Antibiotic Resistance – a growing problem in the US

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015

THE WHITE HOUSE
WASHINGTON

Antimicrobial resistance threats- some you know and some you are going to see

WHO

- *Acinetobacter baumannii* (carbapenem)
- *Pseudomonas aeruginosa* (carbapenem)
- Enterobacteriaceae, extended-spectrum-β-lactamase-producing (carbapenem)
- *Enterococcus faecium* (vancomycin)
- *Staphylococcus aureus* (methicillin, vancomycin)
- *Helicobacter pylori* (clarithromycin)
- *Campylobacter* spp. (fluoroquinolone)
- Salmonellae (fluoroquinolone)
- *Neisseria gonorrhoeae* (cephalosporin, fluoroquinolone)

CDC

Candida *auris*- A multidrug resistant fungus

- Emerging fungal pathogen that can be **resistant to multiple antifungal drugs (Azoles, Echinocandins and Amphotericin)**- overexpression of drug transporters
- CAN BE MISIDENTIFIED AS OTHER SPECIES (most often C. *haemulonii*)
- Invasive fatal infections reported (mostly in adults)
- Survives in environment and reported in outbreaks

'Superbug' fungus new menace in US hospitals, mostly NY, NJ

https://www.cdc.gov/fungal/diseases/candidiasis/candida-auris-qanda.html

What is antimicrobial stewardship?

- An activity that promotes:
  - ✓The right antibiotic
  - ✓At the right dose
  - ✓By the right route and for the right duration

- Antimicrobial stewardship & appropriate antibiotic use have been shown to:
  - ✓**Decrease *Clostridium difficile* infection**
  - ✓Decrease resistance on patient and institution level
  - ✓**Improve infection cure rates**
  - ✓**Decrease antimicrobial costs**

CDC. Core elements of hospital antimicrobial stewardship programs. 2014
CDC. Get Smart: Know when antibiotics work. Get smart for healthcare slides. 2014

- January 1, 2017: *new Joint Commission standards for hospital ASPs*
- Organizations will soon have to report antibiotic use data
- Providers should know:
  - ✓What is antimicrobial stewardship and why it is important
  - ✓What ASP resources are available at their hospital
  - ✓ASP education needs to be provided for all patients being discharged on antibiotics

Antibiotic Stewardship is a Shared Responsibility: EVERYONE ACTS AS A STEWARD

A Assess the patient

- Obtain history and perform physical exam
- Order the appropriate diagnostic studies

C Consider empiric therapy

- Consider appropriate empiric antibiotics based on institutional guidelines and document the indication
- Clarify all antibiotic allergies in detail

T Target therapy

- Re-evaluate and streamline antibiotics based on results of diagnostic studies (i.e., antibiotic time-out after 48-72 hours)
- Clearly define duration of therapy

Prescribing principle:
Do not automatically assume IV is better than oral.

Know which drugs can be converted from IV to PO without loss of efficiency

Some antibiotics are equally effective IV vs. PO

Nurse-Driven Antibiotic Stewardship

Encourage the IV-to-PO Switch

Some antibiotics are just as effective when given IV or PO. If your patient can tolerate PO or enteral feeds and is improving clinically, feel empowered to prompt the IV-to-PO switch with the prescriber.

Did you know?
The prompt IV-to-PO switch results in multiple patient benefits e.g., decreased patient length of stay, costs of antibiotic, and days of IV therapy.

Azithromycin
Ciprofloxacin
Doxycycline
Levofloxacin
Linezolid
Metronidazole
Minocycline
Trimethoprim/Sulfamethoxazole
Voriconazole

Prescribing principle: Be aware of typical presentations and local resistance data

Do we need antibiotics for a drained abscess?

Should we cover for MRSA?

Important points

- Use purulence as a marker for Staph *aureus* infections
- You may not need antibiotics after a complete I&D
- For sensitive Staphylococcus *aureus (MSSA)* Vancomycin is **inferior** to beta lactams (Cefazolin/Oxacillin/Cephalexin)
- In the right setting if your prevalence of MRSA is low , one could possibly start with non-MRSA coverage (Cephalexin) for stable patients with non severe infections
- Bactrim and Clindamycin are often equivalent for MRSA.
- Doxycycline does not have a age restriction anymore

Risk factors for MRSA infection (a bit dated)

- S. *aureus* colonization
- Injection drug use
- Diabetes mellitus
- Chronic dermatologic conditions (e.g., eczema)
- Recent use of antimicrobial agents
- African-American race
- Previous SSTI
- Close contact with an SSTI patient
- Participation in contact sports
- Military personnel
- Prisoners

Infect Dis Clin North Am. 2015 Sep;29(3):429-64.

Standard dosing of drugs for MRSA infection

Drug	Dosing	Adverse Effects	Clinical pearl
Clindamycin	Adults: 450-600 mg IV/PO q6-8H Pediatrics: 10 mg/kg IV/PO q6-8H	Diarrhea, high risk of C-difficile infection	Can be used IN addition to a second drug for syndromes like toxic shock syndrome
Trimethoprim/ Sulfamethoxazole	SSTI: 8-10 mg/kg/day IV/PO divided q6-12H Pneumonia: 15-20 IV/PO mg/kg/ day divided q6-12H	Renal toxicity (crystalluria), hyperkalemia, rash, Steven Johnsons (rare)	Traditionally considered sub-optimal for Group A strep
Doxycycline Minocycline	Adults: 100 mg IV/PO q12H Pediatrics: 2.2 mg/kg IV/PO q12H	Photosensitivity	There is no longer a age restriction! Watch out for DDIs with multivitamins

Vancomycin dosing pearls for pediatrics

- Trough is an imperfect surrogate for efficacy in pediatrics
- 15 mg/kg/dose every 6 hours for severe or invasive disease infections
- Consider a loading dose of 20 mg/kg/dose
- Evidence of increasing renal toxicity with higher troughs and with combination therapy with Piperacillin/Tazobactam
- Target troughs of 15-20 mcg/mL
  - Bacteremia
  - Infective endocarditis
  - Osteomyelitis
  - Meningitis
  - Pneumonia
  - Severe skin and soft tissue infections

Only target troughs of 10-15 mcg/mL for mild-moderate skin and soft tissue infections

Liu C et al. *Clin Infect Dis* 2011;52:1-38.

Vancomycin dosing pearls for adults

- Usual starting dose: 15-20 mg/kg/dose
- Typical dosing interval is every 12 – 24 hours
  - Consider every 8 hour dosing if < 50 years old with severe infection and normal renal function
- A good rule of thumb – morbidly obese patients may require a lower mg/kg/day dose to achieve desired trough levels
- Total daily doses > 4 gm/day are at increase risk of nephrotoxicity

Liu C et al. *Clin Infect Dis* 2011;52:1-38.

New drugs for MRSA infection

Drug	Dosing	Adverse Effects	Clinical pearl
Linezolid	≥12 years: 600 mg IV/PO q12H 1 month to < 12 years: 10 mg/kg/dose IV/PO q8H	Thrombocytopenia (with prolonged courses), lactic acidosis, peripheral neuropathy	Watch out for DDIs with MAOIs, SSRIs (inc serotonin syndrome risk)
Ceftaroline	Adults: 600 mg IV q8-12H Pediatrics: weight & age specific recommendations	Hematologic abnormalities (seen with higher doses), rash	Used in salvage MRSA bacteremia, endocarditis, pneumonia cases Brand only = $$$ Spectrum of activity: MRSA + ceftriaxone
Daptomycin	6-8 mg/kg/dose q24H	Rhabdomyolysis (monitor CPK at least weekly), eosinophilic pneumonia	Cannot be used for pneumonia (inactivated by lung surfactant) Higher doses typically required for E. faecium compared to MRSA

New long acting drugs for MRSA infection

Drug	Adult Dosing (studied for SSTI)	Adverse Effects	Clinical pearl
Oritavancin	1200 mg x 1 single dose	Hypersensitivity reactions, infusion reactions, headache nausea	Exceptionally long half-life (~245 hrs), prolonged infusion (3 hrs), Brand only = $$$
Dalbavancin	Single dose regimen: 1500 mg x 1 Two-dose regimen: 1000 mg x 1, 500 mg one week later	Hepatic effects, hypersensitivity, infusion reactions	Incredibly long half life (~350 hrs), Brand only = $$$

Stewardship principles – Use diagnostic stewardship

My patient has pneumonia and is now **Coronavirus** positive?

Should I give antibiotics?

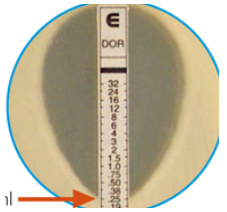
Diagnostic stewardship- what is it? Why does it matter?

- The art and science of using microbiologic tests to guide rational antibiotic use.
- Know how to interpret newly available microbiologic tests
- Know when NOT to treat a positive culture and how to distinguish false positives

Rapid molecular diagnostic methods are revolutionizing clinical microbiology laboratory but this increased sensitivity comes at a cost

Blood cultures Incubation Gram stain Identification Susceptibility testing

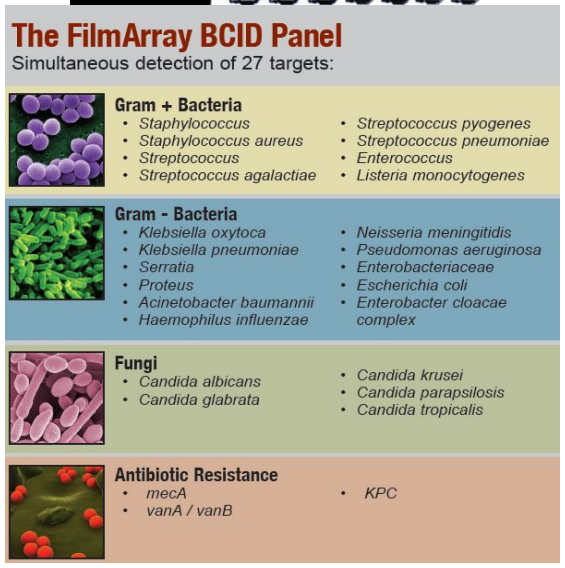
Conventional microbiological diagnosis



Patient with suspected bloodstream infection

~12 hours

24-48 hours



Enterobacter cloacae complex
Method: Vitek Minimum Inhibitory Concentration

Sensitivity	Value
Amikacin	<=2 S
Aztreonam	R
Cefepime	<=1 S
Cefoxitin	>=64 R
Ceftazidime	R
Ceftriaxone	R
Gentamicin	<=1 S
Levofloxacin	R
Meropenem	<=0.25S
Piperacillin-Tazobactam	>=128R
Tobramycin	<=1 S
Trimethoprim-Sulfamethoxazole	<=20 S

Rapid molecular diagnostic technology ~ 2 hours

Now we have PCR assays available for rapid ID for multiple conditions- Respiratory infections

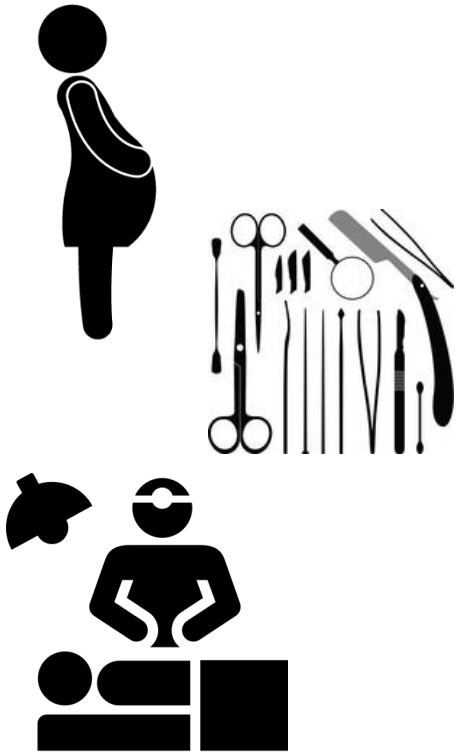
- Multiplex RT-PCR for respiratory viruses
- FilmArray Respiratory panel
- Viral: adenovirus; coronavirus (HKU1,NL63-229E,OC43); metapneumovirus, rhino/enterovirus; influenza (A,A/H1,A/H3, A/H1-2009,B); parainfluenza virus (type 1,2,3,4); respiratory syncytial virus
- Bacterial: *Bordetella pertussis*; *Chlamydophila pneumoniae*; *Mycoplasma pneumoniae*

Rapid Blood Culture Pathogen Identification available at our hospital (so you might get results faster than before)

GRAM POSITIVES	**GRAM NEGATIVES**
Enterococcus, Vancomycin Susceptible	*Acinetobacter baumannii*
Enterococcus, Vancomycin Resistant	Enterics:
Streptococcus pyogenes (Group A)	*Enterobacter cloacae* complex
Streptococcus agalaticae (Group B)	*Escherichia coli*
Streptococcus pneumoniae	*Klebsiella oxytoca*
	Klebsiella pneumoniae
YEAST	*Proteus species*
Candida albicans	*Serratia marcescens*
Candida glabrata	KPC positive/negative
Candida krusei	*Haemophilus influenzae*
Candida parapsilosis	*Neisseria meningitidis*
Candida tropicalis	*Pseudomonas aeruginosa*

Remember that you do NOT have to treat every positive culture…

23-50% of antibiotic days for "UTI" may be unnecessary treatment for asymptomatic bacteriuria.



Whom to treat	Whom NOT to treat
• Pregnant women • Patients undergoing urological procedures in which mucosal bleeding is anticipated	• Diabetic patients • Patients with chronic indwelling urinary catheters • Patients who are immunocompromised • Patients about to undergo non-urologic surgery • Patients with urine cultures that grow MDR organisms

Wald HL JAMA Intern Med 2016. Epub
Trautner BW. Nat Rev Urol. 2012; 9 (2) 85-93

Stewardship principle – Think twice before labeling with an antibiotic allergy

I think my patient has a penicillin allergy and therefore should receive levofloxacin?

Remember : Being labeled with an antibiotic allergy is not trivial and has serious impact on patient outcomes

J Allergy Clin Immunol. 2014 Mar;133(3):790-6. doi: 10.1016/j.jaci.2013.09.021.

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How should vague allergy histories be handled?

When any allergy with an unknown reaction is noted in a patient medical record every effort should be made to clarify the reaction ASAP

85-90% Percentage of reported beta-lactam allergies that **are not true allergies** → reduce antibiotic options unnecessarily.

Patients, their family members, and other care providers can often provide clarity

Park, et al. Ann Allergy Asthma Immunol. 2006;97:681-687.

What do you need to ask?

- Date of reaction
- Timing (immediate vs. delayed)
- Treatment of reaction (epi/steroids)
- Has the patient tolerated other similar classes of medications
- Hives/angioedema/anaphylaxis (Type 1 reaction)
- Oral ulcers (Steven Johnsons syndrome)
- Joint pains (serum-sickness)
- Specific diagnosis given by provider : DRESS/ Acute Interstitial Nephritis/ Hemolytic Anemia

Evolving consensus on true PCN allergy

- PCN allergy is reported by approximately 10–20% of the population in the USA (higher in hospitalized patients)
- **Less than 10% of patients identifying as allergic have positive skin tests to penicillin**
- **90% of patients with labels are able to tolerate the medication without immediate-type hypersensitivity**

JAMA. 2001 May 16;285(19):2498-505.

Curr Allergy Asthma Rep (2017) 17: 40

CROSS REACTIVITY IS LOWER THAN YOU THINK

Cross-reactivity between penicillin and other beta-lactam classes (immediate-type hypersensitivity)

Beta Lactam Antibiotic	Cross Reactivity Rate
Monobactams (i.e., aztreonam)[1]	**0%**
Cephalosporins[2]	**3-4%**
Carbapenems (e.g. Meropenem)	**<1%**

[1] Avoid aztreonam if the patient has had a previous reaction to ceftazidime

[2] Patients with previous reaction to amoxicillin or ampicillin should avoid cephalosporins with identical R group side chains:

Amoxicillin: cefadroxil, cefprozil

Ampicillin: cefaclor, cephalexin

Saxon, et al. J *Allergy Clin Immunol* 1988
McConnell SA, et al. CID 2000
Prescott WA, et al. CID 2004

Cross reactivity charts– Beta-lactams and Cephalosporins (available online)

	Penicillin G	Amoxicillin	Ampicillin	Cephalexin	Cefadroxil	Cefaclor	Cefotetan	Cefoxitin	Cefprozil	Cefuroxime	Cefdinir	Cefixime	Cefotaxime	Cefpodoxime	Ceftazidime	Ceftriaxone	Cefepime
Penicillin G								X									
Amoxicillin			X	X	X	X			X								
Ampicillin		X		X	X	X			X								
Cephalexin		X	X		X	X			X								
Cefadroxil		X	X	X		X			X								
Cefaclor		X	X	X	X				X								
Cefotetan																	
Cefoxitin	X									X							
Cefprozil		X	X	X	X	X											
Cefuroxime								X									
Cefdinir												X					
Cefixime											X						
Cefotaxime														X		X	X
Cefpodoxime													X			X	X
Ceftazidime																	
Ceftriaxone													X	X			X
Cefepime													X	X		X	

X indicates a similar side chain and therefore potential for cross-reactivity

Prescribing principle: You can probably go shorter in terms of antibiotic duration

The New Mantra: Shorter is Better!

Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

Disease	Treatment, Days	
	Short	Long
Community-acquired pneumonia[1-3]	3-5	7-10
Nosocomial pneumonia[6,7]	≤8	10-15
Pyelonephritis[10]	5-7	10-14
Intraabdominal infection[11]	4	10
Acute exacerbation of chronic bronchitis and COPD[12]	≤5	≥7
Acute bacterial sinusitis[13]	5	10
Cellulitis[14]	5-6	10
Chronic osteomyelitis[15]	42	84

Abbreviation: COPD, chronic obstructive pulmonary disease.

Spellberg B. JAMA 2016

Prescribing principles – summary

- Do not automatically assume IV is better than PO.
- Know your local epidemiology and susceptibilities.
- Practice diagnostic stewardship
- Think twice before labeling with an antibiotic allergy
- You can probably do a shorter duration than you think