MRSA

VRE

The ABCs of AROs

VRSA

ESBLs

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BCSLS Tele Health Seminar
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By the end of the session…

- List common organisms of concern for antibiotic resistance
- Explain mechanisms organisms use to become resistant
- Describe how to detect these organisms in the laboratory, with conventional and new methods
- Describe what we do about them
- Explain why we care

Which ABCs of AROs?

- Staphylococci
  - MRSA
  - CMRSA
  - VISA (GISA)
    VRSA (GRSA)
  - MLS_B
- Enterococci
  - HLAR
  - VRE
- Streptococcus pneumoniae
  - PNSSP and DRSP
- Gram negative bacilli
  - AmpC
  - ESBL
  - FQR Salmonella
- Mycobacteria
  - MDRTB
  - XDR

Mechanisms for resistance: intrinsic and acquired

1. Antibiotic inactivation or modification by enzymes
2. Decreased antibiotic uptake or accumulation
3. Antibiotic target altered or not present
4. Circumvention of antibiotic action
5. Uncoupling of antibiotic action and cell death

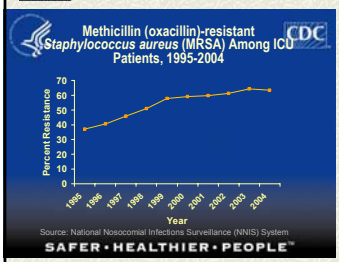
General Introduction

- What are the definitions?
  - S = ?, R = ?
- Current methods may be unreliable to detect developing resistance
  - First need a sufficient number of non-susceptible isolates for developing resistant and intermediate breakpoints
  - Then need to set detection criteria
  - All methods have problems, automated methods in particular
- Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) as reference for procedures

General Introduction: Beta-lactam Antibiotics

- 4 membered ring structure
  - Penicillin, ampicillin, oxacillin, etc
  - Cephalosporins
  - Carbapenems
  - Monobactam
- Beta-lactamases
  - Enzymes that break down beta-lactams
  - Gram negatives: periplasmic space
  - Gram positives: excreted outside of cell
  - Different substrate (antibiotic) profile
  - Genes are on the chromosome of plasmids

MRSA Statistics: Not necessarily complete or comparable



USA, ICU: ~40-60%

Canada*, not ICU:

1995: <1%

2003: ~10%

Europe, 99-02**:

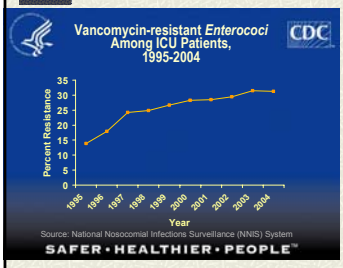
N. Europe: <1%

S & W Europe: >40%

*CCDR, 2005, CNISP

**EARSS, 2004

VRE Statistics:
Not necessarily complete or comparable



USA, ICU: ~15-30%

Canada*, not ICU:

Guestimate?

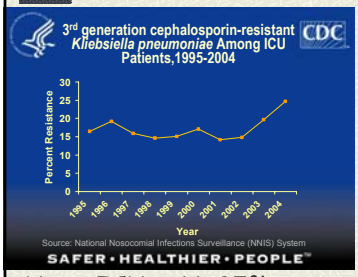
Europe, 2000**:

~2 to 3%

*CNISP

**EARSS, 2000

3rd Generation Cephalosporin R:
Not necessarily complete or comparable



USA, ICU: ~16-25%

SENTRY, 2001*

Canada*: 5%

US: 8%

Europe: 23%

Latin America: 45%

*CID, 2001, May, Supplement 2, S94-103

Which ABCs of AROs?

- Staphylococci
  - MRSA
  - CMRSA
  - VISA (GISA)
    VRSA (GRSA)
  - MLS_B
- Enterococci
  - HLAR
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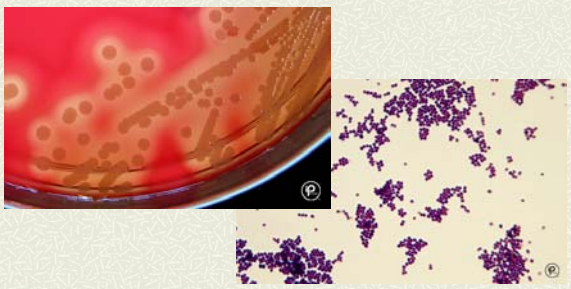
  - ESBL
  - FQR Salmonella
- Mycobacteria
  - MDRTB
  - XDR

Staphylococcus aureus

- Major human pathogen
  - Skin and soft tissue infections
  - Abscesses
  - Pneumonia
  - Toxic Shock
- Also carried normally
  - 30% in anterior nares
- Many other staphylococcal species
  - coagulase negative species, collectively known as "CNS"
  - Common commensal flora

Clinical Images: Staphylococcal Infections

Staphylococcus aureus



Brief history of resistance in Staphylococci

- 1950s
  - Penicillin resistance
  - Beta-lactamase mediated
- 1960s
  - Methicillin resistance
  - Change in structure of cell wall
- 1990s
  - Vancomycin resistance
  - Change in structure of cell wall

MRSA
Methicillin Resistant *S. aureus*

Methicillin:

- 1st antibiotic in the class of "semi-synthetic penicillins"
- No longer used clinically, and not stable in the laboratory
- Oxacillin, cloxacillin, flucloxacillin, etc
- Use of the term persists for Staphylococci resistant to this class of antibiotics
  - "ORSA" – oxacillin resistant *S. aureus*

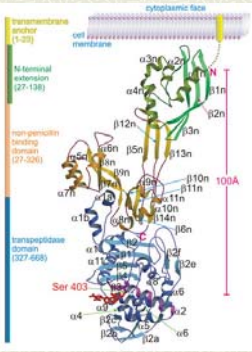
Mechanism of Methicillin resistance

- Chromosomal location, mecA gene
- Changes the cell wall structure
  - Alteration in membrane-bound enzymes called penicillin binding proteins (PBPs)
  - PBPs are the targets of beta-lactam antibiotics
    - PBP2a (PBP2') is the gene product of mecA
  - PBP2a does not allow antibiotic attachment
- Mediates "methicillin" resistance in both *S. aureus* and the coagulase negative staphylococci
- This resistance applies to all beta-lactam antibiotics

MRSA

mecA codes for PBP2a, low affinity for most β-lactams, described by UBC scientists

Authors Natalie Stynadka (left) and Daniel Lim.



Slide from S Porter

Classic MRSA

- Heteroresistant population
- High oxacillin MICs* >256 µg/mL (normal <2)
- Associated with resistance to other antibiotic classes
- Require special procedures for laboratory detection
- Risk Factors for acquisition: hospitalization, prior antibiotics, other

*MIC= Minimum Inhibitory Concentration, lowest concentration that will inhibit growth

MRSA – Laboratory Detection

- Modifications of testing conditions
  - Inoculum: Direct inoculation method
  - Media: supplemented with NaCL
  - Temperature: ≤ 35°C
  - Time: full 24 hour incubation

MRSA – Laboratory Detection

- Phenotypic Methods
  - Oxacillin screening medium
    - 6 mg/L oxacillin plus salt
    - chromogenic media
  - Disk Diffusion (Kirby Bauer)
    - Oxacillin disk ←
    - Cefoxitin disk
  - MIC methods
- Genotypic Methods
  - mecA – gene responsible for resistance
- Gene Product Detection Methods
  - PBP2a detection: latex agglutination

MRSA – Laboratory Detection

- Phenotypic methods
  - Evaluate any growth on screen plate Zone size measurements:
    - Oxacillin ≤ 10 mm ←
    - Cefoxitin ≤ 19 mm
  - MIC: Oxacillin ≥ 4
- Genotypic methods: presence of mecA gene
- Gene product method: positive test with latex agglutination

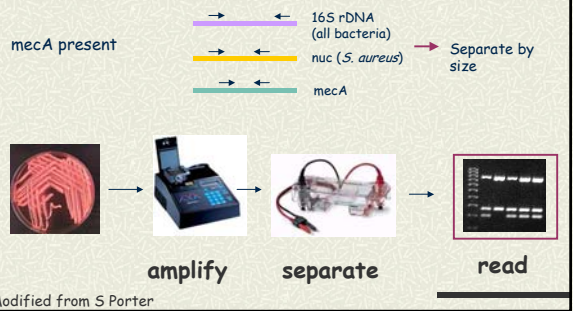
Implications of MRSA

- Considered resistant to all beta-lactam antibiotics
  - Other in vitro results should be ignored
  - Problem: Vancomycin is a second line choice, often only choice for treatment
  - Problem: Drives vancomycin use – Vanco R?
- MRSA isolates should be checked for vancomycin resistance

What about BORSA?

- Borderline "oxacillin" resistant *S. aureus* "BORSA"
- MIC around cut-off, 8-16 µg/mL
- Conflicting results with testing
- Mec A gene or PBP2a negative
- Report as methicillin resistant but not classic MRSA
  - Mechanism hyper-production of beta lactamase?
  - Do not have same infection control implications

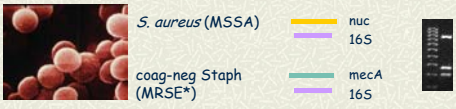
MRSA Identification by mecA



Modified from S Porter

MRSA Detection: Potential problem with mixed culture

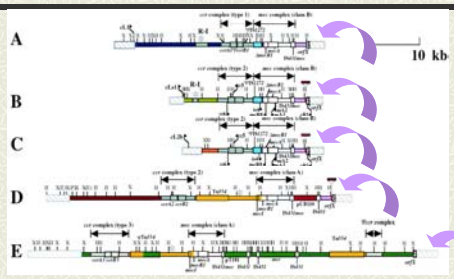
Problem when MSSA and MRSE both present



*methicillin resistant *S. epidermidis*

Modified from S Porter

MRSA Genome



Huletsky et al., JCM 2004

S. aureus - specific integration site

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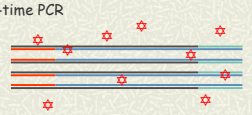
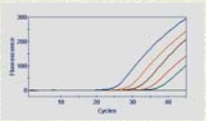
MRSA Detection: Real Time PCR

Conventional PCR- several steps

Real-time PCR





Uses insertion sequence

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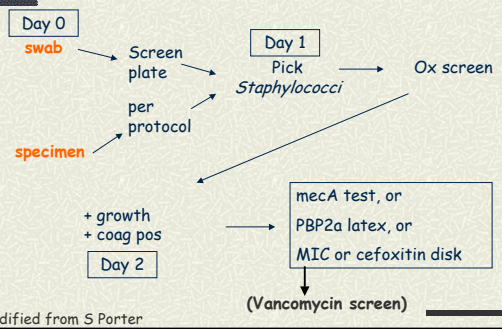
MRSA Identification



Modified from S Porter

Community Acquired MRSA

- Patients presenting with infections without identified risk factors
  - Severe pneumonia
  - Skin and soft tissue infections
- Apparent emergence of a new strain
  - Susceptible to other antibiotics
  - Associated with particular virulence factors:
    - Panton-Valentine Leukocidin "PVL"
  - Primarily one strain type – "clonal"
    - Most PFGE type CanadianMRSA 10 (USA 300)
    - SCC type IV (chromosomal region with mecA)

Community Acquired MRSA

- Many definitions:
  - Place of acquisition?
    - Community versus hospital
  - Susceptibility pattern?
    - Multi-resistant vs susceptible
  - Presence of virulence factors?
    - PVL
    - SCC IV
  - Molecular strain type?
    - CMRSA 10

Strain Typing of Microorganisms

Helpful for:

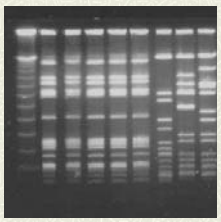
- identifying sources and routes of infection
- monitoring newly evolving strains
- determining contamination
- determining new vs. recurrent infection

Strain Typing of Microorganisms

- Measurement of similarity
- Traditional
  - Antibiograms
  - Biotyping
  - Phage typing
  - Serotyping
- Molecular – Now gold standard
  - Many methods -another alphabet altogether !
  - PFGE: pulsed field gel electrophoresis

PFGE: One method for Molecular typing

MRSA in one ward



index patients

Modified from S Porter

Vancomycin resistance in *S. aureus*: VISA/VRSA

- Brief History
  - 1996: 1st clinical isolate reported from Japan
    - ↓ S to vancomycin (MIC 8 µg/mL)
  - By 2002: 8 patients with VISA reported in USA
    - All patients high risk for AROs
    - Chronic diseases, commonly on dialysis
    - All with MRSA
    - Frequent past treatment with Vancomycin
  - July 2002: 1st clinical isolate R to vancomycin
    - Patient also had MRSA and VRE
    - Vancomycin MIC ≥ 128 µg/mL
    - Van A positive, mec A positive: spread of van A gene resistance determinant from enterococci

Vancomycin

- Glycopeptide antibiotic
  - Hence terms GISA/GRSA, "glycopeptide"
- Active against developing cell wall structure
- Long believed resistance could not develop due to the mechanism of action
- Mainstay of treatment against infections due to "methicillin" resistant organisms
  - MRSA
  - MRSE
  - other

Mechanisms of Vancomycin resistance in Staphylococci

- VRSA
  - All isolates have contained vanA
  - VRE isolated from all patients
  - vanA determinant transferred from enterococci
- VISA
  - Mechanism of resistance?
  - Strains have thicker cell walls
  - Cell walls can bind vancomycin extracellularly
  - Antibiotic can't growing cell wall complex to inhibit cell growth

VISA/VRSA: Laboratory detection

- Defining Vancomycin Resistance (CLSI):
  - Susceptible: MIC ≤ 4 µg/mL* (typically 0.5-2)
  - Intermediate: MIC 8-16 µg/mL
  - Resistant: MIC ≥ 32 µg/mL
- Can we detect these in the Laboratory?
  - Not all susceptibility methods detect VISA and VRSA

*CLSI 2006:

- Proposed change of susceptible category to ≤ 2 µg/mL to enhance the detection of "non-susceptible" isolates

VISA/VRSA: Laboratory detection

- Laboratory Detection
  - Inoculum: direct colony suspension
  - Time: full 24 hours
  - Methods
    - Optimal:
      - Screen medium and non-automated MIC
    - Acceptable
      - Automated method or disk diffusion, PLUS
      - Screen medium with vancomycin 6 µg/mL
        - Check all growth for purity and ID
        - Confirm by MIC method
  - Send isolates with MIC ≥ 4 for reference testing
  - MRSA isolates should be screened for VISA/VRSA

Vancomycin resistance in *S. aureus* - Implications

- Heightened awareness
- Clinical implications for patient
- Infection Control Precautions to prevent spread quite strict (and the cycle repeats)
- Contact tracing
  - No spread to others from previous case reports

Macrolide/lincosamide resistance MLS_B

- Antibiotic classes:
  - Macrolide: Erythromycin
  - Lincosamide: Clindamycin
- Mechanisms of resistance
  - Efflux mediated: *msrA* gene, *mef* gene
  - Ribosomal methylation: *erm* gene, inducible
    - Macrolide-lincosamide-streptogramin B (MLS_B)
    - High rate of mutation to constitutive resistance
- Staphylococci and beta hemolytic streptococci:
  - When Erythromycin R and clindamycin S, do D-test
  - Clinical failures reported in this setting

D test: Detection of inducible MLS_B resistance

- D-test: double disk diffusion assay
- Erythromycin and clindamycin disks placed 15-20 mm apart
- Positive test - "D"

Negative test- no blunting

Which ABCs of AROs?

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  - CMRSA
  - VISA (GISA)
    VRSA (GRSA)
  - MLS_B
- Enterococci
  - HLAR
  - VRE
- Streptococcus pneumoniae
  - PNSSP and DRSP
- Gram negative bacilli
  - AmpC
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- Mycobacteria
  - MDRTB
  - XDR

Enterococci

- Normal GI tract flora
- Many species
  - E. faecalis – 85%
  - E. faecium – 15% (most resistance in this species)
  - Many others – 1%
- Broad range of intrinsic antibiotic resistance
  - Cephalosporins, oxacillin, clindamycin, erythromycin
  - Ampicillin/penicillin, vancomycin & aminoglycosides are not bactericidal alone
  - Require synergistic therapy in serious infections

Enterococci

- Infections include
  - Urinary tract
  - Intrabdominal and pelvic infections
  - Bacteremia
  - Endocarditis
  - Polymicrobial - common
    - Intraabdominal and pelvic
    - Wound
    - Decubitus and diabetic foot ulcers
- Specific directed therapy not always necessary
  - 2nd class pathogen status
  - Hospital-acquired infections, "super-infections"

Clinical Images: Enterococcal Infections

Polymicrobial



Monomicrobial

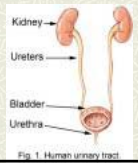
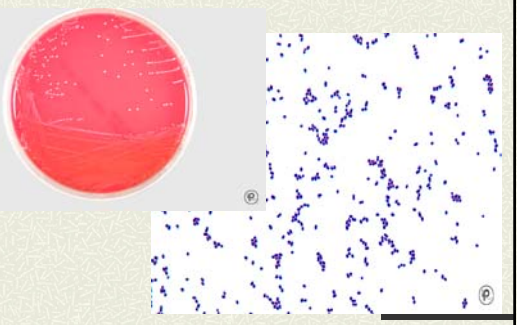


Fig. 1. Human urinary tract

Enterococci



Brief history of antibiotic resistance in Enterococci

1970s and 1980s

- High level resistance to ampicillin
  - Change in PBPs
    - Readily detected by disk or dilution methods
  - Production of beta lactamases (from Staphylococci)
    - May need cefinase test to detect
- High level resistance to aminoglycosides
  - Enzymes which interfere with activity "aminoglycosidases"

1988 through 1990s to present

- 1988 Europe: vancomycin resistance, vanA in E. faecium
- 1989 USA
- 1993 Canada

High level aminoglycoside resistance (HLAR)

Enterococci and Aminoglycosides

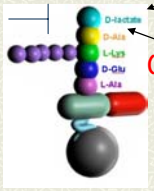
- Enterococci are intrinsically resistant to low-level aminoglycosides
- However, aminoglycosides are important in synergistic combinations with cell wall active agents to treat serious enterococcal infections
- Emergence of HLAR eliminates their use in synergistic combinations
- Laboratory detection fairly easy
  - Test using high level antibiotic: 500 to 2000 µg/mL
  - Disk diffusion or broth/agar dilution
- Interpretive comment (CLSI, other):
  - Resistant, will not be synergistic with cell wall active agents
  - Susceptible, will be synergistic with cell wall active agents

Mechanism of Vancomycin resistance in Enterococci

- Vancomycin
  - blocks the synthesis of bacterial cell walls
  - binds to the D-alanyl-D-alanine terminus of the peptidoglycan stem
  - Resistance to vancomycin is associated with a new membrane-associated protein that inhibits this binding
  - The protein removes the terminal D-ala from pentapeptide, replaces with –D-lactate which prevents vancomycin binding to its target

VRE – new structure of precursor peptidoglycan

Vancomycin



D-ala-D-lactate

(should be D-ala-D-ala)

Peptidoglycan precursor – component of cell wall

Modified from S Porter

Vancomycin Resistance in Enterococci

Organisms	Genes	Intrinsic	Trans ferable	Van MICs
E. gallinarum *E. casseliflavus* *E. flavescens*	Van C-1 Van C-2 Van C-3	Yes	No	2- 32
E. faecium, *E. faecalis*	Van A	No Acquired	Yes	≥ 64 X R: Teico
E. faecalis, *E. faecium*	Van B	No Acquired	Yes	≥4
E. faecium	Van D	No Acquired	No	16-128

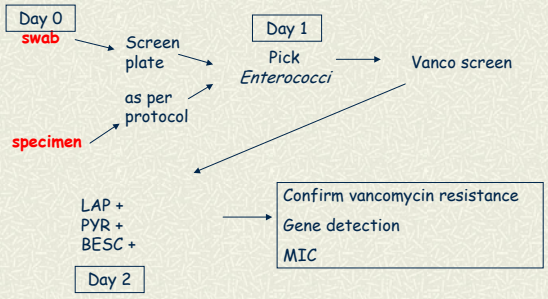
VRE – Laboratory Detection

- Modifications of conditions from usual testing
  - Time: full 24 hour incubation
  - Haze or any growth requires further investigation

VRE – Laboratory Detection

- Phenotypic Methods
  - Vancomycin screening medium with 6 mg/L vancomycin
  - Disk Diffusion (Kirby Bauer)
    - vancomycin disk
  - MIC
- Genotypic Methods
  - Van A, B, C1, C2, D – genes responsible for resistance

VRE Identification



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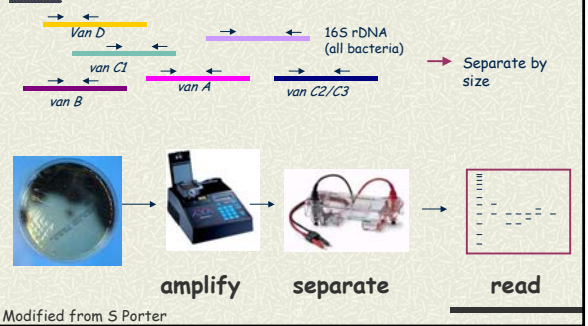

Modified from S Porter

Why we care

IT IS GENERALLY STATED THAT

- These organisms are not more likely to cause infections
- These organisms are not likely to cause more serious infections
- Many patients are colonized only and not infected

HOWEVER

- Decolonization is rarely successful
- Options for treatment if you get an infection are limited
- Serious morbidity and mortality may be associated with these infections
- Represent a significant burden to health care system

Why we care

- Cost to all patients
  - Isolation and isolated
  - Stigma
  - Less attention? – adds to time for care
  - Risk of future infection
- Cost to patients with infections: ABOVE PLUS
  - Prolongs treatment and hospitalization
  - Limited options for treatment
  - Significant morbidity and mortality
- Cost to health care system
  - Extended stays
  - Facility bed availability: acute and extended
  - Cost of surveillance and care

What we do

- Detection
  - Laboratory methods and support
  - Clinical and surveillance specimens
- Surveillance programs
  - High risk areas
  - Patients with recent interaction with health care facilities
- Antibiotic Utilization review
  - Antibiotic use
  - Antibiotic reporting
- Reporting
  - Infection Control Unit and Committee
  - MAC
  - Specific patient care areas

Which isolates to test?

Which patients to screen?

Infection Control

1. Hand washing always first, last, and in-between
2. Patient placement: private or cohort
3. Staff assignments: cohort?
4. Personal protective equipment
   - Gowns, gloves as needed for situation
5. Dedicated equipment
6. Environment - Housekeeping
7. Education
8. Notify other departments as required
9. Decolonization
10. Antibiotic use reviewed by clinicians

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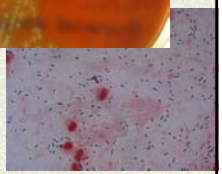
Streptococcus pneumoniae

- Most common cause of acute bacterial pneumonia in the community, meningitis
- Leading cause of illness and death
  - Fatality rate as high as 40% for bacteremia and 55% for meningitis
- Normal flora in upper respiratory tract



Clinical Images: Pneumococcal Infections






PNSSP:Penicillin non-Susceptible *S. pneumoniae*

- 1967 1st reported in Australia, 1977 in South Africa
- Variable geographically, up to 40% "non-susceptible" in some areas, children are biggest reservoir
- Mechanism is due to change in PBPs
- Associated with resistance to cephalosporins, erythromycin, trimethoprim-sulfa (DRSP: drug resistant *S.pneumoniae*)
- Definitions for penicillin susceptibility:
  - Susceptible: MIC ≤0.06 µg/mL
  - "Non-susceptible"
    - Intermediate R: MIC 0.12 to 1 µg/mL
    - High level R: MIC ≥ 2 µg/mL

PNSSP: Laboratory Detection

- Direct colony, MHA with 5% sheep blood, 5% CO_2, 20-24 hours
- Oxacillin disk (1 µg) screen more discriminatory
  - Very sensitive but not specific
- Report results to penicillin, *not* oxacillin
  - Susceptible: zone > 19 mm
  - Further investigation: zone ≤ 19
    - Could be S, I or R
    - Confirm with MIC test
- Isolates from invasive sites
  - Direct to MIC test, do not screen

PNSSP: Clinical implications

- Patients with pneumonia due to "I" strains can be treated with high doses of penicillin
- Patients with meningitis, invasive infections need other therapy
  - Empiric - vancomycin
  - 3rd generation cephalosporin (cefotaxime) if S
- Interpretation of 3rd generation cephalosporins based on clinical presentation
  - Meningitis: Susceptible ≤0.5
  - Non-meningitis: Susceptible ≤1

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Beta-lactamase mediated resistance in Gram negative bacilli

- Gram negative bacilli use many resistance mechanisms
- Beta-lactamase mediated resistance has always existed in gram negative bacilli
  - Low level production of beta-lactamases
  - Many enzymes: Substrate profile, Isoelectric point
  - Resistance to 1st gen cephalosporins and ampicillin
    - TEM-1 and SHV-1
  - Transferred to other species via plasmids

ESBLs
Extended Spectrum Beta-lactamases

- Derive from original beta-lactamases, spread by plasmids
  - amino acid substitutions, change the configuration and increase affinity for broad spectrum cephalosporins and aztreonam resulting in inactivation
  - Resistance to cefotaxime, ceftriaxone, etc.
  - Maintain Susceptibility to
    - Cephamycins (cefoxitin)
    - Carbapenems (imipenem, meropenem)
  - Inhibited by beta-lactamase inhibitors: clavulanic acid
- 1980s: Found in *Klebsiella pneumoniae* and *E. coli*
  - Initially unrecognized, cause of nosocomial outbreaks
- Several hundred known, have their own alphabet soup:
  - Families: TEM, OXA, SHV, CTX-M, etc.

ESBLs: Laboratory Detection

Problems

1. MICs may fall within susceptible range
2. May not be active against the antibiotic you test
3. Require a high index of suspicion
4. Require screening and confirmatory tests against > 1 antibiotic
5. Presence of an ESBL implies resistance to all penicillins, cephalosporins, and aztreonam
6. Presence may be masked by other R mechanisms
7. Confirmation requires molecular methods not widely available

ESBLs: Laboratory Detection*

- Screening method – a few choices
  - Cephalosporin pattern
    - Cefpodoxime
    - Cefotaxime
    - Ceftriaxone
    - Ceftazidime
    - (Aztreonam)
  - S to cefoxitin and imipenem maintained
  - Automated screens – use reduced antibiotic concentrations
- Phenotypic confirmation
  - Test both Ceftazidime and cefotaxime
    - Alone, and
    - With beta-lactamase inhibitor (clavulanic acid)
  - Interpretation:
    Disk test: 5 or greater increase in zone size
    Etest: MIC ratio of 8 or greater

*Methods for *E. coli, Klebsiella pneumoniae,* and *Proteus mirabilis* (bacteremia)

AmpC beta-lactamases: Resistance in Gram negative bacilli

- AmpC: chromosomal gene for beta-lactamases in all gram negative bacilli
- AmpC encodes an enzyme more active in hydrolyzing cephalosporins than penicillins
  - Cephalosporins R, Cefoxitin R
  - Not inhibited by beta-lactamase inhibitors
  - Not difficult to detect in the laboratory
- SPICE organisms: Serratia, Proteus (indole +) Citrobacter, Enterobacter, and Pseudomonas
  - single step mutation to constitutive high level enzyme production: initially susceptible → develop resistance
  - 3rd generation cephalosporins select for resistance
  - Comment added about use of these antibiotics for these organisms

AmpC beta-lactamases: Resistance in Gram negative bacilli

- Now AmpC beta-lactamase genes spread by plasmids to other species world-wide
  - *E. coli*
  - *Klebsiella pneumoniae*
- Laboratory clue:
  - variable R to cephalosporins like ESBLs, BUT
  - R to cefoxitin
- R genes against other antibiotics also present
- Both AmpC beta-lactamases and ESBLs may be present in the same organism
  - Difficult to study
  - Stay tuned

Fluoroquinolone Resistance (FQR) in Salmonella

- Fluoroquinolones inhibit bacterial DNA synthesis
- Resistance:
  - mutations that alter the target (DNA gyrase or topoisomerase IV) or drug's permeability
- Ciprofloxacin common therapy for Salmonella infections
- In-vitro tests may appear susceptible, but
  - clinical failure or delayed response has been noted in bacteremic patients
- Nalidixic acid better agent to detect possible resistance in extra-intestinal isolates of Salmonella
  - Report as Ciprofloxacin resistance

Which ABCs of AROs?

- Staphylococci
  - MRSA
  - CMRSA
  - VISA (GISA)
    VRSA (GRSA)
  - MLS_B
- Enterococci
  - HLAR
  - VRE
- Streptococcus pneumoniae
  - PNSSP and DRSP
- Gram negative bacilli
  - AmpC
  - ESBL
  - FQR Salmonella
- Mycobacteria
  - MDRTB
  - XDR

Multidrug resistance in *M. tuberculosis*: MDRTB

- MDRTB: Resistant to at least INH and rifampin
- 1990s: emerged as a threat
  - Outbreaks in US and worldwide
  - Second-line drugs less effective
  - ~20% of isolates worldwide*
    - 20-50% industrialized nations
  - 2% extensively drug resistant (XDR-R to 3 second line drugs in addition)
    - 2-11% industrialized nations
- Threat to global TB control

*MMWR.55:11, March 2006

It is the end of the session…

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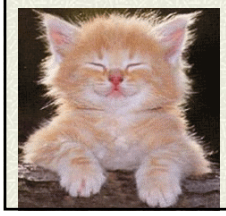
- List the common organisms of concern for antibiotic resistance
- Explain mechanisms organisms use to become resistant
- Describe how to detect these organisms in the laboratory, with conventional and new methods
- Describe what we do about them
- Explain why we care

What about *H.influenzae*, *N. gonorrhoeae*…



Thank you for your attention