Antimicrobial Stewardship Implementing an Effective Program

Ed Septimus, MD, FACP, FIDSA, FSHEA

Therapeutics Research and Infectious Disease Epidemiology,
Department of Population Medicine

Harvard Medical School & Harvard Pilgrim Health Care Institute

Disclosures: consultant bioMerieux

Objectives

- Background
- Regulatory Update
- Summarize the basic principles and strategies of an antimicrobial stewardship program
- Biomarkers and Rapid Diagnostics
- Describe appropriate antibiotic therapy strategies

Question

Which of the following is true?

1. Clinicians perceive antimicrobial overuse is a problem generally, but not locally
2. Other medical specialties responsible for overuse
3. Antimicrobial resistance is a macro problem but of limited concern at the bedside
4. All of the above

Answer is all of the above

Complex problem

1994

2015

OLD

Antibiotics as miracles

("No downside risk, so why not try?")

New

Antibiotics: Good when used well, better when used thoughtfully

Background

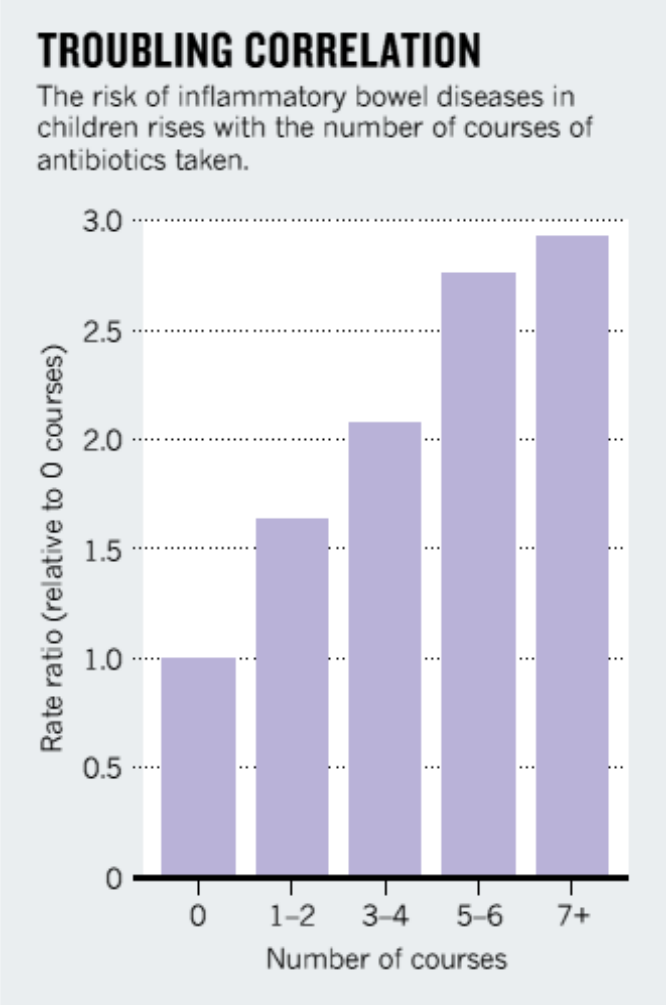
Consequences of inappropriate antibiotic use

Crisis in Infectious Diseases

- Widespread antimicrobial drug resistance
- Increasing number of patients who are immunosuppressed
- Emergence of new pathogens
- Reemergence of older pathogens
- Decrease new drug development
- Dysbiosis due to antimicrobial therapy

Clin Infect Dis 2017; 64:823-828

Collateral Damage of Antibiotic Use



- Average child receives 10-20 courses of antibiotics before age 18
- Antibiotics affect our resident microbiota and may not fully recover after a course of antibiotics
- Overuse of antibiotics may be contributing to obesity, DM, IBD, allergies, and asthma

Nature 2011;476:393

Antimicrobial Resistance

- Increases mortality and morbidity
- Antibiotic-resistant infections have been estimated to cost the US healthcare system over $20 billion annually and over 35 billion in societal costs

Emerg Infect Dis 2001; 7:286
Arch Intern Med 2003; 163:972
Infect Control Hosp Epidemiol 2003; 24:642
Nat Rev Microb 2004; 2:251
Clin Infect Dis 2009; 49:1175-84

Practices That Promote Resistance

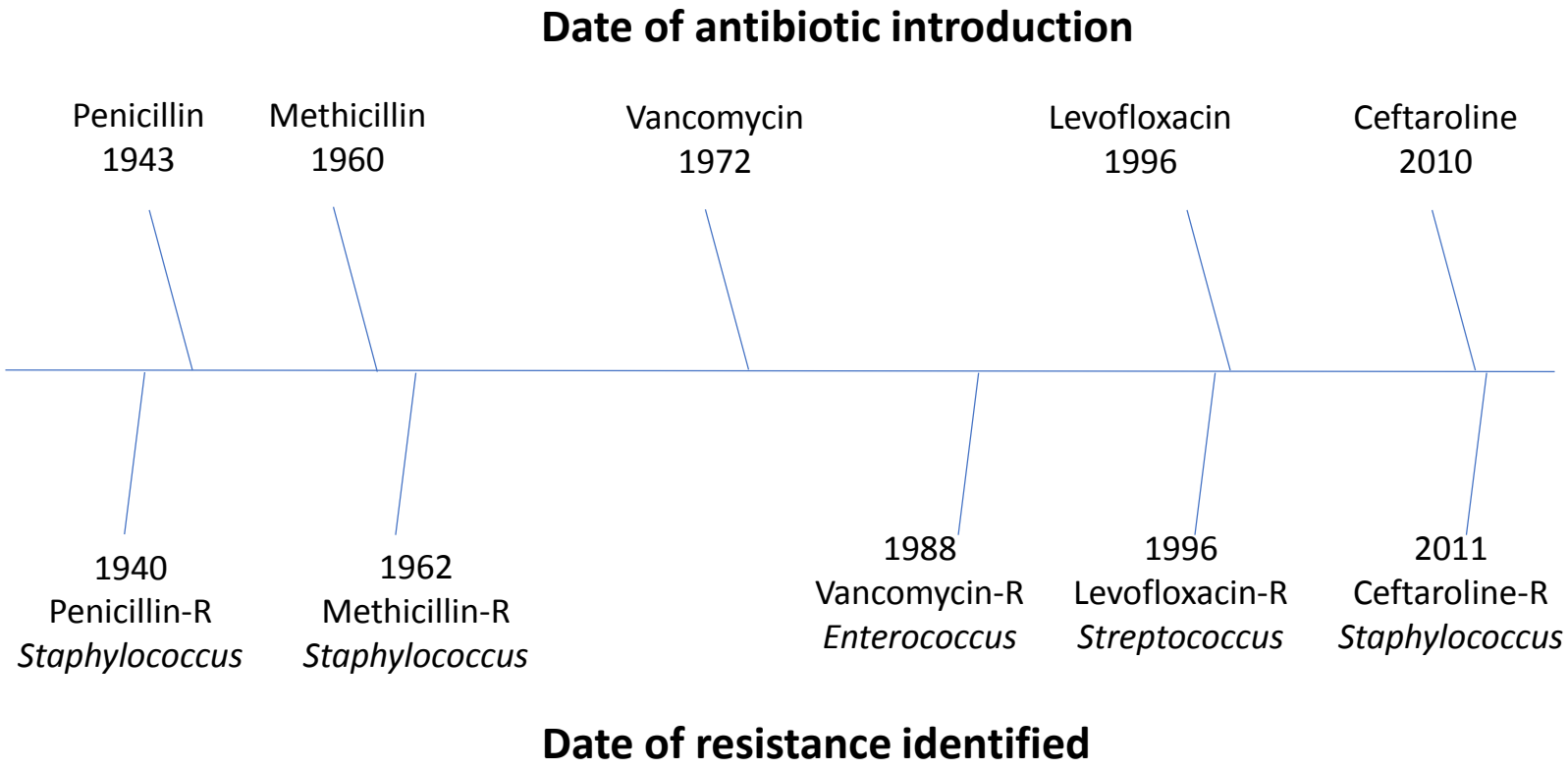
- Misuse of antibiotic(s)
- Overuse of antibiotics in outpatient settings.
- Overuse of antibiotics in hospital settings.
- Poor compliance with regimens.
- Use of antibiotics in animals. (80% of antibiotics sold to farms)

One Health Antibiotic Stewardship Collaborative

- Multi-partner initiative to address antibiotic use
- Inter-agency approach by government
  - MDH, MN Board of Animal Health, MN Ag, Pollution Control Agency
- Stakeholders from academia, human and veterinary clinical practice, professional and industry associations, healthcare systems, producer organizations

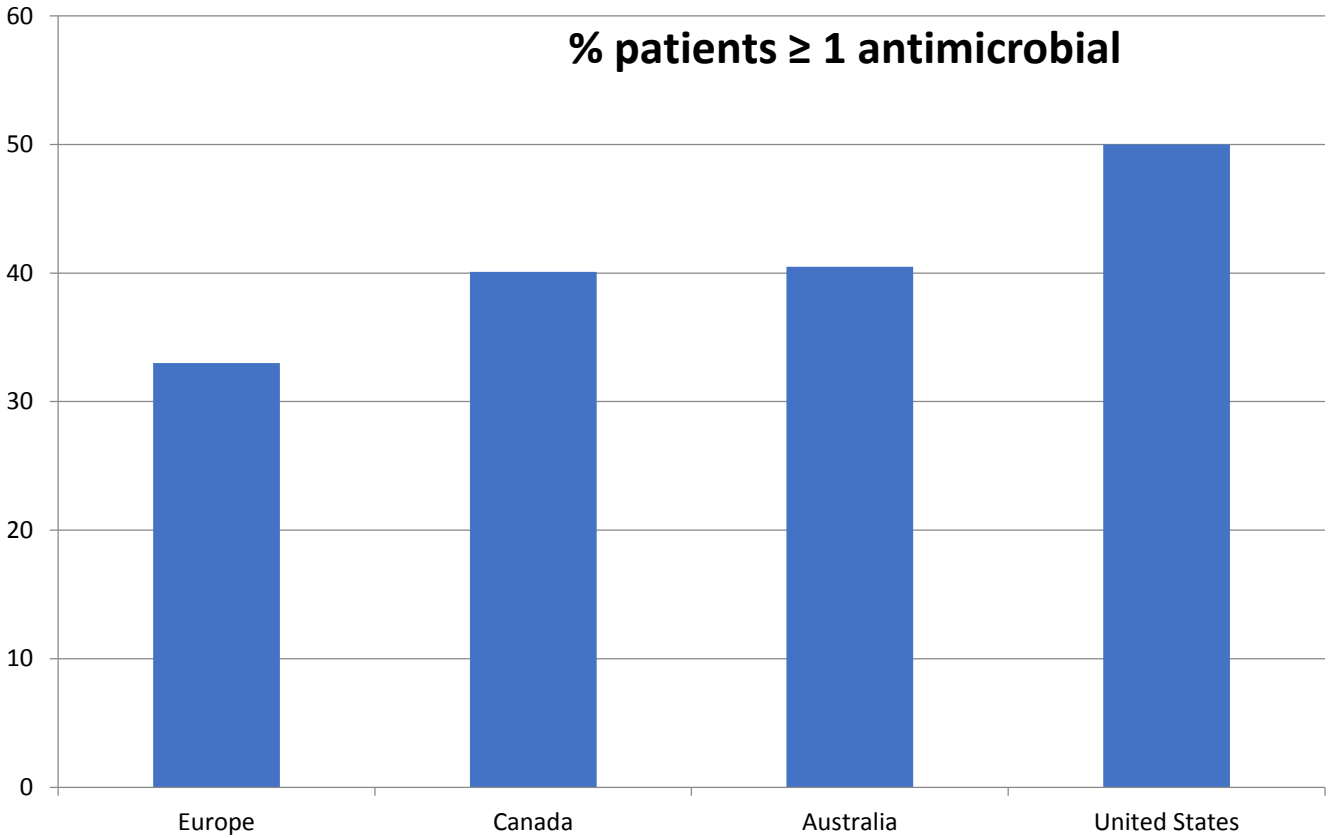
Courtesy Dr Ruth Lynfield

Antibiotic Use Drives Resistance



http://www.cdc.gov/drugresistance/about.html

Prevalence of use in hospitals



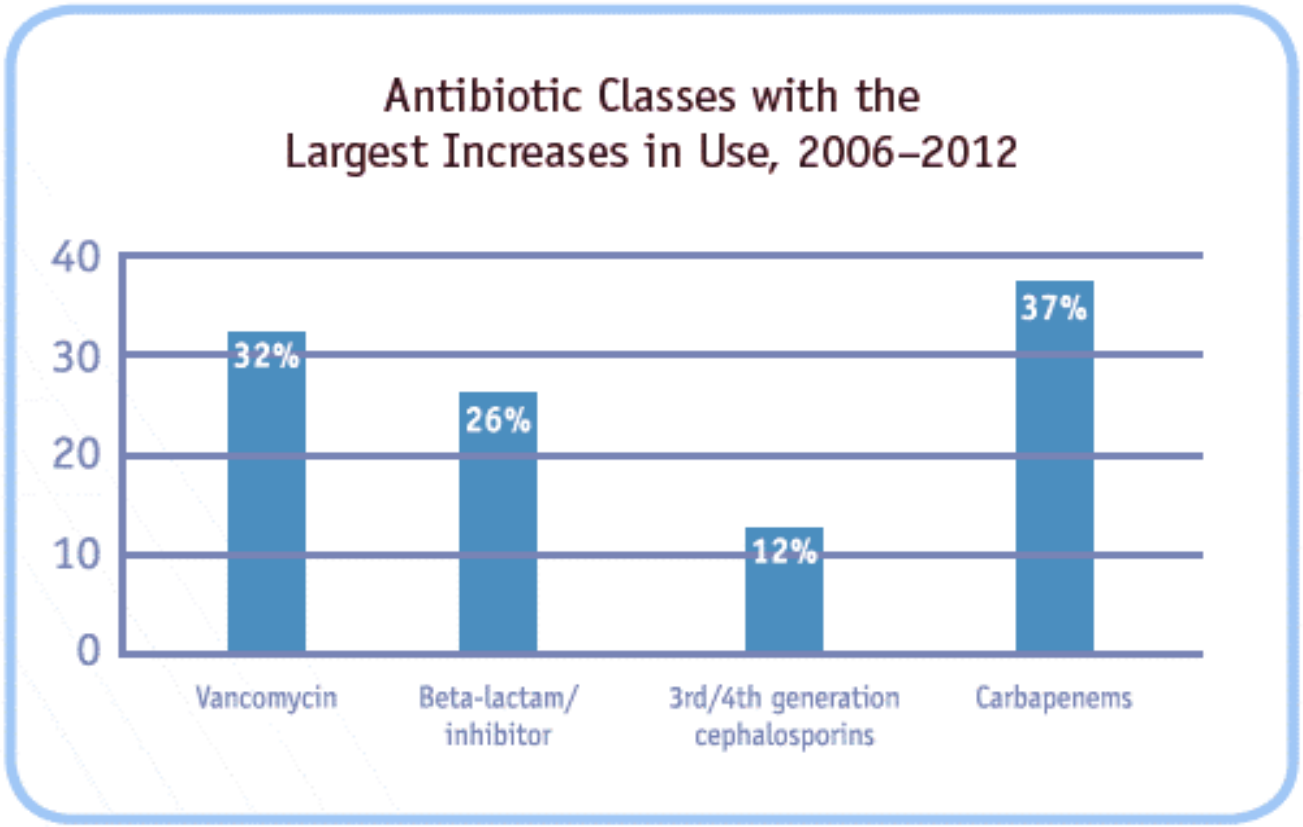
ECDC 2013 Point Prevalence Survey of HAI and antimicrobial use in European hospitals 2011-2012,

Taylor et al Can J Infect Dis Med Microbiol. 2015 Mar-Apr; 26(2): 85–89.

Antimicrobial prescribing practice in Australian hospitals. December 2016.

Magill et al JAMA 2014;312(14):1438-1446

Classes with highest increase in use US hospitals



Source: CDC. Antibiotic Use in the United States, 2017: Progress and Opportunities.
https://www.cdc.gov/getsmart/pdf/stewardship-report.pdf

Misuse of antibiotics

Underuse	• An antibiotic is not used when it could improve health
Unnecessary use	• An antibiotic is not indicated e.g. non bacterial infections
Inappropriate use	• Incorrect timing, choice, dose, route, or duration

Inappropriate use of antibiotics

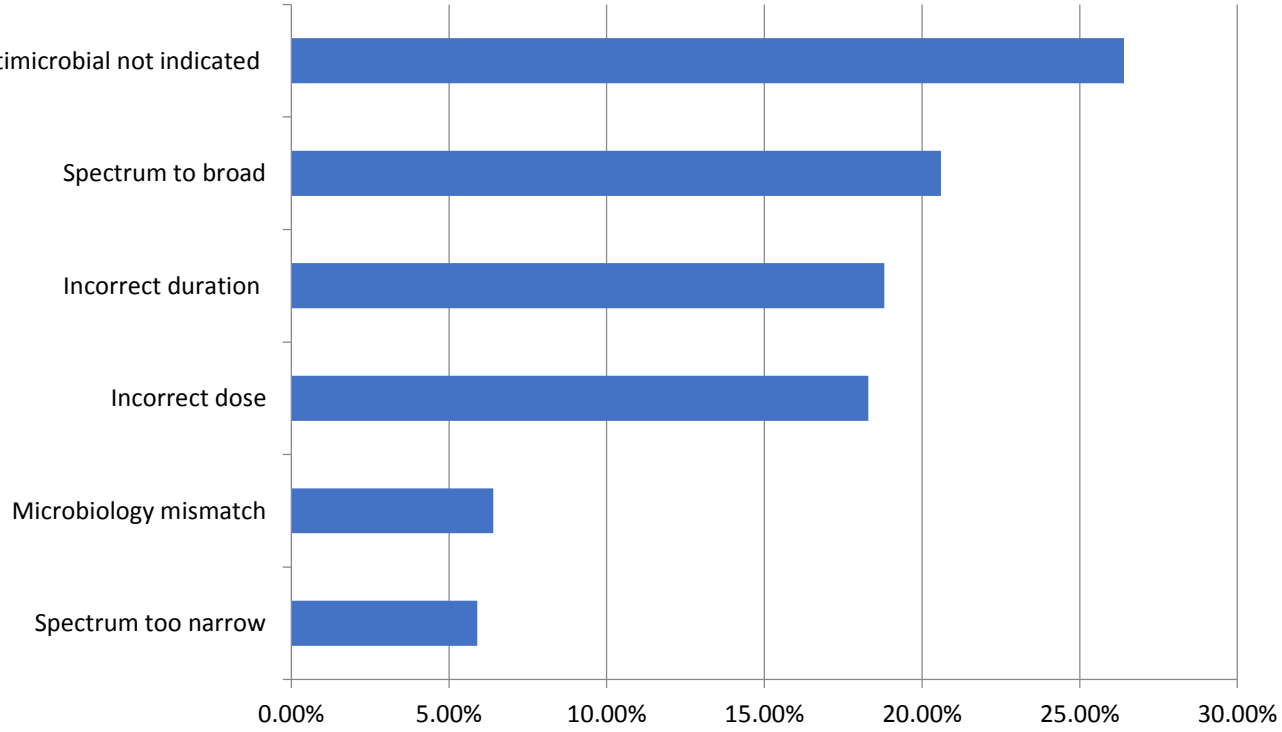
Suboptimal or inadequate use

- administration is delayed in a critically ill patient,
- choice of an antimicrobial with an unnecessarily broad spectrum or too narrow a spectrum
- dose is too high or too low
- duration is too long or too short
- treatment is not streamlined or changed when microbiological culture data become available
- use in patient with an allergy to the agent
- drug – drug interactions
- poor patient adherence to the prescribed treatment

Inappropriate use in hospitals

Common problems

30 - 50% inpatient use inappropriate or suboptimal[1]



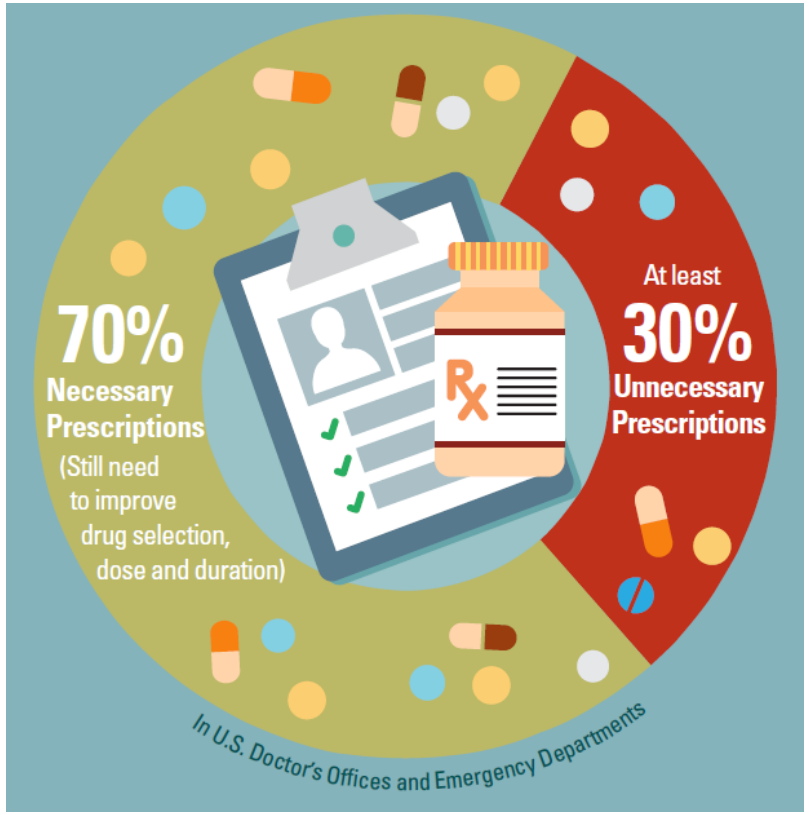
1. CDC Get Smart for Healthcare in Hospitals and Long Term Care https://www.cdc.gov/getsmart/healthcare/
2. Antimicrobial prescribing practice in Australian hospitals. December 2016

Common Outpatient Clinical Syndromes and Overtreatment

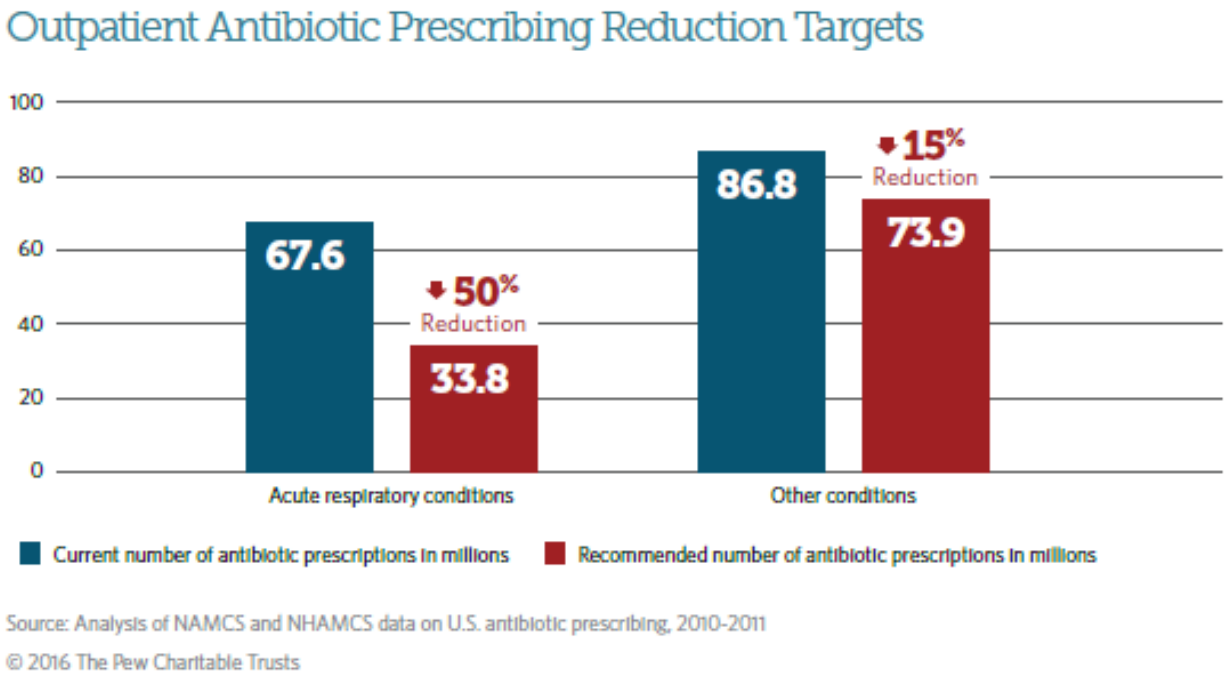
Condition	% bacterial	overtreatment
pneumonia	70%	30%
acute bronchitis	<< 5 %	70%
rhino-sinusitis	<<5 %	95%
UTI	100%	70% in elderly
cellulitis	100 %	30%
Pharyngitis	10%	>60%

Infect Control Hosp Epidemiol 2015; 36:142-152

Setting National Targets: Outpatient Antibiotic Prescribing



47 million unnecessary antibiotic prescriptions per year



By 2020, significant outcomes of Goal 1 will include: **(CARB National Action Plan)**

- Establishment of antibiotic stewardship programs in all acute care hospitals and improved antibiotic stewardship across all healthcare settings.
- Reduction of inappropriate antibiotic use by 50% in outpatient settings and by 20% in inpatient settings.

Fleming-Dutra et al. JAMA 2016;315(17): 1864-1873.
http://www.pewtrusts.org/~/media/assets/2016/05/antibioticuseinoutpatientsettings.pdf; CARB Action Plan

Outcomes of antibiotic misuse

- Development of resistant organisms, *Clostridium difficile* infections
- Patient harm such as treatment failure adverse drug events and increased mortality
- Increase healthcare and societal costs.

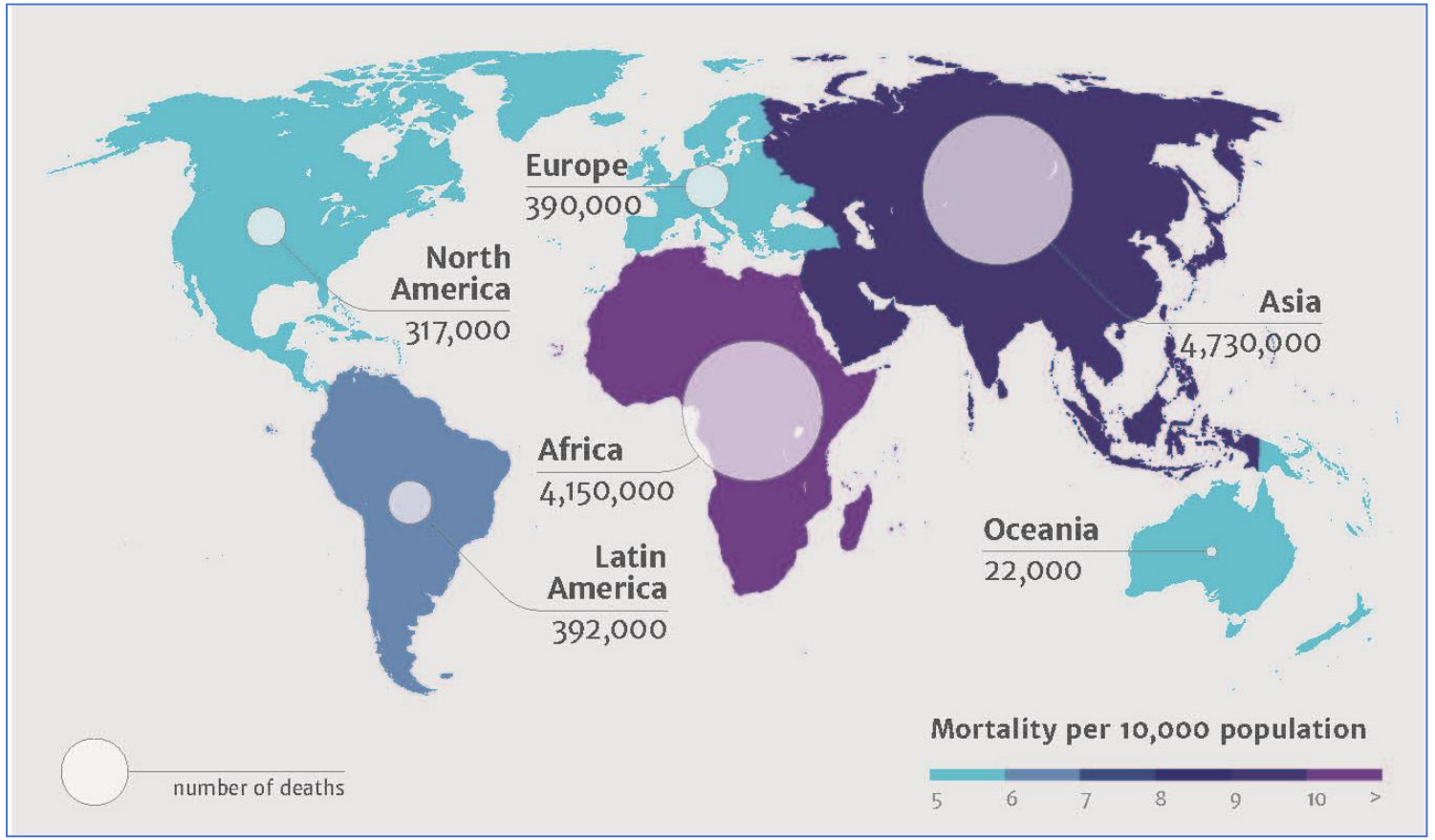
It's a Matter of Patient Safety

- Adverse events from antibiotics range from minor to severe
  - Side effects like rash or antibiotic-associated diarrhea
  - Allergic reactions, including anaphylaxis (life-threatening)
- 1 in 1000 antibiotic prescriptions leads to an emergency department (ER) visit for an adverse event
  - 142,000 ER visits per year for antibiotic-associated adverse events
  - Antibiotics are most common cause of drug-related emergency department visits for children
- Long-term consequences: growing evidence that antibiotics associated with chronic disease through disruption of the microbiota and microbiome

Shehab, et al. *Clin Infect Dis*. 2008 Sep 15;47(6):735-43. Bourgeois, et al. *Pediatrics.* 2009;124(4):e744-50.
Linder. *Clin Infect Dis*. 2008 Sep 15;47(6):744-6. Vangay, et al. Cell host & microbe 2015; 17(5): 553-564.

GLOBAL DIMENSIONS

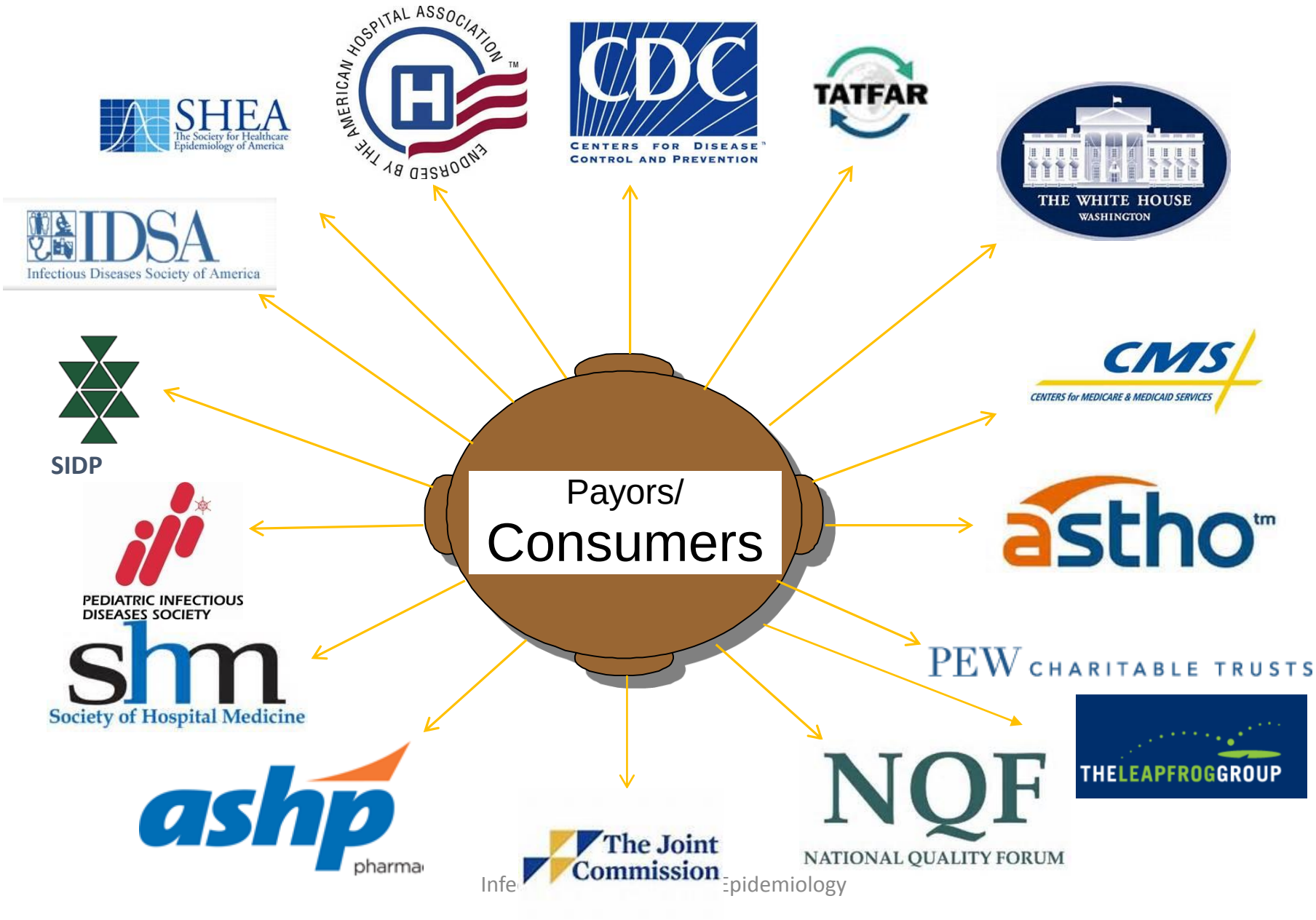
Estimate: By 2050, 10 Million Deaths Attributed to AMR Every Year
Costing World Economy $100 Trillion

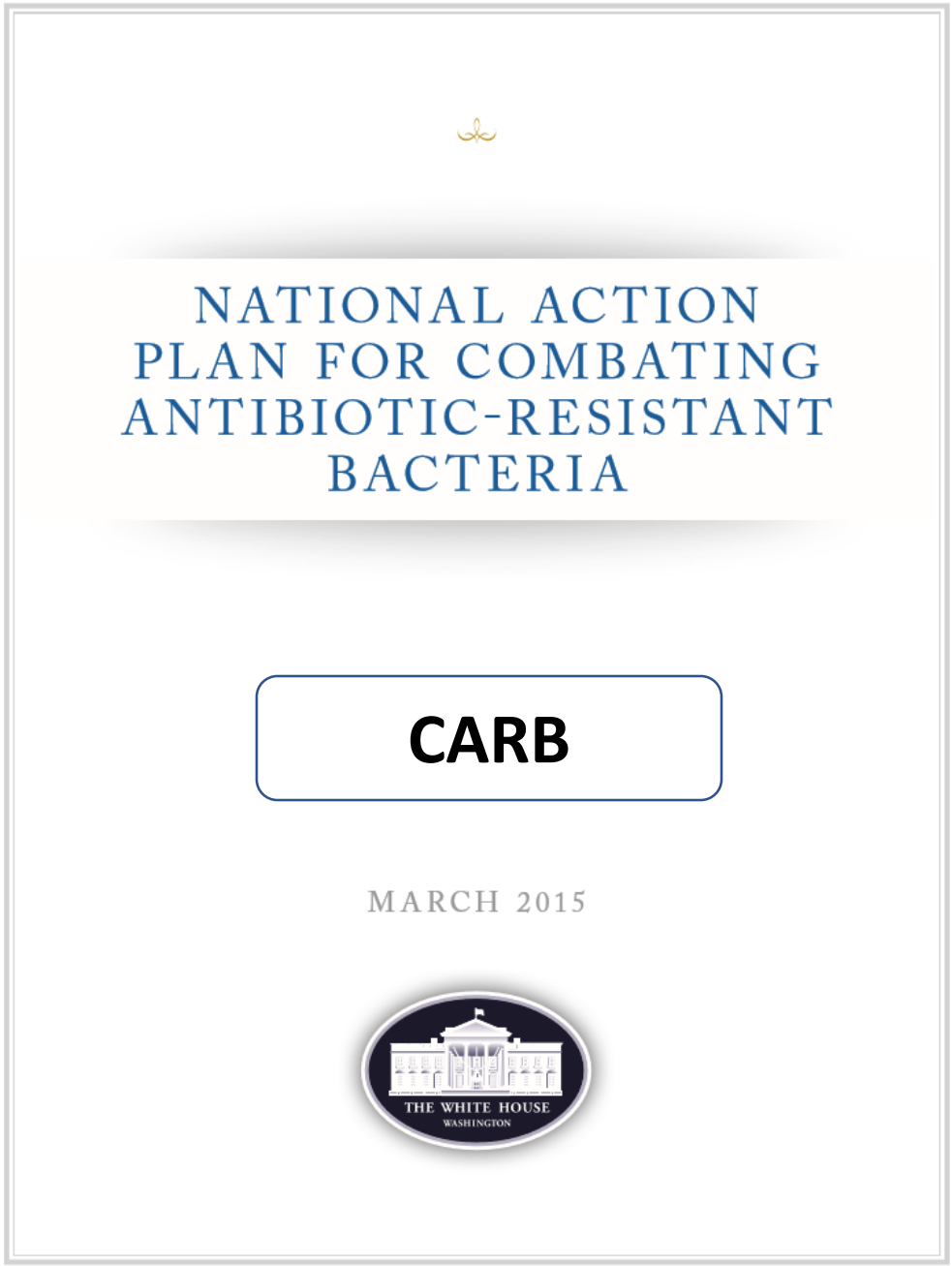


Review on Antimicrobial Resistance (AMR), 2014. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. London, UK http://amr-review.org

Regulatory

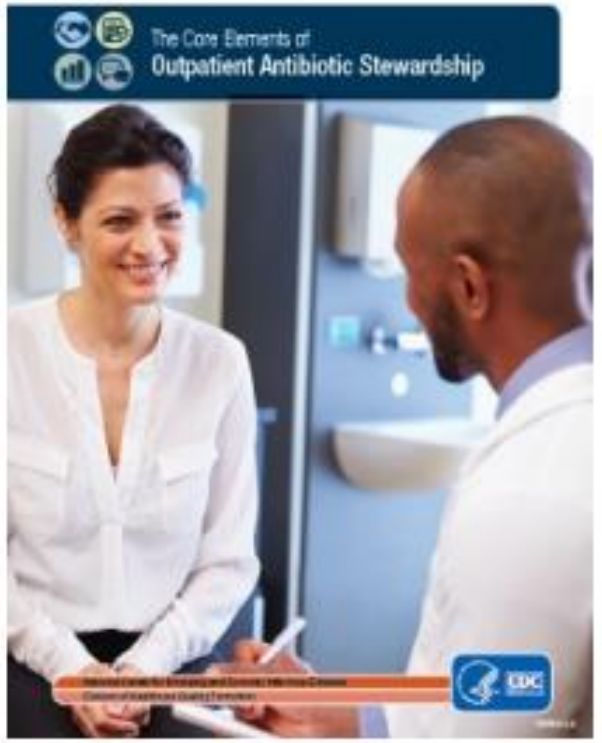
Stewardship Seats at the Table





https://www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

Core Elements for Antibiotic Stewardship Programs



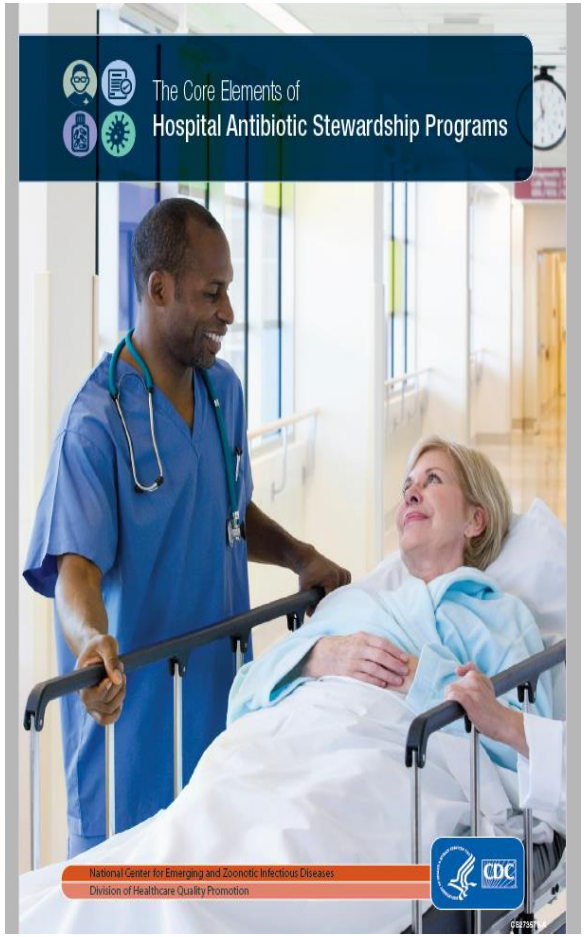
http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html

CDC Core Elements

1. **Leadership commitment**: Dedicate necessary human, financial, and IT resources
2. **Accountability**: Appoint a single leader responsible for program outcomes-this is usually a physician
3. **Drug expertise**: Appoint a single pharmacist leader to support improved prescribing
4. **Act**: Take at least one prescribing improvement action, such as "antibiotic timeout"
5. **Track**: Monitor prescribing and antibiotic resistance patterns
6. **Report**: Regularly report to interdisciplinary team the prescribing and resistance patterns, and steps to improve
7. **Educate**: Offer team education about antibiotic resistance and improving prescribing practice

Centers for Disease Control and Prevention. *MMWR.* March 2014. 63; 194-200.

CDC's Core Elements Adopted by



- The Joint Commission for their antibiotic stewardship standard
- DNV for their antibiotic stewardship standard
- CMS-funded Hospital Improvement Innovation Networks (HIINs)
- AHRQ Comprehensive Unit-based Safety Program (CUSP)

Joint Commission & Antimicrobial Stewardship

Joint Commission

Requirement

Official Publication of Joint Commission Requirements

New Antimicrobial Stewardship Standard

APPLICABLE TO HOSPITALS AND CRITICAL ACCESS HOSPITALS

Effective January 1, 2017

Medication Management (MM)

Standard MM.09.01.01

The [critical access] hospital has an antimicrobial stewardship program based on current scientific literature.

Elements of Performance for MM.09.01.01

1. Leaders establish antimicrobial stewardship as an organizational priority. (*See also* LD.01.03.01, EP 5)

   Note: *Examples of leadership commitment to an antimicrobial stewardship program are as follows:*

   - *Accountability documents*
   - *Budget plans*
   - *Infection prevention plans*
   - *Performance improvement plans*
   - *Strategic plans*
   - *Using the electronic health record to collect antimicrobial stewardship data*

2. The [critical access] hospital educates staff and licensed independent practitioners involved in antimicrobial ordering, dispensing, administration, and monitoring about antimicrobial resistance and antimicrobial stewardship practices. Education occurs upon hire or granting of initial privileges and periodically thereafter, based on organizational need.

3. The [critical access] hospital educates patients, and their families as needed, regarding the appropriate use of antimicrobial medications, including antibiotics. (For more information on patient education, refer to Stan-

https://www.jointcommission.org/topics/hai_antimicrobial_stewardship.aspx

This document is scheduled to be published in the
Federal Register on 06/16/2016 and available online at
http://federalregister.gov/a/2016-13925, and on FDsys.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

42 CFR Parts 482 and 485

[CMS-3295-P]

RIN 0938-AS21

Medicare and Medicaid Programs; Hospital and Critical Access Hospital (CAH) Changes to Promote Innovation, Flexibility, and Improvement in Patient Care

AGENCY: Centers for Medicare & Medicaid Services (CMS), HHS.

ACTION: Proposed rule.

SUMMARY: This proposed rule would update the requirements that hospitals and critical access hospitals (CAHs) must meet to participate in the Medicare and Medicaid programs.

State Antibiotic Stewardship Legislative Policies

- California
  - Senate Bills 1311 (2014) and 361 (2015) require antibiotic stewardship programs in all California hospitals and nursing homes
- Missouri
  - Senate Bill 579 (2016) requires that all non-psychiatric hospitals establish stewardship programs and report antibiotic use to CDC's National Healthcare Safety Network (NHSN) Antimicrobial Use Option

Antimicrobial Stewardship program (ASP)

Basic principles and implementation strategies

The Challenge

- How to initiate and improve antibiotic stewardship efforts
- Proving that it works
  - Clinical outcomes
  - Decrease resistance
- Changing the antibiotic prescribing culture
- Hardwiring the process
- Continuing to show financial benefit to maintain funding and support of efforts


GUIDELINES

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

The Problem with Antimicrobial Stewardship

- Everyone thinks they know what it is

But who knows what it should be?

– Which strategies are most effective?
– How to assess their effectiveness?

Antimicrobial Stewardship: Definition

- A system of informatics, data collection, personnel, and policy/procedures which promotes the optimal selection, dosing, and duration of therapy for antimicrobial agents throughout the course of their use.

- An effective antimicrobial stewardship program will limit inappropriate and excessive antimicrobial use, but more importantly improve and optimize therapy and clinical outcomes for the individual infected patient.

Ohl CA. *Seminar Infect Control* 2001;1:210-21.
Ohl CA. *J. Hosp Med*. In press.
Dellit TH, et. al. Clin Infect Dis. 2007;44:159-177

Antimicrobial Stewardship: Goals

- **Improve patient outcomes**
- Optimize selection, dose and duration of Rx
- Reduce adverse drug events including secondary infection (e.g. *C. difficile* infection)
- Reduce morbidity and mortality
- Prevent or slow the emergence of antimicrobial resistance
- Reduce length of stay
- Reduce health care expenditures

MacDougall CM and Polk RE. Clin Micro Rev 2005;18(4):638-56.
Ohl CA. *J. Hosp Med*. In press.
Dellit TH, et. al. Clin Infect Dis. 2007;44:159-177

Strategies

Appropriate antibiotic therapy

The 5 Ds

1. Right **D**iagnosis
   - What infection syndrome is being treated?
   --Does the patient have an infection?
   - Have appropriate diagnostic tests been collected?

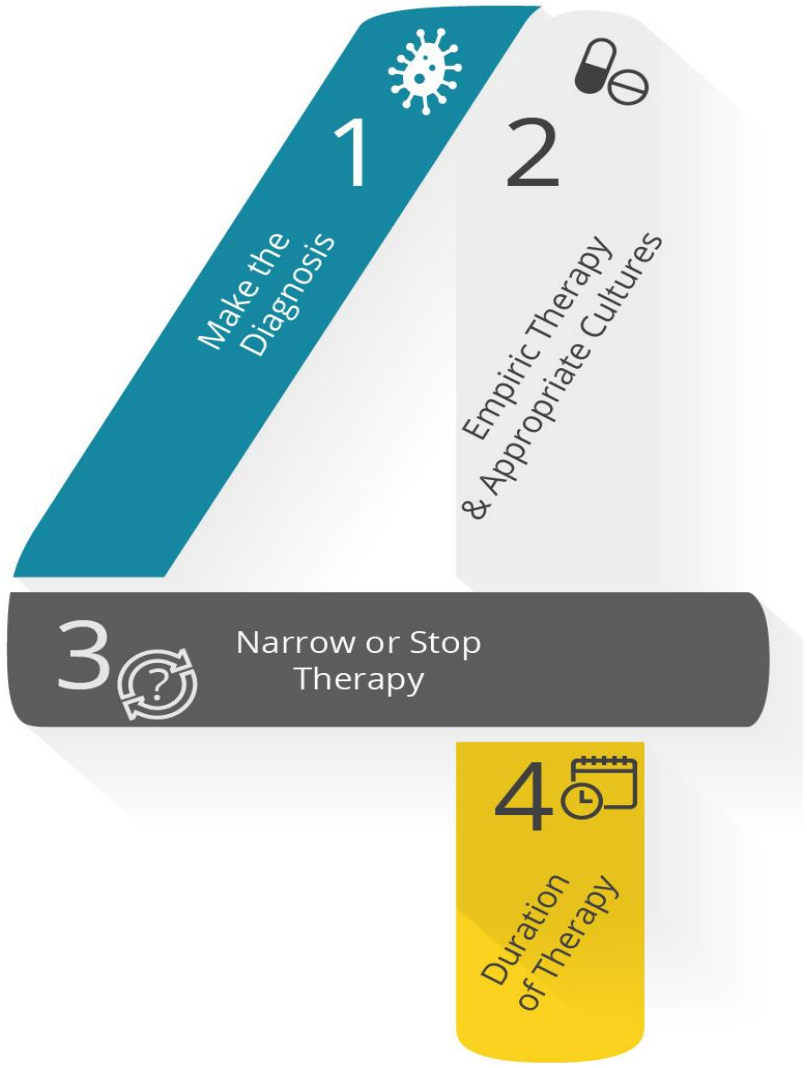
2. Right **D**rug
   - Demonstrated effective per local epidemiology
   - Safest
   - Least “resistance-ogenic” – narrowest spectrum
   - Least expensive

3. Right **D**ose

4. Right **D**uration:
   - Minimal duration undefined for many indications
   - For most: resolution of systemic and improvement in local manifestations

5. Right **D**e-escalation: change to narrowest spectrum/safest/least expensive regimen when:
   - Justified by culture results (positive or negative)
   - Clinical improvement (e.g., IV to PO switch)

Four Moments of Antibiotic Decision Making



1. Does my patient have an infection that requires antibiotics?

2. Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate?

3. A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy?

4. What duration of antibiotic therapy is needed for my patient's diagnosis?

AHRQ Safety Program for Improving Antibiotic Use. 2018.

Obtain Cultures Prior to Starting Antibiotics!

- Develop a process to ensure cultures are properly and consistently ordered
  - Nursing to ensure safe/timely collection of specimens from appropriate source
- Develop processes to ensure cultures are properly and promptly transported and processed

ARHAI. Antimicrobial stewardship: "*start smart-then focus".* Guidance for antimicrobial stewardship in hospitals (England). November, 2011.
Eur J Clin Microbiol Infect Dis. 2009;28(2009):1447-1456.
CDC. Core Elements of Hospital Antibiotic Stewardship Programs. 2014.
Am J Infect Control. 2013;41(2013):365-367.

Clinical Pearl: Appropriate Specimen Collection and Cultures

Culture results guide better patient care decisions

- Wounds
  - Recommend against superficial swab, likely colonizing organisms
  - Preferred samples are pus and tissue
  - Surgical wounds – recommend contacting MD prior to culture collection, consider wound care consult if available for cleansing/debridement prior to sample
- Blood cultures
  - Separate peripheral venipunctures using aseptic technique are preferred
  - Drawing blood for cultures from indwelling catheters should be avoided unless the catheter is thought to be the source of bacteremia
  - Label specimen and collection site and time
- Urine
  - Evaluation of the patient's symptoms is critical before ordering urine culture
  - Screening for asymptomatic bacteriuria (ABU) is not recommended except in pregnancy and before an invasive urological procedure
  - A urinalysis should be performed before a urine culture is ordered. Urine with >10 WBC/HPF with symptoms should have a urine culture if patient has symptoms.

Clinical Pearl: Appropriate Specimen Collection and Cultures (2)

- Stool for *C. difficile*
  - clinically significant diarrhea is defined as 3 or more unformed stools samples within 24 hours
  - Only watery or unformed loose stool should be submitted (Bristol 6 or 7)
  - If patient has been on laxatives in the last 48 hours cancel order and allow at least 48 hours without laxatives to reassess
  - Testing to evaluate for cure is not recommended.
  - PCR does not distinguish colonization versus infection, therefore indications for testing are very important.

Choice of Empiric Agent

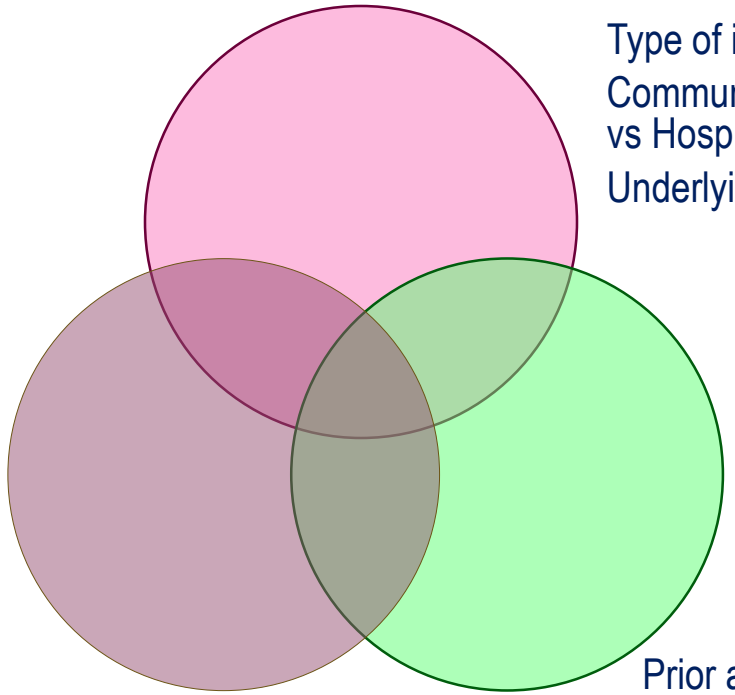
MAXIMIZE COVERAGE

against most likely pathogens

MINIMIZE SELECTION

for resistance

Considerations in Empiric Choice



Host

Type of infection

Community-Acquired vs LTC vs Hospital-Acquired

Underlying comorbidities

Microbe

Local antibiogram

ICU vs Non-ICU

Drug

Prior antibiotic therapy

Selection based on potential for resistance

Need for multiple agents

Front-end Approach

Physician writes order for “Restricted Drug”

Order arrives in pharmacy, pharmacist informs the physician and primary nurse that the drug is “restricted”/”Not part of the pathway”/”non-formulary”

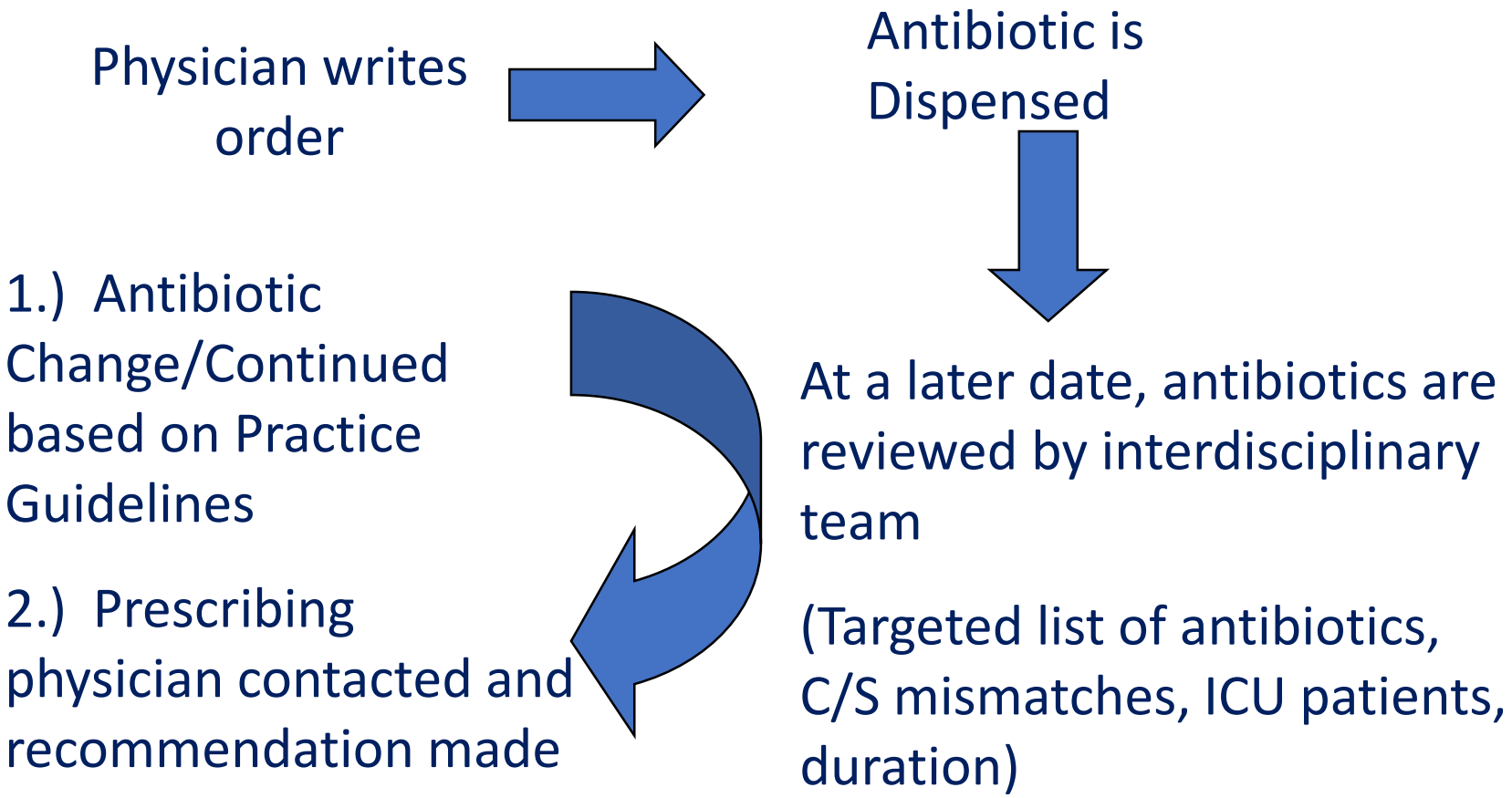
Prescribing Physician and the “GATE KEEPER” converse

Approval or Alternative Antibiotic Selected

Front-end Approach

- **Advantages**
  - Direct control over antimicrobial use
  - Effective control of antimicrobial use during outbreaks
  - Decreased inappropriate use of antimicrobials (and thus costs)
- **Disadvantages**
  - Personnel needs
  - Antagonistic relationship (loss of autonomy)
  - Therapy may be delayed
  - Manipulation of the system
  - ID physicians often exempt
  - Effectiveness in decreasing resistance is less clear
  - No impact on de-escalation or duration

Prospective Audit and Feedback (back-end approach)



Prospective Audit and Feedback

- **Advantages**
  - Prescriber autonomy maintained
  - Educational opportunity provided
  - Patient information can be reviewed before interaction
  - Inappropriate antimicrobial use decreased
  - Impact duration and de-escalation
- **Disadvantages**
  - Compliance voluntary
  - Identification of patients may require computer support
  - Prescribers may be reluctant to change therapy if the patient is doing well
  - Some inappropriate antimicrobial use permitted (with retrospective audit)

Guidelines/ClinicalPathways /EBOS*

- Protocols to guide therapy for a given infection
  - Specific to institutional formulary, patient populations, and resistance patterns
- Evidence-based

- **Advantages**
  - Appropriate antimicrobial use may increase
  - Form of education

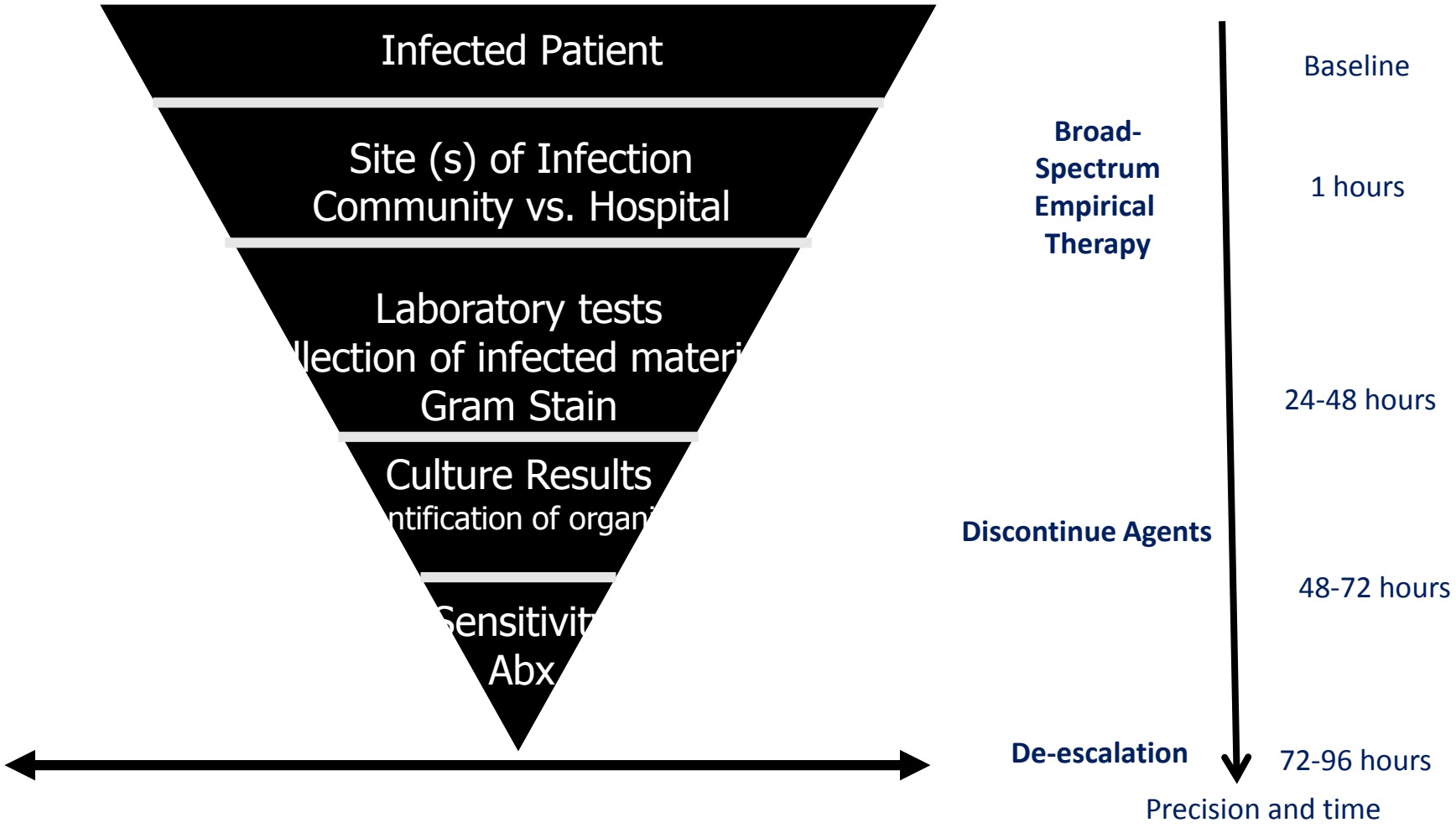
- **Disadvantages**
  - Adherence is usually voluntary
  - “Cookbook medicine”
  - Maintenance is required

*Guidelines may not be appropriate for all situations. Decisions should be based on clinical judgment and consideration for individual patients.

De-Escalation: Goals

- Changing from a broad-spectrum antibiotic to one with a narrower spectrum if appropriate
- Eliminate overlapping or combination therapy targeting causative organism or
- Stopping antimicrobial therapy when a non-infectious etiology most likely
- Administer antimicrobial therapy for the correct duration
- Decrease antimicrobial exposure → reduce adverse events
- Cost savings

De-escalation Timeline



De-escalation of Therapy

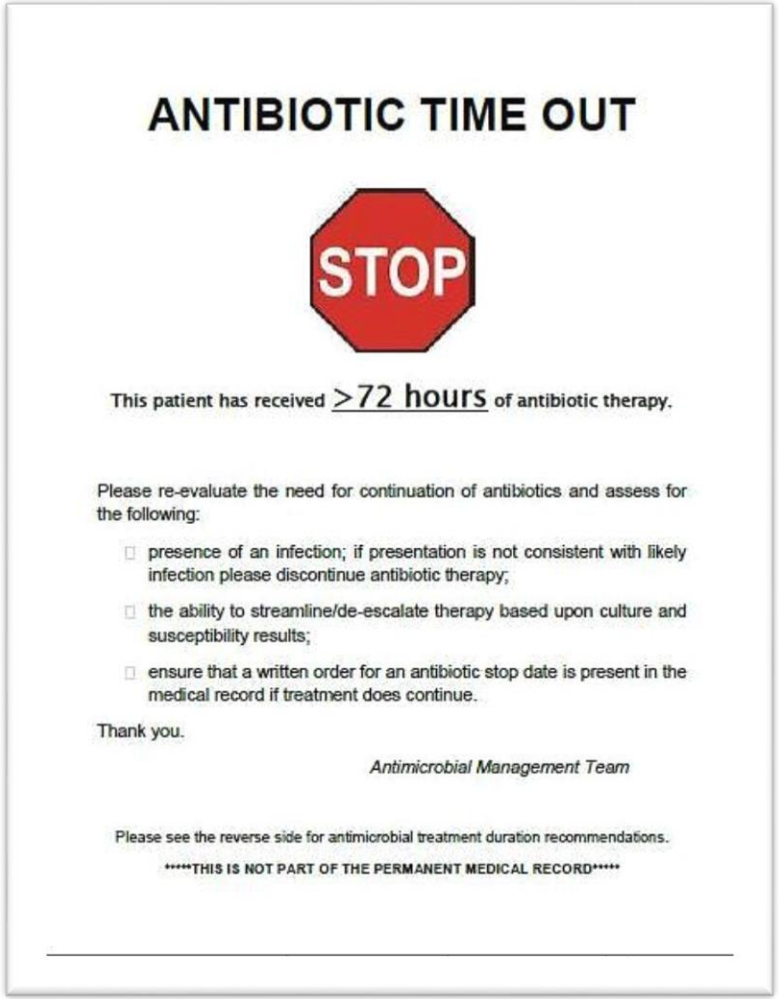
- Decrease number of agents and/or spectrum of activity as appropriate in response to culture results and clinical outcomes
- Optimizing initial therapy may oppose steps to limit use of broad-spectrum agents
  - De-escalation recognizes both aspects
    - **Advantages**
      - Allows initial use of broad-spectrum therapy
      - Narrows therapy when appropriate
      - Improves outcomes
      - Reduces adverse events
      - May influence future prescribing behavior
      - Decreases inappropriate use of antimicrobials
      - Reduces costs
    - **Disadvantages**
      - Prescribers may be reluctant to change therapy if the patient is doing well
      - If not done correctly, may narrow therapy "inappropriately"

De-escalation: Lessons learned

The most common reasons for **not** de-escalating:

- Lack of conclusive microbiology
  - Continued use of broad-spectrum antimicrobial therapy
- Diagnostic uncertainty
  - Treatment of fever, colonization and/or contamination
- Insecurity
  - Treatment of noninfectious syndrome associated with fever
- Duration longer than necessary leading to increase adverse events
  - Highlight duration of therapy for broad-spectrum antibiotics
  - Engage all members of the interdisciplinary healthcare team in monitoring

Antibiotic Time Out



ANTIBIOTIC TIME OUT

STOP

This patient has received >72 hours of antibiotic therapy.

Please re-evaluate the need for continuation of antibiotics and assess for the following:

- ☐ presence of an infection; if presentation is not consistent with likely infection please discontinue antibiotic therapy;
- ☐ the ability to streamline/de-escalate therapy based upon culture and susceptibility results;
- ☐ ensure that a written order for an antibiotic stop date is present in the medical record if treatment does continue.

Thank you.

Antimicrobial Management Team

Please see the reverse side for antimicrobial treatment duration recommendations.

*****THIS IS NOT PART OF THE PERMANENT MEDICAL RECORD*****

- Trigger tool to stop and reassess antibiotic therapy
- Targeted at all providers for Med/Surg patients
- Guided assessment at 72 hrs
- Treatment duration recommendations included for key infections

Duration: Avoid automatic 10-14 Day Courses

- **New Evidence for Duration of Therapy**
  - Uncomplicated urinary tract infection: 3-5 days[1]
  - Community-acquired pneumonia: 3-7 days[2]
  - Ventilator-associated pneumonia: 8 days[3]
  - CR-BSI Coagulase-negative staphylococci: 5-7 days[4]
  - Acute Hem Osteomyelitis in children-21 days[5]
  - Meningococcal meningitis-7 days[6]
  - Uncomplicated secondary peritonitis with source control: 4-7 days[7]
  - Uncomplicated SSTI 5 days[8]

1. *Clin Infect Dis* 1999; 29:745-758
2. *Clin Infect Dis* 2007; 44:S27-72
3. *JAMA* 2003; 290:2588-2598
4. *Clin Infect Dis* 2009; 49:1-45
5. *Pediatr Infect Dis* 2010; 29:1123-1128
6. *N Engl J Med* 1997; 336:708-716
7. *Clin Infect Dis* 2010: 50:133-164
8. *Arch Intern Med* 2004; 164:1669-1674

Case

This is a 46 year old female admitted with hypotension, fever, and flank pain. She has no underlying medical or urologic problems. Her urine showed pyuria and bacteriuria, the peripheral WBC was 16,000/mm^3. She was admitted to the ICU and empirically started on _____.

What would you start?

1. Piperacillin/tazobactam
2. Cefepime
3. Ceftriaxone
4. Levofloxacin

And Now the Rest of the Story

She was admitted to the ICU and started on cefepime. A PICC line was inserted. By day 2, she stabilized and was transferred to the floor. Her urine and blood grew *E. coli* sensitive to all tested antibiotics except ampicillin. The results were not available until after she was transferred to the floor. She was continued on cefepime. On day 7, she spiked a new fever. Blood cultures were drawn and grew_____. Antibiotics were changed to _____. On day 12 her WBC increased to 30,000/mm^3 and she reported unformed stools. Your diagnosis_____

Where there opportunities to improve?

1. de-escalation
2. duration

Effective Implementation

Getting started

In press *Am J Infect Control*

ASP Phase 1 Foundational

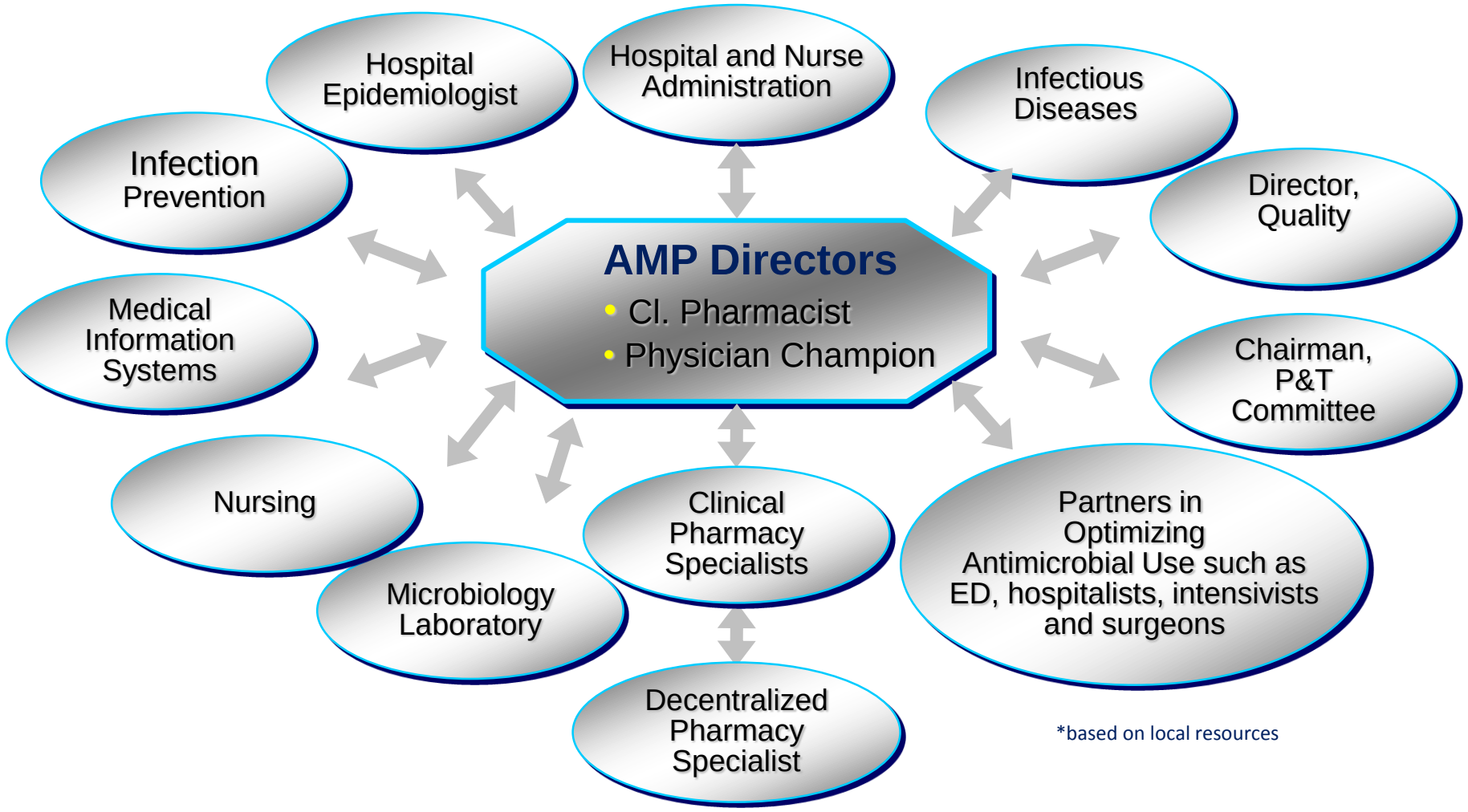
- MD/ PharmD Champion
- Multidisciplinary team
- Gap Assessment
- Assess staff resources
- Competency/Training Planning
- Communication Plan for facility
- CEO support for AMP by approval of gap and action plan

- Selecting Physician Champion
- Complete gap assessment and action plan as a team
- Determine staffing needs to adequately resource AMP activities
- Create competency/training plan for all disciplines based on current knowledge and involvement
- Invite CEO to AMP team meeting to discuss plan, resources, and support

The establishment of a well supported, multidisciplinary ASP infrastructure ensures an ASP is sustainably integrated into facility practices rather than dependent on a single person

Antimicrobial Stewardship Team

Multidisciplinary Team Approach to Optimizing Clinical Outcomes*



*based on local resources

Modified Clin Infect Dis 2007;44:159-177.

Physician To Do List

- Select local physician champion
- Develop an effective antimicrobial stewardship team
- Education the medical staff and administration about the urgency and value of an effective antimicrobial stewardship team
- Assure that microbiology is aware of how to detect new resistance mechanisms (e.g. CREs, NDM1) and new CLSI break points

Clinical Infectious Diseases

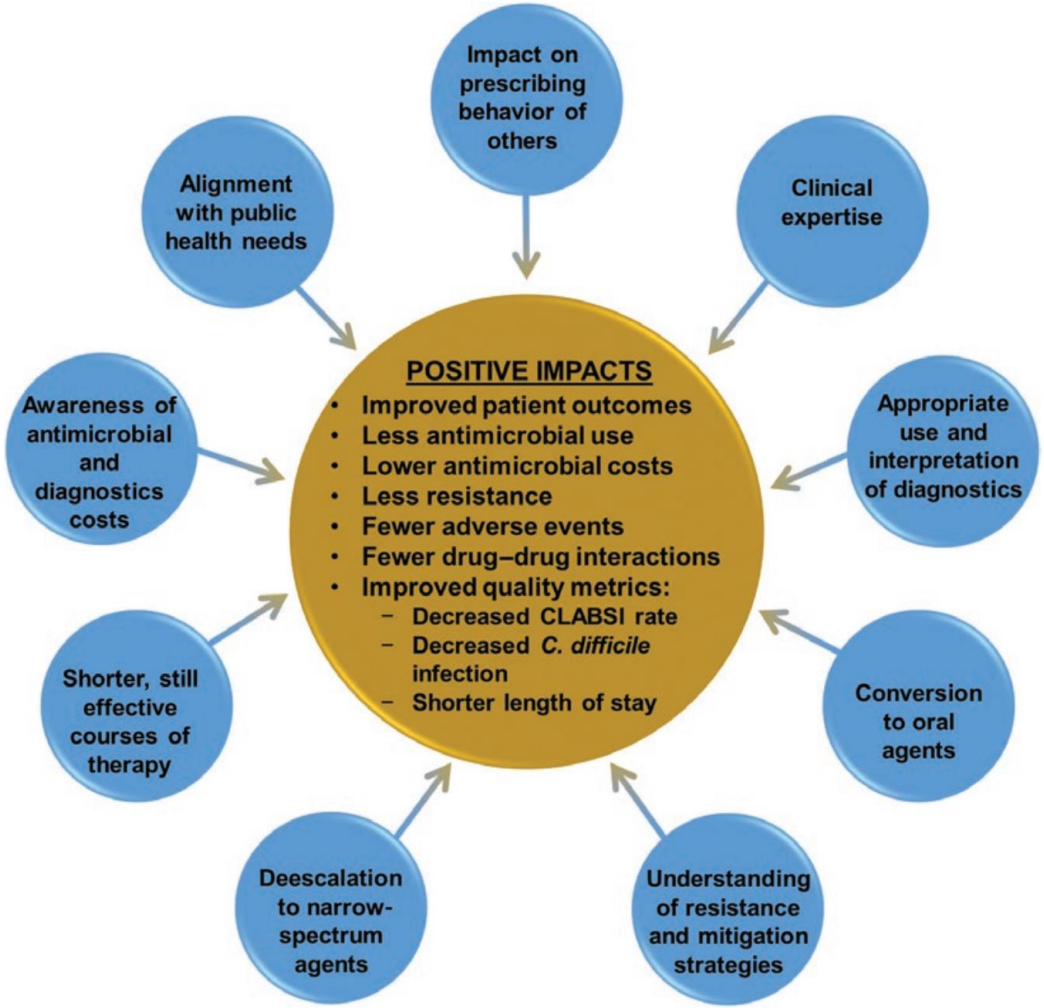
IDSA FEATURES

Infectious Diseases Physicians: Leading the Way in Antimicrobial Stewardship

Belinda Ostrowsky,[1] Ritu Banerjee,[2] Robert A. Bonomo,[3,4,5] Sara E. Cosgrove,[6] Lisa Davidson,[7] Shira Doron,[8] David N. Gilbert,[9,10] Amanda Jezek,[11] John B. Lynch III,[12] Edward J. Septimus,[13,14] Javeed Siddiqui,[15] and Nicole M. Iovine[16]; for the Infectious Diseases Society of America, Pediatric Infectious Diseases Society, and the Society for Healthcare Epidemiology of America

[1]Montefiore Medical Center, Albert Einstein Medical Center, Bronx, New York; [2]Vanderbilt University Medical Center, Nashville, Tennessee; [3]Research and Medical Services Veterans Affairs Medical Center, [4]Departments of Medicine, Pharmacology, Molecular Biology and Microbiology, Case Western Reserve University, and [5]Cleveland Geriatric Research Education and Clinical Center, Case Western Reserve University–Cleveland Veterans Affairs Medical Center, Center for Antimicrobial Resistance and Epidemiology, Ohio; [6]Johns Hopkins University School of Medicine, Baltimore, Maryland; [7]Carolinas Health Care System, Charlotte, North Carolina; [8]Tufts Medical Center, Boston, Massachusetts; [9]Providence-Portland Medical Center and [10]Oregon Health Sciences University, Portland; [11]Infectious Diseases Society of America, Arlington, Virginia; [12]Harborview Medical Center, University of Washington, Seattle; [13]HCA Healthcare, Nashville, Tennessee; [14]Texas A&M College of Medicine, Houston; [15]TeleMed2U, Roseville, California; and [16]University of Florida College of Medicine, Gainesville

Infectious Diseases Physicians: Leading the Way in Antimicrobial Stewardship



Pharmacy Leadership

- Pharmacy leadership is consistently identified as a must for stewardship in hospitals.
- Pharmacists often play a lead role in implementing improvement interventions and monitoring antibiotic use. Should have some training in infectious diseases. (e.g. MAD-ID, SIDP, SHEA)
- Many programs are co-lead by a physician and pharmacist.

Role of Infection Prevention

- Timely communication to team when MDROs are identified
- Prevention of MDRO in health care facilities
- Monitor trends in antimicrobial resistance
- Educate team about NHSN definitions of HAIs
- Collaborate with microbiology, pharmacy, medical staff, and administration to plan and implement effective interventions

AJIC 2012; 40:94

Microbiology Stewardship: Obtain Cultures Prior to Starting Antibiotics!

- Develop a process to ensure cultures are properly and consistently ordered-cultures should have an indication
- Develop a process to ensure cultures are properly and consistently obtained
- Develop processes to ensure cultures are properly and promptly transported and processed
- Develop standards for and assess reliability of processes for ordering and obtaining a culture
- Link molecular diagnostics to stewardship

Are nurses underutilized in ASP?

	RN	PharmD	ID-MD
Patient triage and isolation	X		
Accurate allergy history	X	X	
Timely antibiotic initiation	X		X
Daily progress monitor and report	X	X	X
Preliminary antibiotic dosing	X	X	X
Adverse event monitoring	X	X	
Change in patient condition	X		X
IV to PO adjustment	X	X	X
Patient education	X	X	X

Olans RN et al. *Clin Infect Dis*. 2016; 62:84-89

Defining a Role for Nursing Education in Staff Nurse Participation in Antimicrobial Stewardship. Olans RD et al. *J Contin Educ Nurs*. 2015; 46:318-21.
"Identified a need for more education and also an interest in the area for practicing nurses."

Clinical Infectious Diseases

IDSA GUIDELINE

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1,a] Sara E. Cosgrove,[2,a] Lilian M. Abbo,[3] Conan MacDougall,[4] Audrey N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8] Yngve T. Falck-Ytter,[9] Neil O. Fishman,[10] Cindy W. Hamilton,[11] Timothy C. Jenkins,[12] Pamela A. Lipsett,[13] Preeti N. Malani,[14] Larissa S. May,[15] Gregory J. Moran,[16] Melinda M. Neuhauser,[17] Jason G. Newland,[18] Christopher A. Ohl,[19] Matthew H. Samore,[20] Susan K. Seo,[21] and Kavita K. Trivedi[22]

Evidence-based guidelines for implementation and measurement of antibiotic stewardship interventions in inpatient populations including long-term care were prepared by a multidisciplinary expert panel of the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. The panel included clinicians and investigators representing internal medicine, emergency medicine, microbiology, critical care, surgery, epidemiology, pharmacy, and adult and pediatric infectious diseases specialties. These recommendations address the best approaches for antibiotic stewardship programs to influence the optimal use of antibiotics

Clin Infect Dis 2016;62(10):e51–e77

Suggested Measures

Measurement Area	Measure
Antibiotic consumption	• Days of therapy (DOT) per 1,000 patient days—overall and for specific agents or groups of agents • Defined daily dose (DDD) per 1,000 patient days (if DOT not available) • Standardized Antibiotic Administration Ratio*
Process measures	• Provision of indication with each antibiotic start • Percentage of cases where therapy is appropriate (especially for serious infections, such as sepsis) • Appropriate Treatment of Methicillin-Sensitive Staphylococcus aureus (MSSA) Bacteremia • Frequency at which de-escalation occurs • Timely cessation of antibiotics given for surgical prophylaxis • Antibiotics not prescribed to treat asymptomatic bacteria • Appropriate cultures obtained before starting antibiotics • Adherence to hospital-specific guidelines • Acceptance of ASP recommendations • Frequency of performance of antibiotic time outs or reviews • Timely administration of appropriate antibiotics in cases of suspected sepsis

Modified *Curr Infect Dis Rep* 2014; 16:433

Suggested Measures continued

Measurement Area	Measure
Outcome measures	• Length of stay • Cure of infection • Risk-adjusted mortality • Hospital readmissions for select infections • Hospital-onset C. difficile infections* • Adverse drug reactions (number/percentage/rate) • Antimicrobial resistance- focusing on hospital onset cases would most likely best reflect the impact of ASPs • Provider-level measures if available (e.g., treatment of *S. aureus* and bloodstream infections)
Financial	• Antibiotic cost per patient day • Antibiotic cost per admission • Total hospital cost per admission

*NQF-endorsed measure

Modified *Curr Infect Dis Rep* 2014; 16:433

ASP Phase 2

- Antimicrobial formulary review
- Review metrics (e.g. DOT, CDI, expenditures)
- Review CAP and SCIP core measure
- Microbiology
  - CLSI susceptibility reporting
  - Review new CLSI breakpoints
  - Appropriate use of microbiology document with emphasis on obtaining appropriate cultures before starting antimicrobial therapy for new septic episodes
- Dose optimization
  - Weight-based dosing
  - Renal dosing
  - IV to PO

- **Associated with clinical and economic benefit**
- **Review facility by-laws and state scope of practice for automatic interchanges**
- **P&T and Med Exec approval**
- **Many institutions have these activities implemented (CAP/SCIP)**
- **Routine IV to PO/ Renal Dosing**

ASP Phase 3

- **Kinetic dosing**
  - **Vanc and AG**
  - **Prolonged infusion for pipercillin/tazobactam and carbapenems**
- **Approve institutional guidelines**
  - **CAP, HAP, UTI and ABU, MRSA, VAP, intra-abdominal, surviving sepsis, C. difficile**
- **Timely and appropriate use of antibiotics based on approved institutional guidelines and local antibiograms**
- **Optimize duration based on evidence-based peer review publications**
- **Evaluate use agents based on local needs (front/back-end approach)**
  - **Suggested drugs: daptomycin, linezolid, echinocandins, tigecycline, and carbapenems**
- **Clinical pharmacy rounding with team**

- **Involve nursing staff early in extended infusion work**
- **Meropenem and P/T prolonged infusion recommendation can be combined with formulary change to P&T**
- **Evaluate ability of pharmacist to cover drug regimen reviews and rounding consistently**

ASP Phase 4

- De-escalation “72 hour time-out”
  - Suggestions: review charts with positive blood cultures, 3 or more antibiotics for ≥72 hours, drug-bug mismatches, or antibiotics without a positive culture, duration
- Review and/or implement rapid diagnostics, point of care testing, and biomarkers (PCT)for appropriate use
- Ongoing antibiogram development (e.g. unit specific)
- Report approved metrics to all stakeholders on a regular basis
- Clinical decision support/CPOE

- Overlap will occur with various phases.
- Expectation is for facility to complete elements of each phase in a timely manner.
- Advanced programs can start on other phases before the suggested timelines.
- Synergize ASP with Core Measures and Sepsis Programs
- Provide guidance on use of PCT and rapid diagnostics

Rapid diagnostics

Old

T A T

Turn Around Time

New

T T I

Time To Intervention

Rapid Diagnostic Tests

- Biomarkers of infection/inflammation
  - WBC
  - ESR
  - CRP
  - Lactate
  - PCT
- Gram stain

Procalcitonin Dynamics

PCT Guidance

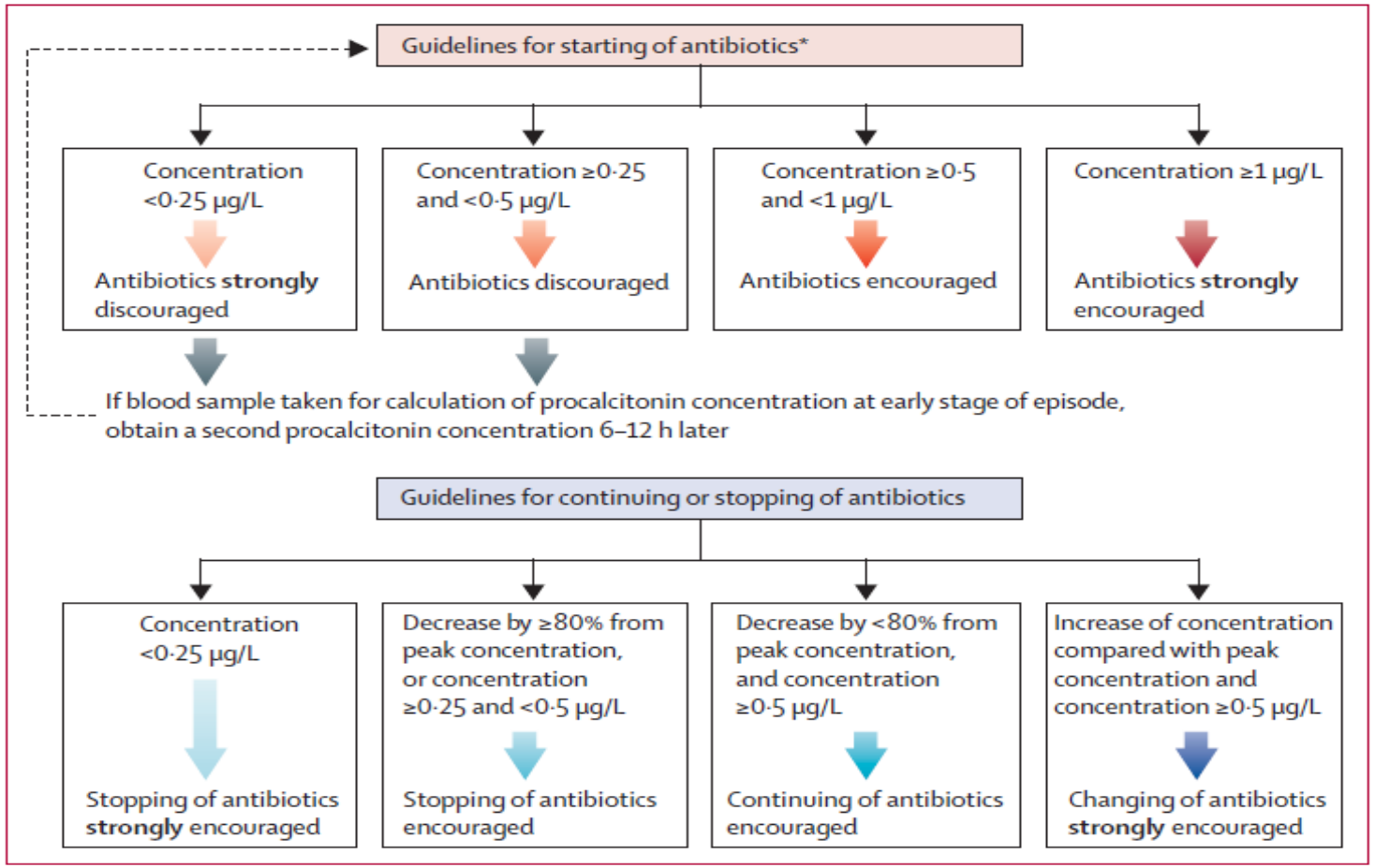


Figure 1: **Guidelines for starting, continuing, or stopping of antibiotics according to procalcitonin concentrations**

*Excludes situations requiring immediate antibiotic treatment (eg, septic shock, purulent meningitis).

Lancet 2010;375:463-74

Rapid Diagnostic Tests (2)

- Culture dependent
  - Rapid biochemical identification
  - Proteomic identification (MALDI-TOF)
  - BCID microarrays, nanoparticle, and PNA-FISH
  - Rapid phenotypic AST
  - Detection of selected resistance genes

Rapid Diagnostic Tests (3)

- Culture independent
  - Direct antigen detection tests
  - Single target or limited multiplex NAATs
    - In lab and now POCTs
  - Syndromic multiplex panels for BSI, GI, RT, and CNS infections
  - Direct detection of BSI by PCR/T2 MRI and PCR/ESI/MS

CASE

This is a 54 year-old female readmitted to the hospital for probably deep sternal SSI. Three weeks earlier she underwent a CAB, MV repair, and an AVR. She received “appropriate” surgical prophylaxis. She is a known diabetic.

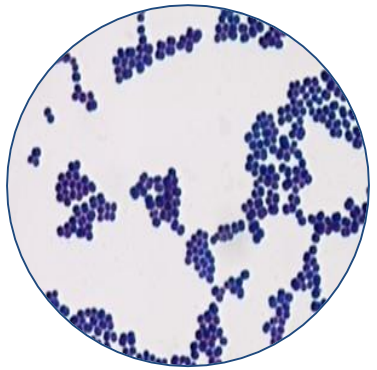
CASE Continued (2)

- On readmission she was febrile (102^{o}), BP 90/60, P-120;
- Lungs--decreased breath sounds on left, no rubs, -- purulence from lower sternum.
- White count was 18,000 with 15% bands, lactate 3.1, creat 2.1, blood cultures were drawn

Case continued(3)

- ID was called in ED
- Gram stain was performed which showed—rapid diagnostic test performed within 2 hours of arrival to ED

What antibiotic(s) would you start?



1. Cefazolin
2. Vancomycin
3. Nafcillin
4. Daptomycin

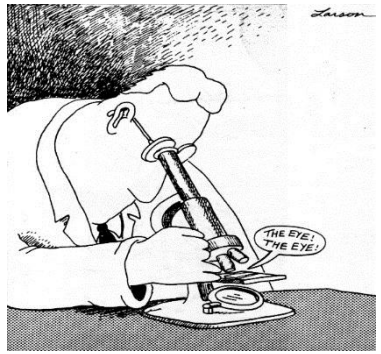
Case continued(4)

- Vancomycin and piperacillin/tazobactam by ED physician was started. ID physician discontinued piperacillin/tazobactam.
- At 12 hours blood cultures were positive for gram-positive cocci in clusters
- Culture from sternum was identified at *S aureus* the next morning sensitivities pending
- Patient was taken to surgery for sternal debridement
- TEE indicated a vegetation on her AV

Scenario #1 Traditional Method -- Suspected Infection

- Fluid or Tissue Sample
- Gram's Stain
  - Bacteria present? If so, Gram - or +
  - Results in minutes
- Sample incubated in culture media
  - Usually 24 hours for growth
- Biochemical testing to determine organism
  - Minutes to 24 hours
- Susceptibility testing
  - Another 24-48 hours
  - **At 48 hours, susceptibilities revealed MSSA**

Scenario #2 Rapid Molecular Methods

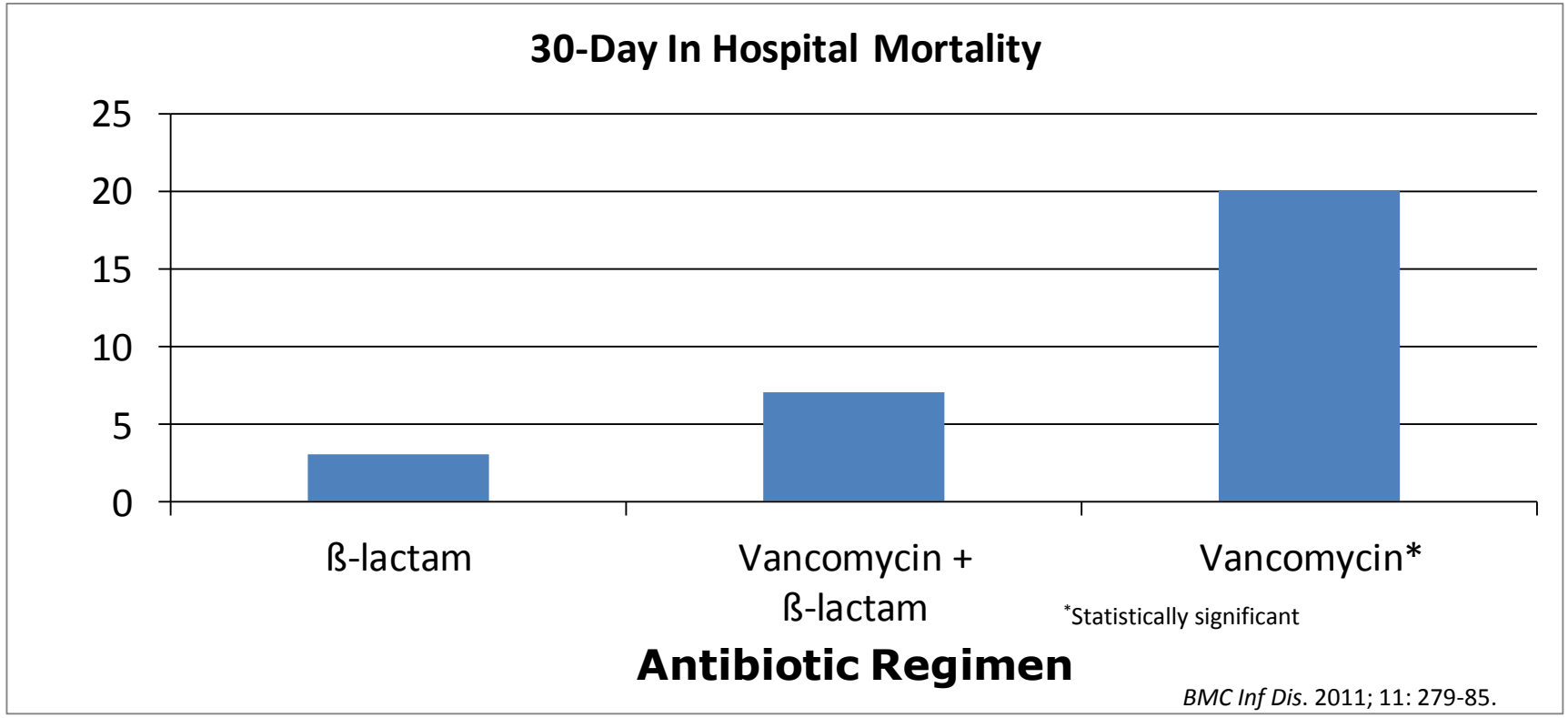


- **Technologies available**
  - Polymerase chain reaction (PCR)
  - Multiplex PCR
  - Nanoparticle Probe Technology
  - Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS)
  - From blood culture MALDI confirmed *S aureus* and PCR indicated this was a MSSA within 4 hours of + blood culture.
  - Total time 16 hours vs 48 hours by traditional methods

What would you do now?

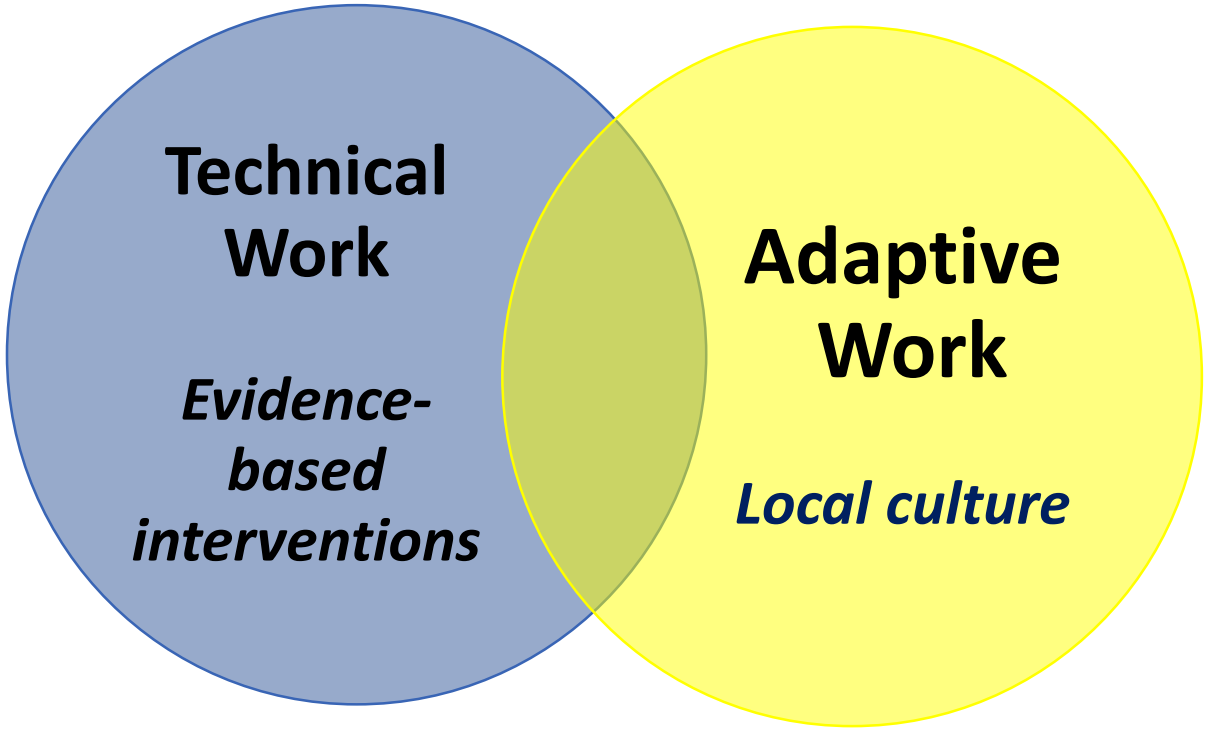
Does it matter since vancomycin covers both MSSA and MRSA?

ß-lactam vs Vancomycin for MSSA Bacteremia



BMC Inf Dis. 2011; 11: 279-85.

How Will We Get There?



Why does Culture Matter?

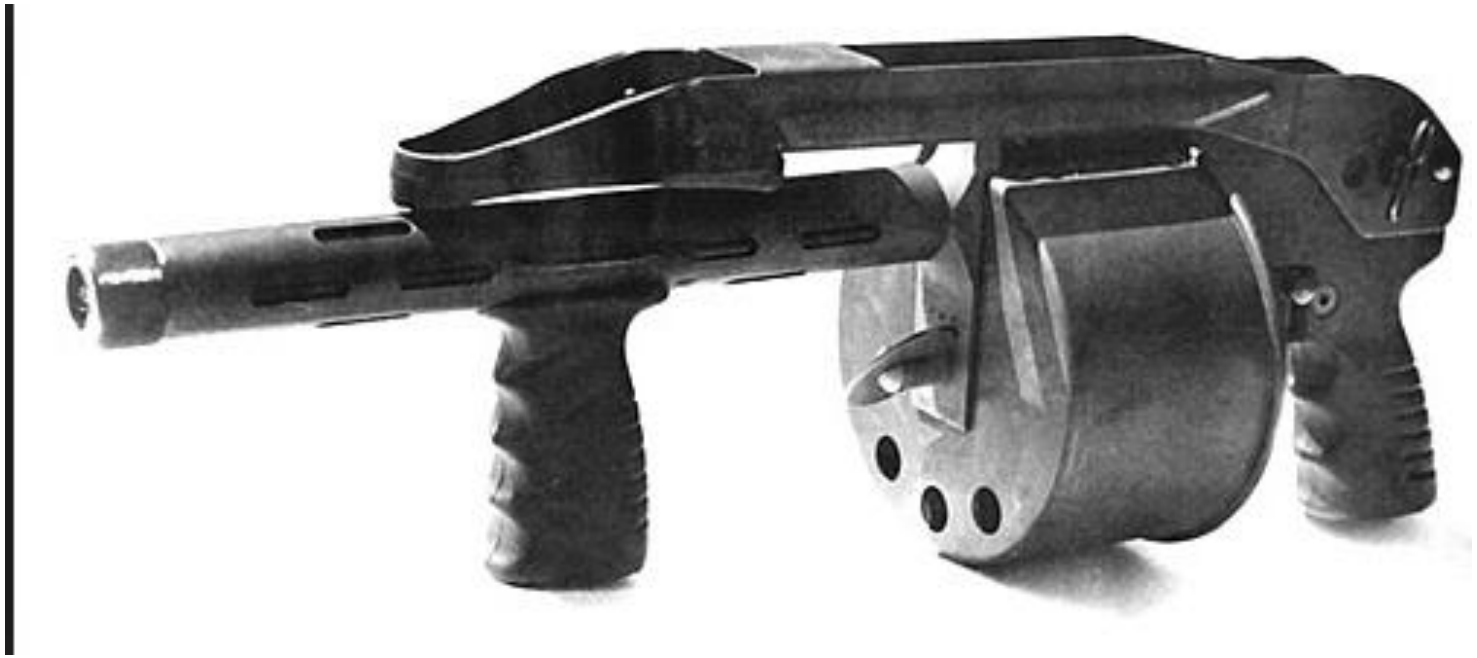
- Safety culture influences the effectiveness of other safety and quality interventions
  - Can enhance or inhibit effects of other interventions
- Safety culture can change through intervention
  - Best evidence so far for culture interventions that use multiple components (e.g.: CUSP, Positive Deviance)

Haynes et al., 2011; Morello et al., 2012; Van Nord et al., 2010; Weaver et al. Ann Intern Med. 2013;158:369-374.

Physician Barriers

- Physician accountability and acceptance of need for improvement
- Misperceptions
- Misalignment of incentives
- Lack of definition of appropriate use of antimicrobial agents
- Lack of standardized, risk-adjusted measures
- Adaptive/behavioral changes needed to change prescribing practices

Surviving Sepsis Campaign Mandate



Treat first and then evaluate later

Intensive Care Med 2018; 44:925-928

Inconvenient Truths

- High rate of overdiagnosis
- Approach promotes excess antimicrobial use and increases unintended consequences
  - *C difficile* infections
  - Acute kidney injury and other side effects (e.g. hepatitis, rash, cytopenias)
  - Missed culture opportunities (antibiotics administered before appropriate cultures obtained)
  - Selection for MDROs
  - Alteration of microbiome-dysbiosis
- Less than 60% of patients admitted to ICU with diagnosis of "sepsis" are confirmed (*Crit Care Med 2015; 19:319)*
- Time to antibiotics matters for septic shock, but evidence is less convincing for patients with possible sepsis without shock
  - Two recent studies confirmed association between delay in antimicrobial administration and mortality in patients with septic shock but little or no association for patients without shock (*N Engl J Med* 2017; 376:2235-2244; *Am J Respir Crit Care Med* 2017; 196:856-863)
  - Randomized trial of antibiotics administered in the ambulance versus administered in ED for patients with suspected sepsis found mortality was the same in both groups. More than 90% of patients enrolled in study had infection alone or sepsis without shock. (*Lancet Respir Med* 2018; 6:40-50)

Key Elements for Successful ASP

- Establish compelling need and goals for ASP
- Senior leadership support
- Effective local physician champion
- Adequate resources and competencies (pharmacy, infection preventionist [IP], microbiology, information technology [IT])
- Primary objectives: optimize clinical outcomes and reduce adverse events, not reduce costs
- Good teamwork
- Agreed upon process and outcome measures
- **ASP should be across the continuum of care**

Stewardship is a Team Sport

- **Indicators of High Performing Teams**
  - A high degree of **interaction and communication** among all members with mutual respect
  - The team directs **energy towards the team vision and goals** and less energy towards individual's own agenda
  - A sense of common ownership
  - Commitment and trust
  - Members **feel great personal satisfaction** from belonging to the team
  - Team members **share loyalty** and group identification

SUCCESS IS NOT FINAL,

FAILURE IS NOT FATAL:

IT IS THE COURAGE TO CONTINUE THAT COUNTS

Winston Churchill