Antibiotic Stewardship

"An Infectious Disease Potpourri"

Nick Zaksek Pharm D., BCPS AQ-ID Infectious Disease
POMA 2019

#POFPS44

Disclosures

I have no relevant financial relationships or conflicts of interest to disclose.

#POFPS44

Objectives

- Practice good "Antibiotic stewardship" and foster the notion of antibiotic stewardship with your patients.
- Use antibiotic stewardship principles to decrease the risk of C.diff infections and adverse effects caused by antibiotics.
- Discuss ways a Post-antibiotic Era could change medicine.
- Understand the workings of an Antibiogram
- Discuss new guideline recommendations for C. diff
- Learn and employ a few clinical tips for treating Cellulitis and skin infections.

#POFPS44

Outpatient Antibiotic Stewardship

- The spread of antibiotic resistant bacteria has placed the world on the precipice of what public health leaders call a "post-antibiotic" era.
  - Simple surgical procedures could become deadly
  - "A child could die from a paper cut or a scratched knee".
- **30% of overall antibiotic use in outpatients is unnecessary**
- How can we start to reduce antibiotic usage?
  - A majority of the reduction could come from reducing unnecessary antibiotic use for respiratory conditions.
  - These conditions account for 44% of antibiotic prescriptions in outpatient facilities. (1/2 of these prescriptions are unnecessary!)

#POFPS44

#POFPS44

YOUR MICROBIOME

"Drop a person in a blender, then count the total cells…
1 in 10 cells will be human and the other 90% are microbes!"

- The microbiome in the GI tract changes after a few days of antibiotics BUT the changes can lasts for months to years and affect us later in life.
  - Individual's microbiome is largely set by age 3 ..antibiotic courses have a greater impact on infants and children versus adults.
- Antibiotics most disruptive to the microbiome are clindamycin, quinolones and 3rd generation cephalosporins
- Microbiome disruption …what really can happen?
  - Disruption in early years can result in obesity in adulthood
  - C. diff
  - Chronic diseases have doubled in the last 20 yrs.
    - Juvenile diabetes, asthma, eczema, and IBS appear to be unrelated but may have the same root cause→ antibiotics disrupting the microbiome

#POFPS44

BRONCHITIS

#POFPS44

Example: Acute Bronchitis

- Routine use of antibiotics is NOT recommended and they don't alter clinical outcomes.
- Acute bronchitis is a Self-limited viral syndrome characterized by:
  - Cough up to 3 weeks duration with or without sputum
  - Absence of signs of pneumonia on chest x-ray
- Common Organisms
  - **Viral** – influenza, Rhonovirus, Coronavirus, parainfluenza virus, Adenovirus etc.
  - **Bacterial** – Account for < 10% of cases
    - Mycoplasma pneumoniae, Chlamydophila pneumoniae, Bordetella pertussis/parapertussis

#POFPS44

Let's do a check ……

- According to studies what percent of outpatient prescription for antibiotics are considered unnecessary?
  - A. 10%
  - B. 30%
  - C. 50%
  - D. 60%

#POFPS44

Bottom line- We're losing our effective antibiotics & have to visualize the enormous impact antibiotic resistance will have.

- A scratch could become deadly
- Minor illness won't be minor anymore
- Surgery would become nearly impossible
- Antibiotics could be rationed or only available to those with means
- IT'S ALREADY HAPPENING
  - 2015- approx. 1.8 million people died of tuberculosis – part because drugs weren't available and in part the drugs didn't work.

#POFPS44

Evolution of Bacteria

How long does it take for bacteria to develop resistance????

#POFPS44

If there were no antibiotics, would you try this?

Pre-op antibiotics decrease risk of infections
.....but must be given appropriately

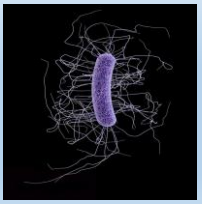

#POFPS44

Let's THINK.....
If there were no antibiotics given before surgery

- C- section - 1 in 100 chance of dying if no antibiotic is given pre-incision
  - Antibiotics decrease risk of obstetric procedures for infection by 70%
- Orthopedic surgery /joint replacement - 1 in 6 chance of infection and possibly dying if no antibiotic is given pre-op
- Dialysis
  - 2008 CDC reported 37,000 bloodstream infections; 1 in 4 of these patients may have died from the infection
  - 2013 CDC reported ↓32% in blood stream infections & ↓54% in vascular access related infections in part from antibiotic use.

#POFPS44

CLOSTRIDIOIDES DIFFICILE
(*formerly Clostridium difficile*)



#POFPS44

Table: Recommendations for Treatment of C. diff (CDI) in Adults 2017

Clinical Definition	Supportive Clinical Data	Recommended Treatment
Initial episode Non-severe	Leukocytosis with WBC of < 15,000 cells/mL and a SrCr. < 1.5 mg/dl	• VAN 125 mg oral QID X 10 days OR • FDX 200 mg BID X 10 days Alternate if above agents are unavailable metronidazole 500 mg TID X 20 days
Initial episode, Severe	Leukocytosis with WBC of > 15,000 cells/mL or a SrCr. > 1.5	• VAN 125 mg QID oral X 10 days OR • FDX 200 mg BID X 10 days
Initial episode, Fulminant	Hypotension or shock, ileus, megacolon	• VAN 500 mg QID oral or by NG tube. PLUS • Metronidazole 500 mg IV q8h, PLUS option of: ▪ Rectal Vancomycin enema 500 mg/100 ml q 6h (especially if ileus)
First recurrence		• VAN 125 mg oral QID X 10 days if metronidazole was used for the initial episode OR • Use prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (e.g. 125 mg QID X 10-14 days, BID X 7days, Daily X 7 days and then every 2 or 3 days X 2-8 weeks) OR • FDX 200 mg BID X 10 days (if VAN was used for the initial episode.)
Second or subsequent recurrence		• Fecal microbiota transplantation OR • VAN in a tapered and pulsed regimen (doses as above) OR • VAN 125 mg QID oral X 10 days followed by rifaximin 400 mg PO TID for 20 days, OR • FDX 200 mg given BID X 10 days

#POFPS44

The Rise and Fall of Metronidazole for *C. difficile*

- Many clinicians still using metronidazole for CDI because of the old 2010 SHEA/IDS guidelines which recommended metronidazole for mild disease and vancomycin for severe disease.
- Metronidazole is inferior to vancomycin esp. in the treatment of severe disease.
- **Metronidazole is NO longer 1st line treatment for adults with CDI**
  - It can be used for non-severe episodes of CDI in patients who cannot tolerate or do not have access to vancomycin or fidaxomicin
  - Still can be recommended to be given IV in addition to oral vancomycin to treat initial fulminant episodes of CDI
  - Prolonged & repeated courses of metronidazole increases the risk of neurotoxicity.
  - Note: metronidazole is still recommended for treatment of CDI in children according to the 2017 IDSA/SHEA guidelines.
  - Note: Metronidazole 500 mg IV q 6 hrs = 2 gm Sodium!

#POFPS44

Antibiotic Stewardship for *C. diff*

- Test patients who have 3 or more unformed/watery stools in 24 hrs.
  - Be sure to evaluate if they have had laxatives in past 48 hrs before testing.
- Assess if patient is presenting with a first episode of CDI, a first recurrence, or more and assess the severity of the illness.
- AVOID THE URGE TO REPEAT THE TEST OR PERFOM A TEST OF CURE.
  - If patient still has symptoms after treatment duration, then a retest may be warranted.
- The duration of therapy should be limited to 10 days for most patients. Some patients may have a delayed response to treatment and clinicians should consider extending the treatment duration to 14 days.

#POFPS44

Careful of who you test !

- RULES:
  - Do Not test asymptomatic patients
    - Positive C. diff tests on asymptomatic patients can result in antibiotics being prescribed. Antibiotics carry risks.
  - Only liquid unformed stools should be sent for testing.
    - 3 or more unformed stools/ 24 hrs
  - Limit retesting … there is no test of cure.
    - Stool assay for toxin may remain positive for several months after treatment! Go by the symptoms!

#POFPS44

Let's do a Check…….

- According to the updated C. diff guidelines (referring to Metronidazole), which of these statements is true?
  - A. Metronidazole is still the first line therapy for an initial C. diff. episode
  - B. Metronidazole should be combined with vancomycin for an initial case of C. diff
  - C. It should be eliminated (or very limited) as a therapy for C. diff
  - D. It should only be given IV for C. diff treatment

#POFPS44

Clinical Practice Guidelines…. Why are they not followed?

- Guidelines are written with the aim of collating the most up to date information into a single document.
  - They aid clinicians in providing the best practice for their patients.
- Evidence suggests that clinicians who adhere to guidelines deliver better outcomes for their patients.
- Barriers why they are not followed:
  - Awareness; familiarity and agreement with the contents
  - Clinician can't overcome inertia of "normal practice"
  - Goals of clinicians are not always the same as each other
  - Equipment, space, educational materials, time, staff and financial resource.

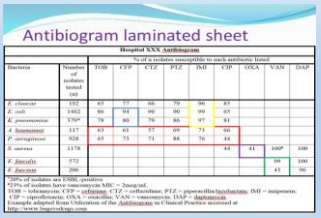
#POFPS44

Real problem: The psychology behind some Antibiotic misuse.

- Doctors prescribe more antibiotics when expectations are high.
  - Unrealistic expectations "magical thinking" can become premeditated resentment on the patient's part. If we think it, it will happen.
- "Tragedy of the Commons"
  - People use resources to their advantage without considering the good of a group or society. This leads to negative outcomes for everybody.
- "Decision fatigue"
  - Drs. Write more prescriptions for antibiotics later in the day. https://www.healthexec.com/node/75980
  - "Patient negotiation fatigue" – it takes time to talk patients out of antibiotics.
  - "Stealth dosing" – order restricted antibiotics after team goes home or on weekends etc.
- Exceptionalism
- "IKEA Effect"
  - People derive great satisfaction from things they build themselves.
    - Backfires: parts left over, things don't align or things fall apart when you try to use it.

#POFPS44

ANTIBIOGRAMS



#POFPS44

What are Antibiograms?

- Tables showing susceptibilities of a series of organisms to different antimicrobials.
- A collection of information obtained from C&S performed in an institution within a given time frame.
- They summarize cumulative proportions of pathogenic organisms that are susceptible to particular antimicrobials.
- They give us a profile of the susceptibilities of specific bacteria to antibiotics.
- Antibiograms help support appropriate and prudent use of antibiotics

#POFPS44

Primary Purpose of the Antibiogram

- Help guide empiric selection of antimicrobials
- An educational tool for prescribers
- To monitor antibiotics resistance trends in bacteria common among the patient populations and in the community
  - Caution here ! reviewing data can vary significantly among institutions even when in close proximity to each other. There can be vast difference in the type of patient population.

#POFPS44

Some basics about Antibiograms

- Antibiograms do not provide:
  - Organism sensitivity to an antibiotic based on site of infection
  - Organism sensitivity based on location in the hospital (ICU vs non-ICU)
  - Average MIC (minimum inhibitory concentration)
  - Antibiotic's ability to kill bacteria at various doses/concentrations
  - Trends of resistance (Unless you compare previous years data)
  - Differences in patient populations, ages of patients, hospital units.

#POFPS44

Parts of an Antibiogram

- ***Far left column:*** Name of bacteria isolated in the lab & tested
- ***Second column from left:***-Number of isolates
  - reflects the number of isolates which have yielded positive for a given organism.
- ***Remaining columns (left to right):*** susceptibility rates in (%) to each of the different antibiotics tested.
- % Susceptible
  - Percentage of isolates of a given organism that are sensitive to a given antibiotic
- Resistance
  - Reflects the percentage of the organism which are resistant to certain antibiotics
  - Resistance = 100 - % Susceptible (from the antibiogram)

#POFPS44

WESTMORELAND HOSPITAL ANTIBIOGRAM
(INPATIENT)

January 2015- December 2015

Data listed is % susceptible

		Penicillins			Cephalosporins			Carbapen		Quinolones		Aminoglyc				
GRAM NEGATIVE	Number Tested	Ampicillin	Ampicillin/Sulbct	Piperacil/Tazo	Cefazolin	Cefepime	Ceftriaxone	Imipenem	Ertapenem	Ciprofloxacin	Levofloxacin	Gentamicin	Tobramycin	Fostomycin (Urine)	Nitrofurantoin (Urine)	Trimeth/Sulfa
Acinetobacter baumanii	35	---	46	20	---	31	9	40	---	21	20	31	48	Mino = 73		31
Citrobacter freundii	19	---	---	93	0	100	95	100	100	89	89	89	89	---	100	89
Enterobacter aerogenes	20	---	---	79	0	100	80	100	100	85	85	85	85	---	7	90
Enterobacter cloacae	49	---	---	67	0	96	71	100	100	82	84	86	86	---	27	75
Escherichia coli	513	51	59	95	92	99	98	100	100	64	64	95	95	---	94	74
Klebsiella oxytoca	38	0	58	77	66	97	97	100	100	100	100	100	100	---	76	100

#POFPS44

Lets try it !

- Pt. has a UTI (no cultures yet). From the following choices of Ampicillin, Cefazolin, or Cipro which is your best bet for empiric therapy to start?
- You got back a culture from another patient and the sputum shows "*Stenotrophas. Maltophilia".* What do you order?
- Pt. at high risk for pseudomonas infections. Lab confirms the patient has Gram negative rods that are non-lactose fermenting. (assume it is Pseudomonas) which Abx is better to start Cipro or Zosyn?
  - Non-lactose fermenting rods - usually one of the 3 "Ps"
    - Proteus, Providencia, Pseudomonas
- Patient has an ESBL E.Coli in the urine. You would like to treat the patient at home with an ORAL antibiotic only. What do you recommend?

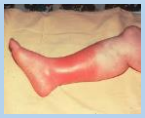
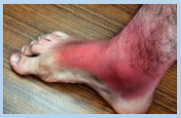
#POFPS44

Let's do a check.....

- Which of the following data pieces would not be found on an antibiogram usually?
  - A. Percentage of sensitive bacteria to antibiotics
  - B. The number of isolates tested per year
  - C. Notes about intrinsic resistance of particular bacteria
  - D. The source where the bacteria were isolated from.

#POFPS44

CELLULITIS

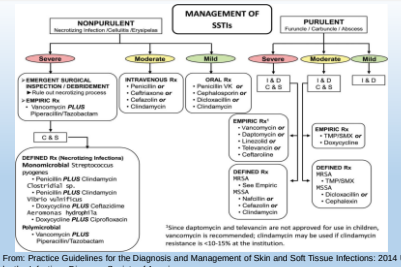




#POFPS44

Cellulitis…….
If it's RED, it's infected…right???

- More than 10% of patients labeled as having cellulitis do not have cellulitis
- Distinguishing true cellulitis from its many imitators is challenging but critical to avoid unnecessary use of antibiotics and delays in treatment.
- A few IMITATORS of cellulitis….which do not require antibiotics:
  - Stasis dermatitis
  - Contact dermatitis
  - Lymphedema
  - Pressure related skin injuries

#POFPS44

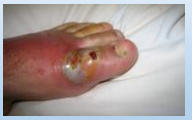


From: Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America
Clin Infect Dis. 2014;59(2):e10-e52. doi:10.1093/cid/ciu296

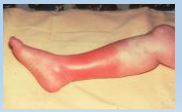
#POFPS44

Skin infections are 2 main categories

- Purulent
  - Uncomplicated abscesses
    - Furuncles, carbuncles
  - Purulent cellulitis



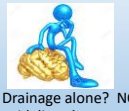
- Non-purulent
  - Necrotizing skin and soft tissue infections
  - Nonpurulent cellulitis
    - Erysipelas, cellulitis



#POFPS44

PURULENT SSTIs – uncomplicated

- What is best?



  - Incision and Drainage alone? NO ANTIBIOTICS
    - The IDSA guidelines lean toward I&D alone….. but the guidelines were last published in "2014".
  - ANTIBIOTICS ? Which ones?
    - TMP-SMX
    - DOXYCYCLINE
    - AMOXICILLIN/CLAVULANATE

#POFPS44

PURULENT Cellulitis

- 1-2 yrs ago "no antibiotics" would have been the correct assumption
- Now 2 newer studies both showed that antibiotics were better for patients with small abscess than incision and drainage alone.
  - 1st study TMP-SMX or clindamycin vs placebo following I&D. (N=786)
    - Results: TMP-SMX and clindamycin had similar efficacy to each other and both were significantly better than placebo.
      - Clinical cure rates were 83% after clindamycin , 82% after TMP/SMX, and 69% after placebo.
      - Adverse effects were more common with clindamycin (22%) versus TMP/SMX(11%)
    - Caution about using TMP/SMX in the older population with poor renal function.
  - 2nd study compared TMP-SMX to placebo following I&D (N=1057)
    - Clinical cure rates were 80.5% TMP/SMX and 73.6% placebo group.

#POFPS44

PURULENT cellulitis

- According to studies MRSA accounts for about 32% of purulent SSTIs while MSSA causes 68%. www.ncbi.nlh.gov/pubmed/23663462
- MSSA infections have become an important consideration as MRSA rates have declined from their peak.
- Purulent indicates *Staphylococcus* while Non-purulent is more indicative of *Streptococcus.* (*Note: Cellulitis can be a mix of Staph. & Strep.)*
  - **Purulent** cellulitis treatment should be directed at ***Staph.*** and I&D if possible.
    - Comes about more slowly
  - **Non-purulent** cellulitis treatment should be directed more toward ***Strep.***
    - Rapidly shows up

#POFPS44

Cellulitis Rx with antibiotics

- PURULENT – Drugs targeting Staph. and MRSA are needed
  - TMP/SMX – 5-10 days . 1 Double strength (DS) tab BID
    - Not good for STREP.
    - Side effects – Hyperkalemia, AKI, allergy
    - Good for *Staph. aureus (*Check your local antibiogram for sensitivity)
  - Doxycycline or Minocycline
    - Not good coverage for Streptococcus
    - Most *Staph. aureus* is susceptible but there is less data backup for it vs TMP/SMX
  - Clindamycin
  - Linezolid

#POFPS44

Cellulitis Rx with antibiotics

- Non-Purulent – Drugs targeting Streptococcus are needed.
  - Cefazolin (IV)
  - Cephalexin (Keflex)
    - 500 mg TID or QID (adjust for renal function)
    - We are seeing failures with Cephalexin outpatient but is the dosing correct?
  - Amoxil, Amoxillicin-clavulanate
    - Dosing might work better if given more frequently versus q 12hrs.

#POFPS44

Antibiotic Selections

- What If coverage for both Strep and MRSA is desired for oral therapy:
  - Conversion to oral therapy in patients receiving Vancomycin need to cover both MRSA and Streptococci.
  - Combination of either BACTRIM OR DOXYCYCLINE with a Beta-Lactam.
    - Beta lactams = Penicillin- like drugs:
      - Penicillin, Augmentin, Cephalosporins (Keflex, Ancef etc,)
  - Clindamycin alone
  - IN CASES of UNCOMPLICATED CELLULITIS, 5 days course is as effective as a 10 days course.
- *Activity of doxycycline and Bactrim against B-hemolytic Strep. is not reliable but is good for MRSA.*
- *If no abscess/ulcer/purulent drainage, B-lactam therapy alone is recommended.*

#POFPS44

IDSA Guidelines

Do you need cultures for Cellulitis?

- "Cultures of blood, tissue aspirates, or skin biopsies are unnecessary for typical cases of cellulitis"
- Prudent to cover MRSA in cellulitis associated with:
  - Penetrating trauma, purulent drainage, concurrent evidence of MRSA infection elsewhere (Nasal swab Positive for MRSA)
- Blood cultures should be obtained & cultures of skin biopsy or aspirate considered for patients with:
  - Malignancy
  - Severe Systemic features (high fever, hypotension etc.)
  - Unusual predisposing factors:
    - An immersion injury, animal bites, neutropenia, immunodeficiency

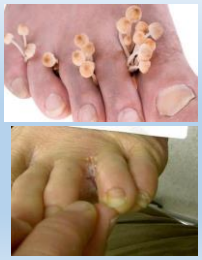
#POFPS44

Ancillary Treatments for Cellulitis

- Elevate the affected limb
  - Destruction occurs to the lymphatics which impairs resorption of inflammatory fluid. Gravity will assist with the drainage
- Anti-inflammatory medications.
  - NSAIDS have been shown to greatly hasten resolution of cellulitis
    - Ibuprofen 400 mg QID X 5 days.
    - Unless there is a clear contraindication, it is recommended to utilize ibuprofen in addition to antibiotics.
- Check for *Tinea pedis*

#POFPS44

Ancillary Treatments for Cellulitis



- Check for *Tinea pedis*
  - Many patients develop cellulitis once the pathogens invade through cracked skin from fungal infections in the web-spaces of the toes and feet.
  - If present… Treat with topical antifungals to seal the portal of entry and reduce recurrences
  - Lotrimin cream or Mycostatin Cream between the toes & affected areas BID

#POFPS44

Let's do a check……

- Select the false statement about Cellulitis.
  - A. Usually there is no need for extended gram-negative or anaerobic coverage.
  - B. Conversion to oral therapy in patients receiving Vancomycin usually needs to cover both MRSA and streptococci.
  - C. Streptococcus is generally associated with purulence and abscesses.
  - D. Ancillary treatments for cellulitis could include ibuprofen & topical antifungals.

#POFPS44

Final Thoughts On Antibiotic Stewardship

- Antimicrobial resistance is increasing; however, antimicrobial drug development is slowing
- By making antimicrobial stewardship part of your daily practice, we can improve patient safety and care, reduce the unnecessary waste of valuable resources , and reduce resistance.
- Antimicrobial stewardship in hospitals reduces the inappropriate use and consequences of antibiotics and improves patient outcomes BUT clearly it needs to be extended to where the greatest use occurs of antibiotics and that is in the community.

#POFPS44

We must all be Stewards of antibiotics
.....for them




#POFPS44

One more thing on my mind !

#POFPS44

#POFPS44

References

1. *Practice Guidelines for the Diagnosis & Management of Skin & Soft Tissue Infections :* 2014 Update by IDSA. Clin Infect Dis. 2014;59(2)

2. Talen,Da. et al. *Trimethoprim-sulfamethoxazole vs Placebo for Uncomplicated* Skin *Abscess*, NEJM 2016:374:823-32

3. Dawn RS. Et al, *A placebo-controlled trial of antibiotic for smaller skin abscesses*, NEJM 2017, Jun 28;376:2545

4. Keller,C., Tomecki K., Alraies, M., *Distinguishing cellulitis from its mimics,* Cleveland Clinic Journal of Medicine Vol79,(8) Aug.2012

5. IDSA/SHEA 'Implementing an Antibiotic Stewardship Program"

6. CDC – Core elements of an Antibiotic Stewardship Program

#POFPS44