

Antibiotics, infection, and the evidence: Update 2018

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Objectives

- ▶ The participant will be able to apply evidence-based guidelines for diagnosis of common infections in acutely ill patients to their current practice.
- ▶ The participant will be able to summarize evidence-based treatment of pneumonia, UTI, soft tissue infections, and bloodstream infections in the acute care environment.
- ▶ The participant will be able to integrate pharmacokinetic/pharmacodynamic principles of antibiotic prescribing into their daily practice.

Disclosures

- ▶ The speaker Has NO conflicts of interest with regard to the topic of this presentation. I do not lecture or receive funding from any pharmaceutical company.



Introduction

- ▶ Infection (known or suspected) is a common reason for hospital admission
- ▶ Hospital acquired infections (HAI) are a continual problem for patients and healthcare institutions
- ▶ Antimicrobial resistant pathogens have a profound effect on inpatient care and outcomes
- ▶ Individual decision making essential
- ▶ Poor decisions can have serious consequences

Factors contributing to the problem:

- ▶ Use and overuse of antibiotics
- ▶ More complex, long-term patients
- ▶ Use of antibiotics in "food animals" to prevent or treat illness, and to promote growth
- ▶ Improper disposal of antibiotics, passing Rx to other persons, incomplete courses, inadequate dosing (esp. in inpatients)
- ▶ Passing antibiotic-resistant infections from one person to the next, via contact or fomites

HAI prevalence study (2014, Magill et al.)

- ▶ Of 11, 282 patients, 4% had 1 or more HAIs
- ▶ Most common types:
 - ▶ Pneumonia, 21.8%
 - ▶ Surgical site infection, 21.8%
 - ▶ GI Infections, 17.1%
 - ▶ Device-associated infections (CLABSI, CA-UTI, VAP) were 25.6% of all infections

HAI prevalence study (cont.)

- ▶ In order of pathogen prevalence:
 - ▶ *C. difficile*, 12.1%
 - ▶ *S. aureus*, 10.7%
 - ▶ *Klebsiella pneumoniae and oxytoca*, 9.9%
 - ▶ *Escherichia coli*, 9.3%

National Healthcare Safety Network

- ▶ CDC's National Healthcare Safety Network is the nation's most widely used healthcare-associated infection tracking system. NHSN provides facilities, states, regions, and the nation with data needed to identify problem areas, measure progress of prevention efforts, and ultimately eliminate healthcare-associated infections.

National Strategy for Combating Antibiotic Resistant Bacteria (CARB)

- ▶ CARB includes a National Action Plan for Combating Antibiotic-Resistant Bacteria, which provides a five-year road map to guide the Nation toward five goals over five years (2015-2020)
(United States Task Force for Combating Antibiotic-Resistant Bacteria, 2017)

Antibiotic Resistant HAIs

- ▶ More virulent and more resistant to the antibiotics typically used to fight them
- ▶ multi-drug resistant organism (MDRO) – an organism resistant to one antibiotic in at least three different classes (Siefert et al., 2013)

Carbapenem-resistant enterobacteriaceae (CRE)

- ▶ Most common types: *klebsiella* spp, *e. coli*
- ▶ CRE have become resistant to nearly all available antibiotics
- ▶ Almost half the hospitalized patients with CRE bloodstream infections die (CDC, 2013)
- ▶ Mechanism of resistance: primarily through extended-spectrum beta-lactamase production, rendering it resistant to all beta-lactam drugs

Enterobacteriaceae

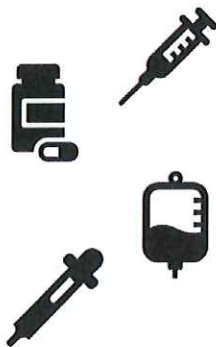
- ▶ Primarily enteric (gut) bacteria
 - *E coli*
 - *Proteus*
 - *Enterobacter*
 - *Serratia*
 - *Citrobacter*
 - *Klebsiella*
 - Many others including *salmonella*, *shigella*, *yersinia pestis*

Newest threats

- ▶ In 2015 the *mcr-1* gene was found on a plasmid in China
- ▶ The *mcr-1* gene confers resistance to colistin
- ▶ In 2016 this was found on an *e coli* bacteria (UTI) of a woman in Pennsylvania
- ▶ Extensive surveillance efforts only revealed one additional finding of this gene (CDC, 2017)

Newest threats

- ▶ *Candida auris* is a multidrug-resistant fungus which is causing invasive fungal infections in hospitalized patients
- ▶ Resistance has developed during treatment with echinocandins
- ▶ As of August 2017, 153 clinical infections have been identified, along with 143 additional patients who are colonized
- ▶ Colonization appears to be long-term and persistent
- ▶ The CDC has developed recommendations for treatment and hospital care in identified cases
<https://www.cdc.gov/fungal/diseases/candidiasis/c-auris-alert-09-17.html>



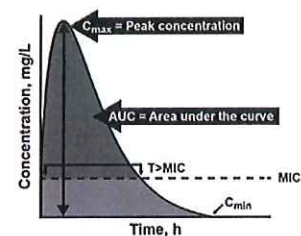
Pharmacology principles and antibiotic therapy

Pharm terms

- ▶ **Pharmacodynamics** – what a drug does to the body, eg. mechanism of action
- ▶ **Pharmacokinetics** – what a body does to a drug, eg. how is the drug metabolized/excreted, regulation of levels
- ▶ **AUC** – Area under the curve
- ▶ **MIC** – mean inhibitory concentration; ie. what level is required to kill the bacteria
- ▶ (Septimus, 2012)

Antibiotic concentration and efficacy

- ▶ **Time dependent** – drug kills at the same rate after achieving a given concentration (surpasses MIC). Also known as concentration independent (dosing more frequent). Examples: beta lactams, vancomycin
- ▶ **Concentration dependent** – drug kills at a greater rate with a higher concentration level. Examples: aminoglycosides, metronidazole, fluoroquinolones



Bacteriostatic or bactericidal?

- ▶ **Bacteriostatic**: stops bacterial growth when above MIC, infection dies off
- ▶ **Bactericidal**: kills bacteria actively when above MIC
- ▶ In most infections, both types of antibiotics kill bacteria at a similar rate, and this should not be a consideration when choosing therapy. Bactericidal antibiotics may have an advantage in certain types of infections (endocarditis, meningitis, febrile leukopenia) but even this is debatable. (Cunha, 2013)

Dosing

- ▶ Dose must exceed MIC (mean inhibitory concentration) for much of the day if time dependent
- ▶ Continuous infusion may be a good option for critically ill (carbapenems, cefepime, pfp/tazo, vanco)
- ▶ Again highly individual
 - ▶ Renal failure?
 - ▶ Penetration of site being treated
 - ▶ Study pharmacokinetics for aminoglycosides (P/T), vancomycin (T only)

Choosing an empiric regimen

- ▶ Local data-based
- ▶ Should cover nearly 100% of potential pathogens
- ▶ Broad spectrum gram negative and gram positive
- ▶ Fungal coverage if strongly suspected, i.e. in the immunosuppressed, GI surgery, TPN

University of Miami/Jackson Memorial Hospital (Main)

ANTIBIOTIC SUSCEPTIBILITY REPORT - January - December 2014

Microbiology Lab 365-555-6300

Date include 1st isolate from patient LAB# 1000

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Dosing and the critically ill patient

- ▶ Risk of suboptimal drug concentrations is higher than the risk of overdosing, especially for hydrophilic drugs (beta lactams)
- ▶ 5 major factors which may cause alterations in drug pharmacokinetics in the critically ill patient:
 - ▶ Increased volume of distribution (Vd)
 - ▶ Alterations in protein binding
 - ▶ Augmented (Increased) renal clearance
 - ▶ Impaired renal clearance
 - ▶ Hepatic dysfunction

(Blot, Pea, & Lipman, 2014)

Dosing and the critically ill patient

- ▶ Critically ill patients often have a greater volume of distribution (Vd) from sepsis, capillary leak, fluid overload
- ▶ Vd describes a relationship between the dose and the resulting serum concentration
- ▶ Most important for hydrophilic drugs (beta lactams)
- ▶ Multiple PK factors may be influencing drug levels
 - ▶ Renal failure, sepsis, drug interactions

(Blot, Pea, & Lipman, 2014)



Diagnosis and treatment of infection: EBP

"Guidelines" and level of evidence

- ▶ Previously, most guidelines consisted of "expert opinion" and constituted a **low level of evidence**
- ▶ NOW, most major societal guidelines are high-level evidence, often done like a **systematic review**

GRADE approach to evidence

- ▶ RCTs start as "High"
- ▶ Observational trials start as "Low"
- ▶ Evidence quality levels (grades):
 - ▶ High
 - ▶ Moderate
 - ▶ Low
 - ▶ Very low

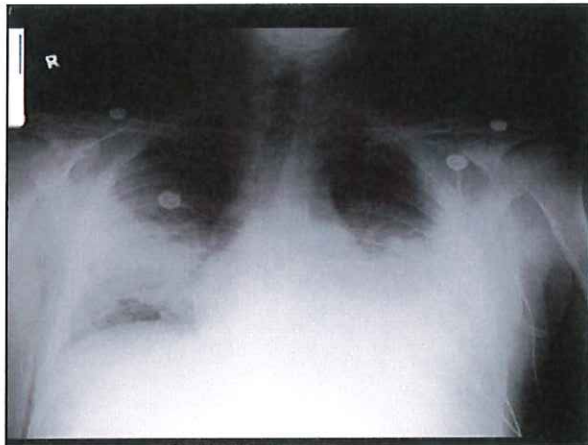
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Procalcitonin and antibiotics

- ▶ Lam, Bauer, Fowler, & Duggal (2018) performed a systematic review and meta-analysis
 - ▶ Focused on three subgroups: use of PCT for initiation of abx, cessation, or both
 - ▶ 15 RCTs were included, significant heterogeneity noted in methods
 - ▶ The use of PCT for cessation and mixed strategies showed decrease in abx use (-1.26 days and -3.1 days)
 - ▶ Only the use of PCT for abx cessation showed a decrease in mortality (RR 0.87)

Most common sites of infection

- ▶ Urinary tract
- ▶ Lungs
- ▶ Invasive devices
- ▶ Bloodstream
- ▶ GI tract
- ▶ Intra-abdominal
- ▶ Skin/skin structure



Pneumonia: CDC clinical diagnostic criteria (2016)

- ▶ For ANY PATIENT, at least one of the following:
 - ▶ Fever ($>38.0^{\circ}\text{C}$ or $>100.4^{\circ}\text{F}$)
 - ▶ Leukopenia ($\leq 4000 \text{ WBC/mm}^3$) or leukocytosis ($>12,000 \text{ WBC/mm}^3$)
- ▶ For adults >70 years old, altered mental status with no other recognized cause

Pneumonia: CDC clinical diagnostic criteria (2016) cont.

- ▶ And at least two of the following:
 - ▶ New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
 - ▶ New onset or worsening cough, or dyspnea, or tachypnea
 - ▶ Rales or bronchial breath sounds
 - ▶ Worsening gas exchange (e.g., O_2 desaturations (e.g., $\text{PaO}_2/\text{FiO}_2$)

Treatment of pneumonia

- ▶ Distinguish CAP/HAP/VAP
- ▶ Treatment
 - ▶ Accurate early empiric therapy essential
- ▶ Need good lung penetration
 - ▶ Quinolones
 - ▶ Beta-lactams
 - ▶ Vanco/linezolid
- ▶ Resistance
 - ▶ Assess risk factors for resistance
 - ▶ Antibiotic use

Diagnosis and treatment of CAP

- ▶ Sputum culture often difficult but nice if you can get it
- ▶ Most important to cover *strep pneumo* (most likely/common pathogen) and the atypicals
 - ▶ Mycoplasma, chlamydiae, legionella (atypicals)
- ▶ IDSA 2007 guidelines (a 2014 Cochrane review made NO new recommendations – Pakhale et al., 2014):
 - ▶ A macrolide for previously healthy patients
 - ▶ A respiratory fluoroquinolone for patients with comorbidities

Diagnosis and treatment of CAP

- ▶ CA-MRSA rates increasing – keep in mind if pt very sick/not improving (s/s – cavitary lesions, pleural effusions, hemoptysis, neutropenia, skin pustules/rash, young healthy patient, severe illness)

Wunderink & Waterer, 2014

Treatment of CAP (hospitalized)

CAP

▶ Inpatient, ICU rx options:

- ▶ Beta-lactam plus azithromycin or fluoroquinolone
- ▶ For poss pseudo (recent HC contact): pfp/tazo or carbapenem plus fluoroquinolone

▶ Inpatient, non-ICU rx options:

- ▶ Respiratory quinolone
- ▶ Beta-lactam plus a macrolide

Duration: min 5 days, 48-72

IDSA/ATS CAP Guidelines, 2007

Resistance concerns

Pseudomonas risk factors

- ▶ pulmonary comorbidities
- ▶ Prior abx therapy/hospitalization
- ▶ Diabetes, alcoholism
- ▶ Immunosuppression

MRSA risk factors

- ▶ Prisoners
- ▶ Athletes
- ▶ Those living in crowded conditions
- ▶ MSM
- ▶ ESRD
- ▶ Rx with fluoroquinolone

Other important CAP data

- ▶ CAP treatment duration of 5 days (if asymptomatic at 5 days) is adequate (Uranga et al., 2016)
- ▶ A beta-lactam monotherapy for cap is non-inferior to combination beta-lactam plus macrolide OR a fluoroquinolone (Garin et al., 2014; Postma et al., 2015)
- ▶ In patients with severe cap and a high inflammatory response, treatment with methylprednisolone resulted in fewer treatment failures than in those with standard abx care. NO difference in mortality (Torres, et al., 2015).

VAP – surveillance definitions

- ▶ Ventilator-associated condition (VAC): resp deterioration after stability or improvement on mech vent
- ▶ Infection-related VAC: above plus fever/ inc. WBC, new abx started
- ▶ Possible VAP: IVAC plus purulent secretions or positive culture
- ▶ Probable VAP: IVAC plus purulent secretions and a positive quant culture, or histopathology
- ▶ (Magill et al., 2013)

VAP – clinical diagnosis (CDC, 2016)

- ▶ Probable VAP: IVAC plus purulent secretions and a positive quanti culture, or histopathology
- ▶ Threshold values for cultured specimens used in the diagnosis of pneumonia
- ▶ Specimen collection/technique Values
 - ▶ Lung tissue* >10⁴ CFU/g tissue
 - ▶ Bronchoalveolar lavage (B-BAL) >10⁴ CFU/ml
 - ▶ Protected BAL (B-PBAL) >10⁴ CFU/ml
 - ▶ Protected specimen brushing (B-PSB) >10³ CFU/ml

HAP/VAP Diagnosis: IDSA 2016

- ▶ NO more HCAP
- ▶ Non-invasive sampling with semi-quantitative cultures (weak rec, low level of evidence)
- ▶ Use clinical criteria alone (NOT PCT) to decide whether to initiate antibiotic therapy in patients with suspected HAP/VAP (strong recommendation, moderate qual evidence)
- ▶ Also, say NO to CRP or use of CPIS to diagnose (not recommended)

Kalil et al., 2016

Empiric VAP recs: IDSA 2016 (where MRSA and MDR gm neg are common)

Gm pos abx with MRSA coverage

Glycopeptides:
Vancomycin 15 mg/kg IV q8-12h
(consider a loading dose of 25-30 mg/kg x 1 for severe illness)
OR
Oxazolidinones:
Linezolid 600 mg IV q12h

Kalil et al., 2016

Gm neg, anti-pseudo, B lactams

Antipseudomonal penicillins:
Piperacillin-tazobactam 4.5 g IV q6h
OR
Cephalosporins:
Cefepime 2 g IV q8h
Ceftazidime 2 g IV q8h
OR
Carbapenems:
Imipenem 500 mg IV q6h
Meropenem 1 g IV q8h
OR
Monobactams:
Aztreonam 2 g IV q8h

Gm neg, anti-pseudo, NON B lactams

Fluoroquinolones:
Ciprofloxacin 400 mg IV q8h
Levofloxacin 750 mg IV q24h
OR
Aminoglycosides:
Amikacin 15-20 mg/kg IV q24h
Gentamicin 5-7 mg/kg IV q24h
Tobramycin 5-7 mg/kg IV q24h
OR
Polymyxins:
Colistin 5 mg/kg IV x 1 (loading dose) followed by 2.5 mg x (1.5 x CrCl + 30) IV q12h (maintenance dose)
Polymyxin B 2.5-3.0 mg/kg/d divided in 2 daily IV doses

Risk factors for MDRO VAP (CDC)

- ▶ Antimicrobial therapy in preceding 90 days
- ▶ Current hospitalization of 5 days or more
- ▶ High frequency of antibiotic resistance in the community or in the specific hospital unit
- ▶ Presence of risk factors for HCAP:
 - ▶ Hospitalization for 2 days or more in the preceding 90 days
 - ▶ Residence in a nursing home or extended care facility
 - ▶ Home infusion therapy (including antibiotics)
 - ▶ Chronic dialysis within 30 days
 - ▶ Home wound care
 - ▶ Family member with multidrug-resistant pathogen
 - ▶ Immunosuppressive disease and/or therapy

VAP treatment

- ▶ Level one evidence supports the use of short-course antibiotic therapy (7-8 days) (Kalil et al., 2016; Pugh et al., 2015)
- ▶ Recommendations for empiric therapy should be based on local antibiogram data when available
- ▶ Empiric therapy:
 - ▶ no risk factors for MDR pseudo or MDR GNR
 - ▶ One gm negative, one MDR gm pos agent
 - ▶ Risk factors for MDR pseudo/other GNR
 - ▶ Two gm negative agents, one for gm Pos (vanco, linezolid, tedizolid)

(IDSA VAP guidelines, 2016; File, 2017)

VAP treatment

- ▶ Inhaled route? Needs to be better studied but:
 - ▶ No nephrotoxicity
 - ▶ Weak evidence supports inhaled colistin (Valachis et al, 2015)
 - ▶ IDSA guidelines (Kalil et al., 2016) suggest using inhaled abx in cases where the pathogen is sens only to aminoglycosides and polymyxin



CA-UTI – Diagnosis by IDSA criteria

- ▶ CA-UTI in patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization is defined by the presence of:
 - ▶ symptoms or signs compatible with UTI
 - ▶ with no other identified source of infection along with:
 - ▶ $\geq 10^3$ colony forming units (cfu)/mL of 1 bacterial species
 - ▶ in a single catheter urine specimen
 - ▶ OR in a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 h
- ▶ (IDSA Guidelines, 2009)

CA-UTI diagnostic criteria (1/16)

- ▶ Patient must meet 1, 2, and 3 below:
 1. Patient had an indwelling urinary catheter that had been in place for > 2 days on the date of event (day of device placement = Day 1) AND was either:
 1. Present for any portion of the calendar day on the date of event
 2. OR Removed the day before the date of event†
 2. Patient has at least one of the following signs or symptoms: • fever ($>38.0^\circ\text{C}$) • suprapubic tenderness* • costovertebral angle pain or tenderness* • urinary urgency ^ • urinary frequency ^ • dysuria ^
 3. Patient has a urine culture with no more than two species of organisms identified, at least one of which is a bacterium of $\geq 10^5$ CFU/ml

Urinary tract infections - treatment

- ▶ Change or remove indwelling catheters
 - ▶ Short course unless deep seated, i.e., pyelonephritis:
 - ▶ 3-5 days uncomplicated may be considered
 - ▶ 7 days if complicated (complicated = presence of foley/other device, or male gender)
 - ▶ longer if late responder (IDSA guidelines, 2009)
 - ▶ Most antibiotics are heavily excreted in the urine, and will work even if the infection is "resistant"
- (Namias & Houghton, 2009)

Asymptomatic bacteriuria

- ▶ Quantitatively positive urine culture in the absence of symptoms
- ▶ **DO NOT TREAT most patients**
- ▶ Treat only select populations such as pregnant women, those with urological procedures, renal transplants

(Fekele and Hooton, 2017)

Bloodstream infections

- ▶ **High mortality if empiric therapy is not appropriate**, as high as 88% in one study (Yamaga & Shime, 2017)
 - ▶ **Identify source and eradicate if possible**
 - ▶ Should always be initially treated IV
 - ▶ 7-14 days depending if (un)complicated
 - ▶ 4-6 weeks if complicated (hardware, endocarditis)
- (IDSA CRBSI guidelines, 2009; Namias & Houghton, 2009)

Bloodstream infections

- ▶ Recommendations for treatment depend on source and type of bacteria (literature is sparse)
- ▶ Recent study of outcomes of *Enterobacteriaceae* bacteremia showed equivalent all-cause mortality between short (6-10 d) and long (11-16 d) treatment courses (Chaliprasitsakul et al., 2018)
- ▶ Follow-up blood cultures likely offer little to no patient benefit (Canzonieri et al., 2017). If the patient is afebrile and doing well...probably not necessary.

Wound/skin

- ▶ Wound, ulcer
- ▶ Cellulitis – usually gram positive
 - ▶ Most important to treat topically with dressing change, local wound care
 - ▶ Underlying nutritional status vital
 - ▶ Also usually a mixed flora

(See IDSA Guidelines for SSTI, 2014)

Necrotizing fasciitis

- ▶ Necrotizing infections/fasciitis require *aggressive* and *immediate* surgical intervention – need to cover gm +/- and anaerobes
- ▶ If in doubt, call a surgical consult



Necrotizing fasciitis – risk factors

- ▶ Diabetes ****
- ▶ Traumatic injury/wounds
- ▶ Obesity
- ▶ Drug use
- ▶ Immunosuppression



Necrotizing fasciitis

- ▶ **Type I infection** – at least one anaerobic species such as *bacteroides*, *clostridium*, or *peptostreptococcus* plus a strep (not group A) and/or an *Enterobacteriaceae* (POLYMICROBIAL)
- ▶ **Type II infection** – common cause is group A *Streptococcus* (GAS). Less common is *aeromonas hydrophilia* (fresh water) and *vibrio vulnificans* (salt water). Could also be CA-MRSA. (USUALLY MONOMICROBIC)
 - Exotoxin production is a hallmark
 - Leads to s/s of shock
 - Tissue destruction, organ failure

Necrotizing fasciitis: diagnosis

- ▶ Physical findings:
 - Skin/soft tissue warmth, redness, edema,
 - Pain, fever, illness out of proportion to apparent skin findings
 - Firm induration palpable beyond the skin area of redness
 - Bullous lesions, skin necrosis
 - Radiology sometimes helpful; air in tissue
- ▶ Definitive:
 - Surgical findings of necrotic tissue
 - Histopathology: extensive tissue destruction, blood vessel thrombosis, presence of bacteria and acute inflammatory cells

Necrotizing fasciitis - treatment

- **Surgery:** repeated OR trips often necessary
- Antibiotic therapy
- **Empiric therapy** should include:
 - a carbapenem or beta lactam/BLI PLUS
 - Consider clindamycin (antitoxin effects – strep/staph)
 - PLUS an agent with MRSA activity
 - **Need to cover GM neg/pos/anaerobes

(Stevens & Baddour, upToDate.com, 2017; Harbrecht & Nash, 2016)



Intra-abdominal infection

- **General principles:** Source control is the most important part of treatment
- **Antibiotic coverage:** Should include broad gram negative to cover enterobacteriaceae, gram positive cocci, and anaerobes
- Classify patients as low or high risk for treatment failure/death
- Classify patients as having community- or hospital-acquired infection
- **Anti-fungal empiric therapy is NOT recommended except in critically ill patients with an upper-GI source (2B)**

(Mazuski et al., 2017)

Complicated intra-abd (non biliary, community acquired)

Low risk patients

- **Single agents:** ertapenem (pref), moxifloxacin
- **Combination:** cefuroxime or ceftazidime (pref), cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole

(Mazuski et al., 2017)

High risk or compromised patients

- **Single agents:** Imipenem-cilastatin, meropenem, doripenem, and piperacillin-tazobactam (pref); tigecycline for resistant organisms
- **Combination:** Ceftazidime (pref), ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole

Complicated IAI, health care acquired

- Use the broad-spectrum agents recommended for high-risk patients
- If high resistance risk/colonized, consider adding an agent for resistant MDROs such as polymyxin or amino, based on local data
- Add an echinocandin if candida suspected or cultured in high-risk, critical patients (1B)
- If MRSA suspected/present, add vanco/linezolid
- If VRE suspected/present, consider daptomycin

(Mazuski et al., 2017)

Complicated IAI: Duration of treatment

- **Surgical debridement:** treat until afebrile and WBC normal (7-14 days)
- **Less than 24 hrs for:** traumatic perfs operated on in less than 12 hrs (1A), G/D perfs operated on in less than 24 hrs (1C), ischemic, non-perf bowel (1C)
- **IAI with source control:** 4 days (1A)
- **IAI with limited/no source control:** 5-7 days (2C)
- **IAI with bacteremia:** 7 days (2B)

(Mazuski et al., 2017; Sawyer et al., NEJM, 2015)

Summary and conclusions

Minimize antibiotic-resistant organisms by:

- ▶ **Responsible prescribing of antimicrobial therapy**
 - ▶ Don't treat colonization
 - ▶ Identify the pathogen responsible if possible
- ▶ **Effective treatment of infection**
 - ▶ Broad empiric coverage based on local data
 - ▶ Narrow ASAP
 - ▶ Shorter treatment courses now well established for most indications



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