DEPARTMENT OF HEALTH AND HUMAN SERVICES

# Understanding Antimicrobial Resistance in Your Facility: the Patient Report and the Cumulative Antibiogram!

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**currently working with CDC's Division of Laboratory Systems through an Interagency Personnel Agreement*

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## At the conclusion of this talk, you will be able to……

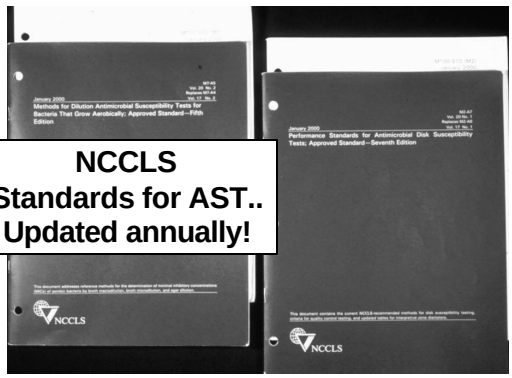
- Discuss use of NCCLS standards for antimicrobial susceptibility testing (AST) and reporting in clinical and public health laboratories.
- Describe effective reporting of antimicrobial resistance on routine laboratory reports.

## At the conclusion of this talk, you will be able to……(con't)

- Discuss analysis and presentation of cumulative antimicrobial susceptibility test data (antibiogram) at local healthcare facilities.

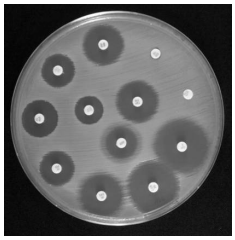
## Current AST Methods NCCLS

NCCLS



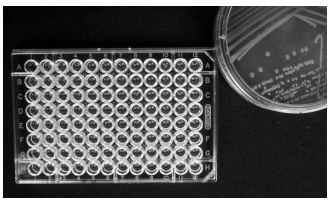

**NCCLS Standards for AST.. Updated annually!**

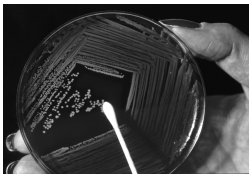
## NCCLS Methods



Disk Diffusion (Kirby Bauer)

MIC





Select colonies

Prepare inoculum suspension

## Disk Diffusion Testing

Remove sample

Swab plate

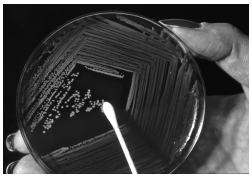
Add disks

Incubate overnight

Measure zones

## NCCLS
## Zone Interpretive Criteria (mm)

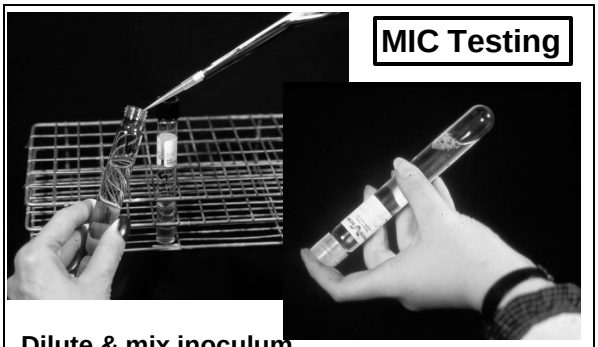
| Drug | Disk content (ug) | Res | Int | Susc |
|---|---|---|---|---|
| cefazolin | 30 | £ 14 | 15-17 | ³ 18 |
| gentamicin | 10 | £ 12 | 13-14 | ³ 15 |



Select colonies

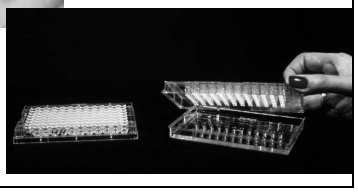
Prepare inoculum suspension

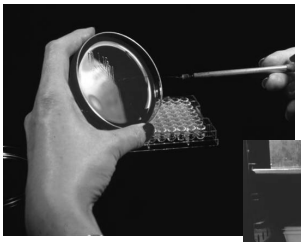
## MIC Testing



Dilute & mix inoculum suspension

Pour inoculum into reservoir and inoculate MIC tray

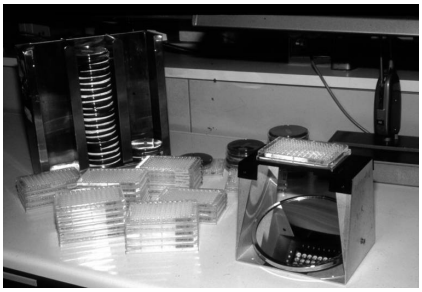




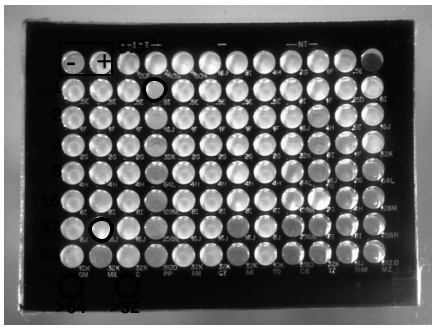
Inoculate purity plate

Incubate overnight

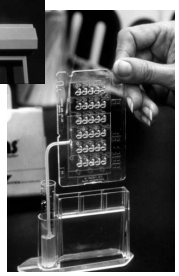
Read MICs



## MICs

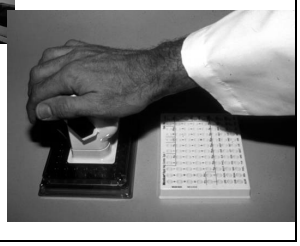



## Vitek



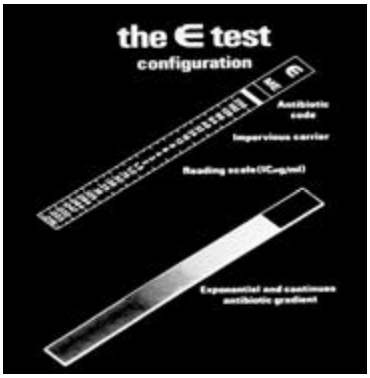
Vitek Automated MIC System

## MicroScan



**MicroScan Automated MIC System**

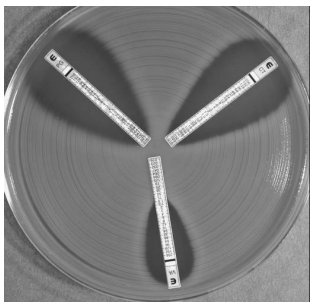
## Etest

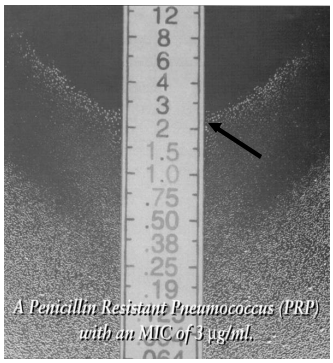



**MIC on a strip**

## *Streptococcus pneumoniae*

**Etest**



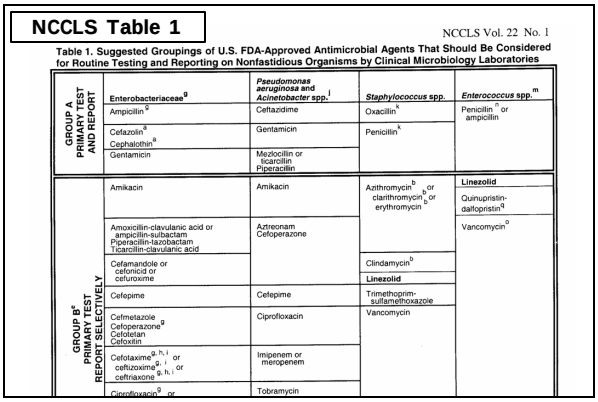



***S. pneumoniae*** **Penicillin MIC = 2 µg/ml**

## NCCLS
## MIC Interpretive Criteria (µg/ml)

| Drug | Susc | Int | Res |
|---|---|---|---|
| cefazolin | £ 8 | 16 | ³ 32 |
| gentamicin | £ 4 | 8 | ³ 16 |

## NCCLS Table 1



NCCLS Vol. 22 No. 1

**Table 1. Suggested Groupings of U.S. FDA-Approved Antimicrobial Agents That Should Be Considered for Routine Testing and Reporting on Nonfastidious Organisms by Clinical Microbiology Laboratories**

| | | | | |
|---|---|---|---|---|
| GROUP A PRIMARY TEST AND REPORT | Enterobacteriaceae[g] | *Pseudomonas aeruginosa* and *Acinetobacter* spp.[l] | *Staphylococcus* spp. | *Enterococcus* spp.[m] |
| | Ampicillin[g] | Ceftazidime | Oxacillin[k] | Penicillin[n] or ampicillin |
| | Cefazolin[g] | Gentamicin | Penicillin[k] | |
| | Cephalothin[g] | | | |
| | Gentamicin | Mezlocillin or ticarcillin Piperacillin | | |
| GROUP B[e] PRIMARY TEST REPORT SELECTIVELY | Amikacin | Amikacin | Azithromycin[b] or clarithromycin[b] or erythromycin[b] | Linezolid |
| | | | | Quinupristin-dalfopristin[q] |
| | Amoxicillin-clavulanic acid or ampicillin-sulbactam Piperacillin-tazobactam Ticarcillin-clavulanic acid | Aztreonam Cefoperazone | | Vancomycin[o] |
| | Cefamandole or cefonicid or cefuroxime | | Clindamycin[b] | |
| | | | Linezolid | |
| | Cefepime | Cefepime | Trimethoprim-sulfamethoxazole | |
| | Cefmetazole Cefoperazone[g] Cefotetan Cefoxitin | Ciprofloxacin | Vancomycin | |
| | Cefotaxime[g, h, i] or ceftizoxime[g, h, i] or ceftriaxone[g, h, i] | Imipenem or meropenem | | |
| | Ciprofloxacin[p] or | Tobramycin | | |

## Detecting and Reporting Antimicrobial Resistance

- *Staphylococcus aureus*
  - MRSA
  - CA-MRSA
  - VISA, VRSA
- Vancomycin-resistant enterococcus (VRE)
- Extended-spectrum b-lactamase producers (ESBLs)
- Others

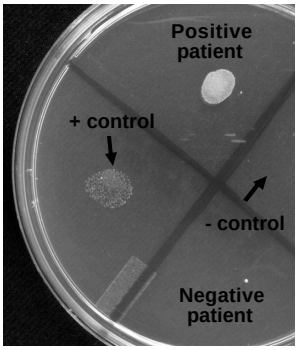
## *Staphylococcus aureus* Testing Methods Reporting

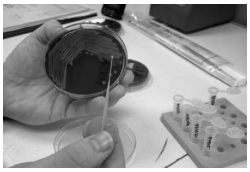
S. aureus

## *S. aureus* Testing

- Disk diffusion or MIC tests (e.g. Vitek, MicroScan)
- Oxacillin-salt agar screen plate
- Detection of gene or gene product
  - "Isolates of staphylococci that are shown to carry the *mecA* gene, or that produce PBP2a, the gene product, should be reported as oxacillin resistant" (NCCLS, 2003)

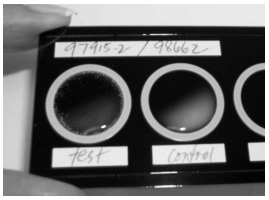
**Oxacillin-salt agar screen for *S. aureus***
**(MHA + 4% NaCl + 6 ug/ml oxacillin)**



**PBP2a rapid latex agglutination assay kit**

- Perform on isolated colonies
- Extract PBP2a
- React with latex antibody to PBP2a




**Report Example (following PBP2a assay): Leg Wound Culture**

**Gram Stain (day 1):**
- Many GPC clusters
- Many WBCs

**Preliminary Culture Report (day 2):**
- Many: *Staphylococcus aureus* , oxacillin-resistant (MRSA)
- "Additional susceptibility results to follow"

## *Staphylococcus aureus*

| | |
|---|---|
| clindamycin | S |
| erythromycin | S |
| oxacillin | S |
| penicillin | R |
| vancomycin | S |

"Cefazolin and other ß-lactams (except amoxicillin, ampicillin, and penicillins) are active against oxacillin-S and penicillin-R staphylococci."

*Consider adding comment to report to further explain ß-lactam results*

## *Staphylococcus aureus*

| | |
|---|---|
| clindamycin | R |
| erythromycin | R |
| oxacillin | R |
| penicillin | R |
| vancomycin | S |

"Oxacillin-R staphylococci are resistant to all ß-lactams. MRSA isolated, please check Infection Control policies."

## *Staphylococcus aureus*

| | |
|---|---|
| cefazolin | R* |
| clindamycin | R |
| erythromycin | R |
| oxacillin | R |
| penicillin | R |
| vancomycin | S |

**If any ß-lactam is tested and tests "S", do not report or change to "R" for MRSA*

## *Staphylococcus aureus*

| | |
|---|---|
| clindamycin | S |
| erythromycin | R |
| oxacillin | R |
| penicillin | R |
| vancomycin | S |

*Historically, MRSA have been multiply resistant to other anti-staphylococcal agents. However, many community associated strains are not multiply resistant.*

## *Staphylococcus* spp. Erythromycin / Clindamycin

| Mechanism | Determinant | Erythro | Clinda |
|---|---|---|---|
| Efflux | *msrA* | R | S |
| Ribosome alteration | *erm* | R | S* |
| Ribosome alteration | *erm* | R | R constitutive |

*msrA* = macrolide streptogramin resistance
*erm* = erythromycin ribosome methylase
*requires induction to show resistance

## *Staphylococcus aureus*

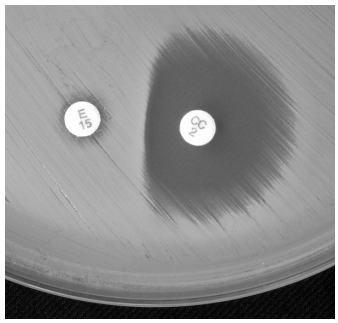
| | |
|---|---|
| erythromycin | R |
| oxacillin | R |
| penicillin | R |
| vancomycin | S |

"Contact laboratory if clindamycin results needed"

*If clindamycin-S, erythromycin-R, do not report as clindamycin-S without performance of "D Test"*

## "D Test"

**Inducible Clindamycin Resistance (*erm*-mediated)**




***"D Test" positive – forthcoming NCCLS comment suggestion***

### *Staphylococcus aureus*

| | |
|---|---|
| clindamycin | R |
| erythromycin | R |
| oxacillin | R |
| penicillin | R |
| vancomycin | S |

**"This *S. aureus* is presumed to be resistant based on detection of inducible clindamycin resistance. Clindamycin may still be effective in some patients."**

***"D Test" negative***

### *Staphylococcus aureus*

| | |
|---|---|
| clindamycin | S |
| erythromycin | R |
| oxacillin | R |
| penicillin | R |
| vancomycin | S |

**"This *S. aureus* DOES NOT demonstrate inducible clindamycin resistance in vitro."**

## *Staphylococcus* spp. Vancomycin

| | MIC (µg/ml) |
|---|---|
| Susceptible | £ 4 |
| Intermediate | 8 - 16 |
| Resistant | ³ 32 |

**VISA = (4) - 16 µg/ml**
**VRSA = ³ 32 µg/ml**

NCCLS M100-S13; Table 2C

## VISA

- 8 cases to date in USA
- Pts. previously had MRSA
- Pt. previously treated with vancomycin
- Most are MRSA

Fridkin et. al. 2001. Clin. Infect. Dis. 32:108.
Fridkin et. al. 2003. Clin. Infect. Dis. 36:429.

## VRSA

- 2 cases to date
  - June 2002 – Michigan
  - September 2002 – Pennsylvania
- Both pts. previously had MRSA and VRE (*vanA*) and were treated with vancomycin
- VRSA had *mecA* and *vanA*
- "S" to other agents (chloramphenicol, linezolid, minocycline, quin-dalfo, TMP-SMZ

MMWR. 2002; 51:565-7.
Chang et al. 2003. NEJM 348:1342

## VISA / VRSA

**Some test methods DO NOT detect VISA or VRSA!!**

**If you suspect vancomycin problems in treating *S. aureus* infection, contact laboratory and suggest further testing!!**

## *Enterococcus* spp.

**Testing Methods**

**Reporting**


## *Enterococcus* spp. Testing

- **AST of isolates from diagnostic specimens:**
  - **Disk diffusion or MIC tests (e.g. Vitek, MicroScan)**
  - **BHI-vancomycin screen plate**
- **VRE surveillance**
  - **Culture media with vancomycin; sub primary specimens (e.g. stool) onto this**

## *E. faecalis* (blood)

| | |
|---|---|
| **ampicillin** | **S** |
| **vancomycin** | **S** |
| **gent syn** | **R** |
| **strep syn** | **S** |

**"Serious enterococcal infections need combination therapy with amp, pen, or vancomycin plus an aminoglycoside. Synergy occurs only when both drugs are susceptible."**

## *E. faecium* (blood)

| | |
|---|---|
| **ampicillin** | **R** |
| **vancomycin** | **R** |
| **gent syn** | **R** |
| **strep syn** | **R** |

**"VRE isolated; Infectious Diseases consult suggested"**

## *E. faecium* (blood)

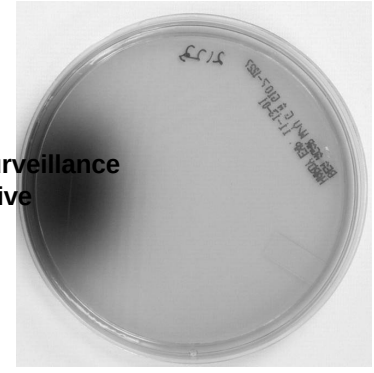
| | MIC (µg/ml) | |
|---|---|---|
| **ampicillin** | **>64** | **R** |
| **chloramphenicol** | **8** | **S** |
| **ciprofloxacin** | **4** | **R** |
| **doxycycline** | **2** | **S** |
| **linezolid** | **1** | **S** |
| **quin/dalfo** | **0.5** | **S** |
| **rifampin** | **8** | **R** |
| **vancomycin** | **>32** | **R** |
| **gent synergy** | | **R** |
| **strep synergy** | | **R** |

## *E. faecium* (urine)

| | |
|---|---|
| ampicillin | R |
| ciprofloxacin | R |
| nitrofurantoin | S |
| tetracycline | R |
| vancomycin | R |

VRE Stool Surveillance
Positive

VRE Stool Surveillance
Negative



## Stool Surveillance Report

Many *Enterococcus faecium*

"VRE isolated; please check Infection Control policy"

# Extended-spectrum b-lactamases (ESBLs)*

*enzymes that destroy extended-spectrum b-lactam drugs

ESBLS

## ESBLs – Testing

- Organisms:
  *E. coli, Klebsiella* spp., (others??)
- Screen test:
  Look for decreased susceptibility (small zone or elevated MIC) to extended-spectrum ß-lactam agents
- Confirmatory test:
  ß-lactam activity restored by the ß-lactamase inhibitor clavulanic acid
  - If positive, must change "S" result to "R" for any penicillin, cephalosporin, or aztreonam

## *Klebsiella pneumoniae* ?ESBL

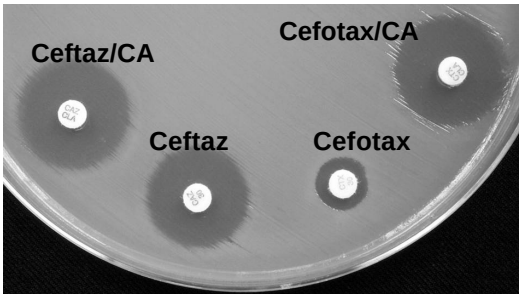
PRELIM:

| | MIC (µg/ml) |
|---|---|
| cefoxitin | 1 S |
| ciprofloxacin | 0.5 S |
| imipenem | £ 0.25 S |
| pip-tazo | 8 S |
| am, cfaz, gm, T-S | R |

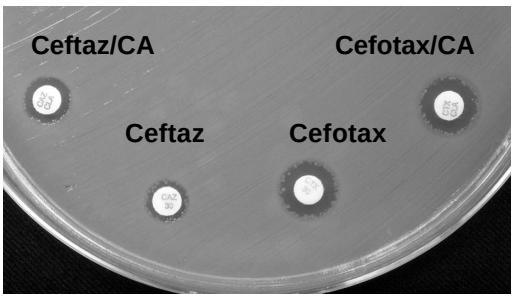
***hold cefepime, cefotaxime if "S"**

"This *K. pneumoniae* is suspicious for extended-spectrum beta-lactamase (ESBL) production; confirmatory tests pending."

## ESBL Confirmatory Test




## ESBL Confirmatory Test




## *Klebsiella pneumoniae* ESBL

FINAL:

| | MIC (µg/ml) |
|---|---|
| cefepime | ~~2~~ S R |
| cefoxitin | 1 S |
| cefotaxime | ~~1~~ S R |
| ciprofloxacin | 0.5 S |
| imipenem | 0.25 S |
| pip-tazo | 8 S |
| am, cefaz, gent, T-S | R |

"Confirmatory tests for this *K. pneumoniae* indicate unusual resistance [extended-spectrum beta-lactamase (ESBL) production]; Infectious Diseases consult suggested."

## *…More report examples*

*…More*

## Throat Culture

**Many Group A Streptococcus**

**"Group A Streptococcus remains universally susceptible to penicillin"**

**Specimen: Anovaginal**
**Test: Prenatal screen**

## Group B Streptococcus

**"Group B Streptococci are susceptible to ampicillin, penicillin and cefazolin, but may be resistant to erythromycin and/or clindamycin. Contact laboratory if erythromycin and/or clindamycin testing is needed."**

## *S. pneumoniae* (blood)

| | MIC (µg/ml) |
|---|---|
| ceftriaxone (meningitis) | 1 I |
| ceftriaxone (non-meningitis) | 1 S |
| erythro, trim-sulfa | R |
| levofloxacin | 0.5 S |
| penicillin | 1 I |
| vancomycin | 0.5 S |

**"Use of cefotaxime or ceftriaxone in meningitis requires therapy with maximum doses. High dose IV pens (e.g. at least 2 mil U every 4 h in adults with normal renal function) or amp are effective in treating pneumococcal pneumonia due to strains in the penicillin "int" category."**

## Blood Culture

**"Coagulase-negative staphylococcus isolated from one culture only. Susceptibility testing is not routinely done. If testing is indicated, please contact lab within 24 h."**


## Sputum Culture

**GS:**

- Many oral flora
- Many WBCs
- Many GNR

**1 potential pathogen**
**Perform AST**

**Culture:**

- Many Normal Flora
- Many *Klebsiella pneumoniae*

## Leg Wound Culture

**GS:**

- Many GPC clusters
- Many pleomorphic GPR

**Culture:**

- Many coag-neg staphylococci*
- Many diphtheroids
- Few *E. coli**
- Few *Proteus mirabilis**

*"Susceptibility results reported per Dr. Jones' request."

## Local Cumulative Antibiogram Report

Antibiograms

## Community Hospital Antibiogram 2002 – Exmp.

| | % Susceptible | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Am | Cf | Ctx | Cip | Gm | Pp | T-S |
| *E. coli* | 729 | 61 | 92 | 95 | 92 | 97 | 66 | 76 |
| *E. cloacae* | 144 | - | - | 71 | 95 | 88 | 65 | 84 |
| *P. aerug* | 221 | - | - | 10 | 76 | 88 | 91 | - |

## NCCLS M39-A Guideline

### "Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data"

- May 2002
- Guide MDs on EMPIRIC THERAPY
- Additional reports may be needed for infection control

## M-39A Recommendations

- Analyze/present data annually
  - Sufficient to GUIDE EMPIRIC THERAPY
- Include only species with ³ 10 isolates
- Include diagnostic (not surveillance) isolates
- Exclude duplicates - include 1st isolate/patient, irrespective of
  - body site, antimicrobial pattern
- Include only drugs routinely tested

## M-39A Recommendations (con't)

- Calculate %S (do not include %I)
- Special circumstances
  - *S. aureus* – all and MRSA subset
  - *S. pneumoniae* - %S and %I (penicillin)
  - *S. pneumoniae* – meningitis, non-meningitis (cefotaxime / ceftriaxone)
  - Viridans *streptococcus* - %S and %I (penicillin)

## Antibiogram 2002 – Exmp.

| | % Susceptible | | | | | | |
|---|---|---|---|---|---|---|---|
| | N | Clin | Ery | Ox | Pen | T-S | Van |
| all SA | 1317 | 80 | 50 | 68 | 9 | 97 | 100 |
| MRSA | 449 | 44 | 4 | 0 | 0 | 94 | 100 |

## Antibiogram 2002 – Exmp.

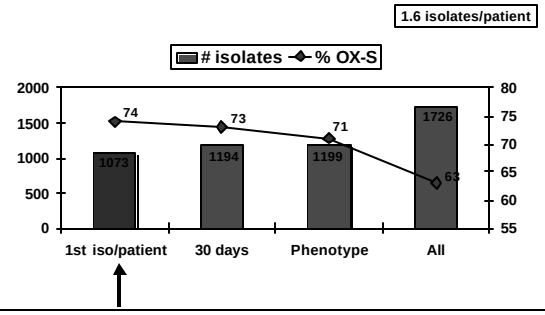
| | % Susceptible | | | | | |
|---|---|---|---|---|---|---|
| | N | Cftrx | Ctx | Ery | Levo | Pen |
| *S. pneumoniae* | 107 | - | - | 65 | 100 | 65* |
| meningitis | | 88 | 90 | - | - | - |
| non-meningitis | | 97 | 96 | - | - | - |

*Susc = MIC £0.06 m g/ml
Non-susceptible includes: 20% Int (MIC 0.12-1.0 m g/ml)
15% high-level Res (MIC >1.0 m g/ml)

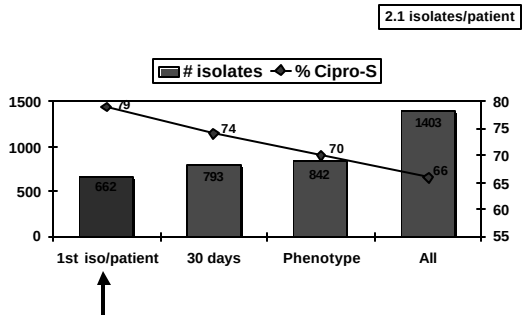
## Limitations M39-A

- Will not identify very unusual phenotype if this is not the "first" isolate on the patient (e.g. VISA)
  - Daily QA checks should catch these
  - Option to additionally search entire database
- Significant Lab Computer limitations
  - Diagnostic test system (e.g. MicroScan, Vitek)
  - Laboratory Information System (LIS) (e.g. Cerner, Meditech, Mysis, etc.)
  - NCCLS is working with vendors to obtain assistance

## *S. aureus* - Oxacillin




## *P. aeruginosa* – Ciprofloxacin




## *P. aeruginosa* – Ciprofloxacin

***Variable results from analysis of single dataset***

| | N | %S | %I | %R |
|---|---|---|---|---|
| 1st iso /pt | 662 | 79* | 7 | 14 |
| All | 1403 | 66 | 11 | 23 |

*M39-A recommendation

**Problem: testing broad-spectrum agents only on isolates resistant to narrower-spectrum agents…**

| | *P. aeruginosa* % Susceptible | | | |
|---|---|---|---|---|
| | N | Cip | Ctaz | Gm | Imip |
| *Hospital A* | 225 | 81 | 88 | 79 | 87 |
| *Hospital B* | 199 | 84 | 85 | 83 | 51* |

*Imipenem only tested on ceftazidime-R isolates (n=29)

**Problem: large number of urine isolates can dilute data….**

| | *E. coli* % Susceptible | | | |
|---|---|---|---|---|
| | N | Ctx | Cipro | Gm | T-S |
| *All isolates* | 2993 | 99 | 92 | 93 | 76 |
| *Urine only* | 2799 | 99 | 93 | 93 | 77 |
| *Excl urine isolates* | 248 | 93 | 83 | 90 | 60 |

**Problem: testing small numbers of isolates may reflect an intermittent resistant clone…**

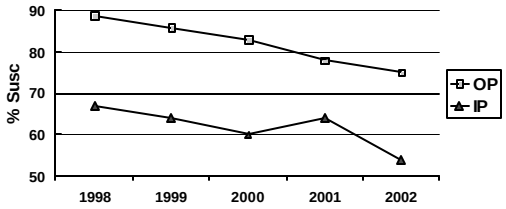
| | *Morganella morganii* % Susceptible | | | | |
|---|---|---|---|---|---|
| | N | Ctx | Cipro | Gm | T-S |
| *Hospital A* | 84 | 86 | 92 | 96 | 89 |
| *Hospital B** | 22 | 10 | 100 | 10 | 10 |

***small hospital that had an outbreak of *M. morganii* in MICU during a 4 week period**

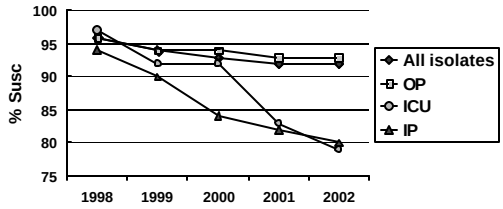
**Problem: how to report VRE?? Not all enterococci are identified to species level…**

| | vancomycin | |
|---|---|---|
| | N | % Susc |
| *E. faecium*-all | 226 | 9 |
| *E. faecium* -bld | 53 | 36 |
| *Enterococcus* spp.– bld | 111 | 71 |
| *E. faecium*-stool | 92 | 0 |
| *Enterococcus* spp.-all | 1144 | 79 |

**Trend Example 1998-2002**
**%S for *S. aureus* - Oxacillin**
***IP vs. OP***




**Trend Example 1998-2002**
**%S for *E. coli* – Ciprofloxacin**
***All and OP, ICU, IP***




**So, is a 18% decrease from 2002 to 2003 in %S of gentamicin for *P. aeruginosa* due to:**

- **Antibiogram calculation artifact?**
- **Infection control issue?**
- **Antibiotic utilization issue?**
- **Change in patient mix?**
- **Other?**

**95% Confidence Intervals for %S with Selected Sample Sizes**

| Sample size | 50% S | 90% S |
|---|---|---|
| 10 | 19-81 | 55-100 |
| 100 | 40-60 | 82-95 |
| 1000 | 47-53 | 88-92 |

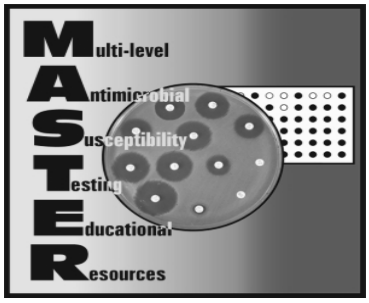
## What's Next for M39 ??

- **Expand suggestions for:**
  - **"Highlighting" certain data points**
  - **Specific presentation of data subsets (e.g., inpatient vs. outpatient)**
  - **Plotting data from year to year**
  - **Use of statistics (will provide table) to help determine significance of "x% change" in %S for "N isolates" from year to year**

## What Can You Do in Your Facility re: our Antimicrobial Resistance Dilemma?

- **Interact with your laboratory**
  - **Exchange "scientific" information**
  - **Communicate your needs (e.g. immediate notification of select resistance results such as MRSA, VRE)**
  - **Develop policies as a team and "test" policies**
- **Interact with clinicians**
  - **Encourage culturing**
  - **Suggest use of AST reports and antibiograms to help in therapy decisions**
- **Maintain awareness of resources for information on antimicrobial resistance and share this with your microbiology laboratory, please!**

Thank you!




**Visit this site and order "FREE": CD ROM**

**www.phppo.cdc.gov/dls/master/default.asp**

**Understanding Antimicrobial Resistance in Your Facility:**
**the Patient Report and the Cumulative Antibiogram**

Reference Material

**Laboratory-oriented:**

http://www.phppo.cdc.gov/dls/master/default.asp
MASTER (multilevel antimicrobial susceptibility educational resource) website!!!
-Includes case studies, Q&A, literature review and more
-describes how to obtain the new and "free" CDC CD-ROM on antimicrobial susceptibility testing

http://www.cdc.gov/ncidod/hip/Lab/LAB.HTM
CDC antimicrobial susceptibility testing fact sheets

Surveillance for Emerging Antimicrobial Resistance Connected to Healthcare (S.E.A.R.C.H.)
Confirmatory Reference Testing
Provides instructions for reporting VISA or VRSA to Public Health Departments.
http://www.cdc.gov/ncidod/hip/ARESIST/search.htm

http://www.asm.org/division/c/index.htm
ASM Division C (clinical microbiology) website includes "Askit" feature.. you can ask any question about clinical microbiology here!!!

**Others:**

http://www.cdc.gov/drugresistance/
CDC drug resistance
CDC Campaign to Prevent Resistance in Healthcare Settings

http://www.cdc.gov/ncidod/hip/ARESIST/visa_vrsa_guide.pdf
Investigating VISA and VRSA – A Guide for Health Departments and Infection Control Personnel

http://www.idsociety.org/
Infectious Diseases Society of America (IDSA)

http://www.tufts.edu/med/apua/
Alliance for Prudent Use of Antibiotics (APUA)

**Text References**

Gilbert, D. N., R. C. Moellering, and M. A. Sande (eds). 2003. *The Sanford Guide to Antimicrobial Therapy, 2003*. 33rd ed. Antimicrobial Therapy, Inc., Hyde Park, VT. (www.Sanfordguide.com)

Isenberg, H. I. (ed). 1998. *Essential Procedures in Clinical Microbiology*. Section 5. ASM Press, Washington, DC. (new edition of "Clinical Microbiology Procedures Handbook" anticipated early 2004)

Mandell, G. L., J. E. Bennett and R. Dolin. 2000. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*, 5th edition. Churchill Livingston, Philadelphia.

Murray, P. R., E. J. Baron, J. H. Jorgensen, M. A. Pfaller, and R. H. Yolken, (eds). 2003. *Manual of Clinical Microbiology*, 8th ed. pp. 1037-1212. ASM Press, Washington, DC. (see www.asmpress.org)

NCCLS Standards (www.nccls.org)

- M2-A8 and M100-S13 (M2). 2003. Performance standards for antimicrobial disk susceptibility tests. Eighth edition. Approved Standard.

- M7-A6 and M100-S13 (M7). 2003. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Sixth edition. Approved Standard.

- M39-A. 2002. Analysis and presentation of cumulative antimicrobial susceptibility test data. Approved Guideline.

**Notes:**