In The Name of God

Treatment of hospital-acquired, ventilator-associated, and healthcare-associated pneumonia in adults

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Critical Care Medicine
*Principles of Diagnosis and Management in the Adult (*Dellinger)

- The Effect of Critical Illness on Pharmacokinetics and Pharmacodynamics (chapter 21)
- Pneumonia: Considerations for the Critically Ill (chapter 40)
- Nosocomial Infection in the Intensive Care Unit (chapter 47)

DEFINITIONS

- **Pneumonia types**
  - Hospital-acquired (or nosocomial) pneumonia (HAP)
  - Ventilator-associated pneumonia (VAP)
  - Healthcare-associated pneumonia (HCAP) is defined as pneumonia that occurs in a nonhospitalized patient with extensive healthcare contact, as defined by one or more of the following:
    - Intravenous therapy, wound care, or intravenous chemotherapy within the prior 30 days
    - Residence in a nursing home or other long-term care facility
    - Hospitalization in an acute care hospital for two or more days within the prior 90 days
    - Attendance at a hospital or hemodialysis clinic within the prior 30 days

- MDR refers to acquired nonsusceptibility to at least one agent in three different antimicrobial classes.

- Extensively drug resistant (XDR) refers to nonsusceptibility to at least one agent in all.

- Pandrug resistant (PDR) refers to nonsusceptibility to all antimicrobial agents that can be used for treatment.

Multidrug resistance (MDR)

- The definition of multidrug resistance (MDR)
  - resistance to at least **two** antibiotics typically used to treat infections with gram-negative bacilli
- Extensively drug-resistant (XDR)
  - resistance to all commonly used systemic antibiotics except colistin, tigecycline, and AG
- Panresistance
  - Pan-resistance refers to gram-negative bacilli with diminished susceptibility to all of the antibiotics recommended for the empiric treatment of HAP and VAP, including cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam, ciprofloxacin, and levofloxacin.

Risk Factors for Multidrug-Resistant Pathogens

Risk factors for MDR VAP:
• IV antibiotic use within the previous 90 days
• Septic shock at the time of VAP
• ARDS preceding VAP
• ≥5 days of hospitalization prior to the occurrence of VAP
• Acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP
• IV antibiotic use within the previous 90 days
Risk factors for MDR *Pseudomonas* and other gram-negative bacilli:
• Treatment in an ICU in which >10 percent of gram-negative isolates are resistant to an agent being considered for monotherapy
• Treatment in an ICU in which local antimicrobial susceptibility rates are not known
• Structural lung disease (bronchiectasis or cystic fibrosis)
Risk factors for MRSA:
• Treatment in a unit in which >10 to 20 percent of MRSA
• Colonization with OR prior isolation of MRSA
• Treatment in a unit in which the prevalence of MRSA is not known

Antibiotic use
HIV infection
Hemodialysis
Long-term care facilities

The importance of providing appropriate therapy

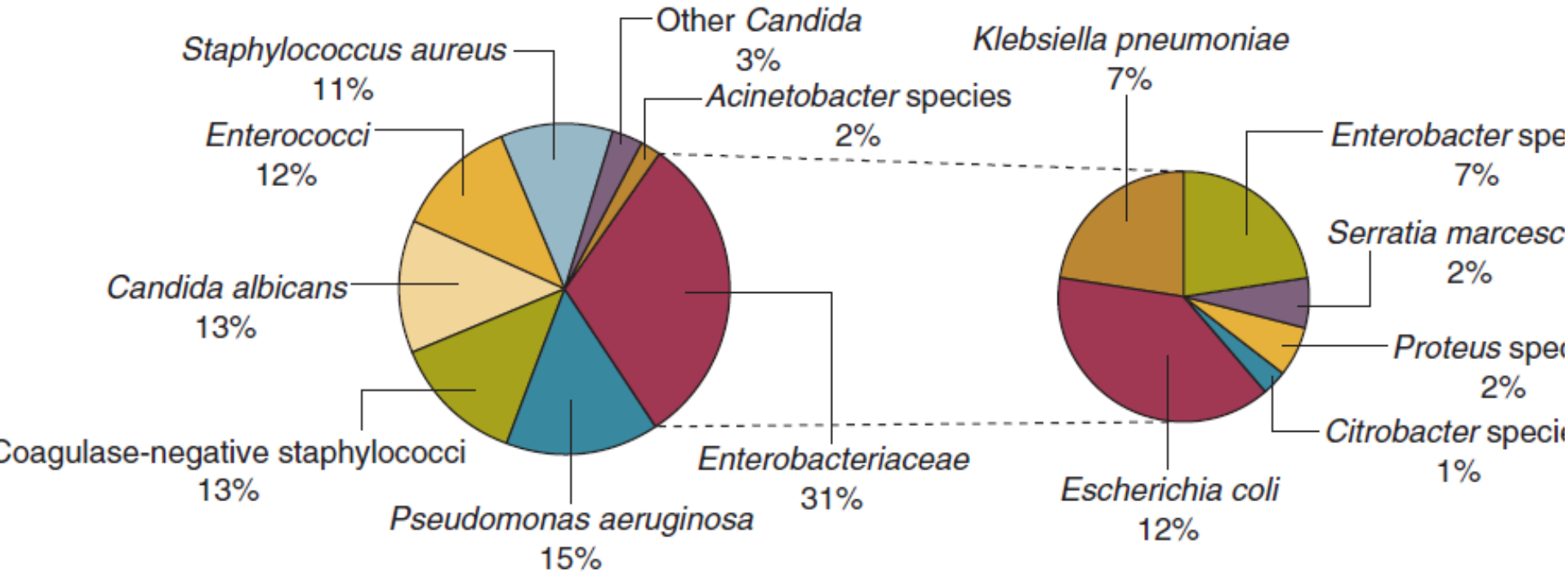
Antimicrob Agents Chemother. 2010 54(11):4851-63.

Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis.

Appropriate empirical antibiotic treatment is associated with a significant reduction in all-cause mortality.

Empiric treatment

(ATS/IDSA guidelines)



• **Fig. 47.1** Microbiology of nosocomial infection in the intensive care unit (ICU). Based on 13,317 infections occurring in ICU patients in 97 participating U.S. hospitals in the Centers for Disease Control's National Nosocomial Infections Surveillance System, January 1992 through July 1997. (Data from Richards MJ, Edwards JR, Culver DH, et al. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. *Crit Care Med.* 1999;27:887–892.)

- All patients with HAP or VAP should be evaluated for clinical response and results of microbiologic studies after initial empiric antimicrobial therapy.
- For patients in whom a pathogen has been identified, the empiric regimen **should be tailored to the pathogen's susceptibility pattern**. Tailoring antibiotic therapy has not been associated with increased mortality, recurrent pneumonia, or longer ICU admission.
- For patients who are clinically improving who do not have an identified pathogen, empiric treatment for S. aureus or multidrug-resistant gram-negative bacilli **can be discontinued** if these organisms have not grown in culture from a high-quality sputum specimen within 48 to 72 hours.

- Patients who have not improved **within 72 hours** of starting empiric antibiotics should be evaluated for **complications, other sites of infection**, and **alternate diagnoses**.

- If the diagnosis of pneumonia appears certain, there is no evidence of a pyogenic complication that requires drainage (eg, empyema, lung abscess), additional diagnostic pulmonary cultures should be obtained and the empiric regimen **can be expanded** to cover additional resistant organisms.

TABLE 40.8 Antibiotics Commonly Used for Treatment of Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia

Class/Antibiotic	Dose	Low Risk for Multidrug Resistance Only	Multidrug Resistance	Extensively Drug Resistant	Combination Only in Multidrug Resistance
Penicillin					
Piperacillin/tazobactam	4.5 g q6h		X		
Ampicillin/sulbactam	3 g q6h	X		X+	
Cephalosporin					
Ceftriaxone	2 g q24h	X			
Ceftazidime	2 g q8h		X		
Cefepime	2 g q8h		X		
Ceftolazone/tazobactam[a]	3 g q8h			X	
Ceftazidime/avibactam[a]	2.5 g q8h			X	
Carbapenem					
Ertapenem	1 g q24h	X			
Imipenem/cilastatin	0.5 g q6h to 1 g q8h		X		
Meropenem	1 g q6–8h		X		
Meropenem/vaborbactam[a]	2 g/2 g q8h			X	
Aminoglycosides					
Gentamicin	7 mg/kg loading dose, then TDM				X
Tobramycin	7 mg/kg loading dose, then TDM				X
Amikacin	20 mg/kg loading dose, then TDM				X
Plazomicin[a]	15 mg/kg q24h				X
Fluoroquinolones					
Ciprofloxacin	400 mg q8h	X			X
Levofloxacin	750 mg q24h	X			X
Polymixins					
Colistin	5 mg/kg IV loading dose, then 2.5 mg × (1.5 × CrCl + 30) IV q12h				X
Polymixin B	2.5–3.0 mg/kg per day in 2 daily IV doses				X
Tetracyclines					
Tigecycline[b]	100 mg, then 50 mg q12h				X
Minocycline	200 mg q12h				X

[a]Not approved by the U.S. Food and Drug Administration (FDA) specifically for pneumonia.
[b]FDA warning for hospital-acquired pneumonia/ventilator-associated pneumonia, + for *Acinetobacter* only.
CrCl, Creatinine clearance; *IV*, intravenous; *q*, every; *TDM*, Therapeutic drug monitoring.

No known multidrug resistance risk factors

For patients with VAP who have **no** known risk factors for MDR pathogens and who are in an ICU in which ≤10 percent of gram-negative isolates are resistant to an agent being considered for monotherapy , one of the following intravenous empiric antibiotic regimens is suggest :

- Piperacillin-tazobactam 4.5 g IV every 6 hours
- Cefepime 2 g IV every 8 hours
- Levofloxacin 750 mg IV daily – When the patient is clinically improved and able to take oral medications, levofloxacin may be administered orally at the same dose as that used for IV administration
- Imipenem and Meropenem

Ceftriaxone (2 g IV daily)
Ampicillin-sulbactam (3 g IV every six hours)
Levofloxacin (750 mg IV daily)
or moxifloxacin (400 mg IV daily).
Ertapenem (1 g IV daily)

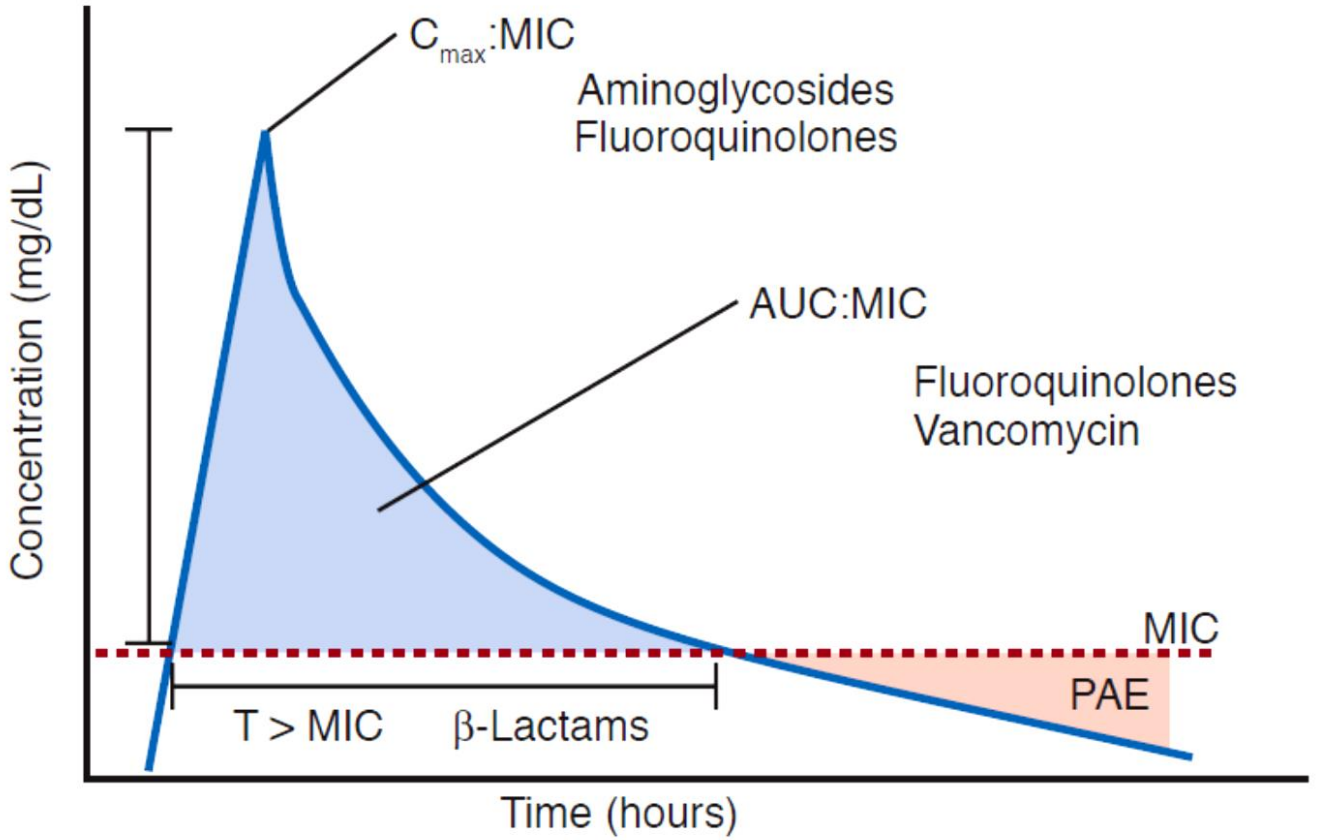
MDR risk factors

- **ONE of the following:**
  - Piperacillin-tazobactam 4.5 g IV every 6 hours
  - Cefepime 2 g IV every 8 hours
  - Ceftazidime 2 g IV every 8 hours
  - Imipenem 500 mg IV every 6 hours
  - Meropenem 1 g IV every 8 hours
  - Aztreonam 2 g IV every 8 hours –is used infrequently since rates of resistance among gram-negative bacilli are typically higher than to the other beta-lactams options
- **PLUS one of the following:**
- An aminoglycoside – Once-daily dosing is only appropriate for patients with normal renal function. A single serum concentration should be obtained 6 to 14 hours after the first dose, and the dose should be adjusted as needed based upon the following nomogram
  - Amikacin 15 to 20 mg/kg IV daily
  - Gentamicin 5 to 7 mg/kg IV daily
  - Tobramycin 5 to 7 mg/kg IV daily

Do **not** routinely use extended-interval dosing for the following patients:

- Patients with burns (>20 percent total body surface area)
- Patients with ascites
- Pregnant women
- Patients with creatinine clearance <40 mL/min (including patients requiring dialysis, although some institutions use a lower threshold)

Extended infusions Vs Once daily administration



• **Fig. 21.6** Pharmacokinetic and pharmacodynamic parameters on a concentration versus time curve. This figure depicts how drug concentration relates to bactericidal effect for various antimicrobial agents. *AUC,* Area under the concentration-time curve; *MIC,* minimum inhibitory concentration; *PAE,* postantibiotic effect; *T,* time.

Extended interval aminoglycoside dose and dosing interval in adults by renal function

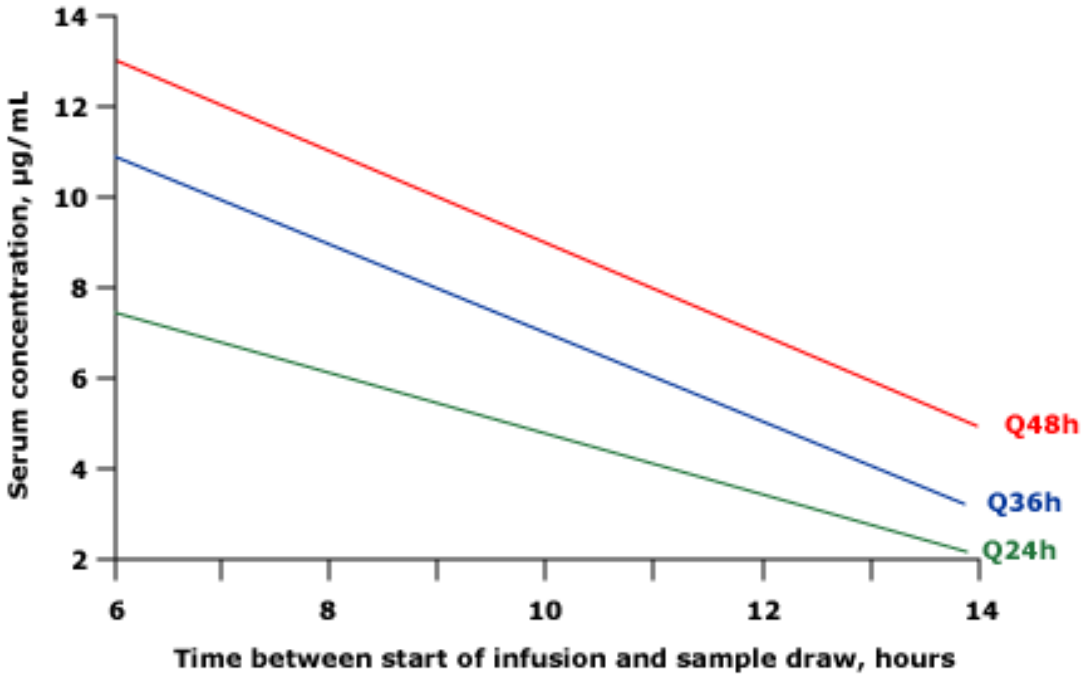
Creatinine clearance* (mL/min/70 kg)	Initial and maintenance dose ¶	Initial dosing interval (hours)
≥120	Use traditional intermittent dosing	
60 to 119	Infuse over 1 hour:	24
	7 mg/kg for gentamicin or tobramycin	
	15 mg/kg for amikacin	
40 to 59	Infuse over 1 hour:	36 (or use traditional intermittent dosing)
	7 mg/kg for gentamicin or tobramycin	
	15 mg/kg for amikacin	
<40Δ	Use traditional intermittent dosing	

* Creatinine clearance may be estimated by use of Cockroft-Gault equation. Calculators for estimation of creatinine clearance are available in UpToDate.

¶ The appropriate dosing weight to use for dose calculation is discussed in the topic on aminoglycoside dosing.

Δ Some institutions use a lower threshold of 20 to 30 mL/min for using traditional intermittent instead of extended interval dosing. In such cases, for patients who have a creatinine clearance between this lower limit and 40 mL/min, the calculated aminoglycoside dose is administered at a 48-hour interval.

Extended-interval dosing nomogram for gentamicin and tobramycin*



The serum gentamicin or tobramycin concentration should be obtained 6 hours (or up to 14 hours) after the initial dose of 7 mg/kg and plotted on the above nomogram. The interval for drug administration of subsequent doses of 7 mg/kg is then determined based on the interval specified on the graph.

* Application of the nomogram for amikacin requires the measured concentration be divided by two. The new value should be plotted on the nomogram in order to obtain the appropriate dosing interval.

Target concentrations

- **Nomogram-based monitoring**
  - a single serum concentration be obtained 6 to 14 hours after the first dose. Results from this measurement are then used to determine the necessary dosing interval.
- To obtain a peak serum aminoglycoside concentration (60 minutes post-infusion) and a second level approximately 6 to 12 hours after the first or second dose.
  - **AMIKACIN :** a peak of 20 to 30 mcg/mL and a trough of <8 mcg/mL (often targeted at 1 to 4 mcg/mL). Higher peak concentrations (up to 40-50 mcg/mL) are often recommended for serious, life-threatening infections such as nosocomial pneumonia.
  - **gentamicin and tobramycin**15 to 20 mcg/mL for in order to target approximately 10 times the MIC of the pathogen. Trough serum concentrations should be less than 1 mcg/mL (are most often undetectable) because of the long dosing interval.

Prolonged infusions

- Beta-lactam antibiotics demonstrate a **time-dependent** effect on bacterial eradication.
- Because of increasing resistance of pathogens associated with VAP and HAP, one potential strategy to enhance the antimicrobial potential of a given agent is to optimize the pharmacodynamic effect.
- As an alternative to traditional intermittent dosing (eg, administered over 30 minutes), prolonged infusions of certain beta-lactam antibiotics may be given in critically ill patients when MDR pathogens are suspected.
- Pharmacologic and clinical data indicate that patients who have an elevated risk of drug-resistant pathogens or who are critically ill in the setting of a severe infection are most likely to benefit.

Dosing for prolonged infusions of beta-lactams

	Creatinine clearance	Dose	Dosing interval	Infusion time
Piperacillin-tazobactam*	>20 mL/min	3.375 or 4.5 g	Every 8 hours	4 hours
	≤20 mL/min or intermittent HD or PD	3.375 or 4.5 g	Every 12 hours	4 hours
	CRRT¶	3.375 or 4.5 g	Every 8 hours	4 hours
MeropenemΔ	≥50 mL/min	1 or 2 g	Every 8 hours	3 hours
	25 to 49 mL/min	1 or 2 g	Every 12 hours	3 hours
	10 to 24 mL/min	500 mg or 1 g	Every 12 hours	3 hours
	<10 mL/min or intermittent HD	500 mg or 1 g	Every 24 hours, given after HD	3 hours
	CRRT¶	1 or 2 g	Every 12 hours	3 hours
Cefepime◇	≥50 mL/min	2 g	Every 8 hours	4 hours
	30 to 49 mL/min	2 g	Every 12 hours	4 hours
	15 to 29 mL/min	1 g	Every 12 hours	4 hours
	<15 mL/min or intermittent HD	1 g	Every 24 hours	4 hours
	CRRT¶	2 g	Every 12 hours	4 hours
Imipenem§	>70	500 mg or 1 g	Every 6 hours	3 hours
	41 to 70	500 mg or 750 mg	Every 8 hours	3 hours
	21 to 40	250 or 500 mg	Every 6 hours	3 hours
	6 to 20 or intermittent HD or PD	250 or 500 mg	Every 12 hours	3 hours
	CRRT¶	500 mg	Every 6 hours	3 hours

FQs in VAP,HAP

- An antipseudomonal fluoroquinolone such as ciprofloxacin (400 mg IV every 8 hours) or levofloxacin (750 mg IV daily) is preferred if *Legionella* is likely. *These agents may be administered orally when the patient is able to take oral medications. The dose of levofloxacin is the same when given intravenously and orally, while the dose of ciprofloxacin is 750 mg orally twice daily.*
- In many institutions, addition of a FQ adds minimal additional in vitro activity against local pathogens.
- The IDSA/ATS guidelines recommend either an antipseudomonal FQ or an AG for the second agent for gram-negative bacilli and they also state that AG should be avoided if alternative agents with adequate activity against gram-negative bacilli are available.
- However, we (uptodate) generally prefer an AG over a FQ if there is not concern for *Legionella,* as AG are more likely to have in vitro activity against gram-negative bacilli in those with risk factors for resistance

Recommendations in the specific FQ:

- Moxifloxacin, levofloxacin, and gemifloxacin are recommend to be avoided in patients with known QT interval prolongation or other risk factors for torsades de pointes, such as **hypokalemia**, **hypomagnesemia**, or the use of class IA (**quinidine, procainamide**) or class III (**amiodarone, sotalol**) antiarrhythmic drugs .
- The prescribing information for moxifloxacin further suggests caution in use by patients with hepatic insufficiency-associated metabolic disturbances, which may lead to QT prolongation

- A polymyxin – Addition of an alternative agent, such as IV colistin may be appropriate if highly resistant *Pseudomonas* spp, *Acinetobacter* spp, Enterobacteriaceae (including *Klebsiella pneumoniae*) is suspected or established
- Aztreonam 2 g IV every 8 hours – Although the use of two beta-lactams is generally avoided, in the absence of other options, it is acceptable to use aztreonam as a second agent for gram-negative bacteria with another beta-lactam because it has different targets within the bacterial cell wall

Dosing of colistimethate sodium

Dosing: Adult Note: Dosage expressed in terms of mg of **colistin base activity (CBA). CBA 1 mg** is defined to be equivalent to **colistimethate sodium (CMS) 30,000 units** which is equivalent to **~2.4 mg CMS**

- **Severe infections (due to multidrug-resistant organisms susceptible to colistin in the critically ill) (off-label dosing):** IV: Loading dose: 300 mg CBA followed by 150 mg CBA twice daily (Dalfino 2012; Plachouras 2009). Additional trials may be necessary to further evaluate the use of this dosing in critically ill patients with this condition
- Target $C_{ss,avg}$ is typically 2.5 mg/L (range: 2 to 4 mg/L [Couet 2012]) and should be based on MIC, site, and severity of infection.
- **multidrug-resistant gram-negative bacilli (eg, *Pseudomonas aeruginosa*, *Acinetobacter spp*) (off-label):**
  - Nebulization (via ventilator circuit): 150 mg CBA every 8 hours delivered over 60 minutes for 14 days or until successful wean from mechanical ventilation (treatment duration range: 7 to 19 days) (Lu 2012). May consider using as an adjunct in patients receiving IV colistin; may improve clinical outcomes (Doshi 2013; Tumbarello 2013; Valachis 2015).

PLUS one of the following:

- Linezolid 600 mg IV q 12 h; may be administered orally when the patient is able to take oral medications.
- Vancomycin 15 mg/kg (based on actual body weight) IV (maximum 2 g per dose initially) q 8 to 12 h for patients with normal renal function, with a target serum trough concentration of 15 to 20 mcg/mL. In seriously ill patients, a loading dose of 25 to 30 mg/kg (maximum 3 g) can be used to facilitate rapid attainment of the target trough concentration.
- We prefer linezolid rather than vancomycin in patients at risk for or with renal insufficiency in whom vancomycin is often underdosed and is associated with a risk of nephrotoxicity. We also prefer linezolid in hospitals in which a substantial proportion of MRSA isolates have a vancomycin MIC ≥2 mcg/mL
- The combination of vancomycin and piperacillin-tazobactam has been associated with acute kidney injury. In patients who require an anti-MRSA agent and an antipseudomonal beta-lactam, options include using a beta-lactam other than piperacillin-tazobactam (eg, cefepime or ceftazidime) or, if piperacillin-tazobactam is favored, using linezolid instead of vancomycin.
- An alternative to linezolid and vancomycin is clindamycin (600 mg IV or orally three times daily), provided that the isolate is known to be susceptible, although there are fewer data to supports its use

Linezolid and vancomycin

- Several trials have compared linezolid and vancomycin, with variable results:
- A meta-analysis of nine randomized trials that compared linezolid to vancomycin for HAP found no differences in rates of death, clinical response, microbiologic eradication, or MRSA eradication. Linezolid was associated with a higher rate of gastrointestinal adverse effects, but there were **no differences** in rates of acute kidney injury, thrombocytopenia, or drug discontinuation due to adverse effects.
- Another meta-analysis, which included eight trials that compared linezolid to vancomycin or teicoplanin for the treatment of suspected MRSA pneumonia, found **no differences** in clinical success, microbiologic success, or mortality .
- It should be noted that the studies included in the meta-analyses described above used a dosing regimen for vancomycin that is significantly lower than what is recommended by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA).
- In a later randomized double-blind trial that compared linezolid with vancomycin for the treatment of HAP or healthcare-associated pneumonia (HCAP) due to proven MRSA, the end-of-study success rate was 58 percent for linezolid and 47 percent for vancomycin . Among patients who had a respiratory specimen available for culture at the end of treatment, 16 of 92 patients (17 percent) who received linezolid had cultures that were persistently positive for MRSA compared with 50 of 109 patients (46 percent) who received vancomycin. In this study, vancomycin dosing was adjusted to achieve target trough levels. Linezolid was noninferior and statistically superior to vancomycin in end of treatment clinical outcome and microbiologic outcome at end of treatment and end of study, but there were no differences in all-cause 60-day mortality or overall adverse events. Nephrotoxicity occurred more commonly with vancomycin than linezolid (18 versus 8 percent).

- ***Acinetobacter baumannii*** – For patients with HAP or VAP caused by *A. baumannii*, a carbapenem or ampicillin-sulbactam should be used if the isolate is susceptible.
- If the isolate is susceptible only to polymyxins (colistin or polymyxin B), one of these agents should be given intravenously together with inhaled colistin ***since intravenous colistin yields low lung concentrations***.

30 to 150 mg CBA via nebulizer 1 to 2 times daily (maximum dose: 150 mg CBA 2 times daily)
Most patients received 1 million units (approximately 80 mg) of colistin twice daily.

Aerosolized antibiotics

- Aerosolized colistin, or aminoglycosides can be used as adjunctive therapy (in combination with IV antibiotics) in patients with VAP or HAP caused by multidrug-resistant gram-negative bacilli, such as *A. baumannii or P. aeruginosa*
- Aerosolization may increase antibiotic concentrations at the site of infection and may be particularly useful for treatment of organisms that have high MICs to systemic antimicrobial agents . **However, the evidence for aerosolized antibiotics is weak and conflicting.**
- In a meta-analysis that included seven observational studies and one randomized trial comparing aerosolized colistin administered with IV colistin to IV colistin alone in the treatment of VAP, there was an improvement in clinical outcome and microbiologic eradication associated with aerosolized colistin, but the level of evidence was low. Similarly, a meta-analysis that included five randomized trials and four observational studies performed as **part of the 2016 IDSA/ATS guidelines found that the addition of aerosolized antibiotics to systemic antibiotics in the treatment of VAP improved the clinical cure rate** (relative risk 1.29, 95% CI 1.13-1.47), but had no effect on mortality or nephrotoxicity.
- In a randomized trial that was published after these meta-analyses and that included 143 patients with VAP due to gram-negative bacilli, aerosolized amikacin and fosfomycin were compared with placebo as adjunctive therapy for VAP; aerosolized therapy was given twice daily for 10 days (or to extubation if it occurred at <10 days). There were **no differences** between the groups in the change from baseline of the Clinical Pulmonary Infection Score, mortality, clinical cure, or the endpoint of no mortality and ventilator-free days

- DEESCALATION
  - after empirical treatment if we have reliable culture result from patient what should we do?
  - If we have g- result of microbiology, what about g+ drugs?
- DURATION
  - (VAP) guidelines recommend a **seven-day** course of antimicrobial therapy rather than a longer duration
  - Serial levels of procalcitonin (procalcitonin was <0.25 mcg/L; a decrease by 80 % baseline)
  - A longer duration than seven days is warranted for patients with other factors such as S. aureus bacteremia, concern for metastatic infection, or more severe disease.
  - failure to improve at 72 hours should prompt a search for infectious complications, other diagnoses, or other sites of infection.

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- Therapy should generally be continued to complete a total course of **seven** days
- Up to 15 days if P. aeruginosa were the etiologic agent
- Up to 21 days for MRSA, depending upon the extent of infection and clinical course. Based on the study of S. aureus VAP, eight days of therapy may be adequate if there is good clinical response early in the course of appropriate therapy

Monotherapy versus Combination therapy

- In a review of available studies (mostly involving patients with VAP), the 2016 IDSA/ATS HAP and VAP guidelines **found no differences** in mortality, clinical response, adverse effects, or acquired resistance between monotherapy and combination therapy
- in a 2016 meta-analysis of randomized trials of patients with VAP, there were no differences between monotherapy and combination therapy in all-cause mortality, clinical cure, length of ICU stay, or adverse events
- In another study of patients hospitalized in an ICU due to trauma, 84 patients with VAP caused by *Pseudomonas* were treated with monotherapy (cefepime 2 g IV every 8 hours); this resulted in microbiologic eradication (based on repeat bronchoalveolar lavage [BAL] showing $<10^3$ organisms/mL) in 94 percent of patients with no recurrences, suggesting that combination therapy is unnecessary when the initial antimicrobial therapy is active against the isolate

Potential toxicities

- All antibiotics increase the risk of C. difficile infection
- AG are nephrotoxic and ototoxic. However, rates of susceptibility among gram-negative bacilli are high, so we often use them as part of the initial empiric regimen. Given the potential toxicity, we typically discontinue the AG after one or two days, especially in patients who have improved clinically and in whom the pathogen (if identified) is susceptible to the beta-lactam.
- Polymyxins (polymyxin B and colistin) are very nephrotoxic. Polymyxins are therefore used rarely and should be avoided if alternative agents with adequate activity against gram-negative bacilli are available.
- The combination of vancomycin and piperacillin-tazobactam has been associated with acute kidney injury. In patients who require an anti-MRSA agent and an antipseudomonal beta-lactam, options include using a beta-lactam other than piperacillin-tazobactam (eg, cefepimeor ceftazidime) or, if piperacillin-tazobactam is favored, using linezolid instead of vancomycin.
- In patients with renal insufficiency, imipenem and cefepime have been associated with seizures. Alternative beta-lactams should be used in patients at risk.
- The fluoroquinolones have multiple potential toxicities, including QT interval prolongation, tendinitis and tendon rupture, and neurotoxicity.

Legionella

- Patients who have
  - diabetes mellitus
  - renal disease
  - structural lung disease
  - have been recently treated with glucocorticoids
- Appropriate coverage for *Legionella* spp Azithromycin or a fluoroquinolone
- Antiinflammatory effects of macrolides

Anaerobes

- Patients who have aspirated or had recent abdominal surgery may warrant coverage for anaerobes
  - Clindamycin
  - beta-lactam-beta-lactamase inhibitor
  - carbapenem