Practical Pearls in Antimicrobial Stewardship

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Objectives

- Define and describe antimicrobial stewardship
- Identify 3 common opportunities for antibiotic stewardship
- List 3 common toxicities or side effects of antibiotic treatment

Disclosures

None

Stewardship

- An ethic that embodies the responsible planning and management of resources (wikipedia)
- The conducting, supervising, or managing of something; especially: the careful and responsible management of something entrusted to one's care <stewardship of natural resources> (Merriam-Webster)

Concept of LIMITED resource and potential HARM of misuse

Antibiotics as limited resource

- Severe ongoing supply shortages in recent years
 - Piperacillin/tazobactam
 - Ampicillin/sulbactam
 - Cefazolin
- Very limited options for some drug resistant infections
 - Carbapenemase producing gram negatives
 - Gonorrhea
 - XDR tuberculosis
- Extreme price manipulation
 - Doxycycline
 - Pyrimethamine

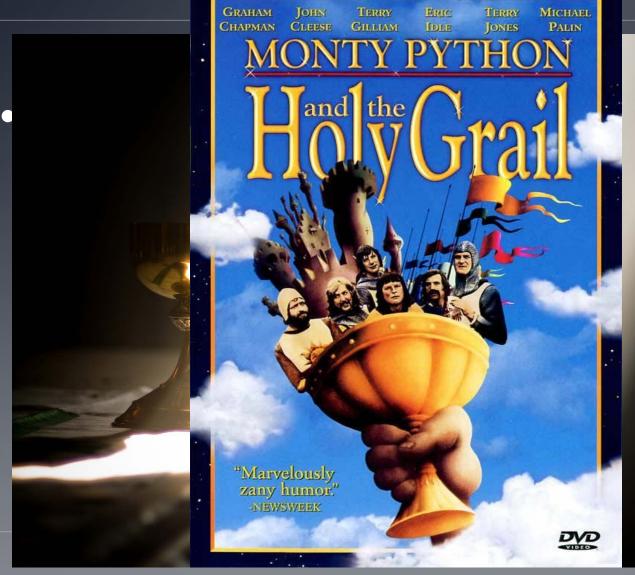
Potential direct harms of antibiotic therapy

- Secondary infections
 - *C. difficile* diarrhea
 - Multi-drug resistant infections
 - MRSA/VRE/ESBL
 - Central line infections
- Non-specific drug toxicities
 - Allergic reactions
 - Severe non-allergic reactions
 - Stevens-Johnson Syndrome, Toxic epidermal necrolysis, DRESS syndrome
- Drug specific toxicities
 - Renal failure
 - Aminoglycosides, vancomycin, amphotericin
 - Photosensitivity, dental staining
 - Tetracyclines

- Drug specific toxicities (continued)
 - Neuropathy
 - Quinolones, linezolid, metronidazole, isoniazid
 - Tendinopathy/rupture, aortic dissection
 - Fluoroquinolones
 - QT prolongation/arrythmia
 - Quinolones, macrolides, azoles
 - Hearing loss
 - Macrolides, aminoglycosides
 - Cytopenias
 - Linezolid, trimethoprim/sulfa, betalactams, vancomycin

The "Holy Grail" of

Anti DELUXE WIDESCREEN PRESENTATION Ship



Antibiotic Stewardship

- Organized approach/programmatic oversight
- Two basic categories of intervention:
 - P&T approved protocols for dosing, route, selection of drug
 - Examples:
 - IV to PO conversion of fluoroquinolones, azithromycin, PPI
 - Formulary swap from non-formulary agent e.g. ertapenem to meropenem
 - Targeted optimization based on review of case and discussion with providers
 - Examples:
 - Formulary restriction- Certain drugs only used with permission
 - Prospective Audit and Feedback by ID/PharmD

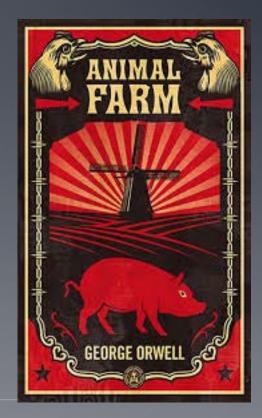
Daily work flow

- ID pharmacist reviews list of targeted antibiotics and cultures (all blood cultures and rapid diagnostics) daily
- Opportunities for optimizing therapy are passed to clinicians in the manner they prefer
 - Some like cell phone calls or pages
 - Some prefer hippa-compliant text messages
 - Some prefer sticky notes in the chart
- Cases rounded with ID MD 2-3x/week and as needed through the day
- Detailed statistics are kept for programmatic quality improvement purposes
 - ~90% of recommended changes are accepted

Pearl #1

Not all allergies are created equal!

• Some are more equal than others.



Case examples

- A patient with with "penicillin allergy" as a child presents with oxacillin sensitive *S αureus* bacteremia. He is treated with IV vancomycin. After 2 weeks of therapy he is discharged but relapses. On re-admission his penicillin allergy is missed and he is given Nafcillin and tolerates the medication well. After 6 weeks of nafcillin therapy he is cured.
- A patient with "vancomycin allergy" is given linezolid for MRSA bacteremia. He develops multifocal MRSA abscesses. After 3 weeks of linezolid he develops thrombocytopenia and peripheral neuropathy. He is switched to vancomycin and tolerates the infusion without incident.

Not all allergies are created equal

- ~9% of patients have a stated "allergy" to penicillin
 - However, 90% of these patients can tolerate PCN and are inappropriately labeled as allergic
 - Nausea, headache etc. are NOT allergies and DO NOT preclude use
- Delayed-onset reaction (>1h) after initial dosing is NOT contraindication to use of different beta-lactam class
 - E.g. If rash on day 2 of amoxicillin, it is OK to use cefazolin
 - Do not challenge if IMMEDIATE reaction (presumed IgE mediated)
 or SEVERE reaction (such as Stevens Johnson Syndrome)
- The medical record rarely documents allergy reaction with required detail. ASK THE PATIENT AND DOCUMENT IT!

Basic Beta-lactam rules

- If distant childhood non-severe rash to amoxicillin, ok to retrial in adulthood
 - Many childhood delayed onset amoxicillin rashes are related to viral illness, risk of severe reaction is the same as the general population
- If delayed onset rash, it is OK to trial a cephalosporin or carbapenem
- If anaphylaxis to PCN, it is OK to use aztreonam
- Cross-reactivity applies to type-I, IgE mediated allergy only
- Cannot desensitize a delayed-onset allergy, only type-I, IgE

Vancomycin "allergy" is usually B.S.

- B.S. = Bogus Stuff
- Vancomycin infusion results in histamine release from mast cells
 - Speed of infusion is correlated with risk
 - Threshold varies patient to patient
 - Histamine causes itching, hives, swelling; Patients hate it
- If there is a history suggestive of "Red-man" syndrome, pre-treat with diphenhydramine and run the infusion SLOWLY (e.g. 1.5g over 3 hours)
- If a patient needed epinephrine/intubation after vancomycin reaction, DON'T RECHALLENGE
- If a patient developed large surface area bullae, DON'T RECHALLENGE

Pearl #2

Bacteria in the urine DOES NOT equal urinary tract infection



Case example

- ID physician called to treat Raoultella planticola "UTI"
- 63 y/o woman with cardiogenic shock s/p IABP, retroperitoneal bleed, prolonged 3 week ICU stay, central lines, urinary catheters, now with severe mitral valve regurgitation awaiting mitral valve replacement
- Urine obtained due to climbing peripheral WBC after initiation of dexamethasone to "perk the patient up"
- Patient denies fever, bladder pain or spasm, dysuria, urgency, hesitancy, hematuria, or back/flank pain
- Antibiotics and dexamethasone discontinued and WBC falls

Asymptomatic bacteriuria (ASB)

- Presence of bacteria in urine in the absence of symptoms
- Women: 2 consecutive voided urine specimens with SAME bacterial strain ≥10⁵ cfu/mL
- Men: Single clean-catch urine with 1 species ≥105 cfu/mL
- Men and women: Single catheterized urine with 1 species
 ≥10²
- Pyuria without symptoms is NOT an indication for antimicrobial treatment

Asymptomatic bacteriuria

Table 2. Prevalence of asymptomatic bacteriuria in selected populations.

Population	Prevalence, %	Reference
Healthy, premenopausal women	1.0-5.0	[31]
Pregnant women	1.9-9.5	[31]
Postmenopausal women aged 50-70 years	2.8-8.6	[31]
Diabetic patients		
Women	9.0-27	[32]
Men	0.7–11	[32]
Elderly persons in the community ^a		
Women	10.8–16	[31]
Men	3.6–19	[31]
Elderly persons in a long-term care facility		
Women	25–50	[27]
Men	15–40	[27]
Patients with spinal cord injuries		
Intermittent catheter use	23-89	[33]
Sphincterotomy and condom catheter in place	57	[34]
Patients undergoing hemodialysis	28	[28]
Patients with indwelling catheter use		
Short-term	9–23	[35]
Long-term	100	[22]

^a Age, ≥70 years.

Clinical Infectious Diseases 2005; 40:643–54

Asymptomatic bacteriuria

- DO NOTTREAT ASYMPTOMATIC PATIENTS!!
 - Not in non-pregnant women, diabetics, old people, institutionalized people, spinal cord injury, or in patients with catheters. Treating even in renal transplant patients is controversial.

UNLESS!!!!!

- 1. Pregnant women should be screened in early pregnancy
 - Treat 3 7 days if positive
- 2. Prior to TURP
 - Start night before or immediately pre-procedure, stop postprocedure
- 3. Prior to urologic procedure where mucosal bleeding is anticipated

Why is asymptomatic bacteriuria over-treated?

- 20 80% of ASB is inappropriately treated
- Survey of 95 resident physicians who managed bacteriuria
 - 32% of ASB inappropriately treated with antibiotics
- Presented with 7 vignettes
 - 37% correct
 - Reasons cited for improperly treating ASB in survey:
 - Concern for post-op infection
 - Elevated inflammatory markers
 - Abnormal urinalysis

Table 2 Summary of clinical vignettes with the corresponding proportions of correct responses

Summary of clinical vignettes		Diagnosis	Treatment
	Expected responses to diagnosis and management	Correct response /total responses (%)	Correct response/ correct diagnosis (%)
 A 50-year-old man with hypertension was seen for annual physical exam, with no urinary symptoms. Routine UA showed pyuria; UC grew ≥10⁵/ml of Escherichia coli. 	ABU, no treatment is needed	31/95 (32.6)	31/31 (100)
 A 70-year-old woman with recurrent UTI history admitted due to trauma, without urinary symptoms. UA showed pyuria; UC grew ≥10⁵/ml of Escherichia coli. 	ABU, no treatment is needed	42/95 (44.2)	39/42 (92.9)
 A 68-year-old man with an indwelling foley catheter had cloudy urine, without urinary symptoms or signs of infection. UA showed pyuria; UC grew ≥10⁵/ml of Klebsiella pneumoniae. 	ABU, no treatment is needed	19/95 (20.0)	18/19 (94.7)
4. A 82-year-old woman without urinary symptoms was seen preoperatively before total knee arthroplasty. A preoperative UC grew ≥10 ⁵ /ml of Klebsiella pneumoniae.	ABU, no treatment is needed	37/95 (38.9)	34/37 (91.9)
 A pregnant woman at 12 weeks' gestation without urinary symptoms presented with pyuria, nitrite positivity on UA. UC grew ≥ 10⁵/ml of Escherichia coli. 	ABU, indicated for antibiotic therapy	29/95 (30.5)	17/29 (58.6)
 A 75-year-old man was about to undergo transurethral resection of the prostate. A preoperative UC grew ≥10⁵/ml of Klebsiella pneumoniae. 	ABU, indicated for antibiotic therapy	34/95 (35.8)	21/34 (61.8)
7. A 68-year-old woman admitted to the ICU with altered mentality due to drug intoxication developed SIRS. She had an indwelling Foley catheter. UC grew ≥10 ⁵ /ml of Escherichia coli. No other suspected infection focus was found.	UTI, indicated for antibiotic therapy	89/95 (93.7)	88/89 (98.9)

Note. Clinical vignettes provided on the questionnaire are virtual cases developed for the purpose of surveying resident physicians

Abbreviation: UA urinalysis, UC urine culture, ABU asymptomatic bacteriuria, UTI urinary tract infection, ICU intensive care unit, SIRS systemic inflammatory response syndrome

Do not screen or treat ASB prior to surgical procedures

No benefit prior to cardiothoracic or spinal surgery

ASB not associated with post-operative joint replacement

infections

Table 6. Microorganisms Isolated in Prosthetic Joint Infection in Patients With Preoperative Asymptomatic Bacteriuria

Patient	ASB Microorganism	PJI Microorganism
1	Enterococcus faecalis	Escherichia coli
2	Klebsiella pneumoniae	Staphylococcus aureus
3	E. coli	Serratia marcescens, coagulase- negative staphylococci
4	E. coli	E. coli, S. marcescens, Proteus mirabilis, Pseudomonas aeruginosa
5	E. coli	Coagulase-negative staphylococci
6	S. aureus	P. aeruginosa
7	E. coli	S. aureus
8	K. pneumoniae	Citrobacter spp.
9	E. coli	Coagulase-negative staphylococci
10	E. coli	Coagulase-negative staphylococci
11	E. coli	Coagulase-negative staphylococci
12	E. coli	Coagulase-negative staphylococci
13	E. faecalis	E. coli

Abbreviations: ASB, asymptomatic bacteriuria; PJI, prosthetic joint infection.

Clin Infect Dis 2014;59(1):41**–7** Interactive CardioVascular and Thoracic Surgery o (2016) 1**–7** J Korean Neurosurg Soc 47 : 265-270, 2010

Pearl #3

 Community acquired pneumonia is often treatable with 5-7 days of antibiotic therapy and rarely requires atypical coverage



Case example

• 45 y/o ethanol-dependent homeless gentleman presents to the hospital with fever and pleuritic chest pain. CXR shows a dense RML opacity. There is no clinical evidence of meningitis. Blood cultures grow S pneumoniae. HIV testing is non-reactive. He is given ceftriaxone 19 IV plus azithromycin 500mg PO daily. On day 3 he is afebrile on room air and wants to leave the hospital. The penicillin MIC of the organism is <0.03. He is discharged with amoxicillin 875mg PO BID to complete 2 additional days of therapy.

AMS at program in Anchorage

- 6,900 interventions since program inception
- 1,900 of 6,900 (28%) relate to respiratory infections
 - By far the most common type of intervention
- Types of interventions
 - Medication class change
 - Duration of therapy
 - IV to PO
- Respiratory-related AMS interventions represent "lowhanging fruit" and are "bread-n-butter" to an active AMS program

Community-acquired Pneumonia

- Pneumonia in patients WITHOUT risk factors for nosocomial organisms
- Subcategories
 - Outpatient
 - Severe (ICU) vs. non-severe
 - Structural lung disease that increases Pseudomonas risk
 - Aspiration pneumonia and lung abscess
- Organisms
 - Pneumococcus, Haemophilus, Moraxella
 - Legionella, Mycoplasma, Chlamydia
 - Structural lung disease: above plus Pseudomonas
 - Alcoholic with bloody sputum: above plus enteric GNR (Klebsiella)
 - Lung abscess or empyema: above plus oral anaerobes

CAP Empiric Rx

- Outpatients: Amox/clav 875/125mg plus azithromycin 500mg
 - No monotherapy with azithromycin (pneumococcus sensitivity ~60%)
 - Amoxicillin monotherapy option in those without comorbidities
- Ceftriaxone 1g plus Azithromycin 500 mg regardless of severity
 - If anaphylactic PCN Allergy: Levofloxacin 750mg (+/- vancomycin if ICU)
- Structural lung disease:
 - Standard regimens, escalate if cultures reveal drug resistant organisms
- Lung abscess and aspiration "pleuropulmonary syndrome":
 - (Ceftriaxone plus metronidazole) OR amp/sulbactam
 - Aspiration at time of intubation/suctioning or from vomiting does
 NOT require anaerobic coverage

"Healthcare-associated" pneumonia

- Abandoned term
- If hospitalized and received IV abx in last 90 days:
 - Non-severe pneumonia: Use standard CAP regimen, escalate if cultures reveal drug-resistant organism
 - If severe pneumonia, add empiric MRSA coverage (vancomycin or linezolid) and use cefepime in place of ceftriaxone
- CAP patients with a history of MRSA or pseudomonas pneumonia should be treated with regimens covering the prior organism and de-escalated based on cultures

Azithromycin

- 500mg PO or IV x 3 days
 - Multiple studies and meta-analysis support short course 500 mg dosing
- Azithromycin is the preferred form of atypical coverage in severe illness
 - Combination therapy decreases mortality in bacteremic pneumococcal illness
 - Azithromycin plus beta-lactam is associated with decreased mortality in ICU-severity CAP vs. quinolone plus beta-lactam
 - Small increased MI risk (OR 1.17) outweighed by survival benefit in elderly veterans (HR 0.73)

Eur Respir J, 1995, 8, 398–402 Journal of Antimicrobial Chemotherapy (2001) 48,691-703 Am J Respir Crit Care Med Vol 170. pp 440–444, 2004 Intensive Care Med (2010) 36:612–620 JAMA. 2014 June 4; 311(21): 2199–2208

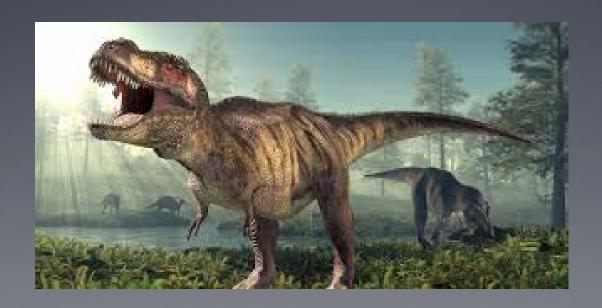
Duration of therapy

- Switch to PO as soon as hemodynamically stable and taking PO
- Stop after the following durations assuming afebrile >24h and hemodynamically stable:
 - 5 days if no immune-compromise* or structural lung disease
 - 7 days if moderate immune compromise or structural lung disease
 - 10-14 days if poor clinical response, inappropriate initial therapy, or severe immune compromise
- Duration for pneumonia with uncomplicated pneumococcal bacteremia is the SAME!! (i.e. 5 days ok if adequate response, ok to swap to PO as per usual protocol)

^{*}Organ transplant, HIV, chemotherapy, chronic prednisone >10mg, immune-suppressing medications

Pearl #4

- Not all cellulitis needs vancomycin, and
- Not all diabetic foot infections need Cephamegakillall or Tyranosauropenem



Case examples

- 65 year old woman with history of lower extremity lymphedema presents with tender erythema of the skin from the ankles confluently to the lower knee of 18 hours duration. She has low grade fever and chills. The WBC count is 21. She is placed on cefazolin 1g iv q8h and improves over the following 48 hours with concomitant leg elevation and NSAID therapy. She is discharged on oral amoxicillin to complete 7 days of therapy.
- 55 year old male with diabetes, neuropathy, and 3 month hx of plantar 5th MTP ulcer presents with erythema spreading to the mid-calf. He has no history of MRSA. He is placed on cefazolin after bedside debridement in the ED; tissue cultures grow group B streptococcus. MRI shows no evidence of bony abnormality. He is discharged on oral cephalexin after 3 days to follow-up with his established podiatrist.

2014 IDSA SSTI Guidelines

- Categorized SSTI by purulent/non-purulent to help guide need for empiric MRSA coverage
- If there is carbuncle/abscess or draining pus = PURULENT :
 - I+D, send culture on first episode
 - MILD = NO ABX
 - MODERATE = Cellulitis > 5 cm diameter
 - Bactrim DS 1 BID x 5 days
 - Clindamycin 300mg po TID if Sulfa allergic
 - SEVERE = Purulent SSTI plus SIRS criteria
 - Blood cultures x 2
 - Vancomycin dosed to goal trough of 10-15
 - PO once source controlled and improved to complete 7d Rx

Non-purulent cellulitis

- MILD
 - Cephalexin or Amoxicillin 1g PO TID
- MODERATE
 - Cefazolin 1-2g iv q8h
 - If not improving after 48-72h, broaden to Vancomycin and evaluate for evolution of unrecognized purulent focus
- SEVERE
 - Evaluate for necrotizing infection
 - Broad abx

ONLINE FIRST

Decreased Antibiotic Utilization After Implementation of a Guideline for Inpatient Cellulitis and Cutaneous Abscess

Timothy C. Jenkins, MD; Bryan C. Knepper, MPH, MSc; Allison L. Sabel, MD, PhD, MPH; Ellen E. Sarcone, MD;

- 169 patient pre-guideline vs. 175 post-guideline³
- Interventions:
 - Selective CRP, x-ray, blood cx use
 - ESR, superficial cultures, CT or MRI imaging DISCOURAGED
 - Vancomycin, total Rx IV + PO 7 days
 - Doxycycline, Clindamycin, or Bactrim on discharge
 - Broad aerobic GNR or anaerobe coverage DISCOURAGED
 - NSAID and elevate legs

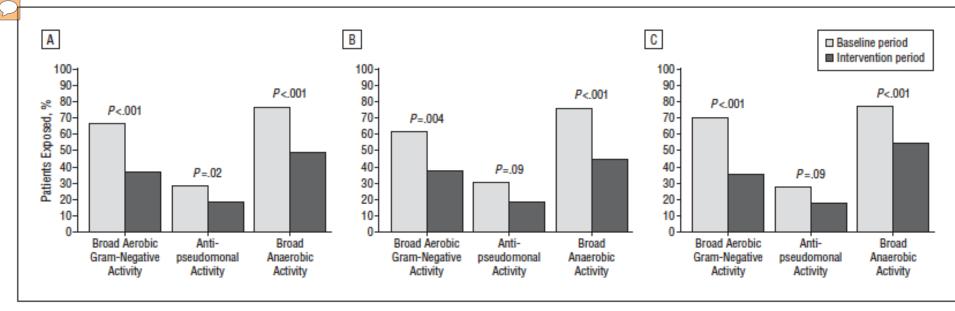
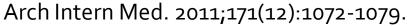


Figure 1. Exposure to antimicrobial classes by time period. Broad aerobic gram-negative activity: β-lactam/β-lactamase inhibitor combinations, fluoroquinolones, ceftriaxone, or imipenem-cilastatin. Antipseudomonal activity: piperacillin-tazobactam, ticarcillin-clavulanate, levofloxacin, ciprofloxacin, or imipenem-cilastatin. Broad anaerobic activity: β-lactam/β-lactamase inhibitor combinations, clindamycin, or imipenem-cilastatin. A, All cases; B, patients with cellulitis; C, patients with cutaneous abscess.



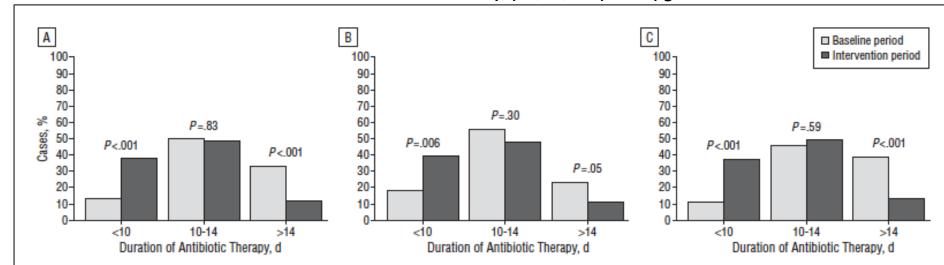


Figure 2. Duration of antibiotic therapy by time period. A, All cases; B, patients with cellulitis; C, patients with cutaneous abscess.

Diabetic Foot Infection (DFI)

- Updated IDSA guideline in 2012
- Not all diabetic ulcers are infected!!
- Signs of infection
 - Redness, warmth, tenderness, pain, induration, or purulent secretions
- MILD
 - Redness ≤ 2 cm around ulcer
- MODERATE
 - Redness >2cm around ulcer OR deep structures involved
 - WITHOUT sepsis
- SEVERE
 - Local infection plus SIRS criteria

Diabetic Foot Infection

- Infected wounds in NON-SEPTIC patients should be cultured BEFORE antibiotics are started
- Cultures should be sent from deep tissue by biopsy or curettage AFTER wound is cleaned and superficial tissues debrided
- All should get plain x-ray
- MRI if x-ray negative and suspicion of osteomyelitis
- If wound probes to bone, patient has osteomyelitis

ABX for DFI

- MILD to MODERATE severity
 - Target aerobic GPC only
 - Mild = Cephalexin pending cultures
 - Moderate = Cefazolin or Vancomycin dosed to goal trough of 10-15 or 24h AUC of 400-600

SEVERE

- Vancomycin PLUS piperacillin/tazobactam or cefepime + flagyl
- Urgent surgical consultation

Duration

- Mild: 1 2 weeks
- Moderate severe: 2 3 weeks
- Osteomyelitis present and not resected: 4+ weeks
- Osteomyelitis fully resected: 2 5 days

Pearl #5

Antibiotics are not useful for bronchitis and should not be offered



Case example

• 54 year old male with no comorbidities comes to clinic asking for antibiotics. He has a cough, sore throat, nose congestion, and says "I need antibiotics because it will go to my lungs." His temperature is 100.1 and his respiratory rate is 18. On exam he is coughing and has a few wheezes in both lungs. He is given albuterol inhaler and tylenol and told that his cough could last up to 3 weeks. He gradually improves.

2017 ANMC Acute Bronchitis in Adolescents and Adults

Presenting Symptoms	Comorbidities	Causes
 Cough > 5 days in a patient <u>WITHOUT COPD</u> 	COPD	 Influenza A and B
 Often productive of purulent sputum 	Asthma	Parainfluenza
 Fever, low-grade (<100.5°F or <38°C) 	Elderly (≥75 years)	Human metapneumovirus
Diffuse wheezes or rhonchi on exam	 Immunocompromised 	Rhinovirus
Mild dyspnea	Heart Failure	
Chest wall pain due to coughing		RSV
		Pertussis

Testing

- Vital signs including SpO2
- Consider influenza PCR during flu season if high risk or <48 hours of symptoms
- Consider pertussis PCR if paroxysms or post-tussive emesis
- Respiratory pathogen testing is discouraged in uncomplicated acute bronchitis
- Obtain CXR if:
 - Hemoptysis
 - III-appearing
 - Focal abnormality on auscultation
 - Age > 75
 - RR >24 or Temperature > 100.5°F or <38°C

Physician. 2016 Oct 1;94(7):560-565; File TM. Acute bronchitis in adults. Oct 2017. Up to date.

 Procalcitonin if patient in UCC/ED and antibiotics are being considered (patients >18 yo) –see ANMC Procalcitonin guideline for interpretation

Main Points

- Antibiotics are not beneficial for uncomplicated acute bronchitis.
 Using antibiotics when not needed could do more harm than good.
- Bacteria are uncommon causes of acute bronchitis
- Expected duration of cough is 2-3 weeks (average 18 days)
- Cough remedies and reassurance are the primary therapies
- Antihistamines are NOT effective for bronchitis
- Narcotic medications should not be used for cough suppression in acute bronchitis
- Avoid over-the-counter cough medications in children <4 years of age

Treatment Options				
	Medication	Education		
Symptoms without comorbidities present < 14-21 days	Guaifenesin 100mg/5ml PO Q4H pm cough (ANMC Non-Formulary, patient responsible for purchasing) Dextromethorphan 10-20 mg Q4H pm cough (max 120 mg/24H) (ANMC Non-Formulary, patient responsible for purchasing) Albuterol inhaler 90 mcg/inhalation 1-2 puffs PO QID pm difficulty breathing and wheezes present on exam in patients with asthma or underlying pulmonary disease	Rationale for no antibiotics Expected duration is 2-3 weeks Smoke free environment Avoidance of irritants Increase fluid intake Rest Humidify air		
Symptoms <u>and</u> comorbidities present	Evaluate for pneumonia or COPD exacerbation or alternative causes If positive evaluation, treat accordingly If negative evaluation, follow guidelines for symptoms without comorbidities	Honey Follow up if symptoms worsen Describe as "viral illness" or "chest cold"		
Adjunctive medications	Ibuprofen 400mg PO Q6-8H pm pain or inflammation Naproxen 500mg PO Q12H pm pain or inflammation Acetaminophen 325mg-650mg PO Q6h prn pain			

Antimicrobial Stewardship Program Approved 2017

References: Braman SS. Chronic cough due to acute bronchitis: ACCP evidenced-based clinical practice guidelines. Chest. 2006 Jan. 129(1 Suppl):95S-103S; Kinkade S, Long NA. Acute Bronchitis: AAFP. Am Fam

Let's take time to discuss any recent cases or infection/antibiotic challenges....

Thanks!