



Carbapenem-Resistant Enterobacteriaceae (CRE): The Public Health Response in Wisconsin

Gwen Borlaug, CIC, MPH, Director,
Healthcare-associated Infections
Prevention Program
Wisconsin Division of Public Health

HAI in LTC Coalition Spring Conference
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Topics

- CRE basics
- Surveillance
- Case studies
- Response and prevention



Enterobacteriaceae



Gram negative rods found in the gut of humans and animals

Common human pathogens

<i>Escherichia coli</i>	} Account for 21% of all HAIs	<i>Salmonella</i>	<i>Shigella</i>
<i>Klebsiella</i>		<i>Yersinia</i>	<i>Serratia</i>
<i>Enterobacter</i>		<i>Proteus</i>	<i>Citrobacter</i>

Practical Healthcare Epidemiology, 3rd edition

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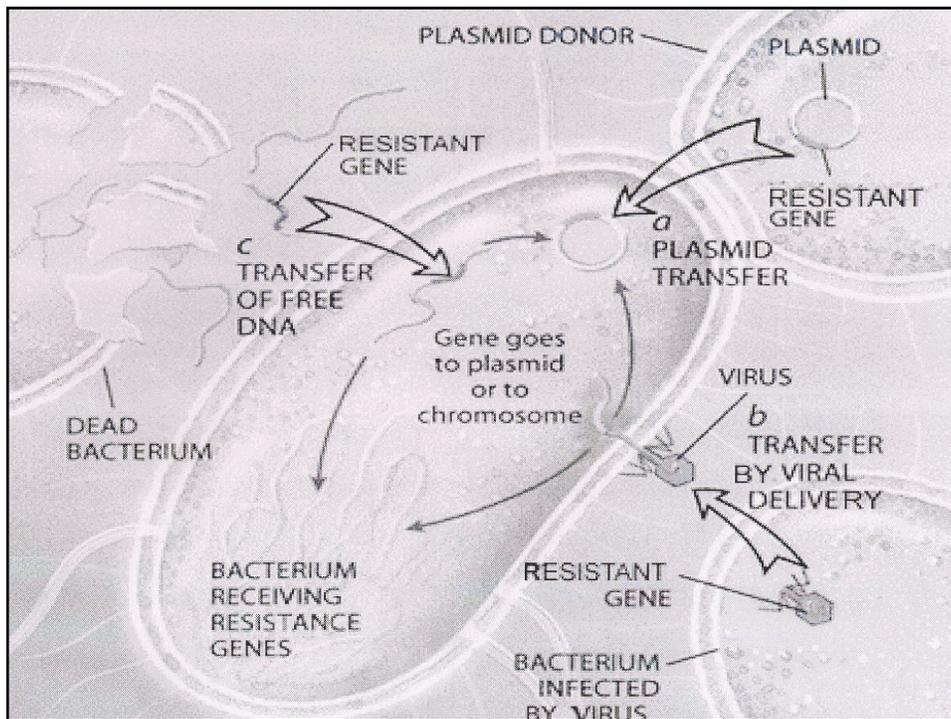


Beta-lactam Antibiotics: Inhibit Cell Wall Synthesis

- Penicillins (penicillin G, penicillin V, ampicillin, amoxicillin)
- Monobactams (aztreonam)
- Cephalosporins (cefadroxil, cefazolin, ceftriaxone, ceftazadime)
- Carbapenems (doripenem, meropenem, imipenem)

Microb. Mol. Biol. Rev. September 2010 vol. 74 no. 3; 417-433

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CRE

- The first KPC producer was identified during 1996 in the eastern U.S.; the organisms spread globally within a few years.
- KPC-producing isolates are most prevalent in the eastern states, and in Puerto Rico, Columbia, Greece, Israel, China.
- *Klebsiella pneumoniae* and *E. coli* are the most common CRE in the U.S.





2013 CDC Threat Report



Microorganisms with threat level of “urgent”

- *Clostridium difficile*
- Carbapenem-resistant *Enterobacteriaceae* (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

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CRE

CDC Antibiotic Resistance Threats in the U.S., 2013

- 9,300 cases of CRE infections annually among hospitalized patients (85% *Klebsiella* spp. vs. *E. coli*)
- 610 deaths
- 11% of infections with *Klebsiella* spp. and 2% of infections with *E. coli* are carbapenem-resistant

<http://www.cdc.gov/drugresistance/threat-report-2013/index.html>

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CRE

- “Triple threat”
 - Invasive infections are associated with high mortality rates (40–50 percent).
 - Many are resistant to almost all antibiotic agents.
 - The potential for community transmission is significant.

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CDC Home Search Health Topics A-Z

MMWR
Weekly
March 20, 2009 / 58(10):266-260

Persons using assistive technology might not be able to fully access information in this of the report in the subject line of e-mail.

...HICPAC recommends an “aggressive infection control strategy, including managing all CRE patients with contact precautions...”

Guidance for Control of Infections with Carbapenem-Resistant or Carbapenemase-Producing *Enterobacteriaceae* in Acute Care Facilities

Infection with carbapenem-resistant *Enterobacteriaceae* (CRE) or carbapenemase-producing *Enterobacteriaceae* is emerging as an important challenge in health-care settings (1). Currently, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is the species of CRE most commonly encountered in the United States. CRKP is resistant to almost all available antimicrobial agents, and infections with CRKP have been associated with high rates of morbidity and mortality, particularly among persons with prolonged hospitalization and those who are critically ill and exposed to invasive devices (e.g., ventilators or central venous catheters). This report provides updated recommendations from CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC) for the control of CRE or carbapenemase-producing *Enterobacteriaceae* in acute care (inpatient) facilities. For all acute care facilities, CDC and HICPAC recommend an aggressive infection control strategy, including managing all patients with CRE using contact precautions and implementing Clinical and Laboratory Standards Institute (CLSI) guidelines for detection of carbapenemase production. In areas where CRE are not endemic, acute care facilities should 1) review microbiology records for the preceding 6–12 months to determine whether CRE have been recovered at the facility, 2) if the review finds previously unrecognized CRE, perform a point prevalence culture survey in high-risk units to look for other cases of CRE, and 3) perform active surveillance cultures of patients with epidemiologic links to persons from whom CRE have been recovered. In areas where CRE are endemic, an increased likelihood exists for importation of CRE, and facilities should consider additional strategies to reduce rates of CRE (2). Acute care facilities should review these recommendations and implement appropriate strategies to limit the spread of these pathogens.

For CRKP, the most important mechanism of resistance is the production of a carbapenemase enzyme, *bla_{KPC}*. The gene that encodes the *bla_{KPC}* enzyme is carried on a mobile piece of genetic material (transposon), which increases the risk for dissemination. Since first described in North Carolina in 1999, CRKP has been identified in 24 states and is recovered routinely in certain hospitals in New York and New Jersey (3). Analysis of 2007 data regarding health-care-associated infections reported to CDC indicated that 8% of all *Klebsiella* isolates were CRKP, compared with fewer than 1% in 2000 (CDC, unpublished data, 2008). CRKP poses significant treatment challenges, and CRKP infections have been associated with increased mortality, length of stay, and increased cost (4). The emergence and spread of CRKP and other forms of CRE is another in a series of successive public health developments involving antimicrobial resistance among gram-negative bacteria and underscores the

Carbapenems: Past, Present, and Future

Krisztina M. Papp-Wallace^{1,2}, Andrea Endimiani^{1,2,3}, Magdalena A. Taracila² and Robert A. Bonomo^{1,2,4,5,*}

Author Affiliations

ABSTRACT

In this review, we summarize the current "state of the art" of carbapenem antibiotics and their role in our antimicrobial armamentarium. Among the β -lactams currently available, carbapenems are unique because they are relatively resistant to hydrolysis by most β -lactamases, in some cases act as "slow substrates" or inhibitors of β -lactamases, and still target penicillin binding proteins. This "value-added feature" of inhibiting β -lactamases serves as a major rationale for expansion of this class of β -lactams. We describe the initial discovery and development of the carbapenem family of β -lactams. Of the early carbapenems evaluated, thienamycin demonstrated the greatest antimicrobial activity and became the parent compound for all subsequent carbapenems. To date, more than 80 compounds with mostly improved antimicrobial properties, compared to those of thienamycin, are described in the literature. We also highlight important features of the carbapenems that are presently in clinical use: imipenem-cilastatin, meropenem, ertapenem, doripenem, panipenem-betamipron, and biapenem. In closing, we emphasize some major challenges and urge the medicinal chemist to continue development of these versatile and potent compounds, as they have served us well for more than 3 decades.

Antimicrob Agents Chemother. November 2011 vol. 55 no. 11 4943-4960

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Accepted manuscript posted online 22 August 2011, doi: 10.1128/AAC.00296-11
Antimicrob. Agents Chemother. November 2011 vol. 55 no. 11 4943-4960

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CRE

- Not all CRE are created equal.
 - Non-carbapenemase producers: resistant to at least one of the carbapenems but are usually susceptible to other antibiotics
 - Carbapenemase producing CRE (CP-CRE): resistant to all B-lactam antibiotics
- The focus of CRE surveillance in Wisconsin is CP-CRE.

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Mechanisms of Carbapenemase Production

- *Klebsiella pneumoniae* carbapenemase (KPC)
- New Delhi metallo-beta-lactamase (NDM)
- Oxacillin-48 (OXA-48)
- Verona integron-encoded metallo-beta-lactamase (VIM)

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CRE

Laboratory-based: 2010
 Hospital: 2011
 Skilled nursing facilities: 2016

Data base: National Healthcare Safety Network

Goals:

- Determine areas of high CRE prevalence
- Identify "high risk" facilities
- Detect incidents of healthcare transmission

Date: September 26, 2011
 To: Infection Preventionists in General Acute Care and Critical Access Hospitals
 From: Jeffrey P. Davis, MD, Chief Medical Officer and State Epidemiologist for Communicable Diseases and Emergency Response
 Re: Hospital Surveillance for Carbapenem-Resistant Enterobacteriaceae

Carbapenem-resistant Enterobacteriaceae (CRE) are emerging in the US as epidemiologically important healthcare-associated pathogens. They are resistant to almost all antimicrobial agents, and infections with these organisms are associated with high morbidity and mortality. In response to this healthcare threat, CDC is urging state health departments to assess CRE prevalence in acute care facilities and to assist in developing prevention strategies.

Associated information regarding CRE isolates obtained from a recent number of state-of-the-art microbiology laboratories includes the presence of CRE in some Wisconsin health...

Date: August 16, 2016
 To: Infection Preventionists in Wisconsin Skilled Nursing Facilities
 From: Jeffrey P. Davis, MD, Chief Medical Officer and State Epidemiologist for Communicable Diseases
 Re: Surveillance for Carbapenem-Resistant Enterobacteriaceae

Carbapenem-Resistant Enterobacteriaceae (CRE) are emerging in the United States as epidemiologically important healthcare-associated pathogens. They are resistant to almost all antibiotic agents and infections with these organisms are associated with high morbidity and mortality. In response to this healthcare threat, CDC is urging state health departments to conduct CRE surveillance among healthcare facilities and to assist in developing prevention strategies.

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CRE Surveillance in LTCF

- The purpose of CRE surveillance is to enable facilities to collect, report and analyze data that will inform infection prevention strategies.
- The multidrug-resistant organism (MDRO) module in the National Healthcare Safety Network (NHSN) is used for CRE surveillance.
- Laboratory results are used without clinical evaluation of the resident.
- Data are collected facility-wide.

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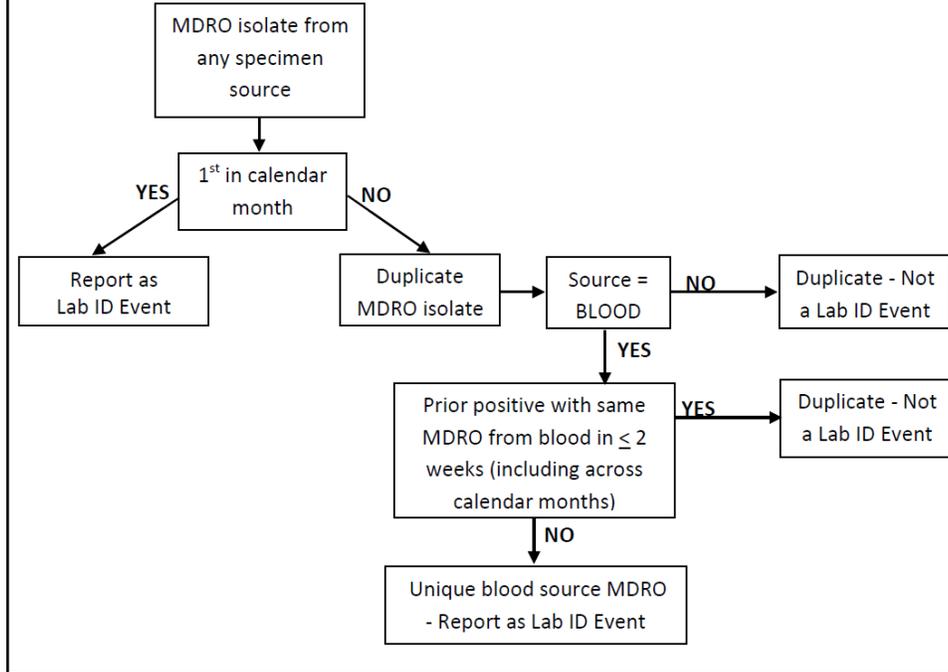
CRE Surveillance Definition

CRE: Any *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, or *Enterobacter* spp. determined to produce a carbapenemase (i.e., KPC, NDM, VIM, IMP, OXA-48) using a recognized test (e.g., polymerase chain reaction, metallo- β -lactamase test, modified-Hodge test, Carba-NP).

Source: National Healthcare Safety Network (NHSN)

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Figure 2. MDRO Test Result Algorithm for Laboratory-identified (LabID) Events.



CP-CRE Surveillance Case Studies



Case 1

6/16: A 70 YO female resident requests a bedside commode and complains of frequent and painful urination. A urine culture is collected via a straight catheter. The resident is afebrile.

6/19: Urine culture is positive for *E. coli* (>100,000 cfu/ml), and antibiotic susceptibility testing (AST) indicates the organism is resistant to imipenem.

6/25: Your reference laboratory flags the final result with the message "KPC gene detected."

What should be reported if you are conducting CP-CRE surveillance?

- A. One CRE LabID event
- B. Two CRE LabID events
- C. Definition of a UTI is not met; therefore, do not report any LabID event
- D. Insufficient information to determine a CRE event

Case 1, con't

6/26: The resident spikes a fever of 101°F and blood cultures X 2 are collected, which grow out *E. coli*, resistant to imipenem. Results from the state lab indicate carbapenemase production.

What should be reported?

- A. No LabID event, a CRE has already been reported for the month for this resident
- B. One CRE LabID event
- C. No LabID event, because the blood isolate is the same species as the urine isolate
- D. Insufficient information to determine

Case 2

A blood culture is collected from an 84 YO male resident on 5/29 and grows out a CP-CRE *Klebsiella pneumoniae*. A second blood culture is collected 6/2 and also grows out CP-CRE *K. pneumoniae*.

How many CRE LabID events should be reported? _____

Why? _____



Identify the CRE LabID Events

Resident	Admit Date	Specimen Collection Date	Source	Lab Result	LabID Event
Jack	6/01/12	06/01/12	Stool	CRE E. coli	Y N
Jack	6/01/12	06/02/12	Blood	CRE E. coli	Y N
Jack	6/01/12	06/12/12	Blood	CRE E. coli	Y N
Jack	6/01/12	06/20/12	Blood	negative	Y N
Jack	6/01/12	07/10/12	Blood	CRE K. oxytoca	Y N
Jack	6/01/12	07/15/12	Blood	CRE K. oxytoca	Y N



Identify the CRE LabID Events

Resident	Admit Date	Specimen Collection Date	Source	Lab Result	LabID Event
Bill	06/15/12	06/16/13	Blood	CRE Klebsiella spp.	Y N
Bill	06/15/12	06/20/13	Blood	CRE E. coli	Y N
Bill	07/02/12	07/01/13	Sputum	CRE E. coli	Y N
Eve	07/02/12	07/06/13	Stool	CRE E.coli	Y N
Eve	07/02/12	07/10/13	Stool	CRE Klebsiella spp.	Y N
Helen	06/01/12	06/06/13	Urine	CRE E. coli	Y N

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DEPARTMENT OF HEALTH SERVICES
 Division of Public Health
 F-XXXXX (06/2016)

STATE OF WISCONSIN

LABORATORY-IDENTIFIED MDRO EVENTS IN LTCF
 (NHSN LTCF MDRO/C. *difficile* protocol http://www.cdc.gov/nhsn/pdfs/ltc/lctcf-labid-event-protocol_current.pdf)

Resident Name		Record No.
Date of Admission		Date of Review
Date of Previous MDRO Culture Result(s)		
Date of Event/Specimen Collection		Type of Specimen Collected
<input type="checkbox"/>	Individual is receiving care at the LTCF at the time of specimen collection.	
AND		
<input type="checkbox"/>	Specimen is collected for clinical assessment purposes (not active surveillance testing).	
AND		
<input type="checkbox"/>	One of the following definitions of a unique laboratory event is met: <input type="checkbox"/> MDRO isolate is the first one obtained in the calendar month from any specimen source (e.g., urine, wound, sputum, blood), for the resident (if source is blood, a prior positive blood culture with the same MDRO must not occur ≤14 days before the current blood culture, even if in different calendar months). <input type="checkbox"/> MDRO isolate is the first obtained from a blood source in the calendar month (with no prior positive blood culture with the same MDRO ≤14 days before the current blood culture). A prior MDRO may or may not have been obtained from another source (e.g., urine, wound, sputum).	

<https://www.dhs.wisconsin.gov/forms/f01887a.pdf>



CRE Denominator Data

- Resident-days
 - Calculated using the daily census of residents in the facility each day of the month and totaled at the end of the month
- Admissions
 - Number of residents admitted each calendar day of the month and totaled at the end of the month
- Must be entered into NHSN every month, even when there are no LabID events



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Denominators for LTC facilities

* Facility ID: DPH NH Location: 4N Month: April Year: 2014

Date	Number of residents	Number of residents with urinary catheter	Number of admissions
1	10	1	2
2	10	1	2
3	10	1	2
4	10	1	0
5	10	1	0
6	8	0	1
7	8	0	1
8	8	3	2
9	9	3	2
<hr style="border: 1px solid red;"/>			
22	10	2	2
23	10	2	2
24	9	1	3
25	7	1	1
26	7	1	1
27	10	2	0
28			
29	10	2	2
30	9	1	3
31			
Total			
	Resident-days	Urinary catheter-days	Resident admissions

Count at same time each day

Total each column at end of month and enter into NHSN

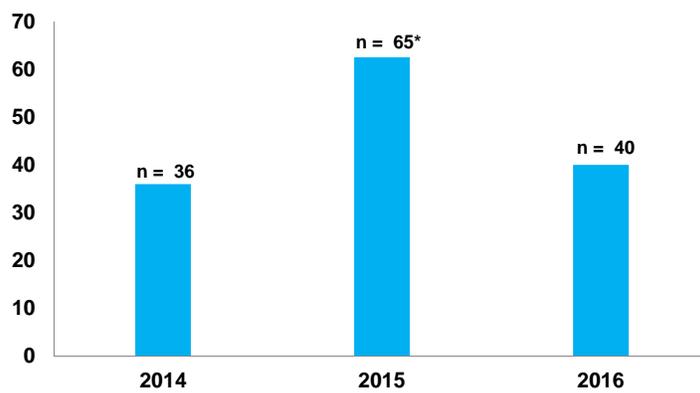
Link to denominator form
http://www.cdc.gov/nhsn/PDFs/LTC/forms/57_142_DenominatorLTCF_BLANK.pdf



CRE Surveillance Data

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Number of Wisconsin patients with at least one reported CRE isolate, 2014-2016

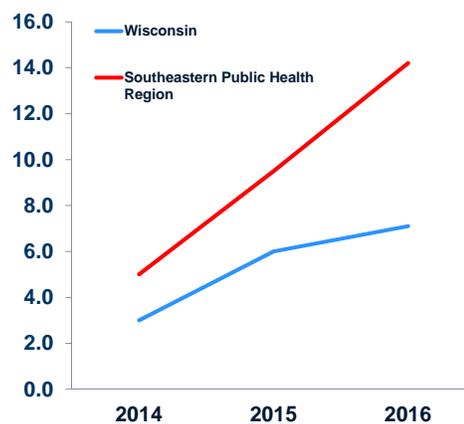


*addition of *Enterobacter* spp. and Emergency Department patients to the CRE case definition

Wisconsin 2016 CRE Surveillance Data Summary

Number of carbapenem-non-susceptible <i>Klebsiella</i> , <i>E. coli</i> , and <i>Enterobacter</i> isolates submitted to WSLH	351
Number (%) of carbapenemase positive isolates	58 (16)
Carbapenemase mechanism	
Number (%) of KPC	56 (97)
Number (%) of OXA-48-like	2 (3)
Number (%) of NDM-1	0 (0)
Specimen source	
Number (%) of urine	34 (59)
Number (%) of skin/soft tissue	16 (28)
Number (%) of sterile sites	6 (10)
Number (%) of respiratory	2 (3)
Organism	
Number (%) of <i>Klebsiella</i> spp.	33 (57)
Number (%) of <i>E. coli</i>	13 (22)
Number (%) of <i>Enterobacter</i> spp.	12 (21)

Laboratory-identified CRE events per 100,000 admissions, Wisconsin 2014-2016



*LabID event = a clinical specimen positive for CRE (*Klebsiella* spp. or *E. coli*) per patient, per month, per facility



CRE Surveillance Summary

- CRE prevalence is highest in the Southeastern Public Health Region.
- One “high risk” facility, located in SE Wisconsin, has been identified. All residents admitted to referring hospital are pre-emptively placed on contact precautions.
- At least 4 incidents of healthcare transmission have been detected.

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Incidents of CRE Transmission in Wisconsin Healthcare Facilities

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Transmission of KPC *Klebsiella pneumoniae* from long-term care to acute care, 2012



Long-Term Care Facility



Patient 1



Patient 2

- Unidentified CRE-positive Patient 1 was transferred from a long-term to an acute care facility.
- CRE was transmitted to Patient 2, located in a hospital room adjacent to Patient 1.
- Rectal cultures of all patients on the affected unit did not reveal additional transmission.
- Patient 2 was not discharged to another facility, thus no follow-up with receiving facilities was required.

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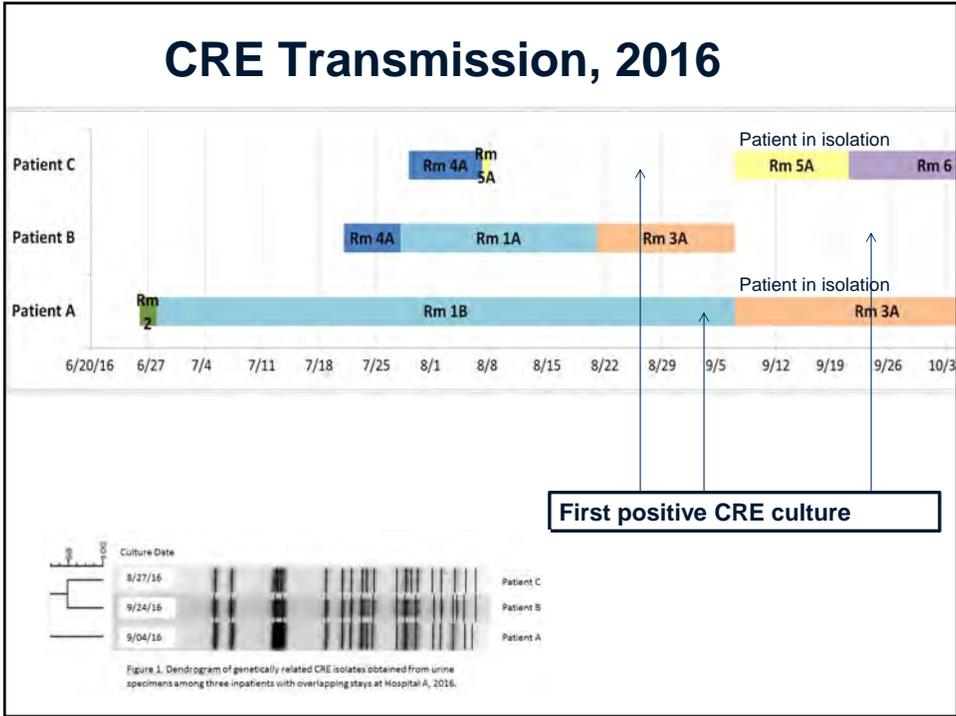


Transmission of NDM-1 *E. coli* via a common duodenoscope, 2013

NDM-1-Positive Index Patient 3



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CRE Transmission in ICU, 2016

A patient being treated in the ICU for several months was infected at multiple sites with KPC *K. pneumoniae*. The isolate was resistant to ALL antibiotics tested.

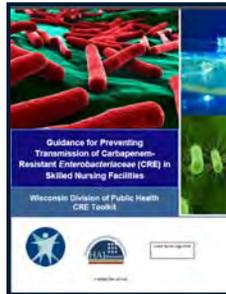
The isolate underwent testing for the mcr-1 gene at CDC, and was negative.

The ICU has been placed on active surveillance, and patients are screened for CRE upon admission, weekly, and at discharge. To date, the same organism was transmitted to 4 additional patients in the unit.

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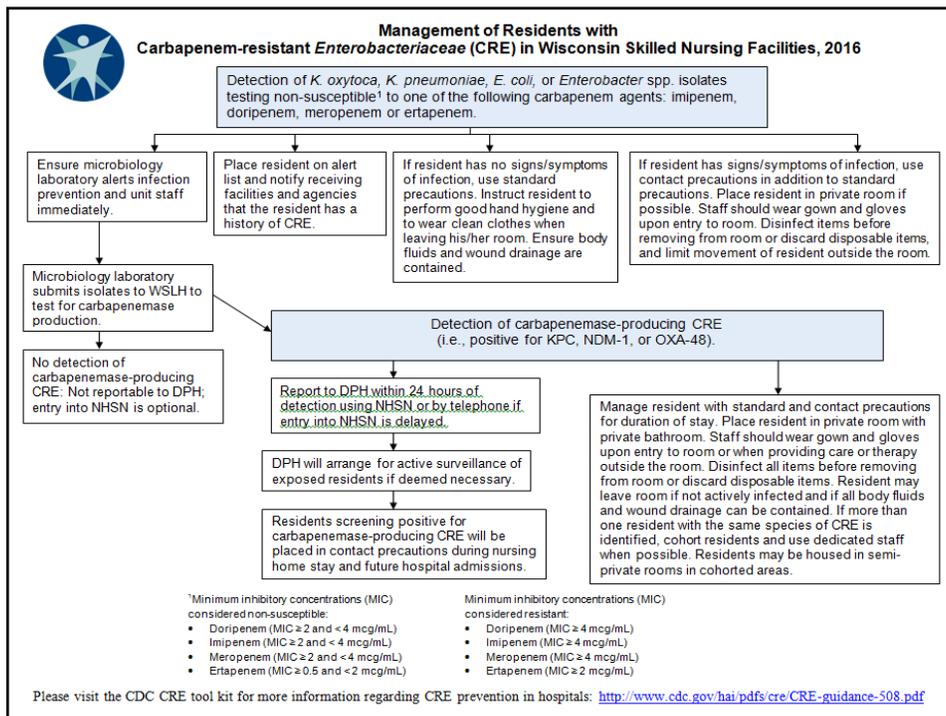


CRE Response: Toolkit for NHs



<https://www.dhs.wisconsin.gov/disease/cre.htm>

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Appendix 1: Sample Nursing Home CRE Policy and Procedures

Management of residents with Carbapenem-resistant *Enterobacteriaceae* (CRE)

Effective date

Department

Dates of review/revision						
Initials						

Background

CRE are a group of bacteria resistant to the last line of drugs that were developed to treat infections with certain drug-resistant organisms. CRE can be divided into two

Appendix 2: Instructions for Collecting and Submitting Rectal Swabs to the Wisconsin State Laboratory of Hygiene (WSLH) to Detect Carbapenemase Production

Supplies

- Culturette,™ ESwab,™ or similar suitable collection system (do not use calcium alginate swabs)
- Disposable gloves
- Alcohol hand sanitizer

NOTE: As an alternative to collecting a rectal swab, a swab of a stool specimen can be obtained and submitted for CRE surveillance testing.

Appendix 3: Sample Scripts to Inform Residents/Responsible Parties of CRE Screening Results

If active surveillance testing indicates the resident is colonized with CRE, the following script may be used to inform the resident/responsible party of the positive test results.

“The results of your CRE screening test indicate you are colonized with, that is you carry, CRE in your intestinal tract. Even though you may not feel any symptoms of illness at this time, we will continue to take precautions to help prevent the CRE from spreading to others. We will place you in a private room, and we will be wearing a gown and gloves whenever we come into your room to care for you. You will also be placed in a private room if you are hospitalized. A more detailed care plan will be provided in the near future. Please read this pamphlet for more information on CRE, and let me know if you or your family members have any questions.”

Appendix 5: Sample Inter-facility Communications Form

Wisconsin Inter-facility Infection Control Transfer Form

Please note that this form is a template and can be adapted to better meet the needs of your facility.

This form is important for ensuring communication among facilities about patients/residents with multidrug-resistant organisms, to help prevent transmission of these organisms across the health care continuum. This form should be completed for transfer to the receiving facility with information communicated prior to or during transfer. Please attach copies of the most recent culture reports with susceptibilities, if available.

Sending Healthcare Facility:

Patient/Resident Last Name	First Name	Date of Birth	Medical Record Number

Is the patient/resident currently in isolation? <input type="checkbox"/> No <input type="checkbox"/> Yes		
Type of Isolation (check all that apply) <input type="checkbox"/> Contact <input type="checkbox"/> Droplet <input type="checkbox"/> Airborne		
<input type="checkbox"/> Other: _____		
Does patient/resident currently have an infection, colonization OR a history of positive culture of multidrug-resistant organism (MDRO) or other organism of epidemiological significance?	Currently Colonized or has history of colonization or infection Check if YES	Active Infection on Treatment Check if YES
Methicillin-Resistant <i>Staphylococcus aureus</i> (MRSA)		
Vancomycin-Resistant <i>Enterococcus</i> (VRE)		
<i>Clostridium difficile</i>		
<i>Acinetobacter</i> , multidrug-resistant		
<i>E. coli</i> , <i>Klebsiella</i> , <i>Proteus</i> , etc. w/Extended Spectrum B-Lactamase		

CRE Educational Resources...

CRE patient and family education pamphlet available at <http://www.dhs.wisconsin.gov/publications/P0/P00486.pdf>

CRE healthcare staff education pamphlet available at <http://www.dhs.wisconsin.gov/publications/P0/P00486B.pdf>

CRE fact sheet available at <http://www.dhs.wisconsin.gov/publications/P0/P00470.pdf>

Aurora Health Care CRE staff education slides available at <https://www.dhs.wisconsin.gov/disease/cre.htm> under the “Healthcare Professionals” tab

CDC CRE website available at <http://www.cdc.gov/HAI/organisms/cre/index.html>

CRE Response Checklist...

- CRE policies and procedures have been written and are available to nursing home staff.
- The clinical laboratory has a mechanism of immediately alerting infection prevention and unit staff when microbiology results identify a CRE isolate.
- During absence of the infection preventionist, back-up staff has been identified and trained to ensure immediate reporting of CRE cases and prompt implementation of infection control measures.
- Infection prevention staff has the authority to collect specimens from residents as part of active CRE surveillance testing and monitoring for transmission.

CRE Response Checklist...

- Staff education regarding CRE prevention has been conducted at least once.
- CRE educational pamphlets are available for residents and their families when needed.

FAQs...

1. Does consent need to be obtained before collecting rectal swabs for CRE surveillance testing?

Because this is a surveillance activity for purposes of preventing disease transmission and is not a research project, no separate consent to test for CRE colonization is required.

2. What should we do if a resident refuses to be screened for CRE colonization?

If screening tests among other residents on the same unit indicate possible CRE transmission, it may be necessary to assume the declining resident is also CRE-positive, and to manage him/her accordingly. The non-tested resident, however, should not be cohorted with other CRE-positive residents.

FAQs...

3. What types of specimens can be collected to conduct CRE screening?

The preferred specimen is a rectal swab, but a perirectal swab or a swab of stool material may also be submitted for testing.

4. Who should order the CRE screening tests?

Infection prevention staff may request an order from the medical director of the facility, or from the individual resident's personal physician.

5. Who usually collects the specimens?

Usually the resident's nurse or other appropriate care provider will explain the purpose of the CRE screening test to the resident/responsible party, collect the specimen and report the results to the resident or his/her family.

FAQs...

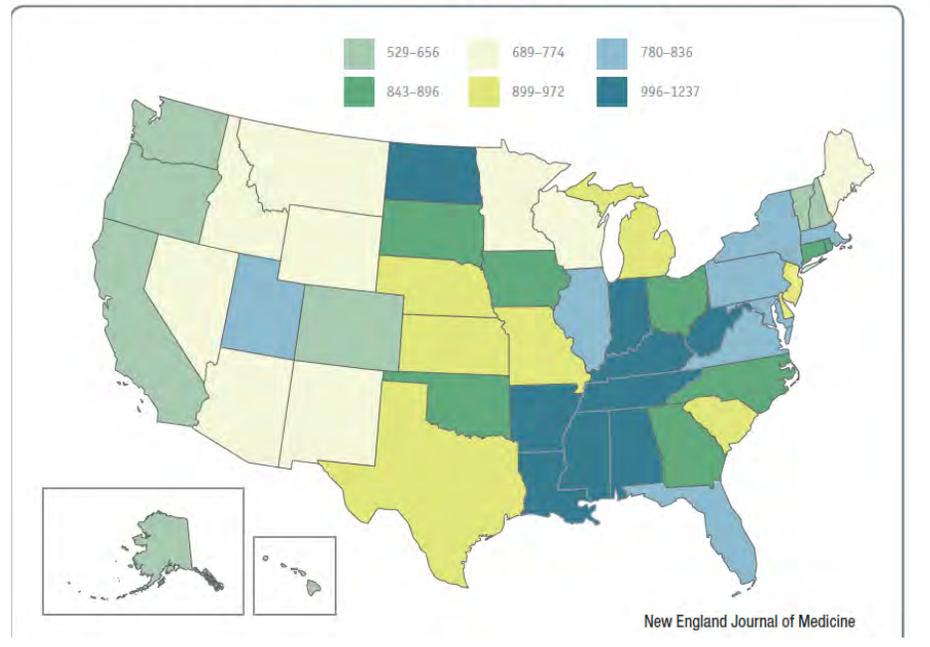
6. Should family members of CRE-positive patients be tested?

It is not usually necessary to test family members, as they are less likely to acquire CRE than hospitalized patients or residents being treated with invasive devices or who are receiving antibiotics. The current CDC recommendations do not include testing of a resident's family members.

7. Should healthcare workers exposed to cases of CRE be tested?

There are no recommendations to test healthcare workers for CRE colonization. Transmission of CRE usually occurs from resident-to-resident due to contaminated hands of healthcare workers. Healthcare workers are usually healthy individuals and are therefore at lower risk of acquiring CRE.

Antibiotic Prescriptions per 1000 Persons of All Ages According to State, 2010



In summary...

- CRE are highly drug-resistant organisms that remain an important public health threat.
- Several incidents of healthcare-associated transmission of CRE have been detected among Wisconsin healthcare facilities.
- Statewide surveillance and prevention strategies have been implemented in Wisconsin to prevent further emergence of CRE.

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DPH CRE Website

<https://www.dhs.wisconsin.gov/disease/cre.htm>



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Gwen Borlaug, CIC, MPH
Director, Healthcare-associated Infections
Prevention Program
Wisconsin Division of Public Health
1 West Wilson Street
Madison, WI 53702
608-267-7711
gwen.borlaug@wi.gov