Overuse of Antibiotics: The Case for Improved Prescribing

Mary Anne Jackson, MD
Professor of Pediatrics
University MO-Kansas City SOM
Division Director, Infectious Diseases
Children's Mercy Hospital & Clinics

UMKC School of Medicine

Children's Mercy HOSPITALS & CLINICS www.childrensmercy.org

Disclosure

- Neither I nor any member of my immediate family has a financial relationship or interest with any proprietary entity producing health care goods or services related to the content of this CME activity
- My content will not include discussion of commercial products or services
- I do not intend to discuss an unapproved /investigative use of commercial products/devices

Objectives

- Identify common pitfalls in antibiotic prescribing
- Recognize components of a successful practice based ASP
- Define targets for ASP practice activities

What's the Big Deal?

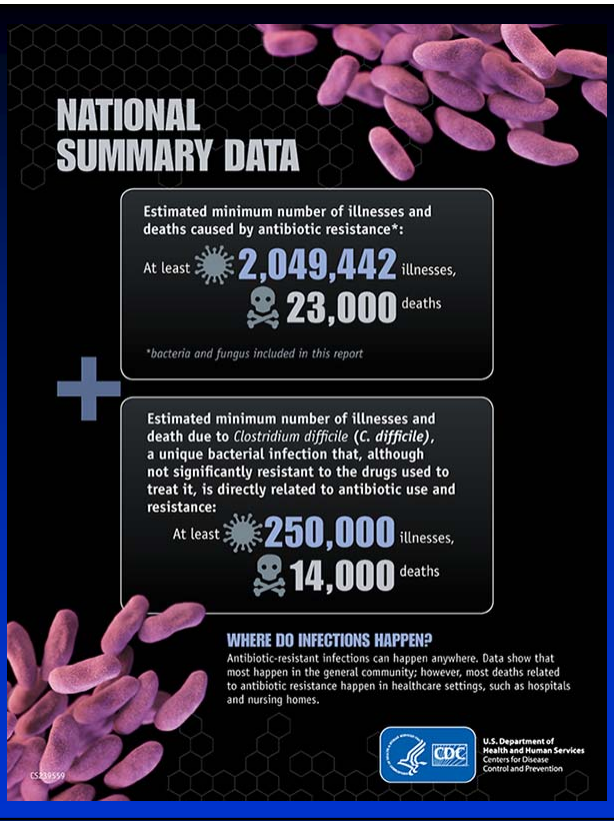
- Although antibiotics have saved countless lives, their use is not benign
  - Antibiotic resistance
  - At least 5% of hospitalized patients experience an adverse reaction
  - *C. difficile* infection
- 50% are prescribed for people who do not need them or are not prescribed appropriately
  - URI, bronchitis, OME
  - AOM, sinusitis, strep throat-diagnostic errors, inappropriate drugs
- Very few antibiotics are being developed

Antibiotics Linked to

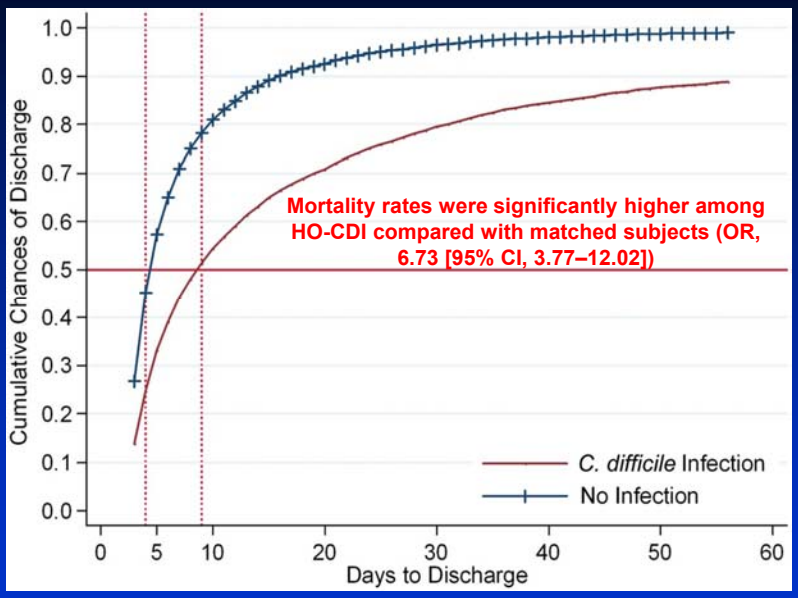
- **Adverse events-outpatients**
  - Estimated ED 142,505 visits/yr for drug-related adverse events attributable to systemic antibiotics
    - beta lactams most common but sulfa most serious
- ***C difficile* disease**
  - High-risk antibiotics-clindamycin, CMCs, and fluoroquinolones
- **Antibiotic resistance**-60% human use is outpatient; animal/food industry (animals=80% of all use)

Shehab, et al. *Clin Infect Dis*. Sept 2008.
Deshpande A, et al. *Antimicrob. Agents Chemother*. May 2013.

TMP/SMX Reaction



Length of stay and *Clostridium difficile* infection in children



Sammons J S et al. Clin Infect Dis. 2013;57:1-8

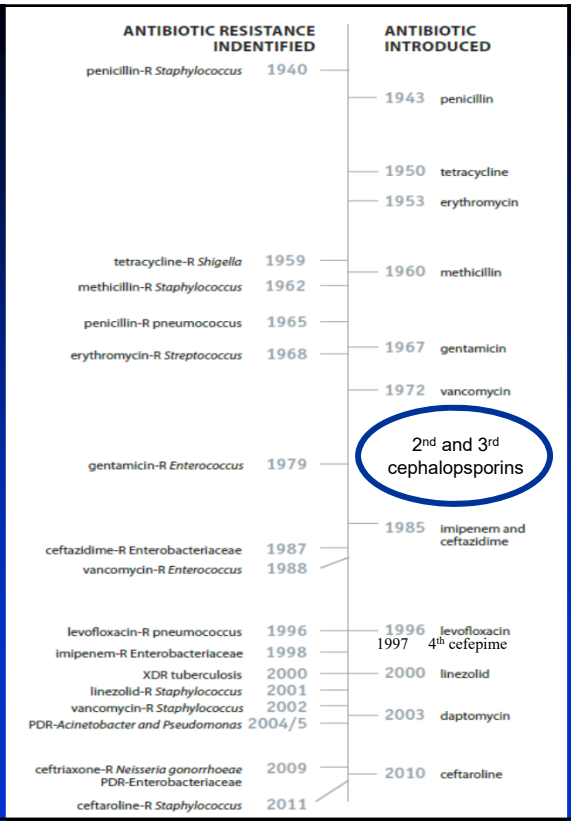
Clinical Infectious Diseases

IDSAPUBLICPOLICY

The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America

Brad Spellberg, Robert Guidos, David Gilbert, John Bradley, Helen W. Boucher, W. Michael Scheld, John G. Bartlett, and John Edwards, Jr., for the Infectious Diseases Society of America

Clinical Infectious Diseases 2008; 46:155–64



Emerging Resistance Patterns-in our own backyard

CRE, or carbapenem-resistant Enterobacteriaceae, have been deemed **"nightmare bacteria"** by CDC, which classified the pathogen as **an urgent threat.**

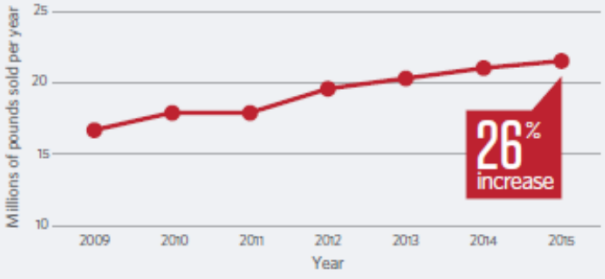
As of **2001**, CRE was reported in **one state.**

As of early **2016**, CRE was found in **48 states.**

Animal Industry

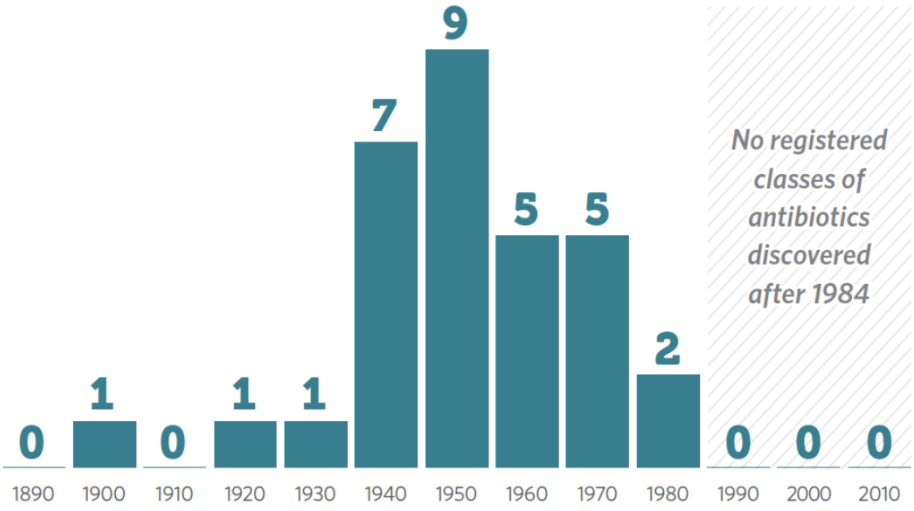
On the farm:

21 **million pounds** of antibiotics important to human medicine were **sold for use in food animals** in 2015.



Every antibiotic in use today is based on a discovery made **more than 30 years ago.**

Number of antibiotic classes discovered or patented



Other Unintended Consequences

Autoimmune and metabolic syndromes

May play a role in JIA, diabetes pathogenesis, ? alterations in the microbiome; Horton, et al. *Pediatrics*, July 2015
Yallapragada, et al. *Pediatr Ann* Nov 2014.

Obesity

Low burden *Actinobacteria* and a high burden *Firmicutes* at 3 mos likely to have high BMI at 5–6 yrs, only if they received several courses of antibiotics
Principi and Esposito. *Int J Antimicrob Agents*; Mar 2016.

Congenital birth defects

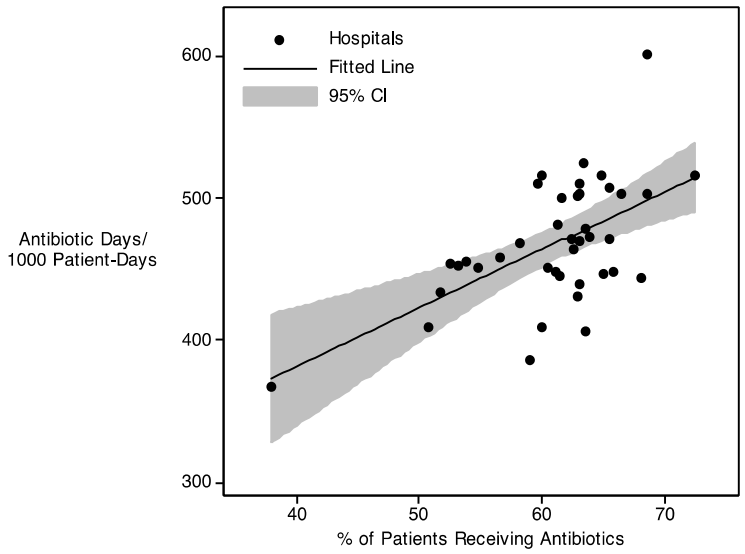
Clindamycin, doxycycline >>quinolones, macrolides, penicillin in utero exposure were linked to ↑malformations; no link amoxicillin, cephalosporins and nitrofurantoin
Muanda, et al. *British Journal of Clinical Pharmacology*, 2017.

- What can the individual practitioner do and why will it make a difference?
- Goals for pediatric outpatients vs inpatients

Most physicians think others misuse antimicrobials while most do not think they themselves misuse antimicrobials

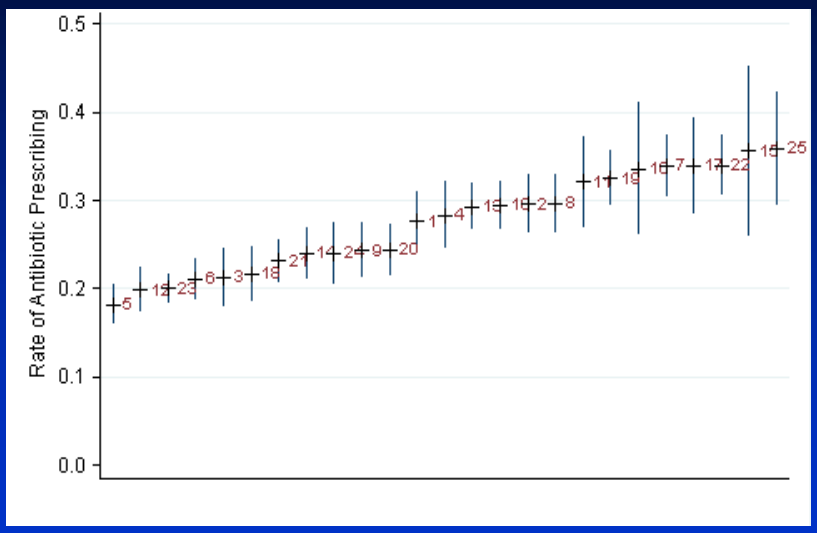
Abbo, et al Evaluation of Faculty and Resident Physicians' Knowledge and Perceptions about' Antimicrobial Use and Resistance: A Web Based Survey 5th Decennial International Conference on Heathcare-Associated Infections 2010

Variability in Antibiotic Use in Hospitalized Children



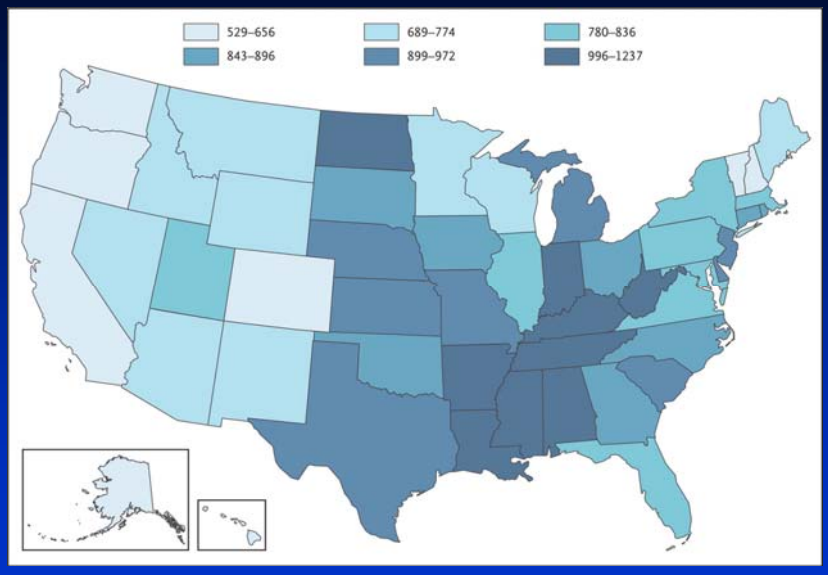
Gerber et al. Pediatrics 2010

Antibiotic Prescribing for Sick Visits



Excluding: preventive visits, CCC
Standardized by: age, sex, age-sex, race, Medicaid

Antibiotic Prescriptions per 1000 Persons of All Ages According to State, 2010.



Hicks LA et al. N Engl J Med 2013;368:1461-1462.

The NEW ENGLAND JOURNAL of MEDICINE

Antimicrobial Stewardship

- Optimizes patient outcomes
  - Improved clinical outcomes
  - Decrease in ADR
- Optimizes patient safety
  - Reduces *C. difficile* infection
- Reduces resistance
- Decreases cost

Carling P et al. ICHE 2003; Fowler S et al. JAC 2007; White AC et al. CID 1997; Staniford HC et al. ICHE 2012

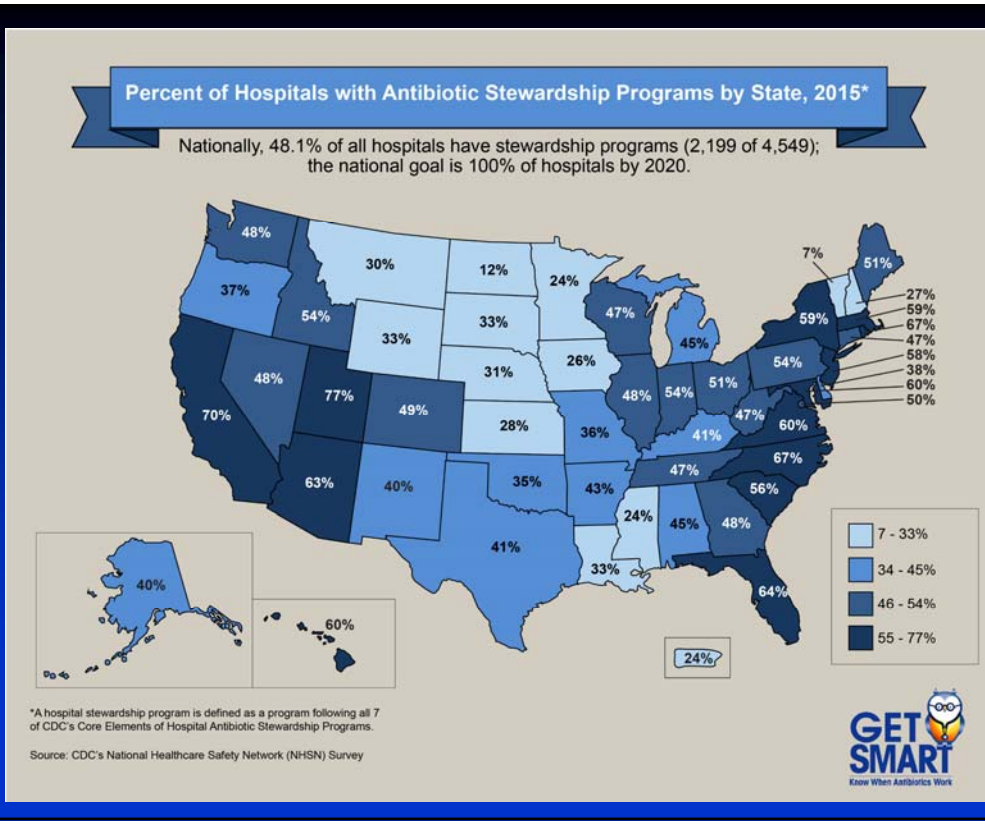
Hospital ASP Call to Action 2007

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

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

[1]Harborview Medical Center and the University of Washington, Seattle; [2]Maine Medical Center, Portland; [3]Emory University, Atlanta, Georgia; [4]Hines Veterans Affairs Hospital and Loyola University Stritch School of Medicine, Hines, and [5]Stroger (Cook County) Hospital and Rush University Medical Center, Chicago, Illinois; [6]University of Utah, Salt Lake City; [7]Mayo Clinic College of Medicine, Rochester, Minnesota; [8]University of Pittsburgh Medical Center, Pittsburgh, and [9]University of Pennsylvania, Philadelphia, Pennsylvania; [10]William Beaumont Hospital, Royal Oak, Michigan; [11]Ochsner Health System, New Orleans, Louisiana; and [12]University of Miami, Miami, Florida

- Leadership resources
  - Human, financial and IT
- Accountability
  - Single leader, physician
- Drug expertise
  - ASP pharmacist
- Action
  - Restriction, prospective audit and feedback
- Tracking-benchmarks
- Reporting-metrics
- Education
  - Regarding resistance and optimal prescribing



Outpatient Call To Action

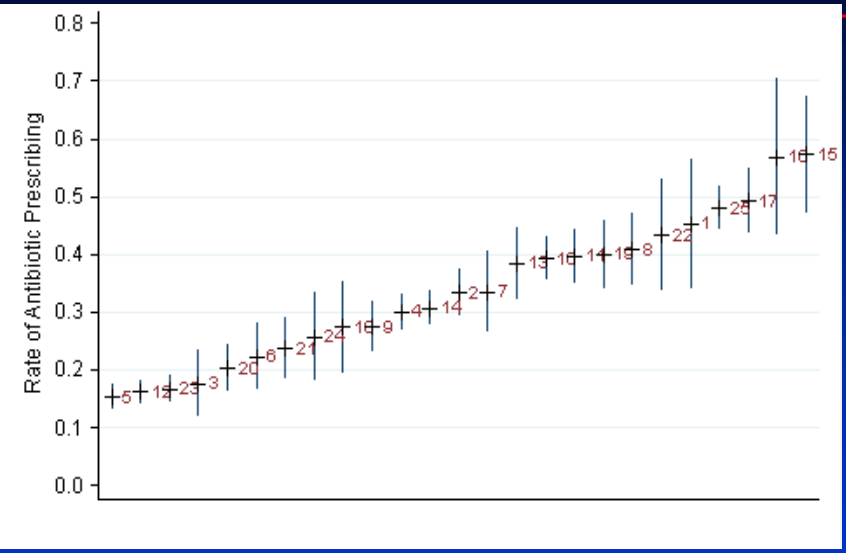
Most antibiotics are used in outpatient setting and up to 50% are unnecessary

- **Improved patient care**
- **Cost savings**
- **Reduction in *C. difficile* infections**
- **Reduction in adverse drug events**
- **Reduction in antimicrobial resistance**

5 at-risk conditions and practice deviation

- **Unnecessary**
  - antibiotics not indicated -- bronchitis, URI
- **Overdiagnosis**
  - when condition dx w/o fulfilling the diagnostic criteria or w/o testing→strep throat
- **Wrong agent, dose, or duration**
  - Wrong agent--azithromycin for AOM
  - Needlessly broad—cefixime for UTI
- **Underuse of watchful waiting**
  - AOM or ABS
- **Need for timely antibiotics is not recognized**

Broad Antibiotic Prescribing



Excluding: preventive visits, CCC, antibiotic allergy, prior abx
Standardized by: age, sex, age-sex, race, Medicaid

How often are broad-spectrum antibiotic used in practice?

- Examined BSA <18 yrs 2006-07
- Amox-clav, 2nd, 3rd gen cephalosporins, macrolides, clindamycin, FQ
- 51% of pediatric visits→abx prescribed
- 38% macrolides, 30% cephalosporins, 27% amoxicillin-clavulanate
- ARTI- most frequent diagnosis
  - In the South & Midwest
  - Children ≤ 5 years

Adam L. Hersh, MD, PhD and Daniel J. Shapiro, BA, U California, San Francisco, CA
IDSA Vancouver, 2010

Principles Judicious Use

- Correct diagnosis=stringent guidelines
  - Diagnosis is a bacterial infection that requires antibiotic rx
- Right drug-most narrow, effective
- Right duration
- Counseling re: potential adverse events, expected outcome

Scenario 1

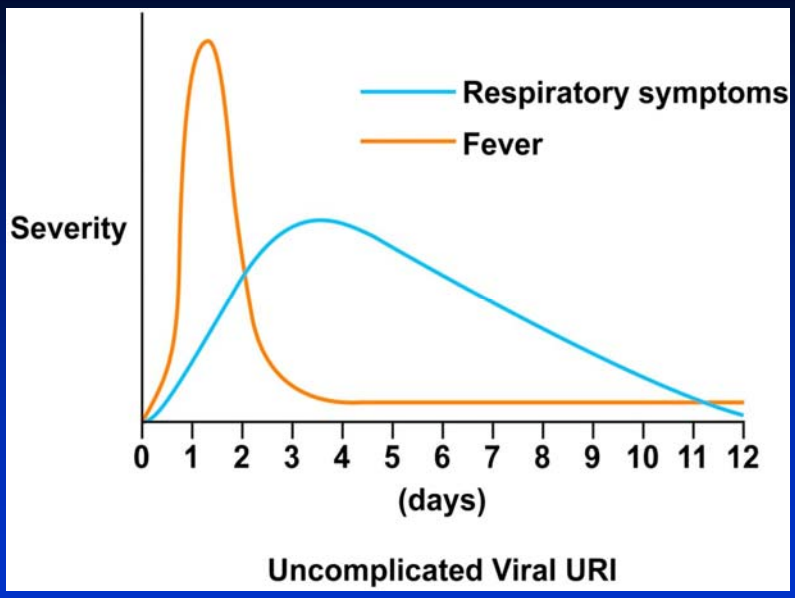
Antibiotic prescribed when none indicated

Antibiotic prescriptions for URI, bronchitis

Judicious Use-URI

- URI-may present with moderate or high fever, cough, congestion, rhinorrhea
- Identify child who can decompensate
- Symptomatic care
- Counsel re: expected course
- No antibiotics

Schematic representation of an uncomplicated viral upper respiratory infection.



Gregory DeMuri, and Ellen R. Wald Pediatrics in Review 2013;34:429-437

PediatricsinReview
AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

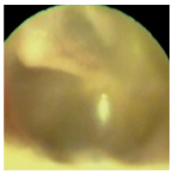
Scenario 2

- Diagnostic criteria?
- Wrong empiric drug based on knowledge of antibiotic susceptibility
- A 2 year old has fever and middle ear effusion
- Given azithromycin

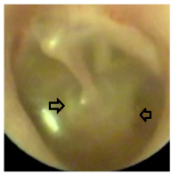
Diagnosing AOM is tricky

Judicious Use-AOM

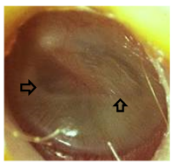
- Acute otitis media-accurate diagnosis; identify when watchful waiting is appropriate, amoxicillin
  - Appropriate vs inappropriate antibiotics



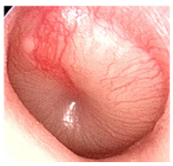
Normal TM
- Ossicles clearly visible
- TM in neutral position
- TM not opaque
- Minimal vascularity
- Color – normal
- No effusion



OME
- Ossicles too prominent
- TM mildly retracted
- TM not opaque
- Central round bubbles
- Effusion



OME 2
- Ossicles too prominent
- TM very retracted
- TM partially opaque
- Large oval bubble
- Modest vascularity
- Effusion



Obvious AOM
- Ossicles not visible
- TM bulging ("bagel")
- TM opaque
- Very vascular
- TM Golden red color
- Effusion

Taking ACTION!

Accurately diagnose acute otitis media
Consider watchful waiting for non-severe cases
Treat pain in all
Identify drug of choice=amoxicillin
Observe for response in all instances
Need for follow up at 72 hours if no better

Amoxicillin for bilateral AOM in 6-23 mos
OR ≥6 mos for unilateral or bilateral OM when temp >102.2°F

Most common respiratory pathogen: *Streptococcus pneumoniae*

2015 Gram Positive Bacteria Antibiogram (% Susceptible)

Organism	# of isolates tested	Ampicillin	Cefotaxime	Ciprofloxacin	Clindamycin	Erythromycin	Gentamicin[a]	Linezolid	Nitrofurantoin[b]	Oxacillin	Penicillin	Penicillin (Oral)	Rifampin[a]	Tetracycline	Trim/Sulfa	Vancomycin
Enterococcus faecalis	234	99	-	94	-	-	-	-	98	-	99	-	-	-	-	100
All Staphylococcus aureus	1914	-	-	-	82	48	100	100	100	64	0	-	100	96	97	100
MSSA	1225	-	-	100	81	66	100	100	[illegible]	100	0	-	100	95	98	100
MRSA	689	-	-	0	82	18	100	[illegible]	100	0	0	-	100	98	97	100
Staphylococcus epidermidis	147	-	-	75	59	31	[illegible]	100	98	34	0	-	99	88	57	100
*S. pneumoniae**	114	-	-	-	93	56	[illegible]	100	-	-	-	67§	-	-	-	100
Meningitis breakpoint		-	89†	-	-	-	-	-	-	-	65†	-	-	-	-	-
Nonmeningitis breakpoint		-	96‡	-	-	-	-	-	-	-	96‡	-	-	-	-	-

**S. pneumoniae* % susceptible was calculated using all isolates based on meningitis, nonmeningitis and oral breakpoints. # of *S.pneumoniae* isolates tested: Pen= 110 cefotaxime= 113 clindamycin=107 erythromycin=87 linezolid=20 vancomycin=26

Trends in Pneumococcal Suscepbitility

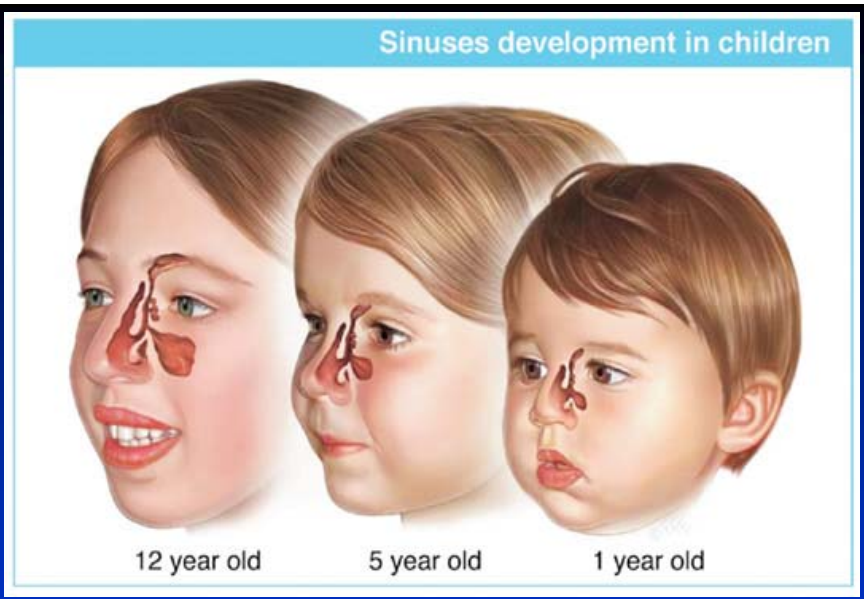
- Pre-vaccine serotypes
  - Penicillin and macrolide R
- PCV7
  - Serotype 19A and others emerge
- PCV13
  - Changing trends once again
  - Increase in penicillin susceptible serotypes

Scenario 3

My child has a sinus infection- just like last time when he got a "Z pak"

Background of Pediatric EBP ABS

- ABS is a complication of URI
- 6% and 7% of children 1-18 years of age seeking care for respiratory symptoms
- Two guidelines both omit < 1 year, anatomic defects, immunodeficiency, CF or ciliary dyskinesia



maxillary:4-5 months; ethmoids:12 months; sphenoid:4 years; frontal: 5-6 years

https://www.google.com/search?q=sinuses+child&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjByO_XtevTAhVm2oMKHW2HDcMQ_AUIBigB&biw=1920&bih=963#imgrc=lDSBxCfrF0AkWM:&spf=1494628671405

Definition: Acute Uncomplicated Bacterial Sinusitis

- Rhinorrhea, daytime cough for 10 days or longer without improvement
- Rhinorrhea with fever >102.2°F for at least 3 days
- Cold worsens after improvement with new fever and cough/rhinorrhea

Scenario 4

- Injudicious testing contributes to injudicious antibiotic use
- Example: streptococcal pharyngitis

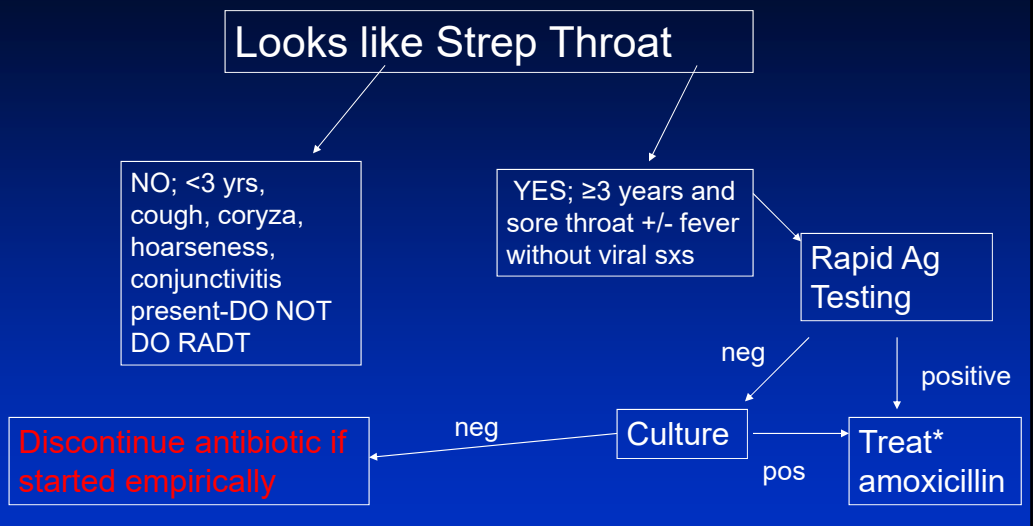
Pharyngitis

80% viral and cannot be distinguished by exam

Judicious Use-Streptococcal pharyngitis

- Group A streptococcus-impact of treatment
  - Speeds recovery
  - Reduces suppurative complications
  - Reduces non-suppurative sequelae
- Test those >3 years with sore throat in the absence of viral symptoms of rhinorrhea, congestion, cough
- Only treat those with positive RADT→amoxicillin single daily dosing

*Most patients who give a history of penicillin allergy are not allergic-explore this history carefully and document in the chart



Typical Clinical Approach to Patient with Pharyngitis

IDSA Guidelines http://www.journals.uchicago.edu/doi/pdf/10.1086/340949

Practice Agreement

- Amoxicillin-drug of choice
- Unless allergy to penicillin, non-adherence risk
  - Confirmation of allergy

Discontinue antibiotics if negative testing

Office Steps

- Diagnose as group A streptococcal pharyngitis using a laboratory test
  - If clinical and epidemiological findings met
- Antibiotics should not be given to a child with pharyngitis only if positive RADT
- Amoxicillin remains the drug of choice
  - Use single daily dose for 10 days
  - Antibiotic should be discontinued if initiated empirically and testing negative

Scenario 5

- Drug bug mismatch or needlessly broad drug choice
- You suspect UTI in a 3 month old
- 10 years ago, TMP-SMX an appropriate choice; resistance rates for E coli >25%

UTI

- ~1.6 million pediatric UTI visits/yr
- TMP-SMX: most commonly prescribed 49%
- 1/3 visits were prescribed broad-spectrum antibiotics
  - 3rd generation cephalosporins
  - Increase risk <1 year and high fever
- Doubling in use of 3rd generation cephalosporins=opportunities to promote more judicious antibiotic prescribing

Copp and Shapiro AAP 2010 Abstract 10063
Antibiotic Prescribing Patterns for Pediatric Urinary Tract Infection:
A National, Ambulatory Assessment of Broad-Spectrum Antibiotic Use from 1998-2007.

Testing for UTI?

- A urinalysis and urine culture should be obtained from children <3 years of age with a fever (>39.0°C rectal) with no apparent source
  - Infants with a fever >39°C for >48 h without another source for fever on examination are highly likely to have a UTI
- For children ≥3 years of age, the presence of urinary symptoms (dysuria, urinary frequency, hematuria, abdominal pain, back pain or new daytime incontinence)
- Right specimen and interpretation of UA
  - negative dipstick for nitrites and LE, pyuria or bacteruria on microscopic examination= <1% chance of UTI

CMH Antibiogram 2015

2015 Gram Negative Bacteria Antibiogram (% Susceptible)

Organism	# of isolates tested	Amikacin	Ampicillin	Amp/sulbactam	Amox/clav*	Cefazolin*	Cefepime	Ceftazidime	Ceftriaxone	Ciprofloxacin	Gentamicin	Meropenem	Pip/tazo	Nirtofurantoin*	Tobramycin	Trimeth/Sulfa
Acinetobacter sp	29	100	-	100	-	-	93	66	28	97	90	100	-	-	97	90
Citrobacter freundii	26	100	IR	IR	IR	IR	-	85	88	96	92	100	-	89	92	88
Enterobacter aerogenes	30	100	IR	IR	IR	IR	100	93	97	100	93	100	-	20	93	100
Enterobacter cloacae	85	100	IR	IR	IR	IR	99	82	84	99	98	100	-	24	96	92
Escherichia coli	1657	100	55	42	85	91	97	97	97	93	94	99	97	96	95	76
Klebsiella oxytoca	55	100	IR	-	100	84	98	96	98	98	98	100	-	79	98	96
Klebsiella pneumoniae	173	100	IR	-	92	90	93	93	93	98	94	100	94	25	94	87
Proteus mirabilis	98	100	94	-	96	98	99	99	99	98	95	-	100	IR	96	94
Pseudomonas aeruginosa	284	100	-	-	-	-	96	97	-	95	95	99	98	-	99	-
Serratia marcescens	38	97	IR	IR	IR	IR	97	97	100	100	97	97	-	IR	87	100

ESBL positive isolates; *E. coli* (55), *K. pneumoniae* (11), *K. oxytoca* (1)

* *Antibiotics tested on* UTI isolates only; *Citrobacter freundii* (19) *Enterobacter aerogenes* (21), *Enterobacter cloacae* (32), *E. coli* (1531), *K. pneumoniae* (111), *K. oxytoc* (28), *P.mirabilis* (89), *P. aeruginosa* (50), *Serratia marcescens* (4)

IR = Intrinsic Resistance mechanism

Feedback Tool

- Visual cues
- Can be educational tool
- Pre-printed scripts
- Trigger tool linked to testing guidelines
- Evaluate/re-evaluate
- Add intervention as needed

Outpatient Stewardship Partners

- Acute care hospitals
- State and local health departments
- Health plans and payers-quality-based payments.
- Health care professional societies
  - Create and share CPG, provide CME, bolster national, local, and regional initiatives
- Community pharmacies and pharmacists
  - Screening for drug interactions and allergies, and patient education
- Local microbiologic laboratories
  - Antibiograms, diagnostic stewardship

Office Nurse's Role in Stewardship Activities

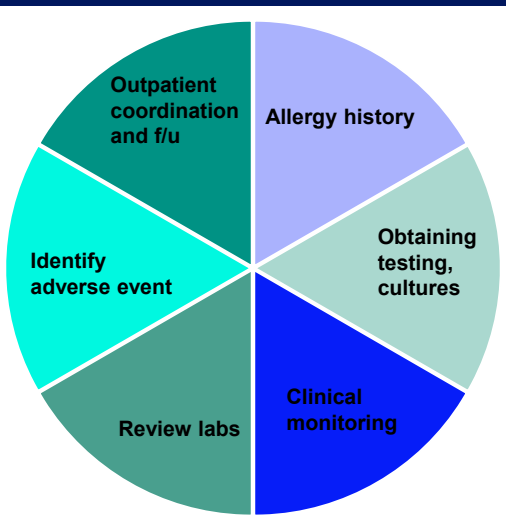


Table. Steps at Which Diagnostic Stewardship May Improve Testing for Common Infectious Disease Tests

	Ordering (Preanalytic)	Collection (Preanalytic)	Processing (Analytic)	Reporting (Postanalytic)
General principles	Test only if clinical presentation is consistent with the infectious etiology (high pretest probability)	Pay attention to sample collection and transport, to optimize yield and reduce contamination	Use adjunctive laboratory tests to distinguish colonization from infection	Report results in a format that guides appropriate practice
Urine cultures	Test only when symptoms suggest urinary tract infection or, if asymptomatic, concordant with guidelines (eg, urologic surgery, pregnancy)	Use aseptic technique—midstream clean catch after periurethral cleansing Obtain catheter sample from collection port (not bag), prefer newly inserted catheter	Only perform urine culture if pyuria present	Text interpreting result, eg, "multiple organisms indicating likely contamination"; "no pyuria, culture not performed" Selective reporting of antibiotic susceptibilities—display preferred antibiotics only
Blood cultures	Test only when symptoms of infection present (fever) Avoid repeat cultures unless concern for persistent or endovascular infection	Use aseptic technique—prefer peripheral samples obtained by trained phlebotomists Avoid catheter draws	Consider rapid testing on initial positive results, eg, polymerase chain reaction, PNA-FISH, MALDI-TOF	Text interpreting result, eg, "likely skin contaminant"; "Staphylococcus aureus, likely pathogen consider infectious diseases consult" Selective reporting of antibiotic susceptibilities
Clostridium difficile testing	Test only when disease likely (eg, recent antibiotic exposure, >3 loose stools/d, duration >24 h, and no recent laxative use) Avoid tests of cure	Only collect and send loose stool (ie, that conforms to the container)	Consider use of a testing algorithm that includes toxin immunoassay	Text interpreting result, eg, "toxin−/PCR+ indicating possible colonization rather than disease"
Molecular detection panels (ie, "syndromic testing")	Test only when pretest probability moderate to high for ≥2 targets on the panel, and when results will influence management	Use recommended collection and transport conditions to reduce contamination and optimize yield	Follow stringent contamination prevention guidance in the laboratory to avoid false-positive results	Selective suppression of results for tests on panel if other testing approach used in the laboratory (eg, *C difficile* testing on stool pathogen panel) Text interpreting results discussing colonization
Forms of automation	Clinical decision support requiring documentation of symptoms Hard stops for contraindications—eg, laxative use within 48 h of *C difficile* test)	Recording site and method of collection Orders requiring supplementary tests—eg, urinalysis before urine culture	Laboratory support systems performing cascades of tests	Prepopulated reports that can be reviewed and modified by laboratory personnel
Clinician education	Yes	No	No	Yes

Abbreviations: PNA-FISH, peptide nucleic acid-fluorescence in situ hybridization; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight.

Morgan, et al. JAMA. Published online July 31, 2017. doi:10.1001/jama.2017.8531

Goals 2017

- Use stringent rules for diagnosis
  - Clinical and laboratory
- Determine if antibiotics needed
- Culture to confirm pathogen
- Use antibiotic susceptibility data to determine appropriate drug
- Counsel every time re: expected course, risks of antibiotics
- Track and improve your antibiotic use-AAP EQIPP module

Clinician Checklist

CDC recommends that outpatient clinicians take steps to implement antibiotic stewardship activities. Use this checklist as a baseline assessment of policies and practices that are in place. Then use the checklist to review progress in expanding stewardship activities on a regular basis (e.g., annually).	
Commitment	
1. Can you demonstrate dedication to and accountability for optimizing antibiotic prescribing and patient safety related to antibiotics?	❑ *Yes* ❑ *No*
If yes, indicate which of the following are in place. ❑ Write and display public commitments in support of antibiotic stewardship.	
Action	
2. Have you implemented at least one practice to improve antibiotic prescribing?	❑ *Yes* ❑ *No*
If yes, indicate which practices which you use. (Select all that apply.) ❑ Use evidence-based diagnostic criteria and treatment recommendations. ❑ Use delayed prescribing practices or watchful waiting, when appropriate.	
Tracking and Reporting	
3. Do you monitor at least one aspect of antibiotic prescribing?	❑ *Yes* ❑ *No*
If yes, indicate which of the following are being tracked. (Select all that apply.) ❑ Self-evaluate antibiotic prescribing practices. ❑ Participate in continuing medical education and quality improvement activities to track and improve antibiotic prescribing.	
Education and Expertise	
4. Do you provide education to patients and seek out continuing education on antibiotic prescribing?	❑ *Yes* ❑ *No*
If yes, indicate how you provide antibiotic stewardship education. (Select all that apply.) ❑ Use effective communications strategies to educate patients about when antibiotics are and are not needed. ❑ Educate about the potential harms of antibiotic treatment. ❑ Provide patient education materials.	

Sanchez GV, Fleming-Dutra KE, Roberts RM, Hicks LA.
Core Elements of Outpatient Antibiotic Stewardship. MMWR Recomm Rep 2016;65(No. RR-6):1–12.