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# Carbapenem Resistant Enterobacteriaceae (CRE)

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**APIC Greater New York Chapter Meeting**
**1/15/20**

# Disclosure

- I have received funding for research through a subcontract that originated with Allergan
- I will briefly mention antibiotics that treat CRE

# Objectives

- Know the definition of CRE – and recent changes to it
- Understand the mechanisms of carbapenem resistance
- Know that the most likely mechanism of resistance varies in different parts of the world
- Understand the implications of CRE for patient care
- Recognize risk factors for carbapenem resistance
- Discuss infection control interventions against CRE organisms
- Discuss screening for CRE organisms

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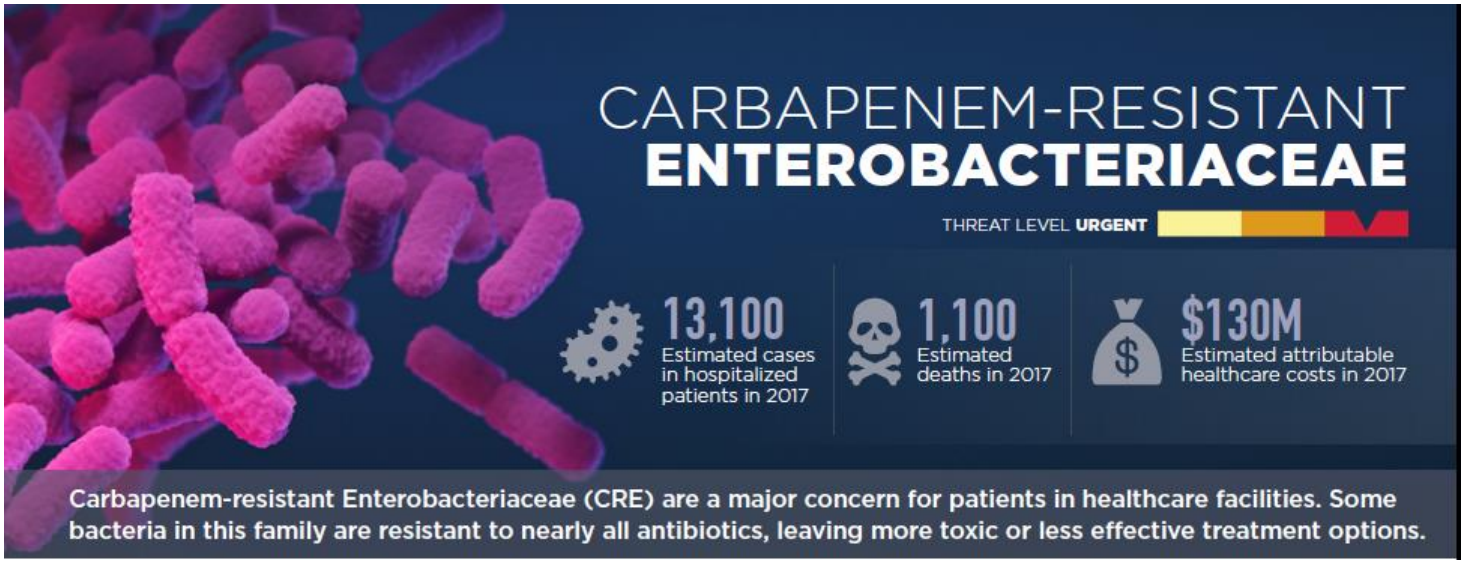


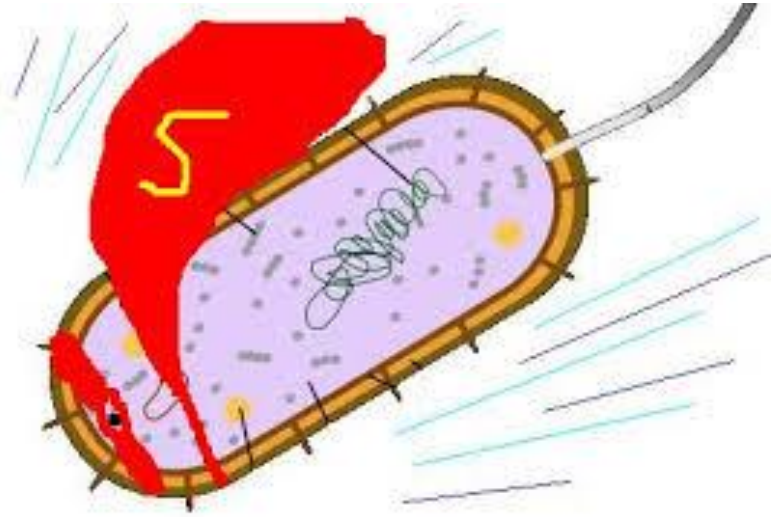


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# CRE Are Tough to Treat

**Blood, Bacteriology Culture (2nd Set, Post-Antibiotic)**

Status: **Final result** Visible to patient: **No (Not Released)** Next appt: **None**

Specimen Information: Blood

Blood, Bacteriology Culture

Growth of

CRE - Klebsiella pneumoniae ssp pneumoniae !

Identification by MALDI-TOF (FDA approved)

Gram Stain

**From Aerobic and Anaerobic Bottles: Gram negative bacilli**

This is an appended report. These results have been appended to

Resulting Agency: MOSES

**Susceptibility**

| | CRE - Klebsiella pneumoniae ssp pneumoniae<br>MIC/INTERPRETATION | |
|---|---|---|
| Amikacin | 32 ug/ml | **Intermediate** |
| Ampicillin | >16 ug/ml | **Resistant** |
| Ampicillin/Sulbactam | >16/8 ug/ml | **Resistant** |
| Aztreonam | >16 ug/ml | **Resistant** |
| Cefazolin | >16 ug/ml | **Resistant** |
| Cefepime | >16 ug/ml | **Resistant** |
| Cefoxitin | >16 ug/ml | **Resistant** |
| Ceftazidime/Avibactam | 3 ug/ml | **Sensitive** |
| Ceftriaxone | >32 ug/ml | **Resistant** |
| Ciprofloxacin | >2 ug/ml | **Resistant** |
| Gentamicin | >8 ug/ml | **Resistant** |
| Identification | Identificat... | |
| Meropenem | >8 ug/ml | **Resistant** |
| Piperacillin/Tazobactam | >64/4 ug/ml | **Resistant** |
| Polymyxin B | 0.38 ug/ml[1] | |
| Tigecycline | 1.5 ug/ml | **Sensitive** |
| Tobramycin | >8 ug/ml | **Resistant** |
| Trimethorprim/Sulfamethoxazole | >2/38 ug/ml | **Resistant** |
| z THIS ORGANISM IS A MDR | | **Resistant** |
| z THIS ORGANISM IS A XDR | | **Resistant** |

[1] Testing done for research purposes only

Linear View

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# Enterobacteriaceae Are Gram Negative Gut Bacteria

| Enterobacteriaceae | Not Enterobacteriaceae |
|---|---|
| *Klebsiella pneumoniae* | *Pseudomonas aeruginosa* |
| *E. Coli* | *Acinetobacter baumanii* |
| *Enterobacter* species | *Stenotrophomonas maltophila* |
| *Citrobacter* species | *Burkholderia cepacia* |
| *Serratia marcescens* | *Enterococcus faecium* |
| *Proteus* species | |

Other types of resistant bacteria are important but this lecture and the label “CRE” deals with Enterobacteriaceae

# CDC Uses a Sensitive Definition for CRE

- Current CDC definition for CRE (post 2015):
  - Resistance to any Carbapenem (includes Ertapenem)

    OR
  - Detection of a Carbapenemase Enzyme

- Prior (2015) CDC definition for CRE:
  - Resistance or Intermediate susceptibility to Meropenem, Imipenem or Doripenem

    AND
  - Resistance to 3rd Generation Cephalosporins (Ceftriaxone)

- The newer definition includes more organisms

- The older definition was more specific to identify organisms with a carbapenemase enzyme

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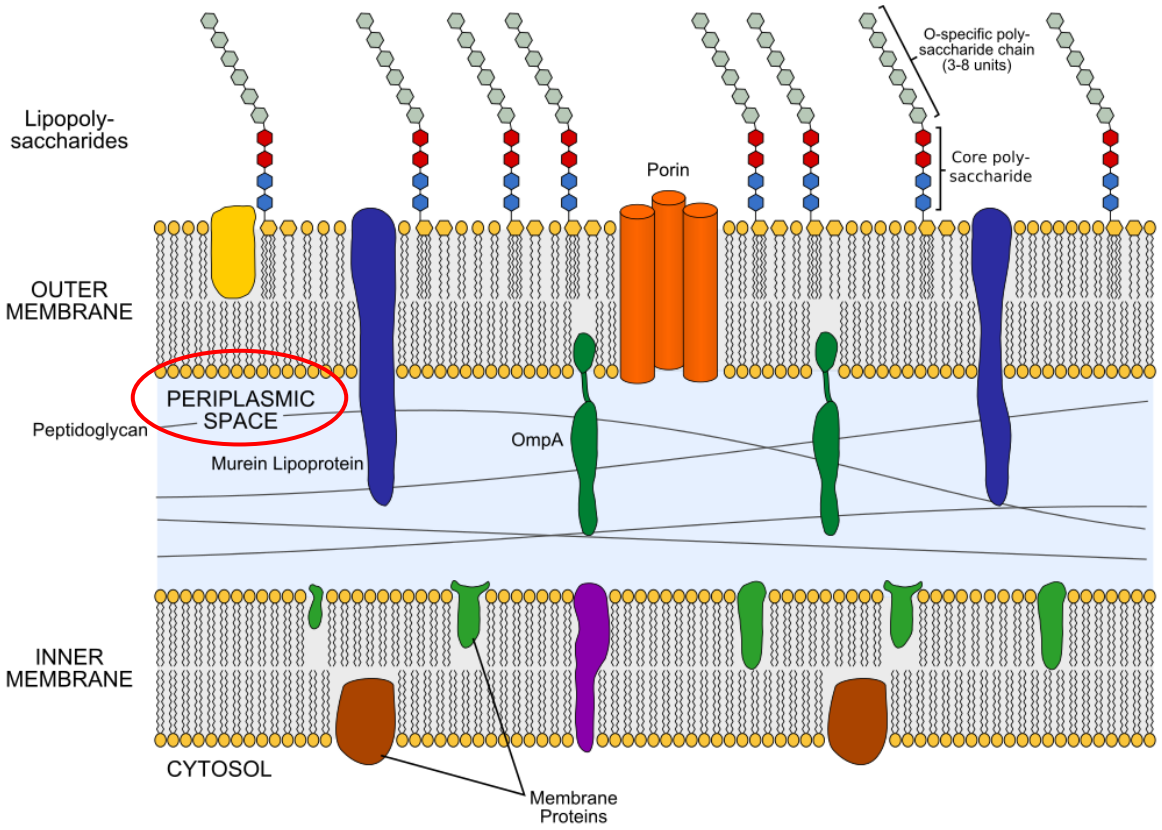
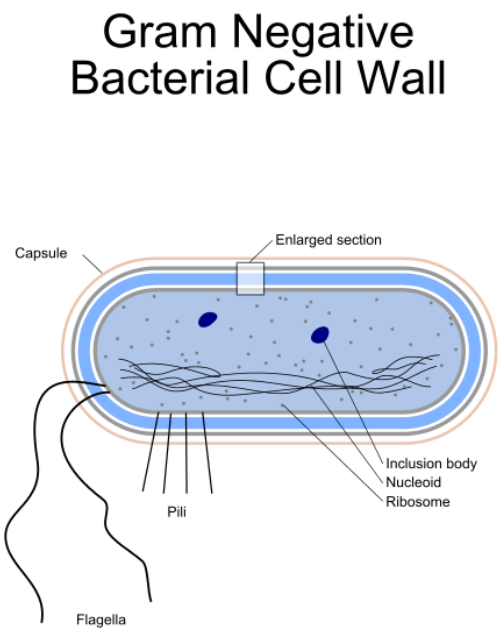
# Beta Lactamases Destroy Beta Lactams in Between the Gram Negative Bacteria Double Membrane

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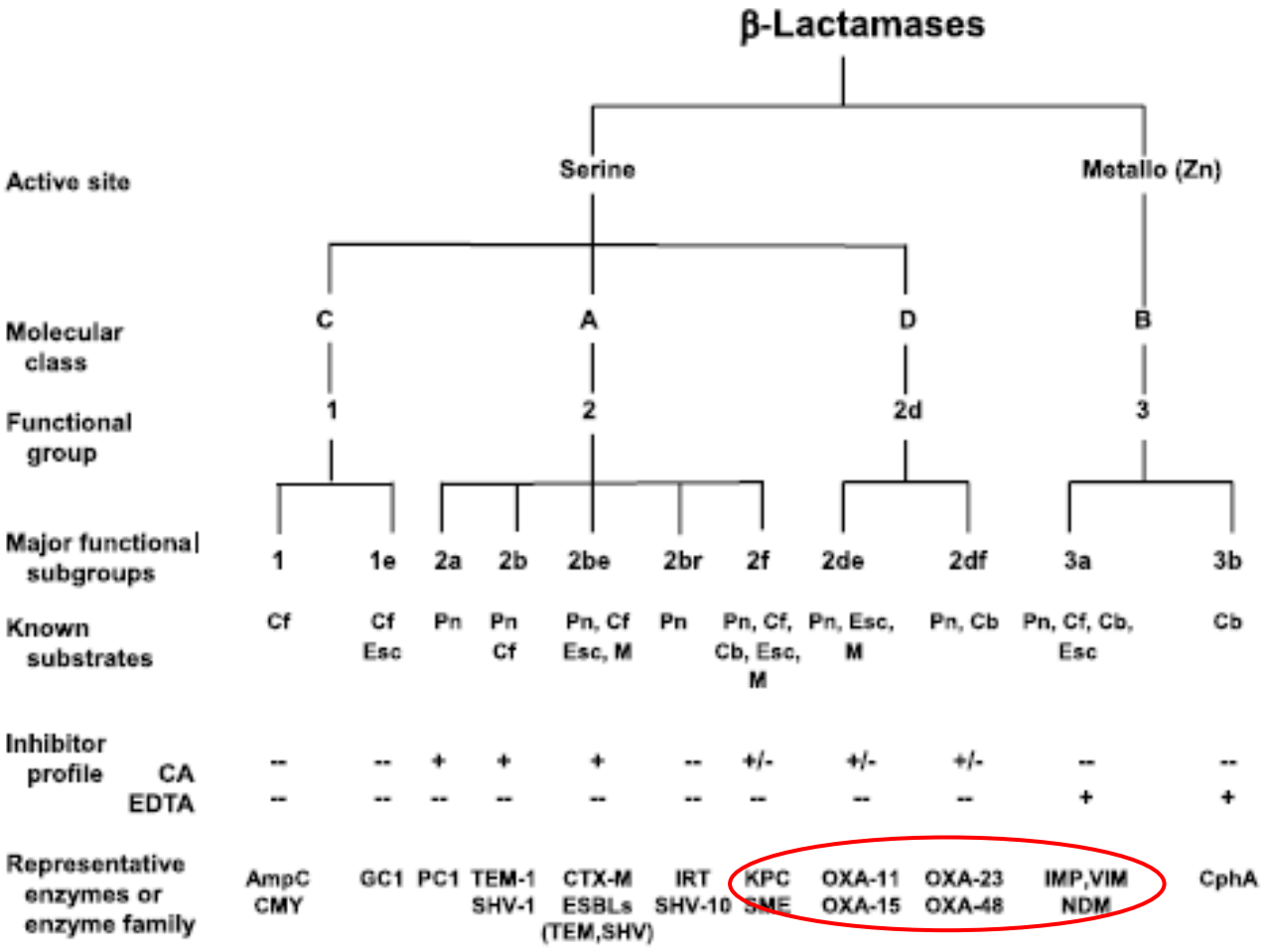
# Carbapenemases are a Subset of Beta Lactamases




Inducible ESBL Carbapenemases

Bush K. Proliferation and significance of clinically relevant B-lactamases. Annals of the New York Academy of Sciences. 2013; 1277: 84-90

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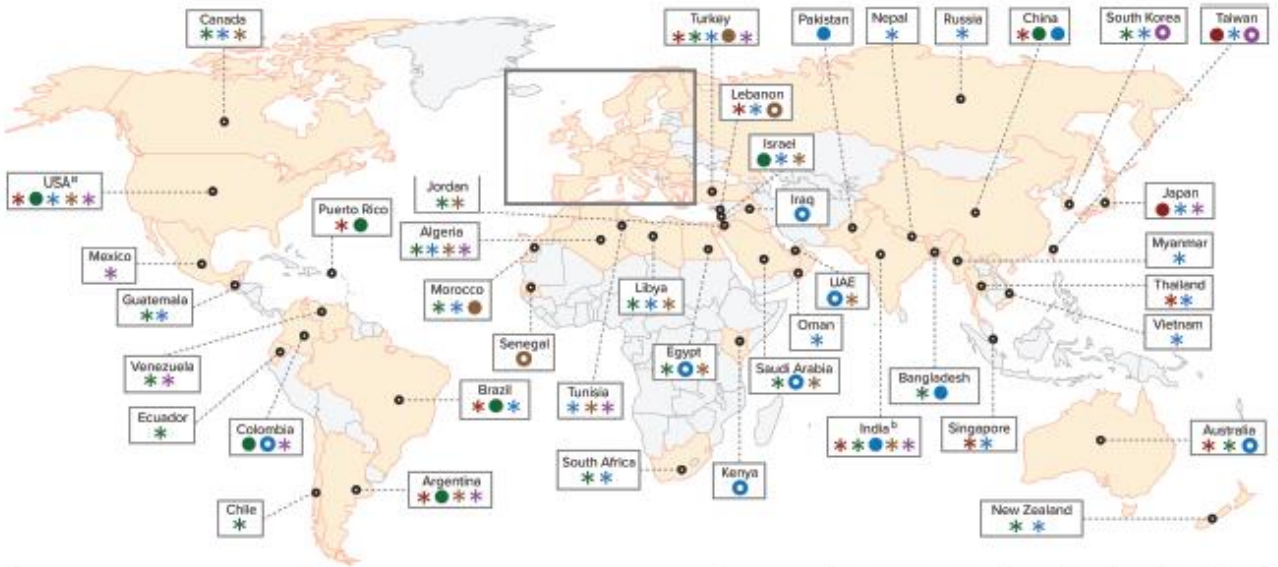
# There Are A Few Types of Carbapenemases

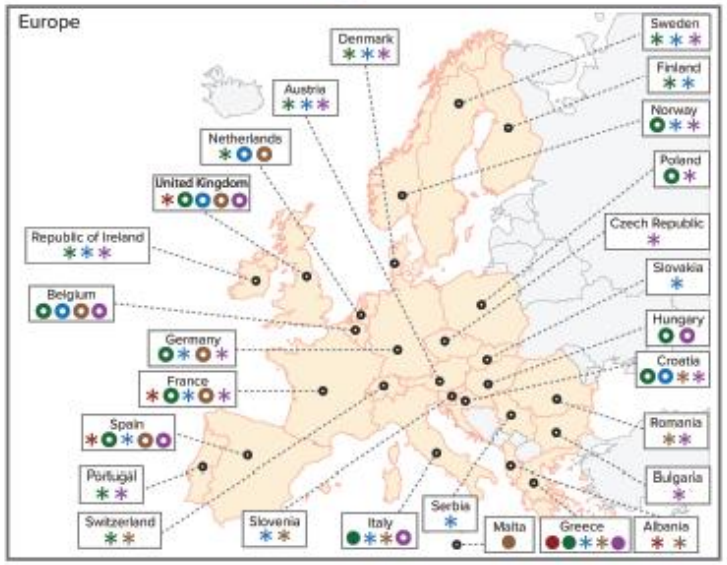
- KPC – *Klebsiella pneumoniae* Carbapenemase
  - KPC-2 and KPC-3 are the most common in NYC and USA
  - Any species can have it (not just *Klebsiella*)

- Oxa Carbapenemases
  - Seen more often in Europe, Turkey, North Africa

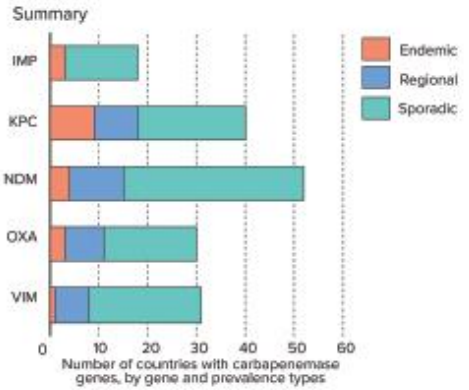
- Metallo Beta Lactamases
  - New Delhi (NDM-1) – From Pakistan, India, China, Mid-East
  - VIM - Europe
  - IMP – Europe, Japan
  - The Metallo Beta Lactamases are resistant to some of the new antibiotics that work against KPC carbapenemases

# Carbapenemase Distribution World Wide




| | IMP | KPC | NDM | OXA | VIM |
|---|---|---|---|---|---|
| Endemic/nationwide distribution | ● | ● | ● | ● | ● |
| Significant outbreaks/ regional spread | ○ | ○ | ○ | ○ | ○ |
| Sporadic outbreak/ occurences | * | * | * | * | * |




Logan L and Weinstein R. The epidemiology of carbapenem-resistant *Enterobacteriaceae* : the impact and evolution of a global menace. Journal of Infectious Diseases 2017; 215

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# KPC-2 and KPC-3 are the Most Common Carbapenemases in NYC

**TABLE 2** β-Lactamases and *Klebsiella pneumoniae* outer membrane porin gene mutations among 106 genotyped CRE[a]

| | No. of isolates (%) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | KPC | | | | | SHV | | | | | |
| CRE pathogen | KPC-2 | KPC-3 | NDM | OXA-48[b] | TEM non-ESBL[c] | non-ESBL | ESBL | CTX-M | AmpC | *ompK35* mutation | *ompK36* mutation |
| *K. pneumoniae* ($n$ = 97) | 44 (45) | 48 (49) | | 1 (1) | 82 (85) | 62 (64) | 31 (32) | 8 (8) | | 81 (84) | 33 (34) |
| KPC-2 ($n$ = 44) | 44 (100) | - | | | 37 (84) | 27 (61) | 17 (39) | 2 (5) | | 35 (80) | 10 (23) |
| KPC-3 ($n$ = 48) | | 48 (100) | | | 43 (90) | 31 (65) | 13 (27) | 2 (4) | | 42 (88) | 21 (45) |
| Other ($n$ = 5)[d] | | | | 1 (20) | 2 (40) | 4 (80) | 1 (20) | 4 (80) | | 4 (80) | 2 (40) |
| *Enterobacter* spp. ($n$ = 5)[e] | 1 (20) | 3 (60) | | | 4 (80) | | | 1 (20) | 4 (80) | N/A | N/A |
| *Escherichia coli* ($n$ = 3)[f] | 1 (33) | | 1[g] (33) | | 1 (33) | | | 2 (67) | 1 (33) | N/A | N/A |
| *Morganella morganii* ($n$ = 1) | 1 (100) | | | | | | | | 1 (100) | N/A | N/A |

Satlin et al. Multicenter Clinical and Molecular Epidemiological Analysis of Bacteremia Due to Carbapenem-Resistant Enterobacteriaceae (CRE) in the CRE Epicenter of the United States. Antimicrobial Agents and Chemotherapy. 2017; 61: e02349-16

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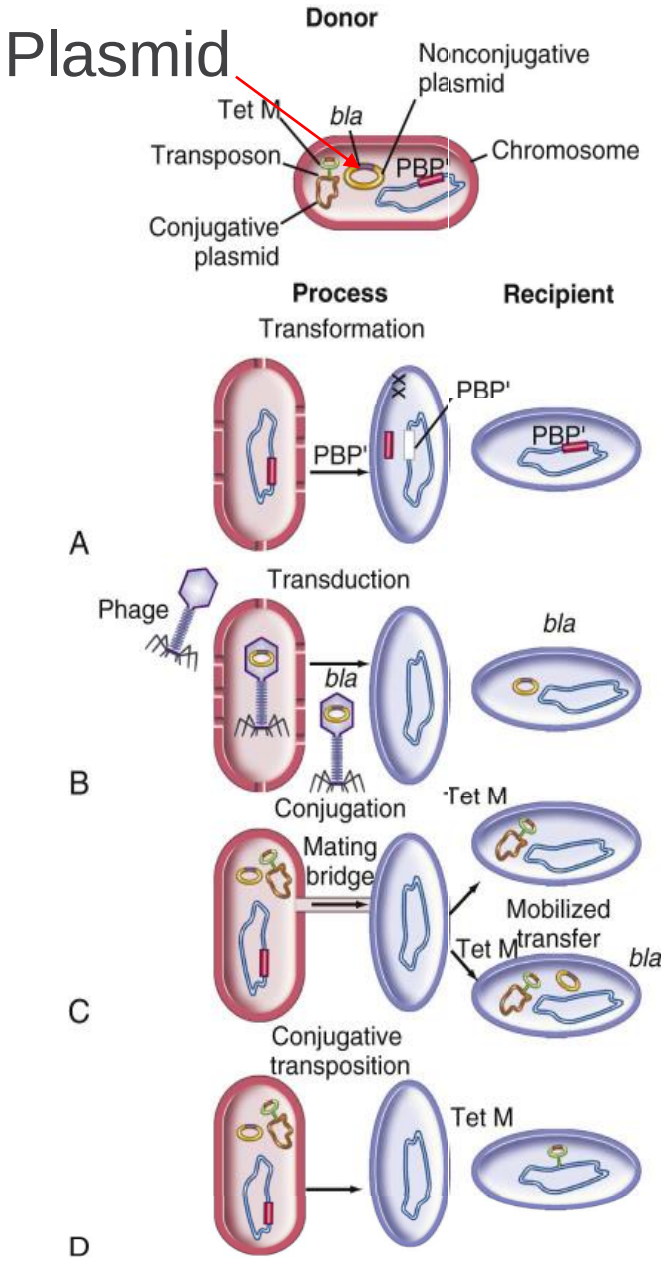
# Carbapenemases on Plasmids can Spread




- Plasmids contain genes but are separate from the bacterial chromosome
- It is easier for a gene on a plasmid to get shared with other bacteria, even across species

Mandell et al. Principles and Practice of Infectious Diseases, 8th ed. Philadelphia: Elsevier, 2015 p 236

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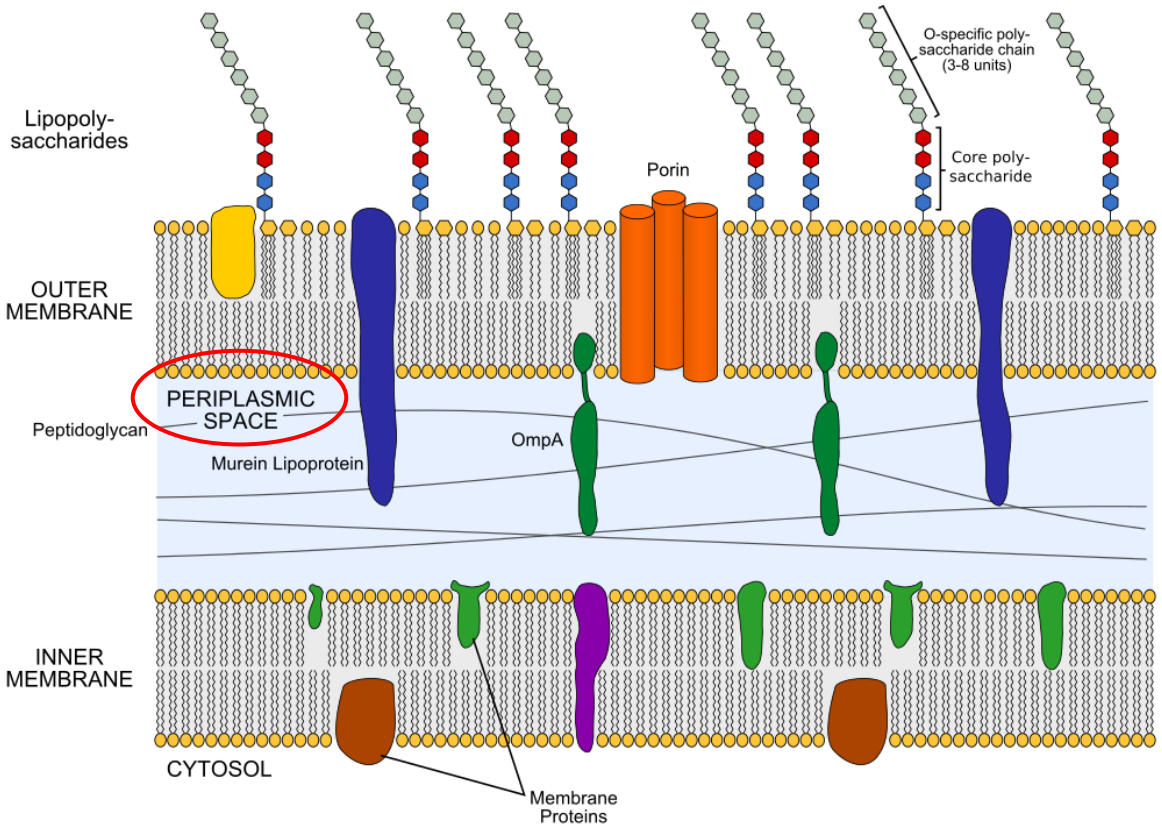
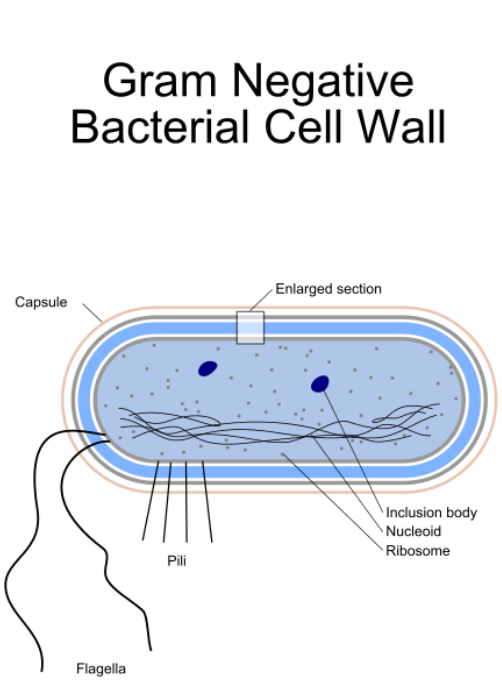
# Carbapenem Resistance without Carbapenemases May involve Porin mutations combined with other resistance elements

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# Species of CRE affects Likelihood of Carbapenemase Production

| Carbapenemase Producing CRE N=37 | Non-Carbapenemase Producing CRE N = 46 |
|---|---|
| Klebsiella pneumoniae<br>28 (76 %) | Enterobacter species<br>27 (59 %) |
| Enterobacter species<br>7 (19 %) | Klebsiella pneumoniae<br>14 (30 %) |
| E coli<br>1 | E coli<br>3 (6.5 %) |
| Citrobacter species<br>1 | Serratia<br>1 |
| | Proteus<br>1 |

Tamma et al. Comparing the Outcomes of Patients with Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant *Enterobacteriaceae* Bacteremia. Clinical Infectious Diseases. 2017; 64: 257-64

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# Carbapenemase Production May Affect Patient Outcome in CRE Infection

**Table 4. Fourteen-Day Mortality for Patients With Carbapenemase-Producing Carbapenem-Resistant *Enterobacteriaceae* (CP-CRE) Compared With non-CP-CRE Bacteremia**

| Covariate | Odds Ratio (95% CI) | *P* Value | Adjusted Odds Ratioa (95% CI) | *P* Value |
|---|---|---|---|---|
| Carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* bacteremia | 3.20 (1.06–9.61) | .04 | 4.92 (1.01–24.81) | .05 |
| Pitt bacteremia score ≥4 | 9.13 (2.39–34.86) | .001 | 11.89 (2.38–59.30) | .005 |
| Active empiric antibiotic therapy | .79 (0.27–2.29) | .67 | 2.46 (0.53–11.48) | .25 |
| Active directed antibiotic therapy | .17 (0.04–0.72) | .01 | 0.10 (0.004–2.22) | .14 |
| Days of combination antibiotic therapy | .89 (0.79–1.00) | .07 | 0.73 (0.59–0.93) | .01 |
| Polymixin therapy administered | 4.61 (1.16–18.3) | .03 | 5.57 (1.07–28.96) | .04 |
| Diabetes | 3.12 (0.99–9.84) | .05 | 3.42 (0.62–19.07) | .16 |
| Immunocompromised | .45 (0.14–1.40) | .17 | – | – |
| Carbapenem therapy administered | .82 (0.27–2.52) | .74 | – | – |
| Meropenem minimum inhibitory concentration ≥16 μg/mL | 1.40 (0.38–5.01) | .61 | – | – |

14 Day Mortality: 12 (32 %) in the CP group and 6 (13 %) in the Non CP group

Tamma et al. Comparing the Outcomes of Patients with Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant *Enterobacteriaceae* Bacteremia. Clinical Infectious Diseases. 2017; 64: 257-64

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# Patient Outcomes in CRE Infections are Poor

- 50% Mortality for Bloodstream Infection – likely improved with newer antibiotics
- Patients are often started on ineffective antibiotics
  - Median time to appropriate therapy 47 hours
- Patients often have multiple comorbidities prior to CRE infection
- Available antibiotics until recently have been poorly effective
  - Polymyxin/Colistin and Aminoglycosides are toxic
  - Tigecycline is associated with failure in bloodstream infection

Satlin et al. Multicenter Clinical and Molecular Epidemiological Analysis of Bacteremia Due to Carbapenem-Resistant Enterobacteriaceae (CRE) in the CRE Epicenter of the United States. Antimicrobial Agents and Chemotherapy. 2017; 61: e02349-16

# Newer Anti-CRE Drugs Are an Improvement, But Not Perfect

| Infection Type | Bloodstream | UTI | Skin/Soft Tissue | Pneumonia |
|---|---|---|---|---|
| 30 Day Clinical Success | 75 % | 88 % | 67 % | 36% |

- Ceftazidime-Avibactam has shown improved results for bloodstream infection – concern about pneumonia results
  - Resistance has begun to emerge
- Meropenem-Vaborbactam and Eravacycline are other new options
- None of these drugs are effective against NDM-1

Shields et al. Pneumonia and renal replacement therapy are risk factors for ceftazidime-avibactam treatment failures and resistance among patients with carbapenem-resistant Enterobacteriaceae infections. Antimicrobial Agents and Chemotherapy. 2018; 62: e02497-17

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# CDC CRE Tool Kit – Basic Interventions

- Hand Hygiene
  - acquisition from the environment
- Appropriate use of PPE
  - acquisition from the environment
- Antimicrobial Stewardship
  - develop resistance from antibiotic exposure
- Environmental Cleaning
  - close attention to sink drains and splash areas around sink drains

# CDC CRE Tool Kit – Specific Interventions

- Contact precautions for all Carbapenemase producing CRE
  - Might use surveillance cultures or a long duration of time without positive culture to stop contact precautions
- Notification system to alert clinicians when a CRE patient returns to the facility, or a new CRE result is identified
- Notify receiving facilities when transferring CRE patient
- Patient and staff cohorting
  - But might want to know mechanism of resistance before cohorting

# CDC CRE Tool Kit – Advanced Interventions

- Screening contacts of CRE patients – for new introduction of CRE or a new carbapenemase
- Point prevalence survey – testing an entire unit in a suspected cluster or outbreak
- Active surveillance testing
  - For facility or a high risk unit or population
  - Patients admitted from outside the US
- Chlorhexidine bathing

# Components of Successful Anti-CRE Interventions From Quasi Experimental Studies

- Contact Precautions
- Active Screening
- Isolation and Cohorting of Staff
- Monitoring and Feedback for Infection Control Practices
- Hand Hygiene Campaign

Tomczyk, S, et al. Control of Carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* in Healthcare Facilities: A Systematic Review and Reanalysis of Quasi-experimental Studies. Clinical Infectious Diseases. 2019: 68; 873-84

# Active Screening in National Israeli Intervention Outbreak Setting

- Acute Care
  - Ward contacts of CRE cases
  - Patients recently admitted to or transferred from other facilities
  - Patients on wards with high incidence of CRE

- Post Acute Care Hospitals
  - Serial point prevalence surveys

Schwaber MJ and Carmeli Y. An Ongoing National Intervention to Contain the Spread of Carbapenem-Resitant Enterobacteriaceae. Clinical Infectious Diseases. 2014; 58: 697-703

# Active Screening in a CRE Endemic US City (Chicago)

- Started with Screening of ICU patients and transfers from other facilities (including LTACH, where CRE prevalence 30%)
  - Screened more than 100 patients for each CRE found

- Stopped ICU screening and continued screening of transfers from other facilities
  - In Medical and Surgical ICU they screened approximately 30 patients per CRE found
  - 10 of 21 patients identified during the first screening period would have been missed

Shimasaki T et al. Active screening and interfacility communication of carbapenem-resistant enterobacteriaceae (CRE) in a tertiary care hospital. Infection Control and Hospital Epidemiology. 2018: 39; 1058-1062

# Regional Coordination to Slow the Rise of CRE

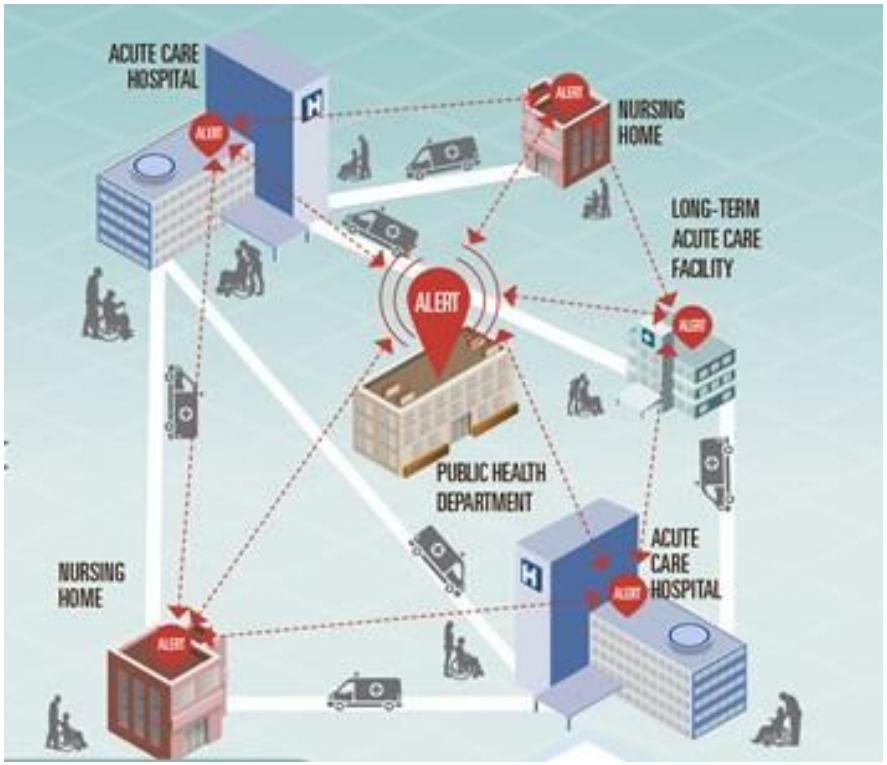
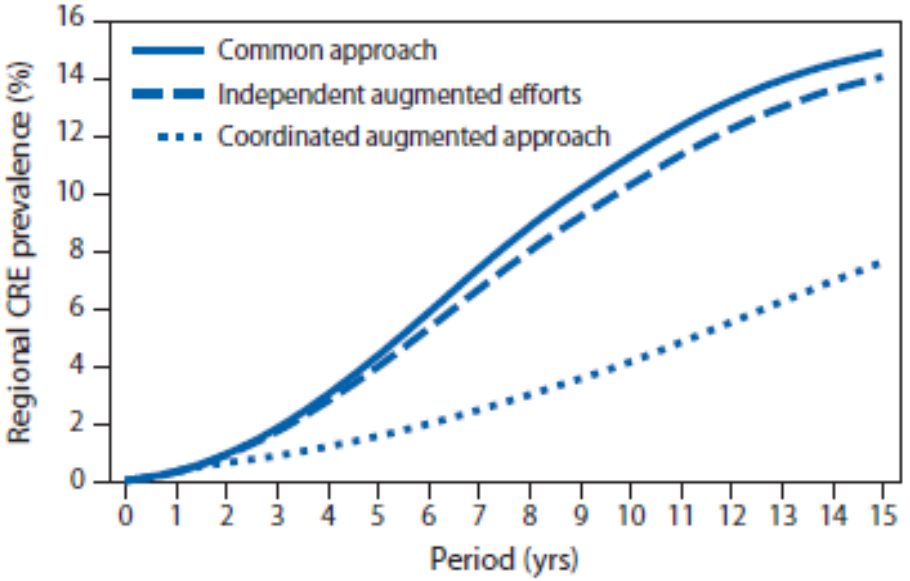



**FIGURE 3. Projected countywide prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) over a 15-year period under three different intervention scenarios — 102-facility model, Orange County, California***




http://www.cdc.gov/drugresistance/solutions-initiative/hai-ar-prevention-program.html

Slayton RB, et. Al. Vital signs: Estimated effects of coordinated approach for action to reduce antibiotic-resistant infections in health care facilities – United States. Morbidity and Mortality Weekly Report. 2015 Aug 7; 64: 826-31

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# Take Home Points

- Implementation of 2015 CDC definition of CRE may cause misleading rise in CRE rate. The 2015 definition identifies a higher percentage of non-carbapenemase producing CRE
- Carbapenemase producing CRE might more easily spread resistance to other bacteria, and may be associated with worse patient outcomes
- KPC is the most common carbapenemase in NY/USA but other parts of the world are different, and other carbapenemases are coming to NY
- Invasive CRE infections are associated with poor patient outcomes – newer antibiotics may not fully solve this problem

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# Take Home Points

- Prior cultures with CRE, residence in SNF, mechanical ventilation, other healthcare exposures are associated with CRE infection – epidemiology in your own institution may determine which patients are more likely to have CRE
- Infection control interventions against CRE include the fundamentals of IPC (hand hygiene, isolation) as well as advanced interventions (ie screening)
- Active screening of CRE has been used in outbreak and endemic settings but the optimal approach is not clear
- Coordination among facilities in the same region can magnify individual infection prevention interventions