Basics of Antibiotic resistance: Focus on Carbapenem-resistant *Enterobacteriaceae*

Nimalie Stone, MD, MS
Division of Healthcare Quality Promotion

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Provide exceptional compassionate clinical care that treats the whole person

- Strive to prevent problems and treat when necessary.
- Change Package Strategies and Prevent Healthcare Acquired Infections Change Bundle (Attachment 4):

https://www.lsqin.org/wp-content/uploads/2015/03/NH-ChangePackage-032615-Final-508.pdf

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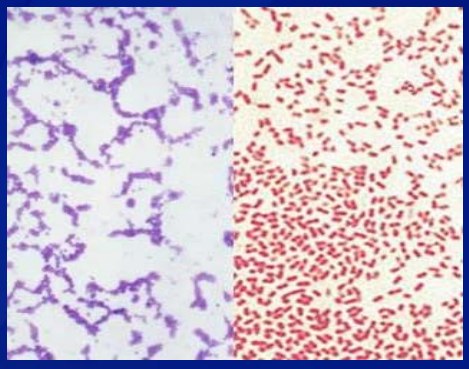
Presentation Objectives

- Review common bacteria identified in nursing homes and antibiotics used to treat them
- Describe mechanisms for antibiotic resistance to develop in bacteria including carbapenem-resistance
- Discuss ways your laboratory can provide information about antibiotic resistance to your facility

Basics on bacteria

Gram Stain Positive (purple)



Gram Stain Negative (pink/red)

- Bacteria have different characteristics that allow us to identify them in the lab
  - Shape, size, gram stain, growth patterns, etc.
- We often use these characteristics to develop antibiotics

Common bacteria in healthcare

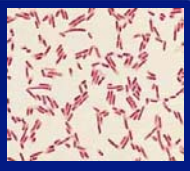
Gram positive

- Many are cocci, "round bacteria"
  - Examples are *Streptococci, Staphylococci, Enterococci*
- *Clostridium difficile* (C. diff) is an anaerobic, Gram positive rod

Gram negative

- Most are bacilli, "rod-shaped bacteria"
  - Examples are: *E. coli, Klebsiella, Enterobacter , Proteus, Pseudomonas, Acinetobacter*

Important gram-negative bacteria



	Genus	Common species	Common culture sites
Enterobacteriacea	*Escherichia sp.*	*E. coli*	Urine
	Klebsiella spp.	*K. pneumoniae and K. oxytoca*	Urine, resp.
	Enterobacter spp.	*E. cloacae* and *E. aerogenes*	Urine
Not ***Enterobacteriacea***	*Pseudomonas sp.*	*Pseudomonas aeruginosa*	Urine, resp., wound
	Acintobacter sp.	*A. baumannii*	Urine, resp.

Antibiotics 101

- Antibiotics are drugs that treat and kill bacteria
- They are grouped into classes based on their structure and activity
  - Narrow-spectrum target a few specific bacteria
  - Broad-spectrum can kill a wide variety of bacteria
- Antibiotic resistance = when the bacteria are no longer fully killed by the antibiotic
  - Bacteria with resistance can cause patients to have more severe infections which are harder and more costly to treat
  - Infection prevention programs track certain "bug-drug" combinations for resistance

Antibiotics: Beta Lactam classes

Penicillin, methicillin, amoxicillin and ampicillin

- Extended spectrum agents: piperacillin, ticarcillin
- Can be combined with a drug to help them overcome bacterial resistance
  - Amoxicillin + Clavulante = Augmentin;
  - Ampicillin + Sulbactam = Unasyn
  - Piperacillin + tazobactam = Zosyn

Cephalosporins

- More gram positive activity: Cephalexin, Cefazolin
- More gram negative activity: Ceftriaxone, Ceftazidime, Cefepime
- New broader spectrum, including MRSA: Ceftaroline

Antibiotics: Carbapenems

- Extremely broad-spectrum, among the most powerful antibiotics we currently have available
- Spectrum includes *Streptococci*, susceptible *Staphylococci*, *Enterobactericeae*, *Pseudomonas*, *Acinetobacter sp.*, and anaerobic bacteria

Drug	Route of Administration
Imipenem	IV
Meropenem	IV
Ertapenem	IM, IV
Doripenem	IV

Antibiotics : Gram positive agents

- Vancomycin
  - Treats methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Oral form is NOT absorbed from gut; only used to treat *C difficile*
  - IV form will get good systemic levels - used to treat all other infections
- Daptomycin
  - Covers resistant gram-positive organisms: MRSA and Vancomycin-resistant *Enterococci* (VRE)
  - Only available as IV formula
- Linezolid
  - Covers MRSA and VRE
  - Both oral and IV forms available and get good systemic levels

Antibiotics: Gram negative agents

Fluoroquinolones (oral and IV forms)

- Ciprofloxacin: Mostly gram negative activity
  - Commonly used for UTI treatment
- Levofloxacin/Moxifloxacin: Broader activity
  - Also used for treating UTIs and infections from gram-negative bacteria
  - Also covers *Streptococcus pneumoniae* and other respiratory bacteria

Aminoglycosides (only IV)

- Examples: Gentamicin, Tobramycin, Amikacin
- Excellent gram negative drugs – especially for urinary tract
- Limited use because of toxicity (kidney, hearing/balance)

Antibiotics: Miscellaneous

- Trimethoprim/Sulfamethoxazole (Bactrim):
  - Mainly given in oral form – must watch renal function
  - Considered narrow spectrum, but has activity against both Gram negative and Gram positive bacteria
  - Commonly used to treat UTIs
  - Also used for MRSA skin infections
- Azithromycin:
  - Commonly given in oral dose pack called "Z-pack"
  - Considered narrow spectrum, used for respiratory/sinus infections
- Metronidazole (Flagyl) (oral and IV form)
  - A primary treatment for C. difficile infections
  - Oral form can cause nausea and stomach upset

Understanding multidrug-resistance

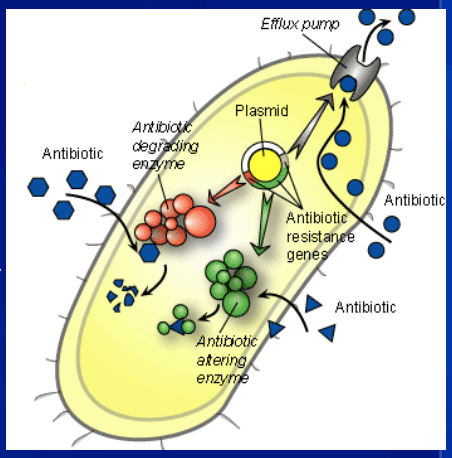
- Multidrug-resistant organisms (MDROs) are a group of bacteria with important resistance patterns
- Sometimes just one key drug will define a MDRO
  - Methicillin-resistance in *Staphylococcus aureus*
  - Vancomycin-resistance in *Enterococcus sp.*
- Gram-negative bacteria can develop resistance to multiple classes of antibiotics
  - Resistance elements travel together so one bacteria can become resistant to many classes: Penicillins, cephalosporins, carbapenems, fluoroquinolones, aminogylcosides
  - Seen in *Enterobacteriaceae, Pseudomonas* and *Acinetobacter*

ABCs of MDROs

Bacteria	Abbrev.	Antibiotic Resistance
Staphylococcus aureus	MRSA	Methicillin-resistance
Enterococcus (faecalis/faecium)	VRE	Vancomycin-resistance
Enterobacteriaceae	ESBL	Extended spectrum penicillins and cephalosporin resistance
Enterobacteriaceae	CRE	Carbapenem-resistance
Pseudomonas/ Acinetobacter	MDR	Multiple drug-resistance

Mechanisms of antibiotic resistance

- Production of proteins that destroy antibiotics
  - Beta-lactamases
  - Cephalosporinases
  - Carbapenemases
- Change their cell structure
  - Blocks binding and function of antibiotics
- Reduce exposure
  - Pump antibiotics out
  - Increase cell barriers to block entry



http://bioinfo.bact.wisc.edu/themicrobialworld/bactresanti.html

Case scenario

- 70 year old admitted from hospital to nursing home
  - Treated with Ceftriaxone for catheter-associated UTI x7 days before transfer
  - Catheter still in place recently transferred
- Repeat urine culture ordered by MD prior to removing catheter
  - Organism: E. coli, $>10^5$ cfu

Drug	Result
Amikacin	Susceptible
Ampicillin	Resistant
Amp/Sulbactam	Resistant
Aztreonam	Resistant
Cefazolin	Resistant
Cefepime	Resistant
Ceftazidime	Resistant
Ceftriaxone	Resistant
Cefuroxime	Resistant
Gentamicin	Susceptible
Levofloxcin	Resistant
Meropenem	Susceptible
Piperacillin/Tazobactam	Resistant
Tobramycin	Susceptible
Trimethoprim/Sulfa	Resistant

Penicillin and cephalosporin resistance in gram-negative bacteria

- Innate: Resistance genes present in bacterial chromosomes (Example: AmpC)
  - Bacteria already had the capability to be resistant
  - Resistance was uncovered with overexpression of the gene
  - *Consider in bugs like Serratia, Pseudomonas, Acinetobacter*
- Acquired: Resistance genes entered bacteria through mobile genetic elements, called plasmids
  - Example: Extended spectrum Beta-lactamases (ESBLs)
  - *Consider in E. Coli, Klebsiella*
- Now we see both types of cephalosporin-resistance expressed in gram-negative bacteria

Case scenario #2

- 70 year old admitted from hospital to nursing home
- Had complicated history including surgery, ICU care, ventilator-weaning
  - On transfer, has tracheostomy, PEG tube, urinary catheter and large sacral pressure ulcer
- MD sends culture from tracheostomy secretions
  - Organism: *Klebsiella pneumoniae*, $>10^5$ cfu

Drug	Result
Amikacin	Intermediate
Ampicillin	Resistant
Amp/Sulbactam	Resistant
Aztreonam	Resistant
Cefazolin	Resistant
Cefepime	Resistant
Ceftazidime	Resistant
Ceftriaxone	Resistant
Cefuroxime	Resistant
Gentamicin	Resistant
Levofloxcin	Resistant
Meropenem	Resistant
Piperacillin/Tazobactam	Resistant
Tobramycin	Resistant
Trimethoprim/Sulfa	Resistant

Carbapenem-resistance in gram-negative bacteria

- Carbapenems are reserved for severe, complicated infections with multiple and often resistant bacteria
  - Recall: "Extremely broad-spectrum"
- Resistance significantly limits treatment options for life-threatening infections
  - No new antibiotics in development for gram-negative bacteria
- Emerging resistance mechanisms can be spread
  - Carbapenemases are found on mobile genetic elements

Carbapenem-resistance: Mechanisms

- There are different ways that gram-negative bacteria become resistant to Carbapenems.
- Some bacteria have to make lots of changes to become resistant.
  - Step 1: Acquire or produce a cephalosporinase (to break down beta-lactam antibiotics
  - Step 2: Lose a porin protein in the cell wall to prevent carbapenems from getting into the cell.
  - Step 3: Gain a pump to remove the carbapenem from the cell
- Others acquire resistance by a plasmid, which carries the genes for carbapenem resistance, "carbapenemases"
  - Examples include: KPC, NDM, VIM, OXA-48

Why focus on carbapenemases?

- The genetic material creating carbapenemases sits on highly mobile elements
  - These resistance elements can be shared between different bacteria very easily
  - Similar to concern with ESBL spreading cephalosporin-resistance
- Two carbapenemases getting lots of attention
  - *Klebsiella pneumoniae* carbapenemase (**KPC**)
  - New Delhi metallo-beta-lactamase **(NDM-1)**
- Identifying/containing bacteria which produce carbapenemase will *prevent the spread of resistance to other people and other organisms*

Microbiology 101: Identification

Growing the bacteria

- Traditional culture, use gram stain and biochemical reactions for identification
- Selective culture media (e.g., CHROMagar)

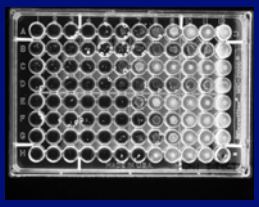
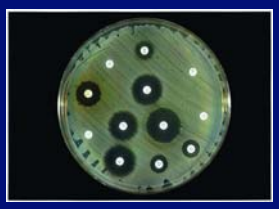
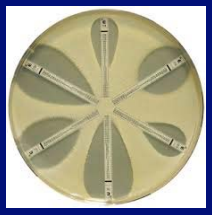
Examining parts of the bacteria

- Molecular diagnostic tests which identify specific fragments of DNA/RNA of organisms
  - Nucleic acid amplification tests (NAAT); Polymerase chain reaction (PCR)
- Matrix-assisted laser desorption/ionization (MALDI-TOF)
  - Very new technology: Uses mass spectrometry to identify bacteria based on weight and charge of ions

Microbiology 101: Susceptibility

Testing the growth in the presence of antibiotic

- Determining the minimum inhibitory concentration (MIC) – lowest amount of drug needed to stop growth
- Broth micro-dilution, Disk diffusion, E-test strips

Identifying resistance genes

- Molecular diagnostic tests – detect presence of specific resistance genes (NAAT, PCR)

Microbiology 101: Automated testing

- Systems with identification and susceptibility in one platform
  - Special growth panels contain biochemicals for identification and antibiotics for susceptibility testing
    - Bacteria of interest are innoculated onto panels and placed into system
  - Computer will identify organism and susceptibility interpretation
    - Uses pre-programmed algorithms based on growth patterns of bacteria on the panel
  - Example systems (trade names): Microscan, Walkaway, VITEK 2, Phoenix, Sensititre

Can laboratories identify carbapenemases?

- Labs look for susceptibility to carbapenems by manual or automatic testing methods

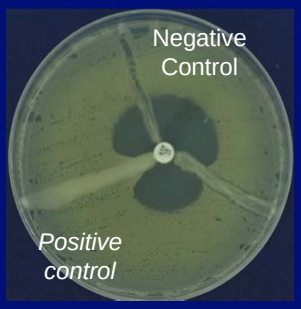
Challenges:

- Identification of carbapenem-resistance varies by which carbapenem is used for susceptibility testing
- Low-levels of carbapenem resistance may not be detected by automated testing
- Even if carbapenem resistance is detected – it may not mean the bacteria produce a carbapenemase

Lab strategies to confirm carbapenemase production

Modified Hodge test

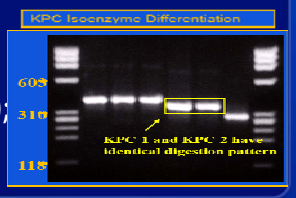
- Create a plate of susceptible E coli
- Place a Carbapenem disc in center
- Negative control has clear zone of inhibition; zone gets distorted when carbapenemase is present



Described by Lee K et al. *Clinical Microbiology and Infection* 7: 88-102, 2001.

Molecular detection of resistance genes

- Nucleic acid amplification tests (NAAT); Polymerase chain reaction (PCR)



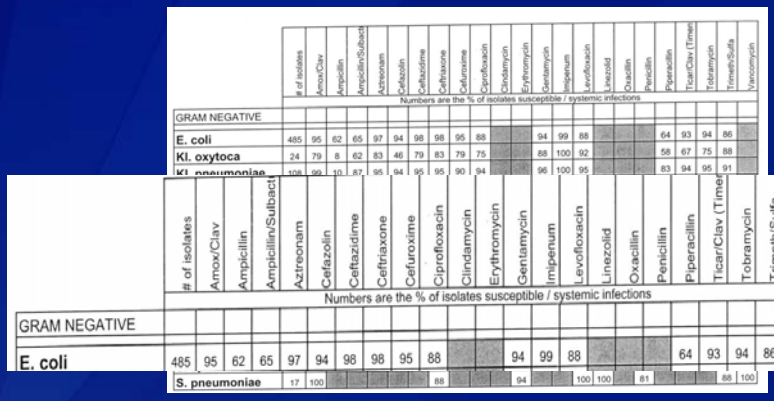
What does it all mean?

- Microbiology labs may use different strategies for identifying carbapenem-resistance
  - Detection of carbapenemase production can vary by testing method being used
- Labs may NOT do the additional confirmatory testing to determine if resistance is from a carbapenemase
  - Requires additional knowledge, supplies/resources, time and technology
- Understanding the testing methods in your laboratory helps you interpret carbapenem-resistance reported in your facility
  - True burden may be over or under-estimated depending on testing methods and lab reporting

Starting the conversation with your lab

- Talk with the director of microbiology for your laboratory
  - Share your interest in understanding the carbapenem resistance in gram-negative bacteria identified in your facility
- Ask what methods are used for identification and antibiotic susceptibility
  - Is it an automated method?
  - Can they easily flag organisms with carbapenem-resistance?
- Ask whether they can perform "confirmatory" testing for carbapenemase-production (e.g., modified Hodge)
  - Could this be done if requested?
- Discuss a strategy for notifying your facility when a carbapenem-resistant bacteria is identified

Snapshot of resistance patterns: Facility antibiograms



	# of isolates	Amox/Clav	Ampicillin	Ampicillin/Sulbact	Aztreonam	Cefazolin	Ceftazidime	Ceftriaxone	Cefuroxime	Ciprofloxacin	Clindamycin	Erythromycin	Gentamycin	Imipenum	Levofloxacin	Linezolid	Oxacillin	Penicillin	Piperacillin	Ticar/Clav (Timen	Tobramycin	Trimeth/Sulfa	Vancomycin
	Numbers are the % of isolates susceptible / systemic infections																						
GRAM NEGATIVE																							
E. coli	485	95	62	65	97	94	98	98	95	88			94	99	88				64	93	94	86	
Kl. oxytoca	24	79	8	62	83	46	79	83	79	75			88	100	92				58	67	75	88	
Kl. pneumoniae	108	99	10	87	95	94	95	95	90	94			96	100	95				83	94	95	91	
S. pneumoniae	17	100							88				94		100	100		81			88	100	

- A yearly summary of the common bacteria from facility cultures and their susceptibility patterns to antibiotics
- Can be developed by your laboratory to show trends in resistance over time

Take Home Points

- Antibiotic resistance is a growing problem across all healthcare settings;
- Carbapenem resistance results in infections which cannot be treated with current antibiotics
- Understand the common bacteria causing infections among residents and the most frequently prescribed antibiotics in your facility
- The microbiology laboratory is a key partner in identifying and communicating when resistant organisms are isolated

Thank you!!

Email: nstone@cdc.gov with questions/comments

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion

Minnesota Resources

- **Minnesota Antimicrobial Stewardship Program Toolkit for Long-Term Care Facilities:** http://www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/asp/ltc/index.html

Recommended nursing-driven core elements

- Identify a stewardship champion (i.e. Consider nursing leadership or IPs)
- Identify a committee/team to incorporate stewardship (e.g. QA, infection control, nursing team meetings)
- Measures antimicrobial use & regularly shares findings with all stakeholders (e.g. EMR, pharmacy records)
- Incorporate relevant clinical guidelines (e.g. Loeb et al, SHEA, IDSA) into policies & protocols
- Provide stewardship-related training to all healthcare personnel & empower all to recognize their role
- Communicate stewardship-related messages to residents, families, & visitors
- Develop clinical algorithms to cue appropriate diagnostic testing, antimicrobial timing, & review of results
- Conduct infection surveillance that is rooted in resident signs and symptoms (e.g. 2012 Stone et al criteria)
- Assess nursing process for 1) recognizing, 2) assessing, 3) communicating, and 4) documenting a resident's change in condition

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Minnesota Resources

Core Tools

- Action Steps and Strategies for Implementing Antimicrobial Stewardship
- http://www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/asp/ltc/apxb.pdf
- Antimicrobial Stewardship Gap Analysis Tool
- http://www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/asp/ltc/apxc.pdf
- Nursing and Provider Antibiotic Use Attitudes and Beliefs Survey
- http://www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/asp/ltc/apxd.pdf
- Antimicrobial Use Assessment
- http://www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/asp/ltc/apxe.pdf
- Nursing Process Evaluation Tool – Resident Change in Condition
- http://www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/asp/ltc/apxf.pdf
- Supplemental Tools: Nursing communication tools, infection surveillance tools, clinical decision-making tools, education modules for nurses and nursing assistants, nursing skills fair questions, antimicrobial stewardship presentations, flyers, table tents, quizzes (see main page above)

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Michigan and Wisconsin Resources

- Michigan Antibiotic resistance Reduction Coalition (MARR) Page:
- http://mi-marr.org/
- Michigan Long-Term Toolkit:
- http://mi-marr.org/LTC_toolkit.php
- Wisconsin Antibiotic Resistance Page:
- https://www.dhs.wisconsin.gov/disease/aro.htm
- Wisconsin Healthcare-Associated Infections in Long-Term Care Coalition Resources (including stewardship)
- https://www.dhs.wisconsin.gov/regulations/nh/hai-resources.htm
- Wisconsin Guidelines for Prevention and Control of Antibiotic Resistance Organisms in Health Care Settings:
- https://www.dhs.wisconsin.gov/publications/p4/p42513.pdf

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National Resources from Centers from Disease Control and Prevention (CDC)

- All long-term care resources

http://www.cdc.gov/longtermcare/index.html

- "The Core Elements of Antibiotic Stewardship for Nursing Homes"

http://www.cdc.gov/longtermcare/prevention/antibiotic-stewardship.html

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Contact the Lake Superior Quality Innovation Network

Michigan: MPRO

Kathleen Lavich

248-465-7399 klavich@mpro.org

Minnesota: Stratis Health

Kristi Wergin

952-583-8561 kwergin@stratishealth.org

Wisconsin: MetaStar

Liz Domiguez

608-441-8271 ldomiguez@metastar.com

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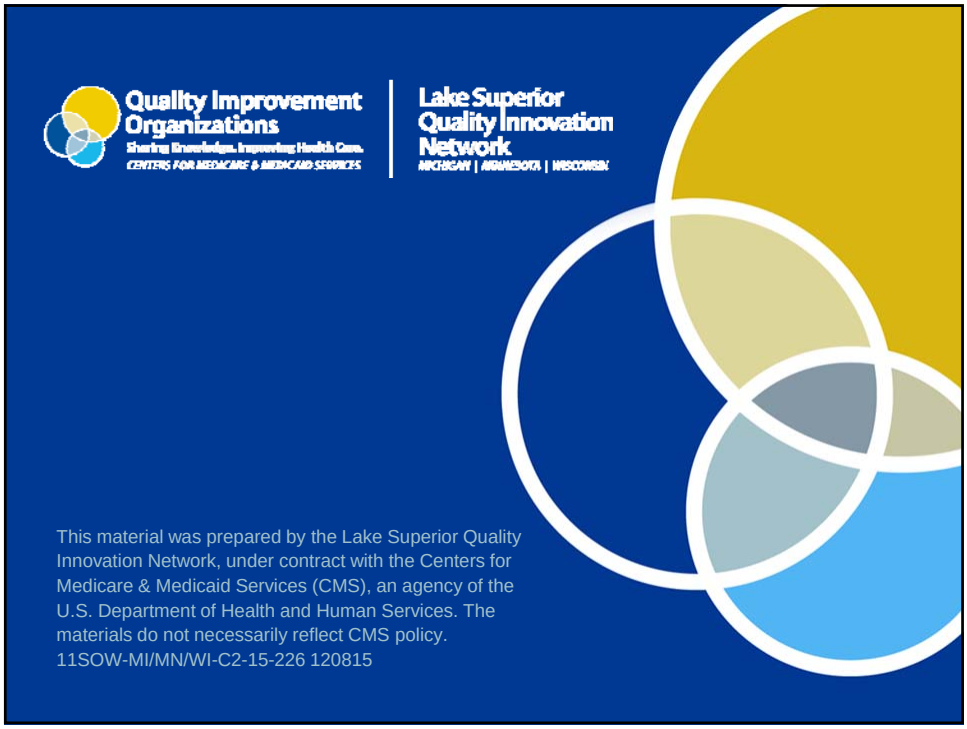
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