Antimicrobial Therapy: Pitfalls, Problems, and Stewardship

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Outline
• Hospital acquired infections overview
• Antibiotic resistance
  • Global issues
  • Community hospital experience
• Antibiotic class review
• Antibiotic susceptibility
• Antibiograms
• Stewardship
• Influenza vaccine mandate

Impact of Hospital-Acquired Infections
• 5-10% of hospitalized patients develop a HAI
  • 90,000 deaths per year
  • $4.5 billion per year
• Risk of serious HAI complications are highest for patients requiring intensive care
• Based on CDC data, the number of HAIs per 1000 patient-days increased by 40% between 1975 and 2005
  • Sicker patient population
  • More complex procedures and equipment
  • Increasing antimicrobial resistance
  • Decreasing LOS relative to severity of illness

Risk Factors for Health Care-Associated Infections
• Hospitalization for ≥ 2 d in preceding 90 d
• Residence in NH or LTCF
• Home infusion therapy, including antibiotics
• Long-term dialysis within 30 d
• Home wound care
• Family member with MDR pathogen

Clinical situations which will promote the emergence of drug resistance
• Overuse of antibiotics
• Unnecessary treatment
• Longer length of treatment
• Repeated courses of rx
• Inadequate dosing
• Broader spectrum
• Excessive use of a single agent in a closed unit
• Inadequate debridement / drainage
• Indwelling foreign body
• Cross-transmission

Impact of Use in the Food Industry
Mechanisms of Antimicrobial Resistance

Crisis in Antimicrobial Drug Development

Trends in Antimicrobial Resistance 2012: ESKAPE pathogens

Vancomycin-resistant Enterococcus
Prevalence of VRE
Stamford Hospital 2009-2012

Burden of *Staphylococcus aureus* Infections in the United States

- 292,045 inpatient stays per year in US due to Staph infections (CDC)
- 0.8% of all inpatients
- 120,000 cases MRSA per year
- MRSA accounts for up to 70% of hospital-acquired Staph. aureus infections
- Patients with MRSA infection have
  - 3 times length of hospital stay (14.3 vs 4.5 days)
  - 3 times total charges ($48,824 vs $14,141)
  - 5 times risk of hospital death (11.2% vs 2.3%)


European Approach to Controlling HA-MRSA

- Netherlands: a national guideline was developed by a Dutch Working Party on Infection Control, and was adopted nationwide in 1988 when MRSA prevalence was >30%.
- Aggressive, “search & destroy” strategy.
  - Private room for MRSA patients
  - Use of masks, cap, gloves and gown for entering room
  - Pre-emptive Isolation & screening cultures of patients admitted from other countries with endemic MRSA
  - If MRSA case found, screen patients/HCW’s
  - Colonized patients and HCW’s are aggressively treated
  - Restrict use of broad-spectrum antibiotics.
- Prevalence of MRSA has remained <1% in the Netherlands despite multiple importations from other countries.


Impact of an “MRSA Bundle” on MRSA VAP and CLABSI rates: Hand hygiene, AST, contact precautions, culture change

Veterans Affairs (VA) Intensive Care Units.


Annual HA Infection Rate and Hand Hygiene
MRSA Prevalence at Stamford Hospital
Microbiology Lab data*

Prevalence of MRSA Stamford Hospital 2009-2012

Results of Active PCR Screening for MRSA

Extended Spectrum Beta-lactamases (ESBLs)

Infection Control Issues for ESBL-producing *K. pneumoniae*

Community acquired ESBL
Treatment of Infections Due to ESBL+ GNRs

- In vitro (laboratory), they may appear susceptible to beta-lactamase inhibitors, such as clavulanate, sulbactam, and tazobactam...but they are not (inoculum effect)
- Fluoroquinolone outcomes have been poor:
  - One study evaluated bacteremia caused by ESBL-producing Klebsiella that were susceptible to ciprofloxacin; Among seven patients treated with ciprofloxacin, five failed treatment and two had a partial response; patients treated with imipenem did much better (complete response in eight of ten)
- The only current proven therapeutic option for severe infections caused by ESBL-producing organisms is the carbapenems and tigecycline
- At the moment, there is no effective way to screen for enteric colonization with ESBLs

Hospital-acquired ESBL+ CAUTI

ESBL+ Isolates at Stamford Hospital

Carbapenems -- The Last Line of Defense?

Klebsiella pneumoniae Carbapenemases (KPCs)

- Carbapenems, have remained effective against most of the Enterobacteriaceae – including ESBL+ organisms – up until now.
  - e.g. ertapenem (Invanz), imipenem (Primaxin)
- KPCs
  - Confer resistance to all β-lactams including carbapenems
  - Usually co-resistant to multiple other agents
  - High mortality due to comorbidities and lack of effective treatment
  - Rx: polymyxin, fosfomycin, tigecycline

Rapid Spread of Carbapenem-Resistant Klebsiella pneumoniae in New York City

Detection and Spread of Escherichia coli Possessing the Human-Borne Carbapenemase KPC-2 in Brooklyn, New York
**Post-op infection**

Stamford MDRO Emergence 2010-2011

**Patient Numbers**

- 110 patients with ESBL E coli, 18 ESBL Klebsiella
  - 26 in 2010; 97 in 2011
  - 17 hospital-acquired
  - 45 community-acquired (hospitalized)
  - 61 out-patient isolates
- 14 patients with KPC Klebsiella
  - 2 patients 2009; 4 in 2010; 8 in 2011
  - 7 of the 14 seen in the last 6 months of 2011
- Many of the ESBL and most of the KPC patients have had other MRDOs (VRE, MRSA, C diff)

**KPC+ Isolates at Stamford Hospital**

**Post-op KPC+ infection**

**Antimicrobial Agents – Class Review**

**Major Antimicrobials**

- Beta-Lactams
  - Penicillins
  - Cephalosporins
  - Monobactams
  - Carbapenems
- Macrolides
- Clindamycin
- Aminoglycosides
- Quinolones
- Tetracyclines
- Vancomycin
- Metronidazole
- Polymyxin
- Novel Antibiotics
  - Linezolid (Zyvox)
  - Synercid
  - Daptomycin (Cubicin)
  - Tigecycline (Tygacil)
  - Fosfomycin (Monural)
**Beta-lactams**

- Bacterial cell walls are made of Peptidoglycan
  - Gram positives: peptidoglycan in the cell wall
  - Gram negatives: have an outer membrane made of lipopolysaccharide which has porins and drugs / chemicals must cross through the porins
- The enzyme that accomplishes the cross-linking of peptidoglycan are PBPs (penicillin-binding proteins)
- Beta-lactams: abx that block the PBPs (prevent cell wall cross-linking)
- Beta-lactamases: bacterial proteins that hydrolyze or bind to beta-lactam antibiotics
- Beta-lactamase inhibitors: block the bacterial beta-lactamases

**Penicillin G (and V)**

- Gram Positive: YES, streptococci, listeria, 10% of staph
- Gram Negative: NO
- Anaerobes: YES, gram positive (clostridium, actinomycyes, anaerobic strep)
- Atypicals: NO
- Miscellaneous: Spirochetes - Syphilis, borrelia

**What is appropriate use?**

- Used for aerobic gram positive infections: Gp A strep, Gp B strep, pneumococcal, and strep viridans group infections
- Anaerobic gram positive infections (esp. clostridium)
- Syphilis, Lyme disease

**Antistaphylococcal Penicillins:**

- IV Nafcillin, Oxacillin; po Dicloxacillin
- Gram Positive: YES for MSSA; not as good for strep
- Gram Negative: NO
- Anaerobes: NO
- Atypicals: NO

**What is appropriate use?**

- MSSA infection: These drugs are more rapidly and completely 'cidal' against MSSA than vancomycin

**Aminopenicillins: ampicillin, amoxicillin**

- Gram Positive: YES like penicillin; but more active against enterococcus
- Gram Negative: LIMITED: Proteus, some E coli, Neisseria Haemophilus
- Anaerobes: YES, gram positive, like penicillin
- Atypicals: NO
- Miscellaneous: Spirochetes- syphilis, borrelia

**What is appropriate use?**

- Equivalent to penicillin (more stable IV, amox better absorbed)
- Dental prophylaxis
- ENT infections
- UTI due to susceptible organisms
- Enterococcal infections (mainly E. fecaelis)

**Penicillins with Beta-lactamase inhibitors**

- IV Unasyn (amp-sulbactam), Timentin (ticar-clavulanate) and Zosyn (pip-tazobactam); PO Augmentin (amox-clavulanate)
- Gram Positive: YES: excellent. Not MRSA
- Gram Negative: YES: Timentin/Zosyn broader (enterobacter, morganella; piperacillin most active for pseudomonas)
- Anaerobes: YES: excellent
- Atypicals: NO

**What is appropriate use?**

- Mixed infections Skin and soft tissue,
- Pulmonary infections: aspiration; Healthcare acquired infections
- Intrabdominal infections
- Unasyn- for above the diaphragm; Zosyn for below

**Cephalosporins**

- Different B-lactam ring. “Generation” concept

<table>
<thead>
<tr>
<th>Photographic Index</th>
<th>IV</th>
<th>PO</th>
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</thead>
<tbody>
<tr>
<td>1st</td>
<td>Cephalexin -Keflex</td>
<td>Cefadroxil- Duracef</td>
</tr>
<tr>
<td>2nd</td>
<td>Cefaclor - Ceclor</td>
<td>Cefuroxime</td>
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<tr>
<td>3rd</td>
<td>Cefpodoxime -Vantin</td>
<td>Cefixime</td>
</tr>
<tr>
<td>4th</td>
<td>Cefepime</td>
<td>Cefaroline</td>
</tr>
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</table>
1st Generation Cephalosporins

Cefazolin IV; Cephalexin PO

Gram Positives: YES, excellent. Strep and MSSA/MRSA
Gram Negatives: LIMITED sensitive E. Coli, Klebs & Proteus
Anaerobes: NO
Atypical: NO

What is appropriate use?
Skin- cellulitis
Surgery- prophylaxis before elective surgery (except bowel)
Can use it for other infections like UTIs or bacteremias if you know the bug and it is sensitive

2nd Generation Cephalosporins

Variable activity within the group

Gram positive: SOME -- but less than first generation
Gram negative: YES – Cefoxitin and cefotetan good enteric
Anaerobes: YES – cefoxitin and cefotetan
Atypicals: NO

What is appropriate use?
Surgical prophylaxis prior to abdominal or GU surgery
Non-life-threatening mixed infections
Respiratory infections (cefuroxime)

3rd Generation Cephalosporins

Gram Positives: YES many Strep and pneumococcus:
variable for Staph; no enterococcus
Gram negative: YES excellent activity; only has pseudomonas activity
Anaerobes: NO
Atypicals: NO
Miscellaneous: Spirochetes (Lyme, syphilis)

What is appropriate use?
CNS infections
Community acquired pneumonia
Serious infections due to GNR
Neutropenic fever (ceftazidime)

4th Generation Cephalosporins: Cefepime

Most stable of all Cephalosporins. B-lactamases. Only IV

Gram Positive: YES, excellent, including MSSA
Gram Negative: YES, excellent
Anaerobes: NO
Atypicals: NO

What is appropriate use?
Serious infections in hospitalized patients
Mixed infections due to aerobic GNR and GPC
Neutropenic sepsis

4th Generation Cephalosporins: Ceftaroline

Very stable. Only IV

Gram Positive: YES, excellent, including MRSA
Gram Negative: YES, excellent, not pseudomonas
Anaerobes: NO
Atypicals: NO

What is appropriate use?
Mixed skin and soft tissue infections where MRSA is a concern
Other mixed infections
Possibly pneumonia where MRSA is a concern (not FDA approved)

Monobactams: Aztreonam

Beta-lactam with no cross-allergenicity to penicillin. Only IV

Gram Positive: NO
Gram negative: YES, aerobic
Anaerobes: NO
Atypicals: NO

What is appropriate use?
Aerobic GNR infections in hospitalized patients (esp Pen allergy)
Substitute for gentamicin in patients with renal insufficiency
### Carbapenems

**Imipenem, Ertapenem, Doripenem, Meropenem**

- Low cross-reaction with penicillin allergy. IV only.
- **Gram Positive**: YES except MRSA, +/− enterococcus
- **Gram negative**: YES, including ESBLs, except KPC, ertapenem not pseudomonas, acinetobacter
- **Anaerobes**: YES
- **Atypicals**: NO

**What is appropriate use?**

- Drug resistant infections in hospitalized patients
- Infections due to ESBL-producing GNR
- Other mixed infections where MDROs are a concern

### Macrolides

**Oral and IV: erythromycin, azithromycin, clarithromycin**

- **Gram Positive**: YES but weak. Increasing resistance
- **Gram Negative**: SOME – enterics (salmonella, campylobacter)
- **Anaerobes**: NO
- **Atypicals**: YES; and legionella
- **Miscellaneous**: Some atypical mycobacteria

**What is appropriate use?**

- Mild to moderate upper respiratory infections; GAS pharyngitis
- Atypical coverage for pneumonia (with ceftriaxone for example)
- Chlamydia, mycoplasma infections (STD)
- MAC infections (and others)

### Clindamycin

**Lincosamide antibiotic**

- **Gram Positive**: YES incl GAS, GBS, some CA-MRSA;
- **Gram negative**: NO
- **Anaerobes**: SOME – many Bacteroides are resistant
- **Atypicals**: NO

**What is appropriate use?**

- Skin and soft tissue infections where Staph aureus is a concern
- Other mixed infection due to gram positive / anaerobes
- Osteomyelitis?
- Gram positive sepsis as an adjunct (inhibits toxin production through protein synthesis inhibition)

### Tetracyclines

**Tetracycline HCl, doxycycline, minocycline (IV and PO)**

- **Gram Positive**: YES including CA-MRSA (mino and doxy)
- **Gram Negative**: YES (variable)
- **Anaerobic**: Weak
- **Atypicals**: YES; rickettsia, chlamydia, mycoplasma
- **Miscellaneous**: Some AFB activity; spirochetes

**What is appropriate use?**

- Skin and soft tissue when CA-MRSA suspect (mino and doxy)
- Respiratory infections, including CA-pneumonia (doxy)
- Atypical infections, including STD
- Lyme disease, syphilis

### Aminoglycosides

**Inhibit protein synthesis. Gentamicin, tobramycin, amikacin**

- **Gram Positive**: YES but only with beta-lactam for synergy.
- **Gram Negative**: YES, aerobic only. G/T resistance may be sensitive to Amikacin
- **Anaerobes**: NO
- **Atypicals**: NO
- **Miscellaneous**: some AFB coverage

**What is appropriate use?**

- In combination for GNR component of mixed infection
- Empiric treatment of GNR (e.g. urosepsis) -- then switch for toxicity
- As double coverage for GNR for synergy or broader coverage

### Fluoroquinolones

**Borad spectrum, for once or twice daily dosing; concentration dependent killing; good oral and IV bioequivalence**

- **Gram positive**: YES; cipro is less active
- **Gram negative**: YES; cipro is most active
- **Anaerobes**: Variable for moxi, levo
- **Atypicals**: Variable; excellent Legionella
- **Miscellaneous**: Good AFB coverage

**What is appropriate use?**

- Urinary tract and GI tract infections
- Respiratory tract infections as an alternative to first line agents (levofloxacin, moxifloxacin)
- Mixed and GNR infections according to sensitivities
- Limit use due to C. difficile risk
### Vancomycin

Old drug; maligned for its toxicity; slowly bactericidal

<table>
<thead>
<tr>
<th>Gram Positive</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaerobes</td>
<td>YES gram positives</td>
</tr>
<tr>
<td>Atypicals</td>
<td>NO</td>
</tr>
</tbody>
</table>

**What is appropriate use?**
- MRSA, MRSE infections – proven or suspected
- C. difficile (orally)
- For GPR/GPC coverage in severe penicillin allergy (esp enterococcus)

### Metronidazole

IV and PO; excellent tissue bioavailability

<table>
<thead>
<tr>
<th>Gram positive</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram negative</td>
<td>NO</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>YES, best coverage</td>
</tr>
<tr>
<td>Atypicals</td>
<td>NO;</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Protozoal activity</td>
</tr>
</tbody>
</table>

**What is appropriate use?**
- In combination for anaerobic component of mixed infection
- Bacterial vaginosis
- C difficile infections
- Amebic infections

### Sulfamethoxazole/Trimethoprim

Bactrim / Septra

<table>
<thead>
<tr>
<th>Gram positive</th>
<th>YES including CA-MRSA; not enterococcus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram negative</td>
<td>YES, enteric GNRs, Haemophilus, Moraxella</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>NO</td>
</tr>
<tr>
<td>Atypicals</td>
<td>Variable; PCP</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Pneumocystis, cyclospora</td>
</tr>
</tbody>
</table>

**What is appropriate use?**
- Skin and soft tissue when CA-MRSA suspect
- Bacterial respiratory infections (esp upper) as an alternate
- UTI
- PCP

### Novel Gram-positive Antibiotics

#### Linezolid (IV and PO) (oxazolidinones class; Zyvox®)

- **Bacteriostatic**
- Spectrum: Gram positive; Staph aureus including MRSA; enterococcus activity including VRE
- Not used for blood-stream infections (failures in line infections)
- Superior to vancomycin for MRSA pneumonia
- Unique side effect: leukopenia and thrombocytopenia

#### Dalfopristin and quinupristin (streptogramin class; Synercid®)

- **Bactericidal**
- Spectrum: Gram positive; Staph aureus including MRSA; E. faecium, including VRE, but not E. fecaelis
- Unique side effect: severe myalgias / arthralgias

### Daptomycin

A Cyclic Lipopeptide. IV only. Once daily

<table>
<thead>
<tr>
<th>Gram positive</th>
<th>YES, including MRSA and VRE (some)</th>
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<tbody>
<tr>
<td>Gram negative</td>
<td>NO</td>
</tr>
<tr>
<td>Anaerobic</td>
<td>NO</td>
</tr>
<tr>
<td>Atypical</td>
<td>NO</td>
</tr>
</tbody>
</table>

**What is appropriate use?**
- Used for Staph SSTI and bone infections
- Bloodstream infections/endocarditis due to MRSA/VRE infections
- Not pulmonary infections due to Staph
- Unique side effect: CPK elevation

### Tigecycline

A glycycline (IV only). Bacteriostatic.

<table>
<thead>
<tr>
<th>Gram Positive</th>
<th>YES including MRSA AND VRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram Negative</td>
<td>YES including ESBLs and KPCs</td>
</tr>
<tr>
<td>Anaerobic</td>
<td>YES</td>
</tr>
<tr>
<td>Atypicals</td>
<td>YES</td>
</tr>
</tbody>
</table>

**What is appropriate use?**
- Complicated intra-abdominal infections with MDROs
- Skin and soft-tissue (especially SSI with MDRO suspect)
- Pneumonia – not hospital acquired.
- **NOT** for bacteremia at this time (tissue levels)
Polymyxin

Polymyxin B and Colistin (polymyxin E). Polypeptides

<table>
<thead>
<tr>
<th>Gram positive:</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram Negative:</td>
<td>YES – may need combination rx due to rapid emergence of resistance – esp KPC, MDRO-acinetobacter</td>
</tr>
<tr>
<td>Anaerobic:</td>
<td>NO</td>
</tr>
<tr>
<td>Atypical:</td>
<td>NO</td>
</tr>
</tbody>
</table>

**What is appropriate use?**

Any site where it is active in vitro and nothing else available. Data mainly on pulmonary, CNS, urinary tract infections. Toxicity: nephrotoxic and neurotoxic potential.

Fosfomycin

Monurol; pyruvyl transferase inhibitor; interferes with cell wall synthesis

<table>
<thead>
<tr>
<th>Gram positive:</th>
<th>YES, mainly Enterococcus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram Negative:</td>
<td>YES -- including MDROs</td>
</tr>
<tr>
<td>Anaerobic:</td>
<td>NO</td>
</tr>
<tr>
<td>Atypical:</td>
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</table>

**What is appropriate use?**

Single dose treatment of lower UTI. Off label use for pyelonephritis due to MDRO. Off label use for MDRO osteomyelitis and potentially other sites, often as a second drug. Well tolerated; only PO form in US.

Antimicrobial Agents – Susceptibility Testing

**Purpose of Susceptibility Testing**

- **As a guide for treatment**
  - Sensitivity of a given microorganism to a known concentration of drug
  - Relative to its concentration in blood, body fluids or tissues
  - Predict success for failure of treatment
  - Sequestered sites are important caveat
    - Prostate, CSF, eye, abscess, bone, macrophage

- **As an epidemiological tool**
  - The evolution of resistance in major global pathogens (e.g., Salmonella, N. gonorrhoea, S. pneumoniae)
  - Surveillance of the susceptibility pattern of the prevalent hospital strains (e.g., Staphylococcus, Gram-negative bacilli)
  - Detection of emergence of resistance through new mechanisms
    - NDM, KPC, etc.

What Does the Laboratory Need to Know about Antimicrobial Susceptibility Testing

- What antibiotics to test?
- Which organisms to test?
- What methods to use?
- How to report results?

Choosing the Appropriate Antibiotic

- **Drugs for routine susceptibility tests:**
  - Primary: the drugs that are available in most hospitals and for which routine testing should be carried out for every strain
    - Basic report
    - Cascade reporting
    - Formulary restriction
  - Secondary: the drugs that are tested only:
    - at the special request of the physician
    - or when the causative organism is resistant to the first-choice drugs (if logistics limit number on primary panel)
    - or when other reasons (allergy to a drug, or its unavailability) make further testing justified
Factors affecting results of susceptibility testing

- Inoculum size used
- Timing of inoculation and incubation
- Size of plate / well
- Depth of agar
- Deterioration of antibiotic in disk / well
- pH of medium or incubation in CO2
- Composition of medium (e.g. calcium)
- Temperature of incubation
- Subjective assessment of growth / zone size
- Breakpoint testing limits
- Fastidious / slow growing / mucoid organisms
- Preferential enzyme testing
  - Direct: Beta lactamase or PBP2a
  - Indirect: D test, ESBL testing, Hodge test (for KPC)

Routine Susceptibility Tests

- Disk diffusion (Kirby Bauer)
- Broth micro-dilution MIC
  - NCCLS reference method
- Etest

Diffusion Method

- Disc diffusion method: The Kirby-Bauer test
  - 1966: Kirby, Bauer, Sherris, and Tuck → Antibiotic-impregnated filter paper disks
  - Demonstrated that the qualitative results of filter disk diffusion assay correlated well with quantitative results from MIC tests
  - Prepare 10⁸ CFU/ml bacterial inoculum
  - Streak plate, apply discs and incubate 18 hours
  - measuring size of "inhibition zone"
    - Correlates with MIC and designation as S, I, R

Dilution Method

- Minimum Inhibition Concentration (MIC)
  - The lowest concentration of antimicrobial agent that inhibits bacterial growth / multiplication
  - Minimum Bactericidal Concentration (MBC) or Minimum Lethal Concentration (MLC)
  - The lowest concentration of antimicrobial agent that allows less than 0.1% of the original inoculum to survive

Broth Dilution Method

- Procedure
  - Make dilutions (2-fold) of antibiotic in broth Mueller-Hinton, Tryptic Soy Broth
  - Add standardized bacterial inoculum
  - Incubation overnight
  - Turbidity visualization → MIC
  - Sub culturing of non-turbid tubes, overnight
  - Growth (bacterial count) → MBC

Broth Dilution Method

Day 2
- Record visual turbidity
- Subculture non-turbid tubes to agar plates (use 0.01 ml standard loop)
- MIC = 16 mg/l

Day 3
- Determine CFU on plates:
  - At 16 mg/l: > 700 CFU/ml
  - 0.1% of 5*10⁵ CFU/ml
- MBC = 32 mg/l
Micro broth Dilution Method

- Micro dilution plates:
  - "Micro dilution/ Micro broth dilutions"
  - 96 wells/ plate: simultaneously performed with many tests organisms/ specimens, less reagent required
  - Combined identification wells and antibiotic susceptibility wells

- Manually prepared
- Commercially prepared
- Frozen or Dried/ lyophilized
- Consistent performance but high cost
- May suffer from degradation of antibiotic during shipping and storage

Clinical Conditions when MICs are Useful

- Endocarditis
- Meningitis
- Septicemia
- Osteomyelitis
- Immunosuppressed patients (HIV, cancer, etc.)
- Prosthetic devices
- Patients not responding despite “S” Reports

The gradient technique, Etest®

- Etest is a well established method in microbiology laboratories around the world. The Etest technique comprises a predefined gradient of antibiotic concentrations on a plastic strip, and can be used to determine the Minimum Inhibitory Concentration (MIC) of antibiotics, antifungal agents and antimycobacterial agents.

MIC of the Bacteria can be read Directly

- E test – MIC Reports are helpful in Critical management decisions
  - Quantitative MIC data is a prerequisite for the management of critical infections with problematic organisms.
  - Penicillin:pneumococcus
  - Vancomycin:staph
  - Daptomycin:staph
  - Anaerobes
Antibiograms

Clinical and Laboratory Standards Institute (NCCLS) recommendations for cumulative antibiogram preparation.

- Analyze and present data at least annually
- Include only species with at least 30 isolates tested
- Include diagnostic, not surveillance, isolates
- Include results only for drugs that are routinely tested
- Include the first isolate per patient in the period analyzed, irrespective of the body site from which the specimen was obtained or the antimicrobial susceptibility pattern
- Calculate the percentage susceptible. Do not include the percentage of isolates with intermediate susceptibility.

For *Streptococcus pneumoniae*, calculate and list both the percentage susceptible and the percentage of isolates with intermediate susceptibility for penicillin; calculate both the meningitis and nonmeningitis breakpoints

For *viridans streptococci*, calculate and list both the percentage susceptible and the percentage of isolates with intermediate susceptibility for penicillin

For *Staphylococcus aureus*, calculate and list the percentage susceptible for all isolates, as well as for the subset of methicillin-resistant *S. aureus*

Stamford Trifold Antibiogram

When using cumulative antibiogram data, you should know that

- Cumulative antibiograms compiled following NCCLS recommendations are a useful guide empirical therapy of initial infections
- The percentage susceptible for a specific drug-pathogen combination will be impacted by patient type and location, culturing practices, specimen collection practices, and laboratory policies
- If some drugs included in the cumulative antibiogram are only tested on selected isolates, the data will be skewed (e.g. enterococcus)
- If repeat isolates are not eliminated from analysis, the percentage susceptible will in most cases be lower than if repeat isolates are eliminated
When using cumulative antibiogram data, you should know that:

- Depending on the method used to eliminate repeat isolates, the percentage susceptible may vary.
- Resistance-phenotype based approaches are highly dependent on local culturing and susceptibility testing practices, and they tend to reflect the results of patients with a higher percentage of resistant bacteria.
- If the sample number is small, the 95% CI will be large; for example, for a sample of 50 isolates, increases or decreases in the percentage susceptible as great as 20% may not be statistically significant.
- Not all clinical laboratories currently comply with current NCCLS Standards, because of software, staffing and financial limitations.

**Stamford Hospital Antibiogram 2011**

<table>
<thead>
<tr>
<th>Percent Susceptible (broth dilution MIC's, mcg/ml)</th>
</tr>
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<tbody>
<tr>
<td>E. coli</td>
</tr>
<tr>
<td>AMP ≤ 4</td>
</tr>
<tr>
<td>OXA ≤ 4</td>
</tr>
<tr>
<td>Van ≤ 4</td>
</tr>
<tr>
<td>CIP ≤ 4</td>
</tr>
<tr>
<td>CAZ ≤ 8</td>
</tr>
<tr>
<td>GM ≤ 16</td>
</tr>
<tr>
<td>TS ≤ 0.125</td>
</tr>
</tbody>
</table>

**Stamford Unit-specific Antibiogram 2011**

<table>
<thead>
<tr>
<th>Mortality Associated with Initially Inappropriate Therapy</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Inadequate Antimicrobial Treatment Infections in the ICU</th>
</tr>
</thead>
</table>

**Stamford Unit-specific Antibiogram 2011**

<table>
<thead>
<tr>
<th>Percent Susceptible (broth dilution MIC's, mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
</tr>
<tr>
<td>AMP ≤ 4</td>
</tr>
<tr>
<td>OXA ≤ 4</td>
</tr>
<tr>
<td>Van ≤ 4</td>
</tr>
<tr>
<td>CIP ≤ 1</td>
</tr>
</tbody>
</table>

**Mortality Associated with Initially Inappropriate Therapy**

<table>
<thead>
<tr>
<th>Critical Ill Patients With VAP or Aspergillus, Severe Septicaemia, or Community-Acquired bloodstream infection</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>20%</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>*Bacteremia within 48h of leakage</td>
<td>*Bacteremia within 48h of leakage</td>
<td>*Bacteremia within 48h of leakage</td>
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<td>*Bacteremia within 48h of leakage</td>
</tr>
</tbody>
</table>

* *P < .001: statistically significant

Antimicrobial Stewardship

Antibiotic Use Facts

- 30%-50% of hospitalized patients at any given time receive antimicrobials
- 1/3 to 1/2 are inappropriate or unnecessary
- Leads to
  - Resistance
  - Increased morbidity/mortality
  - C. difficile
  - Increased costs
- Antimicrobial use is the key driver of resistance.
- This selective pressure comes from a combination of overuse... and also from misuse


Overview of Antibiotic Stewardship

- In the hospital setting, it is estimated that as much as 50% of antibiotic use is unnecessary
  - Antibiotic misuse fosters the development and spread of antibiotic resistance
- Antibiotic stewardship involves limiting inappropriate antibiotic use while optimizing the selection, dose, duration, and route of therapy with the most appropriate drug for the patient
- Stewardship programs have been associated with improved antibiotic use and reduced costs

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SHEA/IDSA/PIDS Policy Statement

- Antimicrobial stewardship programs should be required through regulatory mechanisms
  - Creation of inter-professional stewardship team
  - Limited formulary
  - Clinical guidelines
  - DUE processes
  - Antibiogram dissemination
  - Report to AUR module in NHSN
  - Prospective surveillance for detection of drug resistance
- Antimicrobial stewardship should be monitored in ambulatory healthcare settings
  - Education about antimicrobial resistance and stewardship must be provided for all HCW
  - Antimicrobial use data should be collected and reported to constituents (C-suite, physicians, other providers, community)
- Research on antimicrobial stewardship is needed

Motivation for a Stewardship Program

- Consumers want transparency - public reporting
- Legislative Mandates to Report Quality
  - Medicare Prescription Drug Improvement and Modernization Act of 2003
  - Deficit Reduction Act of 2005
    - Tied 2% of Medicare annual payment update to public reporting of hospital quality measure and gave Secretary of HHS authority to expand measures
  - Tax Relief and Health Care Act of 2006
  - Hospital ambulatory performance measurement
  - Patient Protection and Affordable Care Act of 2010
  - Measurement with accountability works!
    - SCIP measures now 95% nationally
    - MDRO problem (XDR and TDR microorganisms)
  - It’s the right thing to do

Quality Measures for Antibiotic use

- Clinical outcomes - e.g. survival, LOS
- Financial outcomes - e.g. cost per case, drug costs
- Microbiology outcomes - e.g. drug resistance
- Process measures - e.g. guideline compliance
- Mandated measures - e.g. SCIP
- Lack of evidence to support many of these
- Unintended consequences of targets
  - e.g. pneumonia core measures
Active Stewardship Program
- Is not a self-sustaining process
- Computer-assisted algorithms for antibiotic prescribing (LDS)
- Decision support
- Realtime feedback and consultation
- Stewardship team rounding
  - Tailor to the institution
  - Physician involvement is key to success
- Requires C-suite buy-in
  - Resources

Programmatic oversight ideally should include
- Infectious diseases clinician
- Infectious diseases-trained clinical pharmacist
- Medical staff from each hospital department
- Representative from the clinical microbiology lab
- Pharmacists
- Representative from infection prevention program
- Information systems expert

The Devil is in the Development
- Ideal inpatient antibiotic quality measures would
  - Improve practice (maybe not outcomes)
  - Not have unintended consequences
  - Be practical in any healthcare setting
  - Be used by many audiences, stewardship programs, practitioners, accreditation/regulatory groups
  - Measures must be applicable in any hospital
    - Adult, pediatric, large, small
  - Compliance must be relatively easy to assess by someone with no infectious disease training and using tracer methods.
  - Develop measures by consensus and refine with experience
  - Start small and add to achieve comprehensive program
  - Broader measures favored
  - Unfortunate lack of evidence to establish targets

Measures / Interventions - Tier 1
- A multidisciplinary program is in place
  - Antibiotic orders should have an indication (order sheets, hard stops, CPOE)
  - 72 hour review of selected agents (review by stewardship team, or Pharm D, or infectious diseases, automated reordering-stop orders at 72 hours)
  - DUEs followed by peer review process
  - Positive BC review within 24 hours for appropriateness of rx
  - Compliance with treatment guidelines (as available)
  - Antibiotic use measures
    - DOT (days on therapy) or DDD (per patient day)
    - Antibiotic costs (per patient day)
  - Core Measures compliance
  - Resistance rates

CMS Infection Control Worksheet
Quality Measures for Antibiotic Use
- “Systems to prevent transmission of MDROs and promote antibiotic stewardship”
  - 1. C.2.a Facility has a multidisciplinary process in place to review antimicrobial utilization, local susceptibility patterns, and antimicrobial agents in the formulary and there is evidence that the process is followed.
  - 1. C.2.b Systems are in place to prompt clinicians to use appropriate antimicrobial agents (e.g., CPOE, comments in microbiology susceptibility reports, notifications from clinical pharmacist, formulary restrictions, evidenced-based guidelines and recommendations).

CMS Infection Control Worksheet
Quality Measures for Antibiotic Use
- “Systems to prevent transmission of MDROs and promote antibiotic stewardship”
  - 1. C.2.c Antibiotic orders should include an indication for use.
  - 1. C.2.d There is a mechanism in place to prompt clinicians to review antibiotic courses of therapy after 72 hours of treatment.
  - 1. C.2.e The facility has a system in place to identify patients currently receiving intravenous antibiotics who might be eligible to receive oral antibiotic treatment.
**Measures / Interventions - Tier 2**

- BC contamination rate ≈ excess antibiotic use
- C. difficile rates as a measure of antibiotic control
- Prescribing to antibiotic blood level (V, G)
- Streamline combination therapy >72hr (for duplicative & excess therapy)
- Dosing optimization program
  - IV to PO conversion
  - Infusion policies (e.g. continuous infusion of beta lactams)
- Renal dosing program
- De-escalation program (duration and spectrum)
- Bug:drug mismatch assessment
- Culture treatment audits (e.g asymptomatic bacteriuria)
- Procalcitonin measures to support bacterial etiology
- Acceptance of ASP team recommendations

**Assessment of Antibiotic Consumption**

- What is being measured?
  - Pharmacy Purchasing
  - Physician Prescribing
  - Order Entry
  - Dispensing
  - Delivery
  - Administration
  - Billing
- Consumption data from RN & pharmacy records require validation and may be different
- Benchmarking difficult B/C hospitals are measuring different denominators/numerators

**NHSN Role in Antibiotic Use Evaluation**

- AUR option
  - In medication module
  - Aggregate reporting of antibiotic days per month per location
  - Require Emar / bar coding transmission
  - Electronic transmission monthly
  - Vendor partnership
  - SIR for usage based on antibiotic use (DOT) for each mapped unit
  - National benchmark for like hospitals

**CDC Antimicrobial Prevalence Use Survey 2010**

- Collaboration with CDC Emerging Infections Program
  - Network of 10 state health departments and their academic partners (CA, CO, CT, GA, MD, MN, NM, NY, OR, TN)
  - Overall HA/antimicrobial use prevalence survey objectives
    - To estimate HAI prevalence among inpatients of participating acute healthcare facilities
    - To determine the distribution of HAI by pathogen (including antimicrobial-resistant pathogens) and major infection site
    - To estimate the prevalence and describe the rationale for antimicrobial use in acute healthcare facilities.

**CDC Study Antimicrobial Use Prevalence**

- Antibiotic use - point prevalence survey:
  - 50% of patients are receiving an antibiotic on any given day
  - Treatment of infection: 77%; prophylaxis: 13%
  - Vancomycin, cefazolin and pip/tazo were the three top drugs
  - Antimicrobial use prevalence surveys can provide data to inform staff, initiate more detailed surveillance efforts and areas to target for education and stewardship
    - Example: widespread use of vancomycin and pip/tazo for many indications
  - Planning for Phase 4 survey in 2014
    - Larger sample of hospitals, while re-engaging Phase 2/3 hospitals to allow for comparison and validation
    - Refine data collection and assess appropriateness

**Stamford Hospital Antibiotic Stewardship Program**

- Formulary restrictions
  - Prescribing limitations / ID approval required by drug / dose
  - Preprinted orders / pathways (e.g. CAP, febrile neutropenia)
  - Antibiotic prophylaxis standards
  - IV to PO program (pharmacy based)
  - Renal dosing (pharmacy based)
  - Antibiogram review
  - Spot DUE’s
  - Restricted susceptibility reporting (cascade system thru micro lab)
  - Blood culture monitoring daily for appropriateness of antimicrobial Rx
  - De-escalation program in ICU
  - Monitoring MDRO for determining formulary changes and guideline changes
Challenges of an Antibiotic Stewardship Program

- Inadequate laboratory resources or training to produce periodic antibiograms
- Physician “push back” related to monitoring and restricting antibiotic use
- Lack of pharmacists trained in infectious diseases to interact with physicians
- Lack of physician champions to lead program
- Up-front costs to initiate the program
- Pharmacy and therapeutics committee that is not specifically committed to MDRO control
- Lack of IT support to gather aggregate data
- Lack of administrative champions
- Lack of evidence in many areas

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