate or Resistant.
Go look at the footnotes on the Notifiable Conditions list.
CRE: http://www.dshs.state.tx.us/IDCU/health/antibiotic_resistance/Reporting-CRE.doc
Maryland will be added shortly.
Texas will be added once the reporting officially becomes required.
The top graph shows the total percentage of CRE organisms reported through NNIS in 2001 compared to NHSN 2011 data. It increased from 1.2% in 2001 to 4.2% in 2011. What's different about those two years is first that we have more facilities reporting through and using NHSN in 2011 than in 2001. We've also had a change in breakpoints at which CRE is defined.

The second graph shows Klebsiella species as the genera that had the largest increase at 1.6% to 10.4% during that time.

(6)
In NHSN in 2011, CRE represented 4.2% of all organisms. For Texas in 2012 for TxHSN, CRE represented .5% this was only for CLABSI’s. This means we don’t have a true sense of colonization or infection rate in the state. And while any unusual clusters or events are required to be reported, we do not have a formal data collection system for these non-required conditions. So for 2012 data that was reported through NHSN for the required Texas Reporting in TxHSN, we pulled the CRE’s that were reported for SSI’s and CLABSIs.

Of the isolates reported in TxHSN, 538 were Enterobacteriaceae. Of these only 12 were carbapenem resistant enterobacteriaceae’s. **Reportable conditions in 2012: CLABSI, KPRO, HPRO, VSHN, CBGB/C, CARD, HTP**
A break down of these 12 CRE shows that one specific bacteria, *K. pneumoniae* took up almost half at 5 infections. This pie chart shows the bacteria, number of isolates and percentage of CRE.

While these are the number of isolates. No event or infection involved more than one CRE.
Only 6 of these would have been reported under the April 1, 2014 reporting requirements.
Another reason why the definition may not be helpful is that while the breakpoints maybe clearly defined with break point number, they are not yet used. As stated, the current CRE definition is based on the 2012 Clinical and Laboratory Standards Institute (CLSI). To improve CRE detection, these breakpoints have been lowered several times in the past 5 years, most recently in 2012. Using the new breakpoints can help identify patients who should be placed in contact isolation, where with the old criteria the patient may not have been isolated. However, the FDA has not yet approved these new breakpoints, so this means manufacturers cannot update their equipment for hospitals to use these breakpoints (7).

The Modified Hodge Test is a test that can be used to detect carbapenemase production in isolates of Enterobacteriaceae. With the recommended lowered breakpoints the MHT is not necessary, however if a lab is not using the current interpretive criteria/breakpoints then the MHT should be done to confirm an isolate as CRE (7). Not all hospitals are able to perform a MHT due to man power.

You might be asking what about other methods to detect CRE. A polymerase chain reaction (PCR) test can only test for specific carbapenemases, like KPC or NDM. This is not something typically done in a clinical lab and it is not necessary to initiate infection control measures – once the lab ID’s resistance to Carbapenem, appropriate measure should be immediately initiated.
Case Examples
No MIC was listed just for imipenem – this should raise a red flag, ask your lab “Why did this happen?”
Under the preliminary the machine flagged this isolate for additional testing.
They did a Modified Hodge Test and determined that this was not a CRE. That’s why it says “This isolate does not produce a carbapenamase”
This lab did not need to be reported.

Wait for your lab to be final.
ESBL is not a CRE
They can cause a false positive on a modified hodge test
The imipenem is listed as “S”

Notice the second organism is Pseudomonas – this would not be reported!
Pseudomonas is not an Enterobacteriaceae
This report says “CRE” but look at the organism, Enterobacter cloacae – only E.coli and Klebsiella spp need to be reported. This did not have an MIC listed, talk with your lab and ask if this is usual. Or did this happen for a special reason.
Since Enterobacteriaceae are normal gut flora, in healthcare settings they are typically spread person-to-person, such as from the unclean hands of healthcare personnel or through medical devices, such as urinary catheters and intravenous catheters.

- There are many areas and ways to break the chain of infection or even colonization.
- Transmission is the same for MDRA
Patients Most at Risk

- CRE infections are more common in patients who have:
  - Frequent or prolonged hospital stays
  - Prolonged antibiotic use
  - Indwelling medical devices
  - Chronic medical conditions

- We are also collecting this information on our cases.
Facility Level Recommendations

- Lab detection and notification of CRE
  - Facility antibiogram
- Retrospective surveillance
  - Perform surveillance (6-12mos) to find unreported CRE
- Intra and inter-facility communication of patients
- Hand hygiene survey
  - Accessibility of product
- EVS and healthcare worker training
  - High touch areas and practice adherence

- Most of these recommendations come from The CDC CRE Toolkit that was released in 2012. We also have included additional recommendations we have come across through our research. While these are not CDC Core prevention measures, they should be strongly considered by all facilities as basic infection prevention measures.
- It is important to ensure that accurate lab detection of CRE is being implemented so that patients infected or colonized with CRE may be immediately placed on isolation precautions. Facilities should educate and increase awareness of CRE importance among laboratory staff. Are your items sent out? How does your reference lab hold up? Does your lab currently report antimicrobial susceptibility panels to your IP? Laboratory staff should immediately notify infection prevention staff of CRE positive results. Create and use your antibiogram
- Facilities should consider performing a retrospective lab review over a time period of 6-12 months to determine the number of unidentified CRE positive cases. If unrecognized CRE patients are identified, one round of surveillance cultures in units where cases were detected can be considered if there is concern. This will help facilities monitor progress in CRE prevention, identify possible patterns in affected units, and help prevent further transmission.
- There should be prompt communication among laboratory, infection prevention, and healthcare personnel whenever positive CRE specimens are identified. In addition, facilities should communicate CRE status to receiving facilities if patients are being transferred. The CDC has a transfer form if needed
• Conduct a hand hygiene survey at your facility – enough sanitizers located in appropriate areas? easier to install than sinks.

• Ensure your EVS department receives annual training. Do they know what high touch areas are? Provide education to EVS and direct care givers on infection prevention protocols and environmental decontamination. Ensure compliance of routine environmental measures and prioritize room cleaning of patients on contact precautions. Ensure your Infection Preventionist is up-to-date on their knowledge about CRE and are following current guidelines/recommendations.
These core preventative measures should be utilized even for facilities with little or no CRE and can be applied to all MDROs.

1. Hand hygiene should be monitored and feedback should be provided directly to staff. Make sure all units are equipped with hand hygiene supplies.

2. Contact precautions should be used for patients identified as colonized or infected with CRE. Patients may be placed on contact precautions preemptively if being transferred from high-risk settings (ICU, LTACs, or patients who received healthcare from another country within the past six months) until screening culture results are available. Currently there are no recommendations of when to discontinue use of contact precautions for CRE positive patients. Restrict moving the patient outside of the patient room unless necessary—limit diagnostic tests and procedures.

3. Patients colonized or infected with CRE should be cohorted in specific areas, and given single rooms if available. Can use dedicated personnel for affected units.

4. The use of indwelling medical devices can increase risk of CRE infection. Minimizing the use of such devices is encouraged in all healthcare settings. Device use should be reviewed on a regular basis and discontinued asap.

5. Monitor/ensure appropriate use and duration of antibiotics.

6. CRE screening should be used for epi-linked patients as a prevention strategy and in CRE outbreaks. CRE screening might include point prevalence surveys. A point prevalence survey means you’ve identified positive patients and want to look for other CRE positive patients that may exist,
either on the same unit or from patients that were associated with a particular patient. The recommended site for doing this type of surveillance is stool, rectal or peri-rectal cultures, but wound cultures or urine cultures from a urinary catheter have also been used.
Facility Level Recommendations continued...

Supplemental measures

1. Active surveillance testing
   - Reactive vs. Proactive
2. Chlorhexidine bathing

- Supplemental measures can be implemented when core prevention efforts are not effective in reducing CRE.
- We just mentioned screening as a core measure. Active surveillance testing as a supplemental measure is different. CRE screening is “All patients associated with patient X will be screened” This is a reactive approach. You’re reacting to the issue that has arose. Active surveillance testing has been used successfully in other HAI outbreaks when bundled with other interventions. It involves culturing patients who meet a specific criteria, but are not necessarily epidemiologically linked to CRE patients. For example, you might culture all patients admitted, from facility X. This would be an example of a proactive approach. You want to catch the patients upon admission before they can spread CRE to your other patients.

- The proactive approach means resources are given upfront and will allow early detection and containment. Reactive means the resources are given post-outbreak. The resource cost is dependent upon the size of the outbreak. It is up to a facility to decide which approach they prefer.

- Chlorhexidine bathing is the process of using 2% diluted liquid chlorhexidine or 2% chlorhexidine wipes to bath patients and is not usually used above the jaw or on wounds. It has been used successfully in reducing MDROs including CRE when bundled with other interventions. In acute-care settings, the bathing will usually be used on all patients regardless of CRE status. In long-term care settings, this
intervention might only be used on patients known to be infected or colonized with CRE. Other products may exist on the market, research is pending.
For the prevention and management of CRE in LTACs, the same 6 core measures on the previous slide should be followed, but might be modified due to LTAC setting differences.

Resident placement – if private rooms are not available, CRE positive patients should be cohorted with other CRE positive patients or patients with low risk of acquiring infection such as residents that are:
- Not significantly immunocompromised
- Are continent of urine and feces
- Have no invasive devices (urinary catheters, lines, track, drainage devices)
- You do not want to put someone who is neutropenic in a room with someone who is known or at risk of carrying of CRE. In addition, someone who is totally dependent upon medical care or a care giver to daily living would be considered high risk.

Contact precautions – The use of contact precautions may be “relaxed” for patients with low risk of transmission. LTACs should consider risk of transmission and CRE carriage before discontinuing contact precautions. Staff should ensure visitors follow facility policy as well. Will your visitors follow a different practice?

Therapy – CRE positive patients with high risk of transmission should have therapy and treatments performed in the patient’s room if possible. If therapy must be done outside the patient’s room, certain precautions should be taken to reduce the risk of transmission to other patients. If possible:
- Use dedicated resident equipment or disposable equipment
• Clean all equipment immediately after use
• Schedule CRE positive patients for the last sessions of the day
• Ensure excretions/secretions are contained and that they are clean – the patient can leave the room and participate in activities
• Just like resident place and modified precautions, you need to consider social activities. You should consider the patients level of function both cognitive and physical, and the site of the infection/colonizations.
• Lastly, a facility should not deny admission of a patient solely based on the CRE status. With proper precautions, appropriate care can be given to these individuals without transmitting it to other patients
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References


