Antimicrobial Impact

(A) Mortality rates for erysipelas at Cook County Hospital 1929-1938

(B) Mortality of erysipelas from Norwegian national registry

The Conquest of Infectious Diseases

“Nearly all experts agree, by the year 2000 bacterial and viral diseases will be eliminated; in addition, atherosclerotic heart disease will have been eliminated too.” TIME Magazine. Feb 25, 1966

“Its time we close the book on Infectious Diseases.”
  W.H. Stewart, U.S. Surgeon General, 1969

“I cannot conceive of a need for more infectious diseases experts unless they spend their time culturing each other.”
  R.G. Petersdorf, M.D. NEJM 1978
TIME

REVENGE OF THE
Killer Microbes

Are we losing the war against infectious diseases?

1,000 SUPERBUG VICTIMS A WEEK

Hospital infection soars by 22 per cent in just three months

To halt spi kills 4,000

Super Bug

Dangerous drug-resistant germ spreads across U.S.
Antimicrobial resistance is a growing problem
- Running out of antimicrobial agents
- Results in:
  - Use of less effective, more toxic agents
  - Increased mortality, morbidity, and costs
The Cost of Resistance: Bad For Patients, Bad for Healthcare

Analysis of 188 patients with antimicrobial-resistant infections in a group of 1391 hospitalized patients

- Medical Costs: $18,588 to $29,069 per patient
- Excess LOS: 6.4 – 12.7 days
- Attributable Mortality: 6.5%
- Overall Increased Cost 1 year: $13.35 million

Where Does All This Resistance Come From?

“It is not difficult to make microbes resistant to penicillin... moral: If you use penicillin, use enough.”
(Alexander Fleming, Nobel Prize Acceptance Speech, 1945)

“Antibiotic use is the key driver of resistance.”
(WHO Global Strategy for Containment of Antimicrobial Resistance, 2000)

What Do We Do?

• Options
  1. Create new drugs
  2. Learn to use what we have more wisely

ANTIMICROBIAL STEWARDSHIP
What is antimicrobial stewardship (AMS)?

• “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration”

• **Primary goal:** optimize clinical outcomes while minimizing unintended consequences of antimicrobial use
  – effective antimicrobial stewardship **PLUS** infection prevention = limit emergence and transmission of antimicrobial-resistant bacteria

Clin Infect Dis 2007;44: 159-77.
Why is AMS important?

• Annually in the United States:
  – 30% of hospital admissions due to infection
  – 2 million people develop hospital acquired infections (HAIs)
• 30-50% of hospitalized patients receive antibiotics
• 50% of antibiotic orders: unnecessary or inappropriate
• Antimicrobials are usually 30% or more of hospital pharmacy budgets

Pharmacotherapy 1999;19:1369
Clin Infect Dis 2007;44:159
Antimicrobial Resistance

• Antimicrobial resistance identified by United Nations (UN) leaders as health crisis requiring attention (9/2016)
  – only the fourth time a health issue has been taken up by the UN General Assembly

• Antimicrobial resistance poses a fundamental threat to human health, development, and security

• If not successfully addressed, predict significant social, health, security, and economic repercussions that will seriously undermine the development of countries

http://www.un.org/pga/71/event_latest/high-level-meeting-on-antimicrobial-resistance/
Increased Focus on Antimicrobial Stewardship

• Joint Commission released new Antimicrobial Stewardship Standard for all hospitals that requires compliance with starting January 1, 2017

• **Why now?** *Per Joint Commission:*
  - Current scientific literature emphasizes the need to reduce the use of inappropriate antimicrobials in all health care settings due to antimicrobial resistance
  - AMS can help prevent the development of multidrug resistant organisms, and reduce unnecessary drug use and costs associated with expensive, broad-spectrum therapies used to treat HAIs
AMS Outcomes in Literature

Systematic review of 24 selected studies

• Decreases seen in:
  – Antibiotic use
  – Costs
  – Length of therapy
  – Inappropriate use
  – Adverse drug reactions
  – Resistance

• No increases seen in:
  – Nosocomial infection rates
  – Length of stay (some studies showed decreased LOS)
  – Mortality

Decreased Toxicity and Improved Clinical Outcomes

Clinical Outcomes in a Randomized Trial Comparing an ASP to Usual Care

Decreased Toxicity and Improve Clinical Outcomes

Clinical Outcomes for Patients Treated with Aminoglycoside or Vancomycin with and without a Pharmacist-led Antimicrobial Stewardship Program

- Death: No ASP 15% vs. ASP 10%, *P* < 0.0001
- Hearing Loss: No ASP 5% vs. ASP 2.5%, *P* < 0.0001
- Renal Impairment: No ASP 35% vs. ASP 25%, *P* < 0.0001
- Deaths in Patients with Complications: No ASP 30% vs. ASP 20%, *P* < 0.0001

Mean carbapenem use (DOT/1,000 PD) was significantly lower in hospitals that restricted (shaded bars) versus did not restrict (open bars) carbapenems (P = 0.04)

Core AMS Program Strategies

- **Prospective review/audit with feedback**
  - Improve antibiotic use
  - Reduce antibiotic resistance
  - Reduce *Clostridium difficile* infection (CDI) rates
  - No increase in negative patient outcomes

- **Other options to enhance AMS:**
  - Prior Authorization
  - Education
  - Facility-Specific Clinical Practice Guidelines
  - Computerized Clinical Decision Support Systems
  - IV to PO
  - Micro lab – selective/cascade susceptibility reporting, rapid diagnostic testing
How to implement AMS program

• Guidelines published by IDSA and SHEA 2016

• Core members of AMS team:
  – Infectious disease physician
  – Clinical pharmacist (preferred with ID training)
  – Clinical microbiologist
  – Infection prevention professional

• Need support/collaboration of administration and local providers
Ways to Optimize Antimicrobial Use

• Use local hospital/system antibiogram to improve empiric therapy choices for common infections

• Interpret microbiology lab susceptibility report and de-escalate therapy to least broad agent that can treat infection when culture results are known
ANTIBIOGRAMS - *Interpretative*

- Percent of strains (≥ 30 isolates) tested which are sensitive to a given antibiotic
- Published annually

**Problems:**
- duplicate isolates
- non-pathogens tested
- sampling bias
- nosocomial vs community acquired strains
- retrospective
- qualitative
# ANTIBIOGRAMS - Example

| GRAM NEGATIVE ORGANISM          | # of isolates | Amikacin | Ampicillin | Ampicillin/Sulbactam | Aztreonam | Ceftazolin | Ceftazolin\(^2\) | Ceftiofur | Ceftiraxone | Cefturoxime | Ciprofloxacin | Chloramphenicol | Erythromycin | Gentamicin | Levofloxacin | Metronidazole | Nitrofurantoin | Piperacillin/Tazobactam | Tetracycline | Tobramycin | Trimethoprim/Sulfamethoxazole |
|--------------------------------|---------------|----------|------------|----------------------|-----------|------------|-------------------|-----------|-------------|------------|---------------|----------------|--------------|-------------|---------------|--------------|----------------|----------------|----------------|-----------------------------|
| Acinetobacter baumannii       | 86            | 85       | 81         |                      | 65        | 66         | 52                | 50        | 58          | 52         | 81                    |              |             |               |              |                |                |              | 59            | 64           | 56            |
| Bacteroides fragilis group    | 36            | 89       | 72         |                      |           |            |                   |           | 56          |            | 100                    |              |             |               |              |                |                |              | 96            | 79           | 90           |
| Citrobacter freundii          | 304           | 100      | 90         |                      | 99\(^+\)  | 88         | 86                | 91        | 99          | 90         | 93                    | 100          |              |              | 94          | 96            | 79            | 90            |
| Citrobacter koseri            | 124           | 100      | 93         | 98                   | 98        | 89         | 81                | 86        | 100         | 98         | 88                    | 100          |              |              | 84          | 100           | 93            | 100 |
| Enterobacter aerogenes        | 197           | 100      | 86         |                      | 99\(^+\)  | 84         | 82                | 97        | 94          | 98         | 96                    | 100          |              |              | 21          | 90            | 87            | 99            | 97            |
| Enterobacter cloacae          | 447           | 99\(^+\) | 82         |                      | 97        | 82         | 77                | 94        | 93          | 98         | 95                    | 99\(^+\)     |              |              | 27          | 86            | 85            | 97            |
| Escherichia coli              | 9754          | 99\(^+\) | 54         | 59                   | 94        | 94         | 92                | 90        | 76          | 92         | 77                    | 100          |              |              | 97          | 97            | 75            | 92            |
| Klebsiella oxytoca            | 374           | 100      | 69         | 91                   | 59        | 97         | 96                | 93        | 87          | 92         | 99\(^+\) 99\(^+\) | 94          | 100         |              | 94          | 93            | 90            | 99\(^+\) 96   |
| Klebsiella pneumoniae         | 1650          | 99\(^+\) | 83         | 95                   | 96        | 95         | 95                | 91        | 94          | 99\(^+\) 96 | 97                    | 100          | 61          |              | 97          | 83            | 96            | 90            |
| Morganella morganii           | 150           | 99\(^+\) | 92         |                      | 99        | 87         | 88                | 53        | 98          | 80         | 60                    | 100          | 100         |              | 100         | 89            | 53            | 95            |
| Proteus mirabilis             | 1259          | 99\(^+\) | 85         | 93                   | 96        | 97         | 98                | 97        | 51          | 99\(^+\) 87 | 58                    | 100          | 99\(^+\) 90 |              | 92          | 100           | 98            | 99            |
| Providencia retgeri           | 50            | 100      | 84         |                      | 98        | 78         | 100               | 84        | 100         | 100        | 88                    | 100          | 92          |              | 92          | 100           | 98            | 99            |
| Providencia stuartii          | 63            | 100      | 100        |                      | 100       | 93         | 100               | 21        | 95          | 52         | 21                    | 100          | 100         |              | 44          | 71            | 71            | 98            |
| Pseudomonas aeruginosa        | 1264          | 95       | 74         |                      | 83        | 89         | 69                | 77        | 68         | 86         | 96                    | 92           | 96          |              | 96          | 92            |                |               |
| Serratia marcescens           | 175           | 99       | 87         |                      | 98        | 85         | 87                | 84        | 98          | 97         | 92                    | 98           | 85          | 17           | 93          | 95            |                |               |
| Stenotrophomonas maltophilia\(^2\) | 129        |          |            |                      |           |            |                   |           | 79          |            |                      |              |             |              | 98          |                |                |               |

1. Urine isolates only
2. Routinely only trimethoprim/sulfamethoxazole and levofloxacin are reported.
3. Partial year results due to panel change
ANTIBIOGRAMS - *Interpretative*

- **What are they used for?**
  - Guide empiric therapy to local hospital susceptibility patterns
  - Help clinicians avoid using antimicrobial agents that have higher reported resistance to most likely pathogens for infection being treated (i.e. *E. coli* for UTI)
When is antimicrobial susceptibility testing (AST) performed in micro lab?

1) Isolate must be clinically significant, i.e. a (potential) pathogen

2) Antimicrobial susceptibility pattern of isolate is unpredictable

3) A standardized method is available for AST performance and interpretation on the isolate
AST – Very Important Points

• In vitro AST results do not necessarily predict clinical efficacy

• The purpose of AST is to detect phenotypic RESISTANCE → this has a high correlation with clinical failure
Important AST Definitions

• **MIC** – Minimum Inhibitory Concentration, lowest concentration of antibiotic which prevents growth of the bacteria; µg/mL

• **MIC Breakpoints** - critical antibiotic concentration (µg/mL) that the organism’s MIC is compared with, to determine if the organism is susceptible, resistant or intermediate to the antibiotic. Determined by serum or body compartment (e.g. csf) concentration and other PK/PD data, after routine safe doses.
  
  – **MIC breakpoints specific for each drug/organism – cannot directly compare MIC results between drugs**
Important AST Definitions

• **Susceptible** (sensitive) - MIC of the antibiotic against the organism is at or below the susceptible breakpoint; *the antibiotic has a high probability of clinical effectiveness*

• **Resistant** - MIC of the antibiotic against the organism is at or greater than the resistant breakpoint; *the antibiotic has a low probability of clinical effectiveness (not recommended for use)*

• **Intermediate** - MIC of the antibiotic against the organism falls between the susceptible and resistant breakpoints; “gray zone”, *the clinical efficacy of antibiotic is questionable (not recommended for use except in extraordinary circumstances)*
What is YOUR role in AMS?

• Include an indication with every antibiotic order

• Prescribe the narrowest spectrum antibiotic for the condition you are treating

• Review your antibiotic orders every day to make sure they are still indicated and appropriate

• Use evidence based treatment guidelines in determining choice of antimicrobial agent and length of therapy
Summary

• AMS is now required per CMS in hospital setting starting January 1, 2017

• Can see great outcomes with reduced costs and increase in patient safety and quality of care

• CHI Health hoping to expand AMS in 2017 to more hospital sites

• AMS is a team approach with ID physicians, clinical microbiology, and pharmacy staff working together

• Core principal for success ➔ prospective review/audit with feedback and real time education to health care providers