Implementation of NCCLS Antimicrobial Susceptibility Testing Standards

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Role of AST in Clinical Microbiology

- Data used to manage therapy for infections in individual patients
- Guidance for empiric therapy
- Basis for infection control activities
- Used in local, regional, and national databases to evaluate trends in emerging resistance

NCCLS AST Standards Provide:

- Methods for antimicrobial susceptibility testing (disk diffusion, MIC, screen tests)
- Interpretive criteria for results (breakpoints)
  - Susceptible, Intermediate, Resistant
- Quality control, quality assessment
- Recommendations for reporting results
  - Report first line drugs before more expensive and potentially more toxic agents

NCCLS AST Documents

- M2 – Disk diffusion document
- M7- MIC document
- M11- Anaerobe document
- M23 – Development of in vitro test criteria and quality control ranges
- M39 – Antibiogram document
- M100- Tables (updated annually)

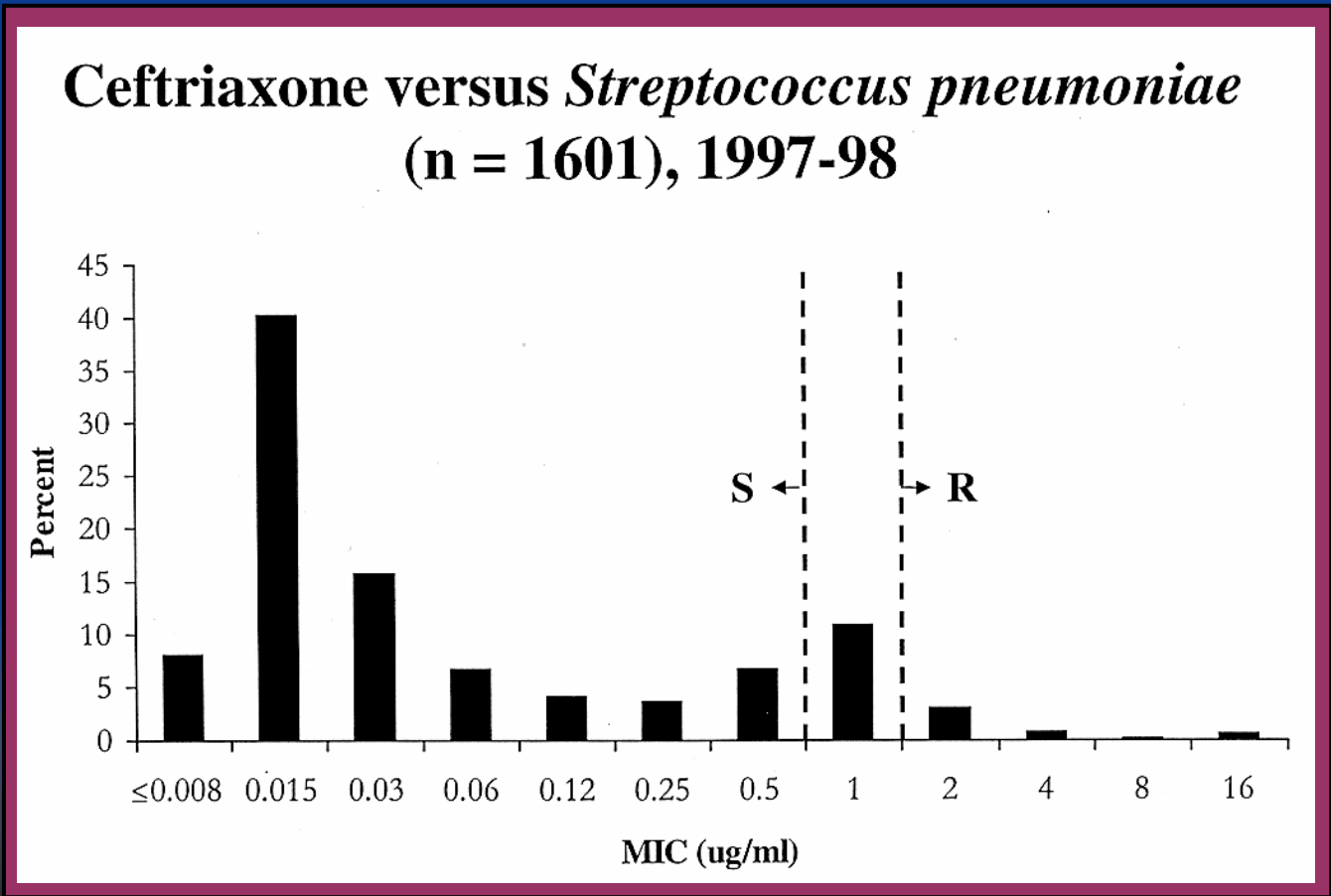
College of American Pathologists Requirements

- Lab should have up-to-date NCCLS standards
- Methods documents (M2 and M7) updated every three years
- M100 Tables updated every year
  - Breakpoints for new drugs
  - Revised breakpoints for older drugs
  - New screening tests
  - Clarifications of testing methods

Establishing Breakpoints

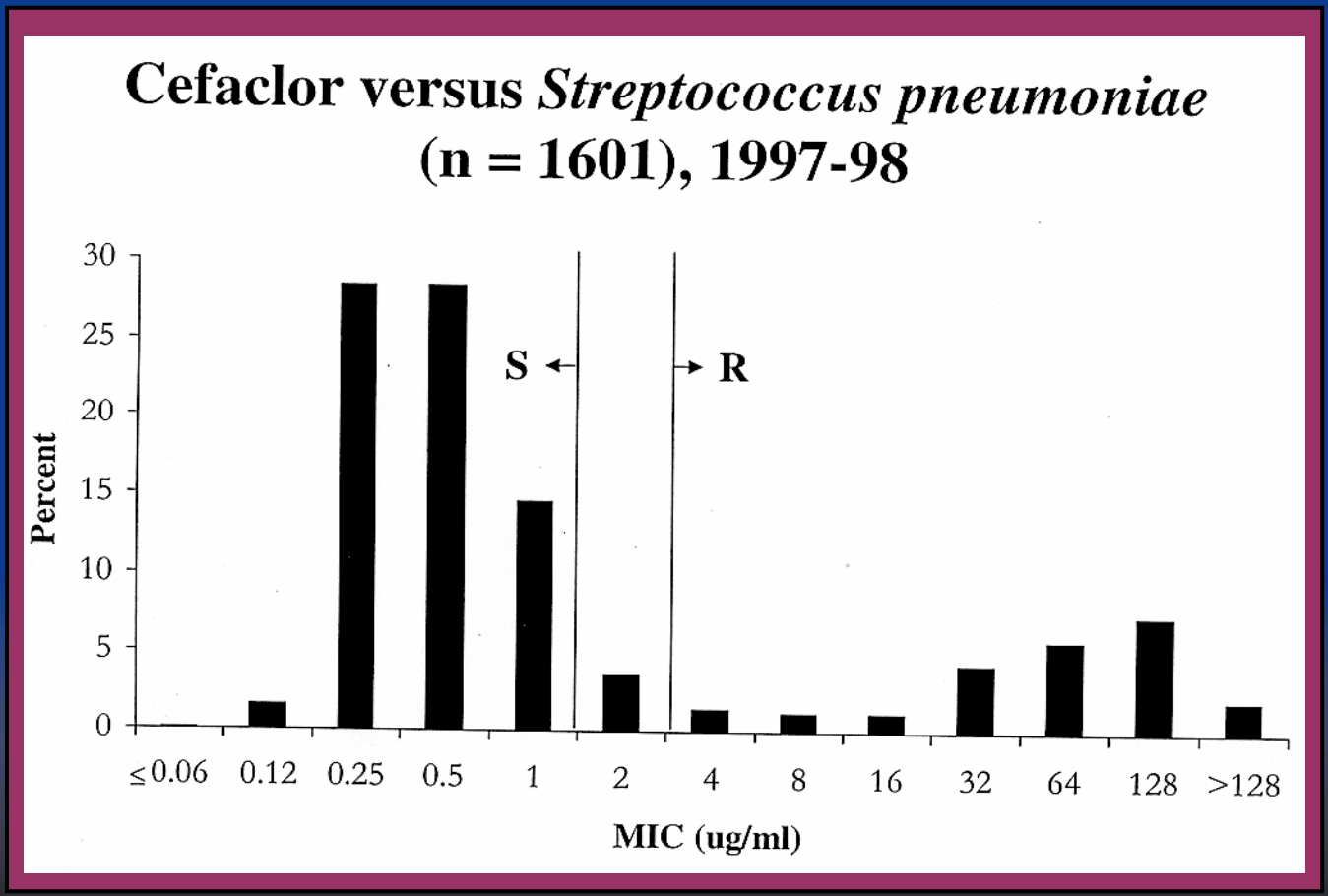
- Population distributions
  - **Surveys of large numbers of susceptible and resistant organisms**
- Pharmacokinetics and pharmacodynamics
  - **Achievable blood and CSF levels, clearance of drugs, toxicities**
- Clinical data
  - **Validation that proposed MIC and disk diffusion breakpoints have predictive value**
- Conflicts among these three are common

Ceftriaxone MIC Distribution for Pneumococci



Note location of susceptible breakpoint; data shows efficacy for meningitis good penetration in CSF

Cefaclor MIC Distribution for Pneumococci



Very different PK/PDs and clinical efficacy data account for differences

Our AST Methods Are Far from Complete

- Defined methods and defined breakpoints
  - *E. coli* and ampicillin
- Defined methods and breakpoints, but often requiring additional testing
  - *S. aureus*; oxacillin, vancomycin
  - *Klebsiella pneumoniae*; extended-spectrum beta-lactamases

The Problems

- Defined methods, but lacking quality control ranges or defined breakpoints
  - *Enterococcus faecium* and daptomycin
- Defined methods, but no breakpoints and no quality control ranges
  - *Neisseria meningitidis* and penicillin
- No methods, no breakpoints, no quality control
  - *Corynebacterium* species

NCCLS Responses

- *Enterococcus faecium* and daptomycin
  - New breakpoints to be published in Jan 2005
- *Neisseria meningitidis* and penicillin
  - New Table devoted totally to *N. meningitidis* in Jan 2005 (10 drugs)
- No methods, no breakpoints, no quality control for *Corynebacterium* species
  - New NCCLS document in development on testing of fastidious and infrequently isolated organisms (Jan 2006)

Sources of Information Regarding What Antimicrobial Agents to Test

- NCCLS guidelines (M2/M7 Tables 1 and 2)
- FDA product inserts (www.fda.gov)
- The Sanford Guide to Antimicrobial Therapy
- Clinical practice guidelines from professional societies (IDSA, ATS, etc.)
- Physician's desk reference
- Peer-reviewed literature
- Medical Letter

An Example Showing How NCCLS Could Improve: Testing *Gemella* species

- Case of native valve infective endocarditis caused by *Gemella haemolysans*
- Physician wants assurance that penicillin therapy plus an aminoglycoside is best option
- *Gemella* is not in NCCLS guidelines
- What approach would you take?

Gemella endocarditis: Questions to Ask

- Is it clinically relevant to patient management?
- Are their NCCLS guidelines for similar types of organisms that might apply?
- Can I adequately control the medium and test conditions?
- Is there sufficient information available to interpret the results?

Addressing the Questions

- Answers will affect therapy
- Could use NCCLS non-pneumococcal streptococcus guidelines; some strains require blood, so use MH broth + 5% LH blood (document says to peform MICs if necessary)
- *S. pneumoniae* ATCC 49619 used for Quality control
- No interpretive criteria available

What To Do?

- Report MICs without interpretations
  - No MICs were obviously in the "resistant" or "susceptible"
- Add comment that no interpretive criteria are available for this organism
- Suggest Infectious Disease or Pharmacy Consultation as described in document M100
- This process could be better explained in NCCLS documents

Other Helpful NCCLS Comments: Urinary Tract Pathogen

"Routine testing of urine isolates of *Staphylococcus saprophyticus* is not advised because infections respond to concentrations achieved in urine of antimicrobial agents commonly used to treat acute, uncomplicated urinary tract infections (e.g., nitrofurantoin, trimethoprim/sulfamethoxazole, or a fluoroquinolone)."

NCCLS Document M100, 2004

Are NCCLS AST Standards Responsive to Customers' Needs?

- Annual M100 supplements includes a summary of major changes (additions and deletions)
- Each M100 document has section of "Comments and Responses".
- Provides to questions raised by users regarding test methods or breakpoints
- Documents are conservative. Proposed changes undergo considerable study

Who submits data for consideration by NCCLS?

- Pharmaceutical industry
  - Proposed breakpoints for new drugs
  - Revisions to existing breakpoints
- Government
  - Public health warnings, ESBLs, VRSA screening tests
- Academia
  - PK/PD data; Monte Carlo simulations
- Individual microbiologists

CONCLUSIONS

- The goal of AST is to generate accurate and meaningful results
- NCCLS standards provide a structure for testing and reporting
- Feedback is continuous to NCCLS headquarters
- Questions often redirected to AST Subcommittee members; answers published annually
- The system appears to work slowly but well