Antimicrobial Stewardship and Core Elements: Where to Start

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Learning Objectives

- Evaluate the principles and objectives of antimicrobial stewardship programs

- Identifying barriers to implementation of a successful stewardship program

- Discuss antimicrobial stewardship strategies that can be effectively implemented

- What metrics should be used?

Antimicrobial Stewardship Concepts

- Not new concept

- Sir Alexander Fleming addressed in 1945 Noble Prize acceptance speech

- Documented ASPs since 1970s in US hospitals

- In 1996, John McGowan, Jr, MD, and Dale N. Gerding, MD, at Emory University School of Medicine in Atlanta, coined the term "Antimicrobial Stewardship."

Scheckler, W.E.,Bennett, J.V. *JAMA*. 1970; 213: 264-267
McGowan, J.E. Jr, Finland, M. *J Infect Dis*. 1974; 130: 165–168
McGowan JE Jr, Gerding DN. New Horizons 1996;4:370 –376

Public Awareness of the Problem

Rationale for Starting a Stewardship Program

Patient care

"The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as Clostridium difficile infection), and the emergence of resistance."

Financial

"Effective antimicrobial stewardship programs can be financially self-supporting and improve patient care. Comprehensive programs have consistently demonstrated a decrease in antimicrobial use (22% - 36%), with annual savings of $200,000 - $900,000 in both larger academic hospitals and smaller community hospitals."

Dellit T, et al. *Clin Infect Dis.* 2007;44:159-177.

Rationale for Starting a Stewardship Program

- Approximately, 25%–50% of hospitalized patients receive antibiotics, with between 30% and 50% of antibiotic use being inappropriate

- Research demonstrates a strong link between antibiotic use and the development of resistance

- Recent reports indicate that patients with infection caused by drug resistant bacteria have a two-fold increase in mortality compared to those with infection with sensitive bacteria

http://www.cdc.gov/vitalsigns/antibiotic-prescribing-practices/

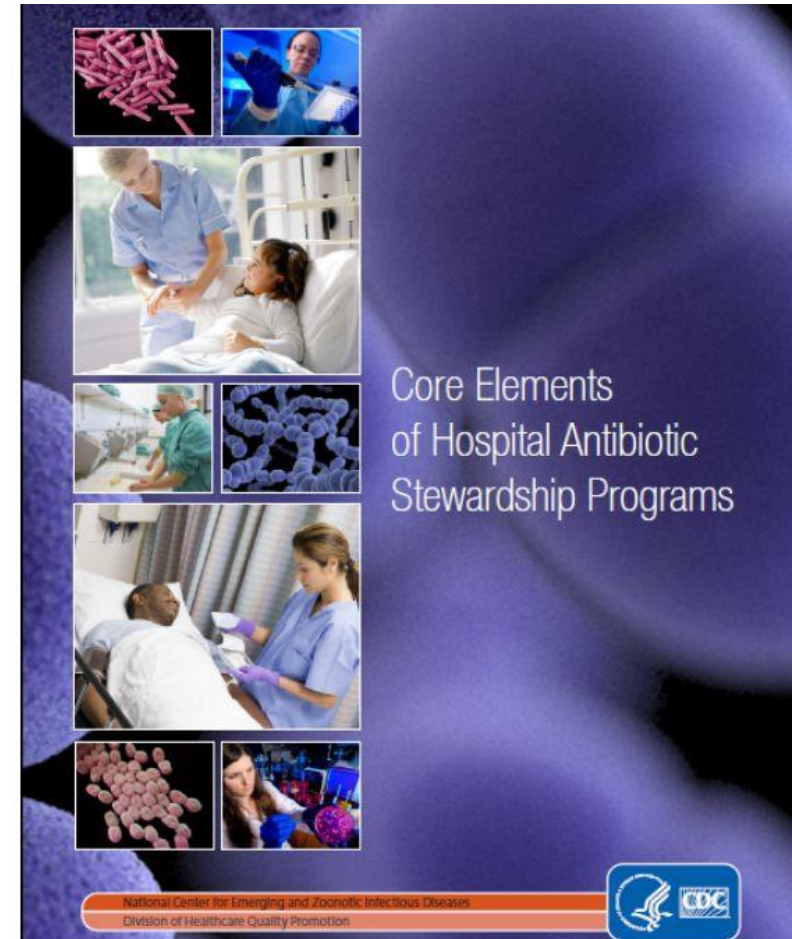# Rationale for Starting a Stewardship Program

- Improve Patient Care and Safety

  - Prevent *collateral damage* (ie; *C. Difficile* infections)

  - Minimize adverse events

- Antimicrobial stewardship programs attempt interventions aimed at improving the use of antibiotics in various settings

- Reduce Resistance

  - Preserve antimicrobial effectiveness

  - Decrease excess deaths

While all changes do not lead to improvement, all improvement requires change

Institute for Healthcare Improvement. Knowledge Center. [cited 2011 August 15]; Available from: http://www.ihi.org/knowledge

CDC Core Elements for Antibiotic Stewardship Programs

- Guidance to assist hospitals in starting or expanding Antimicrobial Stewardship Programs to improve prescribing

- Emphasizes Antimicrobial Stewardship Programs can be implemented effectively in a wide variety of hospitals

- "No single template".. Success depends on defined leadership and a coordinated approach....

Core Elements of Hospital Antibiotic Stewardship Programs

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion

http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html

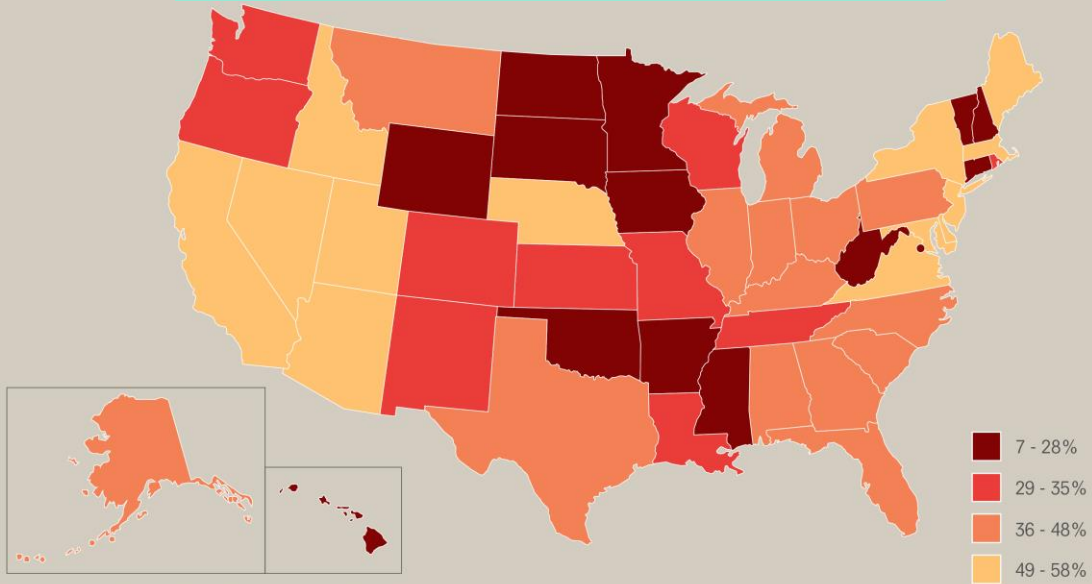# CDC Core Elements for Antibiotic Stewardship Programs

- Leadership commitment from administration

- Single leader responsible for outcomes

- Single pharmacy leader

- Antibiotic use tracking

- Regular reporting on antibiotic use and resistance

- Educating providers on use and resistance

- Specific improvement interventions

Hospitals With Stewardship Programs

Percent of Hospitals with Antibiotic Stewardship Programs by State, 2014*

Nationally, 39.2% of all hospitals have stewardship programs (1642 of 4184)

7 - 28%
29 - 35%
36 - 48%
49 - 58%

*A hospital stewardship program is defined as a program following all 7 of CDC core elements of antibiotic stewardship programs.

AE, AP, AS, GU, VI data are not shown due to 7 or fewer hospital respondents but are included in the overall percentage.
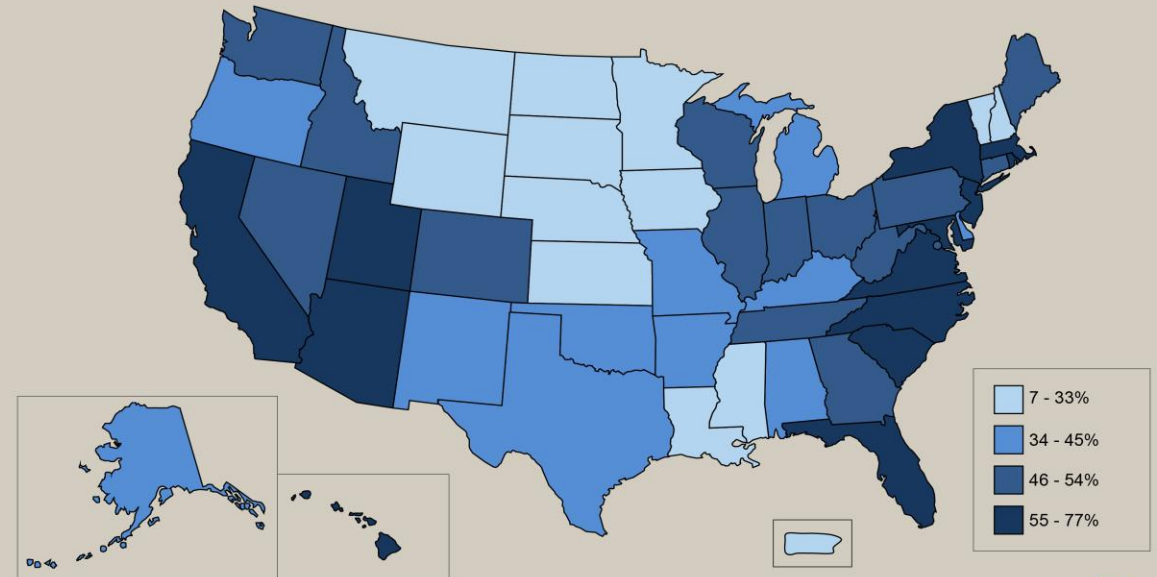
Source: CDC's NHSN Survey

Nationally, 39.2% of all hospitals have stewardship programs (1642 of 4184); the national goal is 100% of hospitals by 2020.

Percent of Hospitals with Antibiotic Stewardship Programs by State, 2015*

Nationally, 48.1% of all hospitals have stewardship programs (2,199 of 4,549); the national goal is 100% of hospitals by 2020.
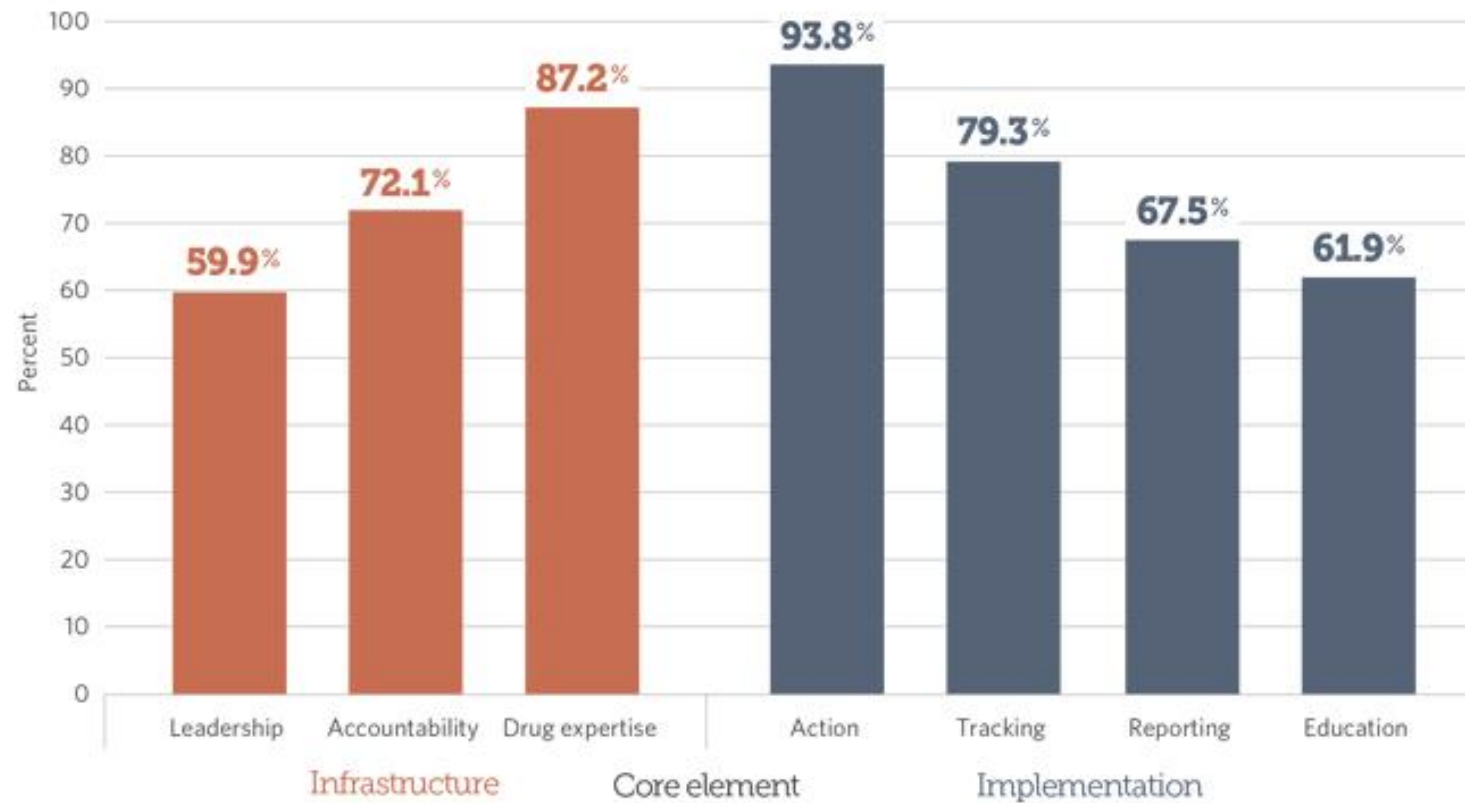
7 - 33%
34 - 45%
46 - 54%
55 - 77%

*A hospital stewardship program is defined as a program following all 7 of CDC's Core Elements of Hospital Antibiotic Stewardship Programs.

Source: CDC's National Healthcare Safety Network (NHSN) Survey

https://www.cdc.gov/getsmart/healthcare/evidence.html
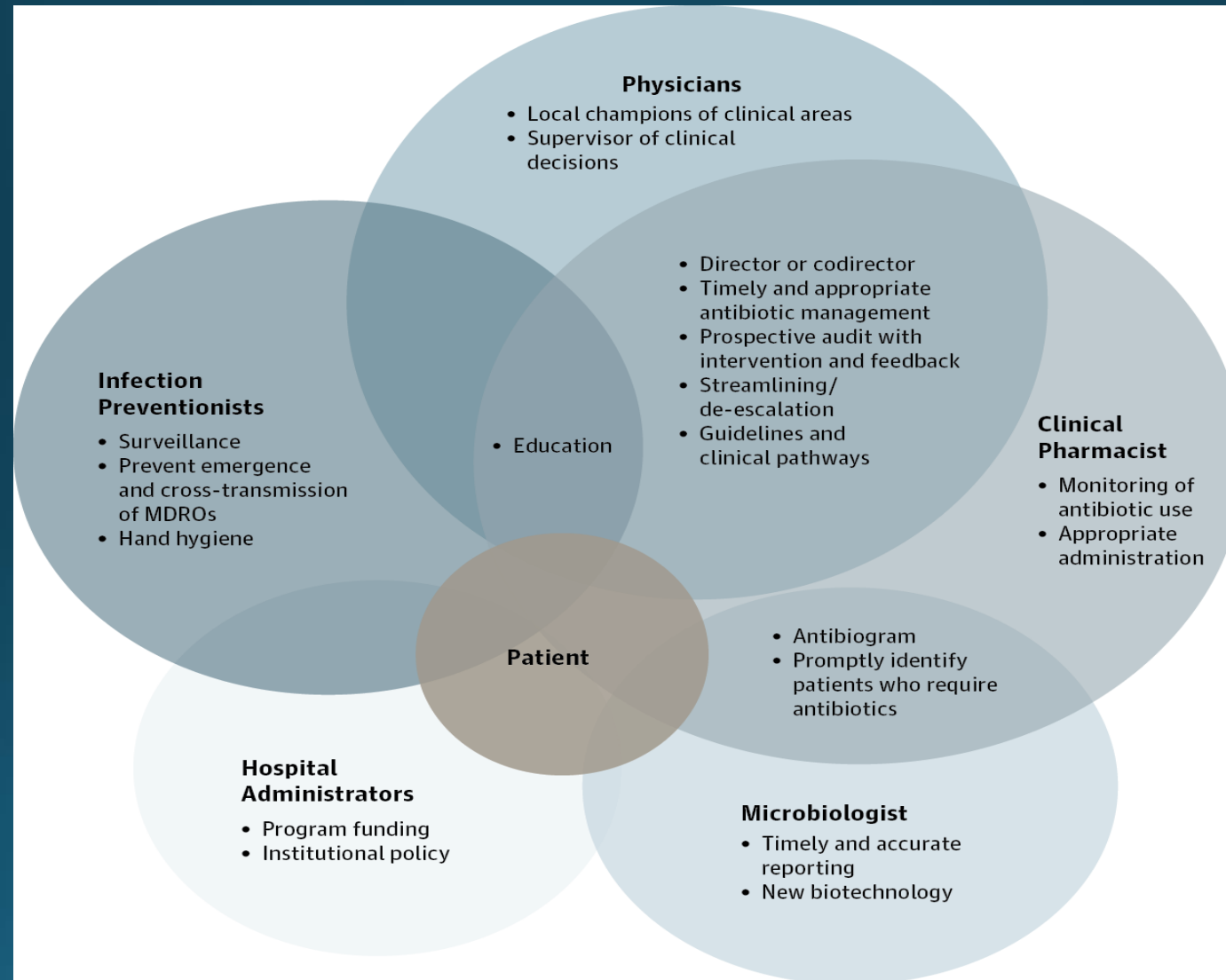PEW Charitable Trusts 2016

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Percentage of Hospitals Reporting Implementation of Core Elements

Data From 2014

CDC and Pew Charitable Trust 2016

Antimicrobial Stewardship Team
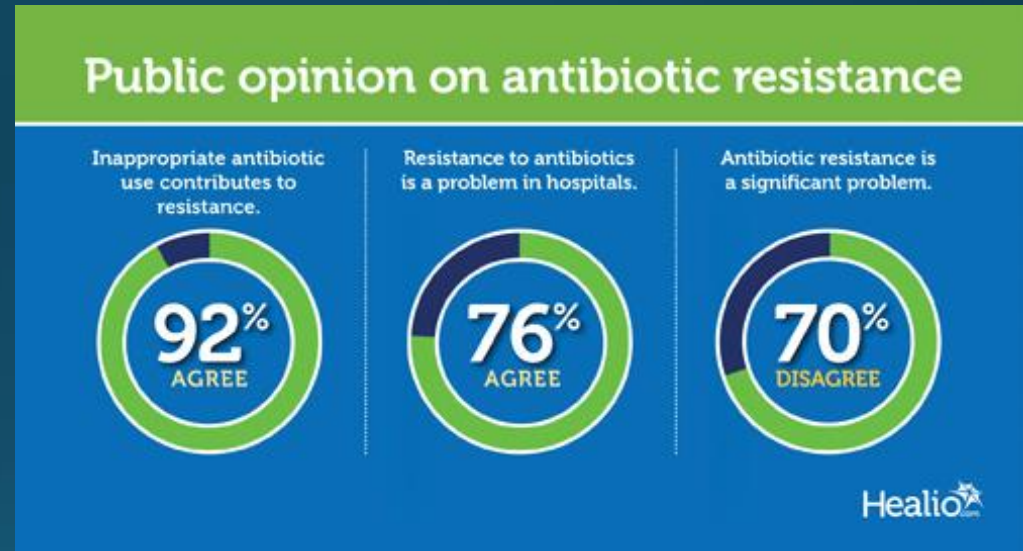
Multidisciplinary Team Approach

Stewardship: How to Get Started

- Establish a core planning committee
  - Subcommittee of P&T Committee?
  - Subcommittee of Infection Control Committee?
  - Add other interested stakeholders
- Establish goals and mission statement
- Draft an idea
  - Program structure
  - Program elements
  - Write a strategic (business plan) - work with CFO
- Identify existing and needed resources

Infect Control Hosp Epidemiol. 2012; 33:322-327
Doron S & David L. *Mayo Clinic Proceedings.*2011, 86:1113-1123

Stewardship: How to Get Started

- Present ideas to Pharmacy Director

- Vet your ideas with Chief Medical Officer (CMO) and/or key medical staff leadership

- Establish a working budget

- Meet with VP for patient safety/quality

- Meet with CEO and CO when above complete

- Present to key medical staff committees and get approval from the Executive Committee

Infect Control Hosp Epidemiol. 2012; 33:322-327
Doron S & David L. *Mayo Clinic Proceedings*.2011, 86:1113-1123

Antimicrobial Stewardship: WHY???

Antimicrobial Stewardship Goals

- Improve patient outcomes

- Selection of the right drug, dose and duration of treatment and when not to use an antibiotic

- Minimize adverse drug events including secondary infection (such as: *C. difficile* infection)

MacDougall CM and Polk RE. *Clin Microbiol Rev.* 2005; 18(4):638-56.
Dellit TH et. al. *Clin Infect Dis.* 2007; 44:159-177.
Doron S & David L. *Mayo Clinic Proceedings.*2011, 86:1113-1123.

Antimicrobial Stewardship Goals

- Reduce morbidity and mortality

- Limit emergence of antimicrobial resistance

- Reduce length of stay

- Reduce health care expenditures

MacDougall CM and Polk RE. *Clin Microbiol Rev.* 2005; 18(4):638-56.
Dellit TH et. al. *Clin Infect Dis*. 2007; 44:159-177.
Doron S & David L. *Mayo Clinic Proceedings*.2011, 86:1113-1123.

Antimicrobial Stewardship
Core Strategies

Preauthorization
Restricted formulary

"Front end" strategies

- Effective strategy to decrease use of targeted antimicrobials
  - Changes are immediate and significant
- May be most useful in controlling outbreaks of infection
- Long-term beneficial impact on emergence of resistance has not been demonstrated
- May result in cost savings

Prospective audit
and feedback

"Back end" strategy

- Requires that information about infecting pathogen is available
- Performed by either an infectious diseases physician or a clinical pharmacist
- Can target specific units or services where problems exist when facilitated by computer surveillance of antimicrobial use
- May result in cost savings

Dellit T, et al. *Clin Infect Dis.* 2007;44:159-177. 2. MacDougall C, Polk RE. *Clin Microbiol Rev.* 2005;18:638-656.

Antimicrobial Stewardship
Supplemental Strategies

- Guidelines and clinical pathways antimicrobial cycling

- Scheduled antimicrobial switch

- Antimicrobial order forms

- Automatic stop orders

- Streamlining or de-escalation of therapy

- Look at specific infections

- Dose optimization:
  - Conversion from parenteral to oral therapy
  - Adjustment for hepatic or kidney function "*renal dosing*"

- Computer surveillance and decision support

Antimicrobial Stewardship

Infection and syndrome specific interventions

Community-acquired pneumonia

Urinary tract infections (UTIs)

Skin and soft tissue infections

Tailoring treatment to culture results

Clostridium difficile infections

Antimicrobial Stewardship
Interventions

- **Guidelines, policies, and protocols alone will probably not change practice**

- **Active interventions are most effective**

  - **Prospective audit**

  - **Formulary restriction and preauthorization**

  - **Antibiotic 'Time Out'**

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Antimicrobial Stewardship
Interventions: Prospective Audit

Physician or pharmacist reviews orders and intervenes with modification of order and feedback to prescriber
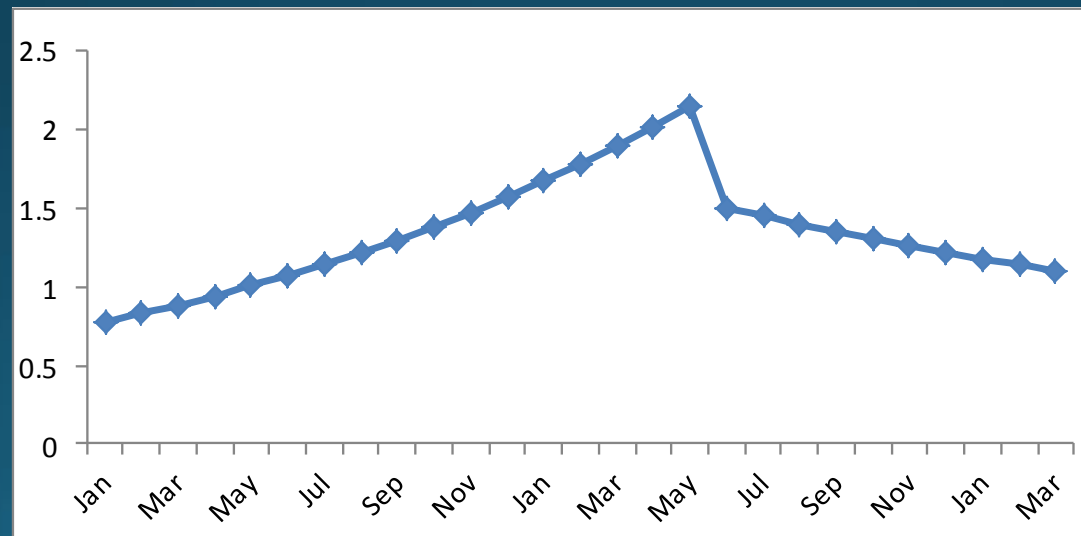
Results in improved use, decreased costs

Caveats:

- Time and labor intensive

- Many settings do not have capacity

- Providers may not be receptive

Antimicrobial Stewardship
Interventions: Formulary restriction and preauthorization

Specific antibiotics cannot be ordered without authorization

Useful in response to healthcare-associated outbreak

Impact of Fluoroquinolone Restriction on Rates of *C. difficile* Infection

Kallen et al. Infect Control Hosp Epidemiol. 2009 Mar;30(3):264-72.

Antibiotic Stewardship

Intervention: An Antibiotic '*Time Out'*

The 'time out' concept is borrowed from surgery

A concrete point in time dedicated to reviewing antimicrobial choice and duration

- Reappraise therapy when more clinical data are available (usually in 48-72 hours)

- Decide about continuation, narrowing therapy and specify a duration

Recommended changes are better received and more likely to be followed at a later time point
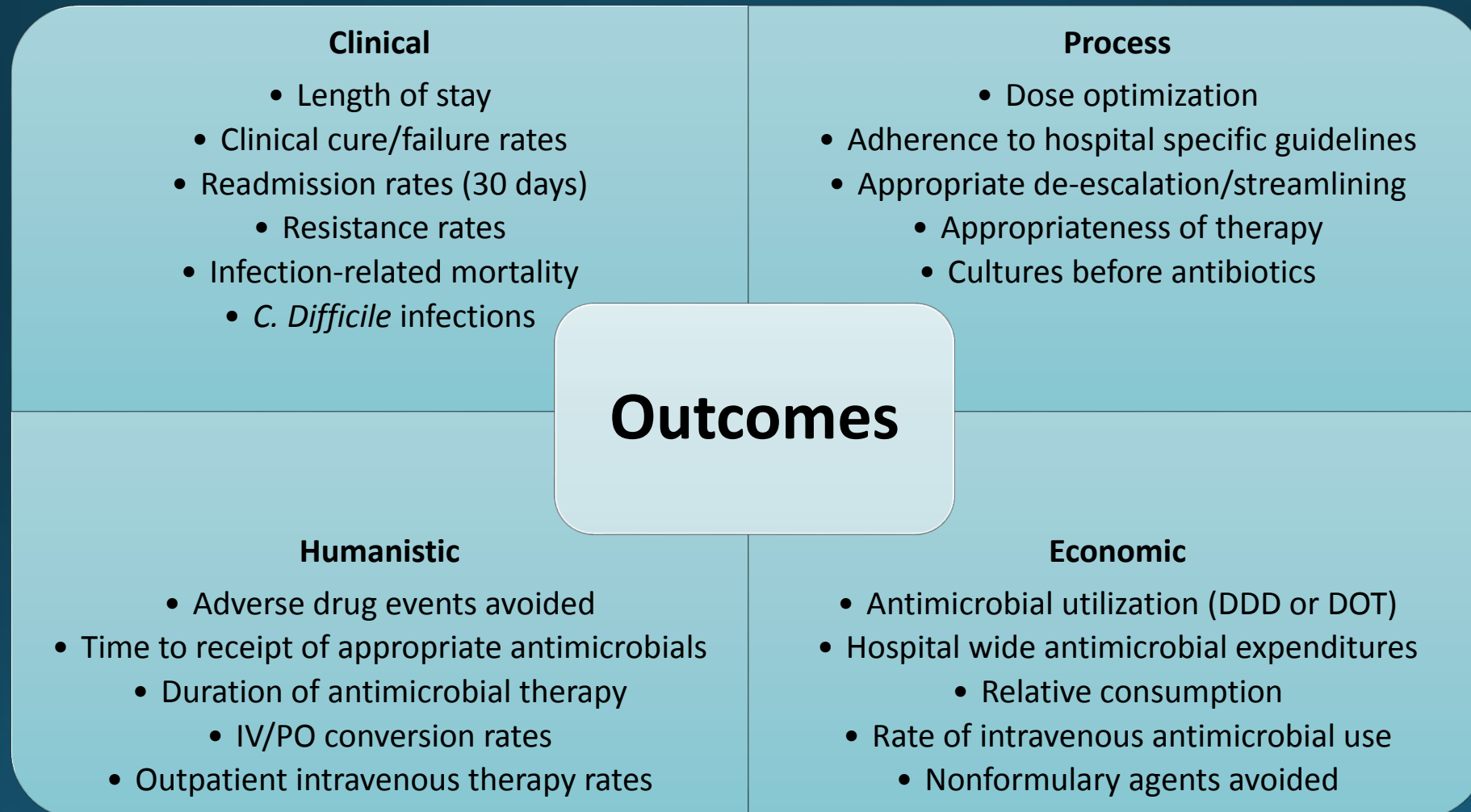
Antimicrobial Stewardship
Potential Measurements

- Antimicrobial use
  - Defined daily dose
  - Days of therapy
- Antimicrobial costs
- Timely antibiotic administration and duration
- Cultures obtained before antibiotic(s) administered
- Adverse drug events
- Antimicrobial resistance patterns
- *C. difficile* rates

Antimicrobial Stewardship
How It All Works

Clinical

- Length of stay
- Clinical cure/failure rates
- Readmission rates (30 days)
- Resistance rates
- Infection-related mortality
- *C. Difficile* infections

Process

- Dose optimization
- Adherence to hospital specific guidelines
- Appropriate de-escalation/streamlining
- Appropriateness of therapy
- Cultures before antibiotics

Outcomes

Humanistic

- Adverse drug events avoided
- Time to receipt of appropriate antimicrobials
- Duration of antimicrobial therapy
- IV/PO conversion rates
- Outpatient intravenous therapy rates

Economic

- Antimicrobial utilization (DDD or DOT)
- Hospital wide antimicrobial expenditures
- Relative consumption
- Rate of intravenous antimicrobial use
- Nonformulary agents avoided

DDD=Defined daily dose, DOT=Days of therapy

Examples

Antimicrobial Utilization Measures

Metric	Definition	Sample Calculation	Advantages	Disadvantages
Grams of Antimicrobials used	Grams of antimicrobial based on: acquisition (purchased), dispensed or administered over a defined time period Serves as an integral step in determining Defined Daily Doses (DDD)		Relatively easy to determine grams of antimicrobial from purchasing records Grams adjusted by patient days for comparisons so may help to broadly identify potential areas for stewardship initiatives Grams of use is not affected by changes in price of antimicrobials over time so may be a more accurate reflection of the impact of antimicrobial stewardship initiatives compared to before and after analyses comparing cost	Provides a very rough approximation of antimicrobial use

Antimicrobial Utilization Measures

Metric	Definition	Sample Calculation	Advantages	Disadvantages
Antimicrobial Expenditures	Antimicrobial costs can be based on: acquisition (purchased), dispensed or administered over a defined time period Costs can be expressed as absolute dollar value, percent of total (purchased, dispensed or administered) and/or per patient-days Antimicrobials can be tracked monthly and annually hospital wide, for specific clinical services (e.g. ICU), classes of antimicrobials (e.g. fluoroquinolones), individual drugs (e.g. linezolid), or types of infections/indications (e.g. ventilator-associated pneumonia)	Pharmacy drug budget of $3,000,000 Antimicrobial acquisition costs $750,000 (25% of budget) Cost savings (percent reduction in antimicrobial costs): ——————— a) overall antibiotic acquisition costs 2015 $750,000 2016 $675,000 Absolute decrease of $75,000, equals 10% reduction ——————— b) ICU antibiotic acquisition costs 2015 $100,000 (patient days = 2000, $50/patient-day) 2016 $75,000 (patient days = 2000, $37.50/patient-day) Absolute decrease of $25,000, equivalent to a reduction of $12.50/patient-day	Expenditures are easily understood by and relevant to administrators May be viewed favorably in offsetting costs of stewardship program Relatively easy to determine acquisition costs from purchasing records Costs adjusted by patient days for comparisons between clinical services may help to broadly identify potential areas for stewardship initiatives	Purchased and dispensed costs are used as surrogate markers fro administration costs Difficult to retrieve data and accuracy of actual consumption Costs fluctuate with contracts/suppliers, generics, so calculated cost reductions may not necessarily be reflective of interventions Dispensed costs may not account for "returns" Difficult to retrieve antimicrobial costs for specific clinical services depending on the capability of the pharmacy computer system

Evaluating Specific Antimicrobial Use
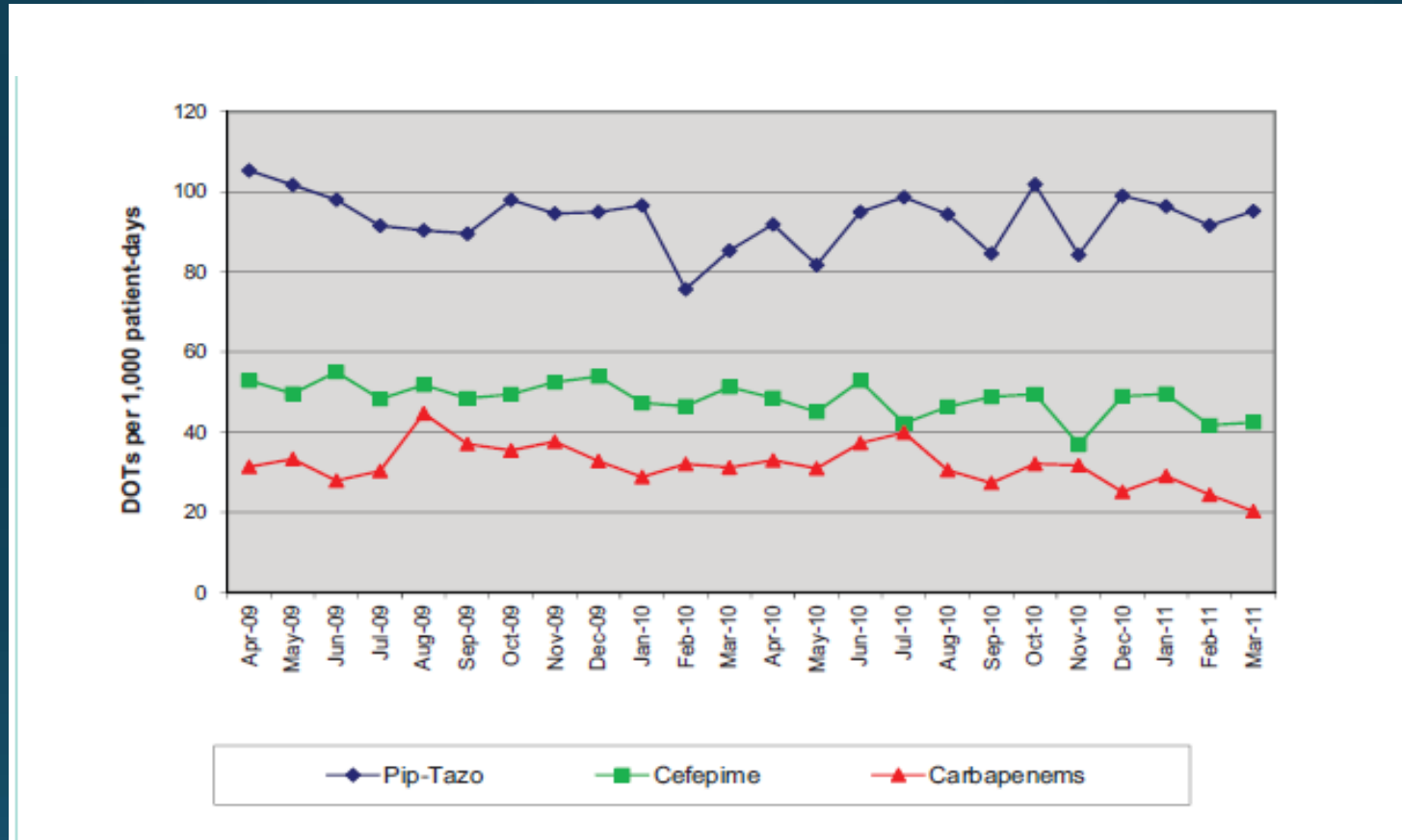
Usage of three beta-lactam antimicrobials commonly used to empirically cover gram-negative organisms is plotted over time. This type of analysis shows whether changes in the usage of a single antimicrobial are offset by a reciprocal change in another. (Pip-Tazo: piperacillin-tazobactam)

Antimicrobial Utilization Measures

Metric	Definition	Sample Calculation	Advantages	Disadvantages
Days of Therapy (DOT) **Is currently the preferred measure of antibiotic use and is used by CDC and National Healthcare Safety Network (NHSN)**	The number of days that a patient receives an antimicrobial agent (regardless of dose) Any dose of an antibiotic that is received during a 24-hour period represents 1 DOT The DOT for a given patient on multiple antibiotics will be the sum of DOT for each antibiotic that the patient is receiving DOT is often standardized to 1000 patient days (DOT/1000 patient days) to allow comparison between hospitals or services of different sizes	Rx: Levofloxacin 500mg po od x 7 days DOT = 1 DOT x 7d = 7 DOT Rx: Levofloxacin 750mg po od x 7 days DOT = 1 DOT x 7d = 7 DOT Rx: Levofloxacin 750mg po q48h x 7days = 4 DOT Rx: Cefazolin 2 g q8h iv X 1 day = 1 DOT Rx: Cefazolin 1 g iv X 1 dose = 1 DOT Rx: Levofloxacin 750mg po od x 7 days + Vancomycin 1g iv q12h x 7 days: DOT Levofloxacin = 1 DOT x 7d = 7 DOT DOT Vancomycin = 1 DOT x 7d = 7 DOT Total DOT = 14 DOT	Provides a method of measure to benchmark both within and between institutions if normalized to patient days. Caution should be exercised when making comparisons between services and institutions with different case mixes. Allows for multiple patient populations to be compared accurately Is NOT affected by change in dosing (e.g. Levofloxacin 500mg vs. 750 mg) or WHO DDD	The denominator of patient days is required to standardize DOTs for benchmarking between institutions or services Requires computerized pharmacy records to obtain data. Manual determination of days a patient receives antimicrobials, although more precise, is not practical Favors those who use broad spectrum mono-therapy over those who use narrow spectrum combination therapy. For example, meropenem x 7 days = 7 DOTs, ceftriaxone + metronidazole x 7 days = 14 DOTs Since 1 DOT is any dose of antibiotic received during a 24 hour period, the DOT for patients that receive a dosing interval >24 hours (e.g. renal failure patients) does not reflect patient exposure; it only reflects antibiotic administration Overestimation with one time doses (e.g. surgical prophylaxis) since one dose of a multi-daily dose regimen counted the same as multiple doses received in a day

Antimicrobial Resistance Measures

Metric	Definition	Sample Calculation	Advantages	Disadvantages
Antibiotic Resistance Trends	Number of patients with specific drug resistant organism divided by the total number of patients admitted to the area of interest. Antibiogram based on unique isolates and susceptibility to given antibiotics	Meropenem resistant *Pseudomonas aeruginosa* in critical care: In 2015, of 500 patients admitted to critical care unit, 100 patients had meropenem resistant *P. aeruginosa*: 100/500 = 20% 60 patients with meropenem resistant *P. aeruginosa* in 2016 with 600 patients admitted to critical care unit in 2012: 60/600 = 10% Therefore, the rate of meropenem-resistant *P. aeruginosa* was reduced from 20% in 2009 to 10% in 2016	Enables quantification of resistance trends as a measure of the advantage of antimicrobial stewardship and infection prevention and control Easier to do than a per patient approach, since the information can be obtained directly from a microbiology database without a patient denominator	Improvements in resistance patterns lag behind decreases in antimicrobial use and therefore, should be assessed over extended periods (e.g. > 1 year). Since multiple interventions typically take place concurrently (e.g., related to Infection Control) it is difficult to attribute observed changes specifically to antimicrobial use Requires the ability of microbiology or another data base to track susceptibility and a data base to track patient admission to ward, service or unit of interest

Create Antibiograms

- Information system design
- Data analysis
- Data presentation
- Use of cumulative antimicrobial susceptibility reports
- Limitation of data, data analysis and data presentation

- Patient location
- Specific ward, clinic, inpatient, outpatient, intensive care unit
- Clinical service
- Specimen type
- Certain organism subgroups
- Special populations

Sample Antibiograms

Antibiotic Tested	Escherichia coli	Klebsiella pneumoniae	Proteus mirabilis	Pseudomonas aeruginosa		Staphylococcus aureus nonMRSA	MRSA †	Staphylococcus coag. Neg	Enterococcus sp
# of Isolates‡	165	75	39	33		10*	35	18	68
Oral or Oral Equivalent						**Oral or Oral Equivalent**			
Ampicillin	46%	0%	62%			50%	0%	50%	96%
Amox / Clav	77%	96%	100%						
Cefazolin	70%	93%	88%			100%	0%	50%	
Cefoxitin	82%	100%	100%						
Ceftriaxone	85%	79%	92%						
Ciprofloxacin	58%	79%	62%	56%			0%	0%	47%
Levofloxacin	59%	79%	62%	57%		33%	20%	0%	64%
Nitrofurantoin	100%	0%	0%			100%	100%	100%	100%
TMP / SMX	64%	79%	54%			67%	100%	100%	
Tetracycline	64%	60%	0%			100%	100%	80%	38%
Oxacillin						100%	0%	50%	
Clindamycin						50%	50%	100%	
Erythromycin						50%	0%	0%	
Linezolid						100%	100%		100%
IV Only						**IV Only**			
Pip / Taz	98%	96%	100%	100%					
Cefepime	89%	95%	92%	91%					
Ceftazidime				91%					
Gentamicin	85%	83%	92%	91%		100%	100%	67%	
Imipenem	100%	100%	100%	71%					
Vancomycin						100%	100%	100%	100%

Antimicrobial Resistance Measures

Metric	Definition	Sample Calculation	Advantages	Disadvantages
C. difficle Infection (CDI) rate	CDI rate per 1,000 patient days: Number of patients newly diagnosed with institution acquired CDI, divided by the number of inpatient days in that time period, multiplied by 1,000 May also be expressed as the number of new CDI cases per 1000 patient admissions	2014: 75 cases *C. difficile* and 90,000 patient days in 2009 = (75/90,000)*1000 = 0.83 2016: 43 cases *C. difficile* and 85,000 patient days in 2011 = (43/85,000)*1000 = 0.5 Reduction in *C. difficile rate* = (0.83-0.5)/0.83 = 40% reduction in *C. difficile* rate in 2016 compared to 2009	CDI is a publicly reportable patient safety quality indicator for hospitals in Illinois. Rates are readily accessible and can be compared between institutions. Given mandatory public reporting hospitals are highly invested in reducing rates.	Changes in CDI rate are impacted by a number of factors, including clinical, IPAC and ASP practices. Difficult to attribute a change in rate to a single intervention.

Antimicrobial Process Measures

Metric	Definition	Sample Calculation	Advantages	Disadvantages
Interventions	Tally of the number and type of interventions made and acceptance rate Potential types of interventions are listed in the sample calculation and the notes below	1000 antimicrobial orders were reviewed by the stewardship team in 2016 and recommendations were made for 750 (75%) The overall acceptance rate was 650/750 (87%) The types of interventions and their acceptance rates were: Dose optimization n= 152/160 (95%) Escalation of therapy n=45/50 (90%) Discontinuation of therapy n=112/140 (80%) De-escalation of therapy n=250/300 (83%) Route change (eg. IV to PO) n=89/100 (89%)	Cost savings/avoidance (in concert with improved patient outcomes – e.g. reduced *C. difficile*) with documentation of accepted interventions, lends support to the changes being a result of antimicrobial stewardship activities Ideally this will be viewed favorably by administrators in offsetting costs of stewardship program	

Antimicrobial Stewardship Programs
Timeline for Implementing

Joint Commission and CMS Requirements for Antimicrobial Stewardship

REQUIREMENT	CMS	JOINT COMMISSION
Program implementation	ASP should be implemented based upon national guidelines and should promote evidence-based usage of antimicrobials.	The ASP should include core elements as defined by the CDC and utilizes multidisciplinary protocols
Committee Members	Unspecified. The program should promote a coordinated multidisciplinary approach that includes all staff and prescribers involved in antibiotic selection, administration, and monitoring	The organization should have a multidisciplinary antimicrobial stewardship team with an ID physician, pharmacist, infection preventionist, and practitioner.
Organizational By-In	Hospital leadership should establish an ASP as an organizational priority.	The organization should establish an ASP as a priority and provides necessary resources.
Leadership	A program leader with appropriate expertise in infectious diseases and/or antimicrobial stewardship should be.	One leader should be responsible for program outcomes.
Documentation	All stewardship activities should be documented, including evidence-based use of antibiotics	ASP data should be collected and analyzed.

ASP, antimicrobial stewardship program; CDC, Centers for Disease Control and Prevention; CMS, Centers for Medicare & Medicaid Services; Infectious disease

Joint Commission and CMS Requirements for Antimicrobial Stewardship

REQUIREMENT	CMS	JOINT COMMISSION
Reporting	Unspecified	ASPs should report metrics monitored to relevant healthcare.
Program Monitoring	Unspecified	The ASP should track antibiotic resistance and antibiotic prescribing patterns.
Patient Education	Unspecified	Patients and their families should be educated, as needed, regarding appropriate use of antimicrobials
Improvement	The program should demonstrate improvement in appropriate antibiotic use.	The program should act upon opportunities for improvement as identified through program monitoring.
Provider Education	Training and education should be provided to relevant staff and prescribers regarding practical applications of an ASP.	Staff and providers involved in antibiotic orders from initiation to administration and monitoring should receive education about antibiotic resistance and stewardship.

ASP, antimicrobial stewardship program; CDC, Centers for Disease Control and Prevention;   CMS, Centers for Medicare & Medicaid Services; Infectious disease

Antimicrobials Stewardship:
The Challenges

- How to initiate and improve antibiotic stewardship efforts
- Proving that it works
    - Clinical outcomes
    - Decrease resistance
- Medicolegal implications of responsibility for patients
- Hardwiring the process
- Literature often not clear in Infectious Diseases

Antimicrobials Stewardship:
The Challenges

- Changing the antibiotic prescribing culture

- Everyone thinks they know how to use antibiotics

- Providers perceive autonomy is lost

- Continuing to show financial benefit to maintain funding and support of efforts

- Difficulty proving impact of program(without national measures)

- Financial pressures dictating decisions
  - Pharmaceutical manufacturers / Hospitals
  - Payers: Insurance providers/ CMS / Patients

Summary

- Antibiotic stewardship promises attainable goals and outcomes
  - Reduction in healthcare costs without adversely impacting the quality of care
  - Programs require support from hospital administration
- Focus on optimal initial antibiotic therapy, dosing, and discontinuing therapy when clinically indicated

  The most expensive antibiotic is the one that doesn't work!

  - Initiate appropriate empiric therapy early
  - Provide optimal dose based on sound PK/PD principles
  - Reduce duration of therapy and/or stop therapy to limit unintended consequences
- The need for strategies to contain antimicrobial resistance and to preserve our antimicrobial arsenal

Conclusion

A pessimist sees the difficulty in every opportunity, an optimist sees the opportunity in every difficulty

Winston Churchill