HAP/VAP Guideline Update: It's A Balancing Act

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Objectives

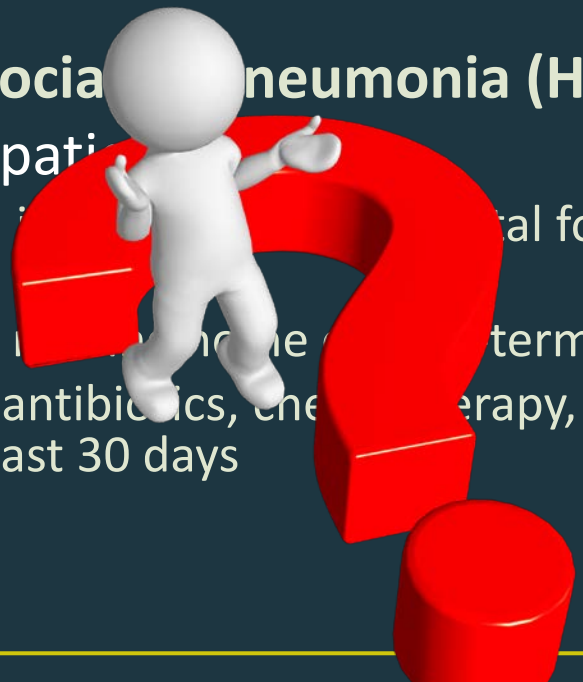
- Discuss the risk factors for ventilator-associated pneumonia, hospital-acquired pneumonia, and multi-drug resistant organisms.
- Design an empiric and definitive antibiotic treatment regimen based on cultures, susceptibilities and optimized antimicrobial dosing.
- Summarize alternative risk assessment strategies for patients who may have traditionally been treated for healthcare-associated pneumonia.

Definitions

- **Hospital Acquired Pneumonia (HAP):** a pneumonia that occurs 48 hours or more after admission; which was not incubating at the time of admission

- **Ventilator Associated Pneumonia (VAP):** a pneumonia that arises more than 48-72 hours after endotracheal intubation

- **Healthcare Associa[illegible]neumonia (HCAP):**
  - Includes any pati[illegible]
    - Hospitalized i[illegible]tal for two or more days within 90 days
    - Resided in a [illegible]term care facility
    - Received IV antibi[illegible]ics, che[illegible]erapy, wound care or hemodialysis within the past 30 days



Kalil AC, et al. Clin Infect Dis. 2016;63(5):61-111

Where is HCAP?

- Patients meeting “HCAP” definition are not at a high risk for multi-drug resistant (MDR) pathogens
- HCAP could be in the upcoming community-acquired pneumonia (CAP) guidelines
  - Coverage for community-dwelling patients who develop pneumonia would be based on validated risk factors for MDR pathogens
- The HAP/VAP guideline authors voted unanimously to not include HCAP in the 2016 HAP/VAP guidelines

Kalil AC, et al. Clin Infect Dis. 2016;63(5):61-111

Etiology of HAP & VAP

- Caused by a wide-spectrum of bacterial pathogens
- The most common bacterial pathogens are:
  - *P. aeruginosa, E. coli, K. pneumoniae* and *Acinetobacter*
  - *Staph aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Polymicrobial infections can occur especially with acute respiratory distress syndrome (ARDS)
- Viral or fungal pathogens are rare in immunocompetent patients

Kalil AC, et al. Clin Infect Dis. 2016;63(5):61-111

Multidrug-Resistant Organisms (MDRO)

VAP	HAP	MRSA	*Pseudomonas*
• Prior IV antibiotics in 90 days	• Prior IV antibiotics in 90 days	• Prior IV antibiotics in 90 days	• Prior IV antibiotics in 90 days
• Septic shock at time of VAP • ARDS preceding VAP • 5 or more days of hospitalization prior to occurrence of VAP • Acute renal replacement therapy prior to VAP onset			

Kalil AC, et al. Clin Infect Dis. 2016;63(5):61-111

Use of an Antibiogram

- Use antibiogram to guide empiric treatment
  - Antimicrobial flora and resistance patterns vary among countries, regions, hospitals, intensive care units (ICUs) within a hospital, specimen sources
  - Balances early appropriate coverage with avoiding superfluous treatment
- Regularly disseminate a hospital antibiogram
  - ICU specific antibiogram
  - Separating clinically important findings

Kalil AC, et al. Clin Infect Dis. 2016;63(5):61-111

VAP Epidemiology

- VAP occurs in about 10% of all intubated patients
- All-cause mortality 20-50%
  - Attributable mortality of ~13%
- Prolongs length of mechanical ventilation by 7.6-11.5 days and hospitalization by 11.5-13.1 days
- Excess cost associated with VAP ~$40,000 per patient

Wang Y, et al. N Engl J Med. 2017; 370:341-51
Melsen WG, et al. Lancet Infect Dis. 2013; 13:665-71
Muscedere JG, et al. Clin Infect Dis. 2010; 51(suppl 1):S120-5
Kollef MH, et al. Infection Control Hosp Epidemiol. 2012; 33:250-6

HAP Epidemiology

- HAP accounts for 25% of all ICU infections
- 50% of patients have serious complications
  - Pleural effusions
  - Septic shock
  - Renal failure
  - Empyema
- Mortality of HAP approaches that of patients with VAP if developed in ICU
- Increases hospital stay by 7-9 days
- Attributable mortality 33-50%
  - Higher with *Pseudomonas* or *Acinetobacter*

Kalil AC, et al. Clin Infect Dis. 2016; 63(5):61-111
Sopena N, et al. Chest. 2005; 127:213-9
Esperatti M, et al. Crit Care Med. 2013; 41:2151-61
Am J Respir Crit Care Med. 2005;171:388-416

Risk Factors

	VAP	HAP
MRSA coverage	• Patients in units with >10-20% *S. aureus* isolates are MRSA • Patients in units where the prevalence of MRSA is not known • Risk factor for resistance	• Prior IV antibiotic use within 90 days • Hospitalization in a unit where >20% of *S. aureus* isolates are methicillin resistant • Prevalence of MRSA is not know • High risk for mortality*
Double coverage of *Pseudomonas*	• Patients in units where >10% Gram negative isolates are resistant to the antibiotic considered for monotherapy • Patients in ICU where local susceptibility rates are not available • Risk factor for resistance	• Prior IV antibiotic use within 90 days • High risk for mortality*

High risk for mortality =septic shock or needing ventilatory support due to pneumonia

Kalil AC, et al. Clin Infect Dis. 2016;63(5):61-111

Empiric Drugs of Choice- HAP and VAP

Initial antibiotic	Risk factors for MRSA add one of the following:	Risk factors for MDR *Pseudomonas* add one of the following:
Piperacillin/tazobactam	Vancomycin	Aminoglycoside (amikacin, tobramycin or gentamicin)*
Cefepime or ceftazidime	Linezolid	Fluoroquinolone (levofloxacin or ciprofloxacin)
Carbapenem (imipenem or meropenem)		Colistin or polymyxin B (VAP only)
Aztreonam		
Levofloxacin		

Aminoglycosides should not be used as monotherapy

Kalil AC, et al. Clin Infect Dis. 2016;63(5):61-111
Vidal L, et al. JAC. 2007;60:247-57

When Do We Need Double Pseudomonal Coverage?

- Bliziotis, et al 2005
  - Meta-analysis of randomized controlled trials
  - Compared aminoglycoside + Beta-lactam vs Beta-lactam monotherapy
  - Monotherapy arm had less super infections (OR, 0.62; 95% CI, 0.42-0.93) and fewer treatment failures (OR, 0.62; 95% CI 0.31-1.01)
  - No difference in emergence of resistance, treatment failure attributable to resistance or super-infection, all cause morality, or mortality due to infection
- Conclusion: double coverage not necessary

Bliziotis IA, et al. Clin Infect Dis. 2005;41:149-58

Double Coverage in VAP

- Heyland, et al 2008
  - Multicenter randomized trial of 740 critically ill patients
  - Stratified according to Acute Physiology and Chronic Health Evaluation (APACHE) II score $\leq$24 or >24
  - Combination meropenem and ciprofloxacin vs meropenem alone
  - Relative mortality at 28 days was not statistically different at 1.05 (0.78-1.42, p=0.74)
  - Proportion of patients receiving adequate empiric antibiotics greater in combination group (93.1% vs 85.1%, p=0.01)
- Conclusion: monotherapy likely adequate empirically for VAP

Heyland DK, et al. Crit Care Med. 2008;36(3)737-43

Not Without Risk…

- Fluoroquinolones
  - *C. difficile* diarrhea, tendon rupture, hypo- and hyperglycemia, altered mental status, prolonged QTc, peripheral neuropathy, muscle weakness, photosensitivity, GI upset
- Aminoglycosides
  - Nephrotoxicity
  - Ototoxicity
  - Monotherapy associated with treatment failure

Stevens, et al. Clin Infect Dis. 2011;53(1)42-8
FDA Briefing Document 2015. Available at: https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm467383.pdf
Vital L, et al. JAC 2007;60:247-57

Use of Biomarkers

- **Use clinical criteria alone** to determine whether or not to initiate therapy
  - Not PCT + clinical criteria
  - Not sTREM-1 + clinical criteria
  - Not CRP + clinical criteria
  - Not CPIs + clinical criteria
- More helpful in de-escalation

Kalil AC, et al. Clin Infect Dis. 2016;63(5):61-111

What is Procalcitonin (PCT)?

- Pro-inflammatory biomarker
  - Stimulated by cytokines and endotoxins →procalcitonin produced throughout the body
- Rapidly increases in bacterial infection but not viral or fungal infections
  - Levels rise 2-4 hours after onset of infection
  - Peak at 6-24 hours
- Normally undetectable in healthy persons (<0.05 ng/mL)
- Positive cut off varies between studies
- Not affected by neutropenia or immunosuppression
  - Some non-bacterial conditions may also increase PCT (false positives)
- Correlation with severity of illness

Kalil AC, et al. Clin Infect Dis. 2016;63(5):61-111
Christ-Crain M, et al. Am J Respir Crit Care Med. 2006;174:84-93
Kibe S, et al. J Antimicrob Chemother 2011;66(S2):33-40
Schuetz P, et al. BMC Medicine. 2011;9:107
Meisner M. Ann Lab Med. 2014;34:263-73

What Does the Data Say About PCT in HAP/VAP?

- No head-to-head studies comparing clinical criteria alone vs PCT + clinical criteria
- The guideline authors looked at 6 studies (meta-analysis)
  - Reported how well PCT assisted in diagnosing HAP/VAP
  - Sensitivity 67% and specificity 83%
  - False negative 33% and false positive 17%
- Currently not enough literature to support its use in guiding diagnostic decisions

Kalil AC, et al. Clin Infect Dis. 2016;63(5):61-111

Optimizing Pharmacokinetics

- Determine antibiotic dosing by pharmacokinetic (PK)/pharmacodynamic (PD) data rather than manufacturers prescribing criteria
  - Examples: weight-based dosing, use of serum concentrations
- Meta-analysis of 3 studies determined PK/PD optimized dosing reduced mortality and ICU length of stay (LOS)
- Meta-analysis of 5 studies found that it improved the clinical cure rate

Kalil AC, et al. Clin Infect Dis. 2016;63(5):61-111

How to Optimize Pharmacokinetics and Pharmacodynamics

- Concentration vs time-dependent
- Vancomycin and aminoglycosides: pharmacy dosing protocol with monitoring serum levels
- Beta lactams
  - Extended infusion piperacillin/tazobactam
  - Continuous infusion nafcillin, penicillin, ampicillin, cefepime
- Antifungals: Serum drug monitoring
- Bactrim: weight-based dosing for *Pneumocystis jirovecii* pneumonia, *Stenotrophomonas maltophilia*

Mah GT, et al. Ann Pharmacother. 2012;46:265-75
Kaufman SE, et al. NEJM. 2011;68:1521-1526
Rybak M, et al. Am J Health-Syst P harm. 2009;66:82-9
Pasucal, et al. CID. 2008;46:201-11

General Treatment Concepts

- Early, appropriate antibiotics in optimized doses
  - Cultures before treatment
  - Quicker time to antibiotic administration = better outcomes
- Variability exists among institutions
  - Use local microbiological data to guide empiric antibiotic therapy
- Treat the patient
  - Allergies
  - Previous history
  - Comorbidities

Kumar, et al. Crit Care Med. 2006; 34(6)1589-96

Case #1

- GH is a 69 year old male with NKDA taken to the hospital via EMS for chest wall pain. Upon arrival the patient was found to have a STEMI and be in cardiogenic shock. He was intubated upon admission and sent to the CICU after the cath lab (with DES placement). Two days after admission, the patient had increased ventilator requirements and a fever to 38.6, WBC 17.1, procal 0.37. RR is 24 but patient is not hypotensive. CXR showed developing consolidation on RUL suggestive of pneumonia.
- The attending asks you to start antibiotics, which ones do you order?

Case #1

A. Piperacillin/tazobactam + vancomycin + levofloxacin
B. Levofloxacin + ceftriaxone
C. Cefepime + vancomycin
D. Cefepime + tobramycin + vancomycin
E. Cefepime alone

Management of Definitive Treatment, Duration of Therapy and Patients in Limbo

Definitive therapy

- De-escalation is recommended over fixed therapy
- Use confirmed susceptibilities to provide targeted therapy
- Optimize pharmacokinetics and pharmacodynamics of the antibiotics based on available evidence

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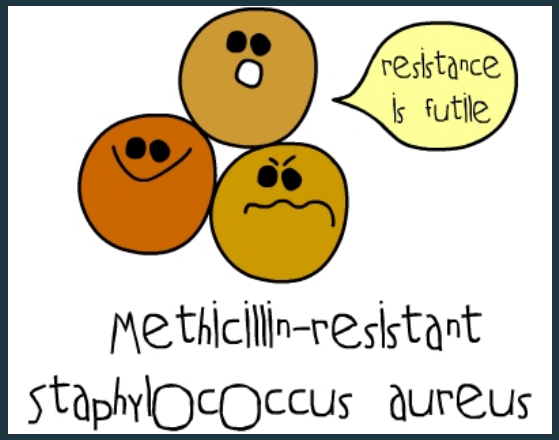
MRSA Treatment Recommendations

- "We recommend that MRSA HAP/VAP be treated with either vancomycin or linezolid rather than other antibiotics or combinations *(strong recommendation, moderate quality evidence)"*



	Staphylococcus aureus, methicillin resistant	
Drug	Interp	MIC-
Amoxicillin/Clavulanate	R	>4/2
Ampicillin	BLac	>8
Ampicillin/Sulbactam	R	16/8
Cefazolin	R	>16
Cefepime	R	>16
Cefotaxime	R	>32
Ceftriaxone	R	>32
Cephalothin	R	>16
Chloramphenicol	I	16
Erythromycin	R	>4
Imipenem	R	>8
Linezolid	S	<=2
Oxacillin	R	>2
Penicillin	BLac	>8
Synercid	S	<=1
Tetracycline	S	<=4
Trimethoprim/Sulfa	S	<=2/38
Vancomycin	S	<=2

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Vancomycin vs Linezolid

- Wunderink, et al 2008
  - Prospective randomized trial
  - Microbiologic response after 72-96 hours as confirmed by quantitative BAL cultures
    - Linezolid 56.5% vs Vancomycin 47.4%
  - Clinical cure
    - Linezolid 66.7% vs Vancomycin 52.9%
  - Survival rate
    - Linezolid 86.7% vs Vancomycin 70 %

Wunderink RJ, et al. *Chest. 2008;134(6):1200-7.*

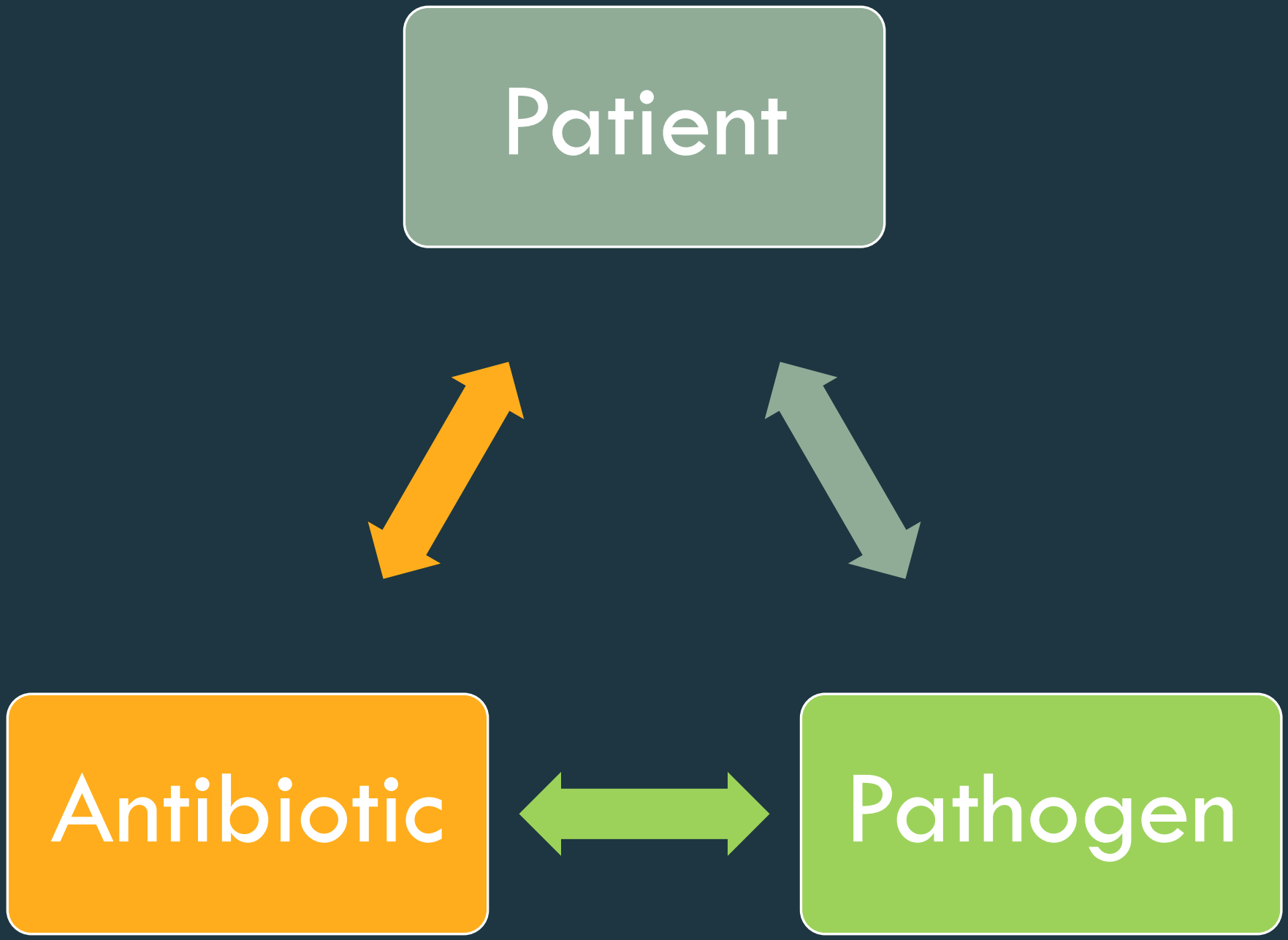
Vancomycin vs Linezolid

- Wunderink, et al 2012
  - Prospective, double blind cont
  - Dose optimized vanco
  - Clinical succes
    patients
  - C

No significant differences in mortality have been demonstrated

…ezolid
…tients, P=.042
… linezolid and 17%

Wunderink RJ, et al *Clin Infect Dis. 2012;54(5):621-9.*


Patient
Antibiotic
Pathogen

What about Pseudomonas?

- Use susceptibility results
- Choose wisely
  - MIC matters!

	Pseudomonas aeruginosa	
Drug	Interp	MIC-
Amikacin	S	<=16
Aztreonam	I	16
Cefepime	R	>16
Ceftazidime	I	16
Ciprofloxacin	R	>2
Gentamicin	I	8
Levofloxacin	R	>4
Meropenem	I	8
Piperacillin	R	>64
Piperacillin/Tazobactam	R	>64
Tobramycin	S	<=4

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MIC Matters

TABLE 5. Meropenem target attainment against *P. aeruginosa* using four different dosing regimens

MIC	% of isolates inhibited by:				
	1 g q8h (3 h)[a]	1 g q8h (1 h)	500 mg q8h (3 h)	500 mg q8h (1 h)	500 mg q6h (1 h)
0.008	100	100	100	99.95	100
0.016	100	100	100	99.8	100
0.125	100	99.99	100	99.45	100
0.25	100	99.97	100	98.65	99.84
0.5	100	99.82	100	95.4	99.36
1.0	100	99.28	100	89.65	97.04
2.0	100	96.21	99.25	65.45	88.04
4.0	99.1	81.08	79.6	31.9	63.02
8.0	79.6	23.12	14.2	4.4	19.08
16.0	14.2	0	0	0	0
32.0	0	0	0	0	0
Target attainment	86.4	79.5	79.3	67.5	76.4

[a] Values in parentheses are infusion times.

Lomaestro BM, et al. Antimicrob Agents Chemother 2005. 49(1):61-111

MIC Matters

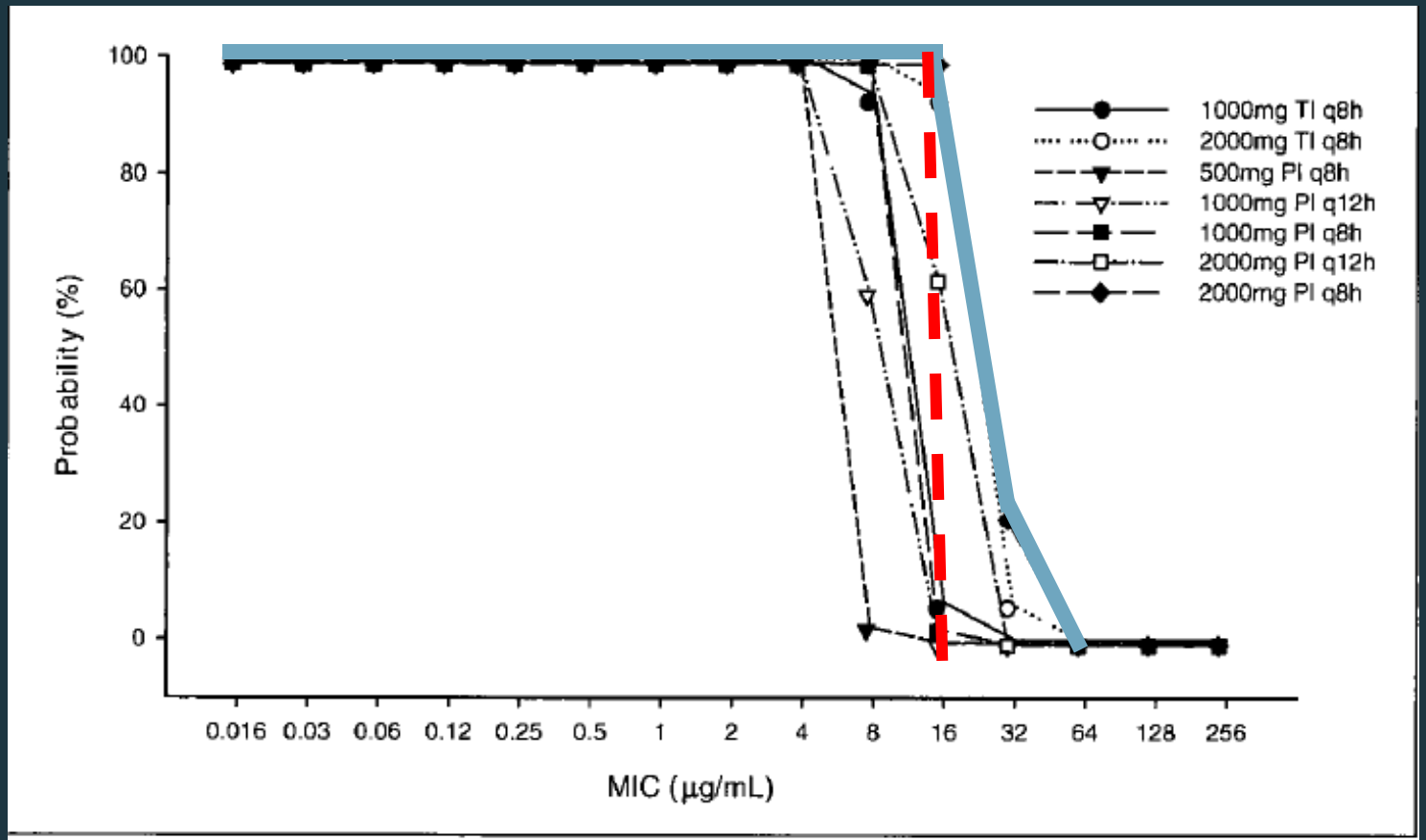

Figure 2. Target attainment rate for 30% time above the minimum inhibitory concentration (MIC) for each meropenem dosage regimen at each MIC.

Kuti JL, et al. Journ Clin Pharm 2003. 43:1116-23.

Combination Therapy for *Pseudomonas sp.*

- Recommendation *against* aminoglycoside monotherapy
- Two drugs for persistent septic shock or high mortality risk
- Consider combination for organisms with elevated MICs

Kalil AC, et al. Clin Infect Dis 2016. 63(5):61-111

Combination Therapy for Other Organisms

- Acinetobacter species
  - Ampicillin-sulbactam or carbapenem preferred
  - Combine intravenous polymyxin with inhaled colistin when only susceptible to polymyxins

- Carbapenem resistant organisms
  - Combine intravenous polymyxin with inhaled colistin when only susceptible to polymyxins

*All are weak recommendations with low quality evidence

Kalil AC, et al. Clin Infect Dis 2016. 63(5):61-111

What About Culture Negative Patients?

Infectious history	• Previous cultures • Rapid diagnostic testing
Recent antibiotics	• During and prior to onset of HAP/VAP • Response to empiric therapy
Clinical presentation and resolution	• Septic shock • Time to resolution of symptoms

Diagnostics and De-escalation

- Procalcitonin recommended *in combination with clinical criteria* for discontinuation
  - Significantly shorter duration of antibiotic therapy

    (9.1 days vs. 12.1 days; P<.00001)
  - No difference detected for
    - Duration of mechanical ventilation
    - ICU or total hospital length of stay
    - Recurrence
    - Resistance

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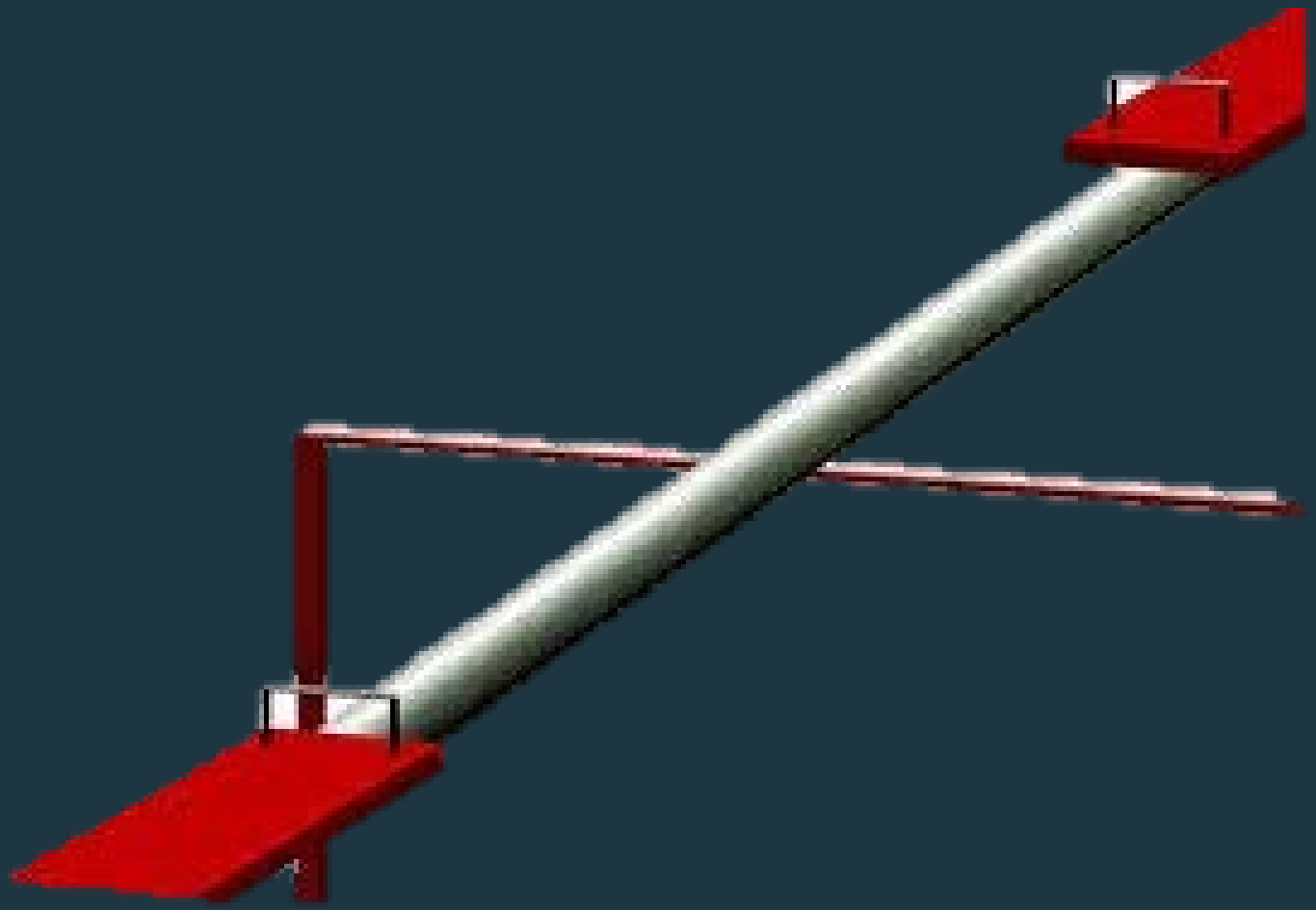
Duration of therapy



"You want me to treat for how long?!"

- "For patients with VAP, we recommend a 7-day course of antimicrobial therapy rather than a longer duration." *(strong recommendation, moderate quality evidence)*

- Also recommended for HAP but with very low quality evidence.
  - Extrapolated from VAP data

- This includes non-lactose fermenting Gram negative rods such as *Pseudomonas sp.* or *Acinetobacter sp.*

Kalil AC, et al. Clin Infect Dis 2016. 63(5):61-111

Duration of Therapy

- Pugh R, et al. Cochrane Review, 2015
  - Included 6 randomized trials
  - Short course of 7-8 days reduced recurrent VAP due to MDR pathogens as compared with extended duration of > 9 days (42.1% vs 62.3%; OR 0.44; 95% CI .21 - .95)
  - *No difference* in:
    - Mortality
    - Recurrence
    - Treatment failure
    - Duration of mechanical ventilation
    - Hospital length of stay

Pugh, et al. Cochrane Database Syst Rev 2015.8:Cd007577

VAP with Non-lactose Fermenting Gram Negative Organisms

- Hedrick, et al. 2007
  - Observational
  - Included only non-fermenting Gram negative bacilli
  - Short course (7-8 days) vs long course ($\geq$ 9 days)
    - No difference in recurrence
    - No difference in mortality

Hedrick TL, et al. Surg Infect 2007. 8:589-97.

VAP with Non-lactose Fermenting Gram Negative Organisms

- Meta analysis of systematic reviews
- Short course (7 to 8 days) vs long course (10 – 15 days)
  - No difference in recurrence

    OR, 1.42 (95% CI .66 – 3.04); P= .37
  - No difference in mortality
    - OR 0.94 (95% CI 0.56 – 1.59); P= .83

Kalil AC, et al. Clin Infect Dis 2016. 63(5):61-111

How low can we go?

- Klompas, et al. 2017
  - 1290 patients with suspected VAP
    - 259 patients received 1-3 days of therapy
    - 1031 patients received > 3 days of therapy
  - Minimal, stable ventilator settings for 3 consecutive days after antibiotics initiated
    - Positive end expiratory pressure (PEEP) of $\leq$ 5 cm H_2O
    - Fraction of inspired oxygen (FiO_2) of $\leq$ 40%
  - Outcomes
    - Time to extubation alive
    - Ventilator death
    - Time to hospital discharge alive
    - Hospital death
  - Propensity score matched (PSM) subgroup analyses

Klompas M, et al. Clin Infect Dis 2017. 64(7):870-6.

Results

		Time to extubation alive		Ventilator Death		Time to Hospital Discharge Alive		Hospital Death	
Patient Population	No.	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
All patients (1-3 days vs. < 3 days)	1290	1.16 (.98-1.36)	0.08	0.82 (.55-1.22)	.32	1.07 (.91 –1.26)	.43	0.99 (.75 –1.31)	0.96
PSM population	514	1.15 (.97-1.38)	.12	0.89 (.57-1.38)	.60	1.08 (.88-1.32)	.45	0.92 (.67-1.27)	.62
VAP diagnosis code, PSM	104	1.27 (.86-1.88)	.24	0.69 (.26-1.79)	.44	0.94 (.59-1.51)	.80	1.24 (.66-2.34)	.51
Gram stain with > 25 neutrophils and positive cultures, PSM	100	1.00 (.67-1.49)	.98	0.85 (.29-2.50)	.77	1.33 (.85-2.07)	.21	0.60 (.27-1.31)	.20

***Bottom line:* no significant differences in outcomes between groups**

Klompas M, et al. Clin Infect Dis 2017. 64(7):870-6.

Determining duration

7 days for most patients

3 days may be sufficient for a small subset of VAP patients

Consider patient specific needs

- Resolution and stability
- Mortality risk

It's the End of HCAP as We Know It?

- Inconspicuously absent from the guidelines
- Significant practice changes necessary
- What about the community acquired pneumonia patients who may have drug resistant CAP pathogens?
  - Combination of risk assessment and patient factors?

New Risk Factors?

- Prospective, observational study performed at 10 institutions
- Identify factors that are associated with infection with pathogens that are resistant to first line therapy typically used for community acquired pneumonia including
  - Ceftriaxone
  - Ampicillin-sulbactam
  - Macrolides
  - Respiratory fluoroquinolones

Shindo Y, et al. AM J Resp Crit Care Med 2013. 188(8):985-95.

Risk Factors of CAP Drug Resistance

	Univariate Analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Hospitalization for >2 days in the preceding 90 days	4.63 (3.03 – 7.09)	2.06 (1.23 – 3.43)
Immunosuppression	2.68 (1.40 – 5.13)	2.31 (1.05 – 5.11)
Use of antibiotics in previous 90 days	3.60 (2.40 – 5.40)	2.45 (1.51 – 3.98)
Tube feeding	6.15 (3.41 – 11.10)	2.43 (1.18 – 5.00)
Non-ambulatory status	3.89 (2.60 – 5.84)	2.45 (1.40 – 4.30)

Shindo Y, et al. AM J Resp Crit Care Med 2013. 188(8):985-95.

Prospective Risk Stratification

"A New Strategy for Healthcare-Associated Pneumonia**: A 2-Year prospective Multicenter Cohort Study** Using Risk Factors for Multidrug-resistant Pathogens to Select Initial Empiric Therapy"

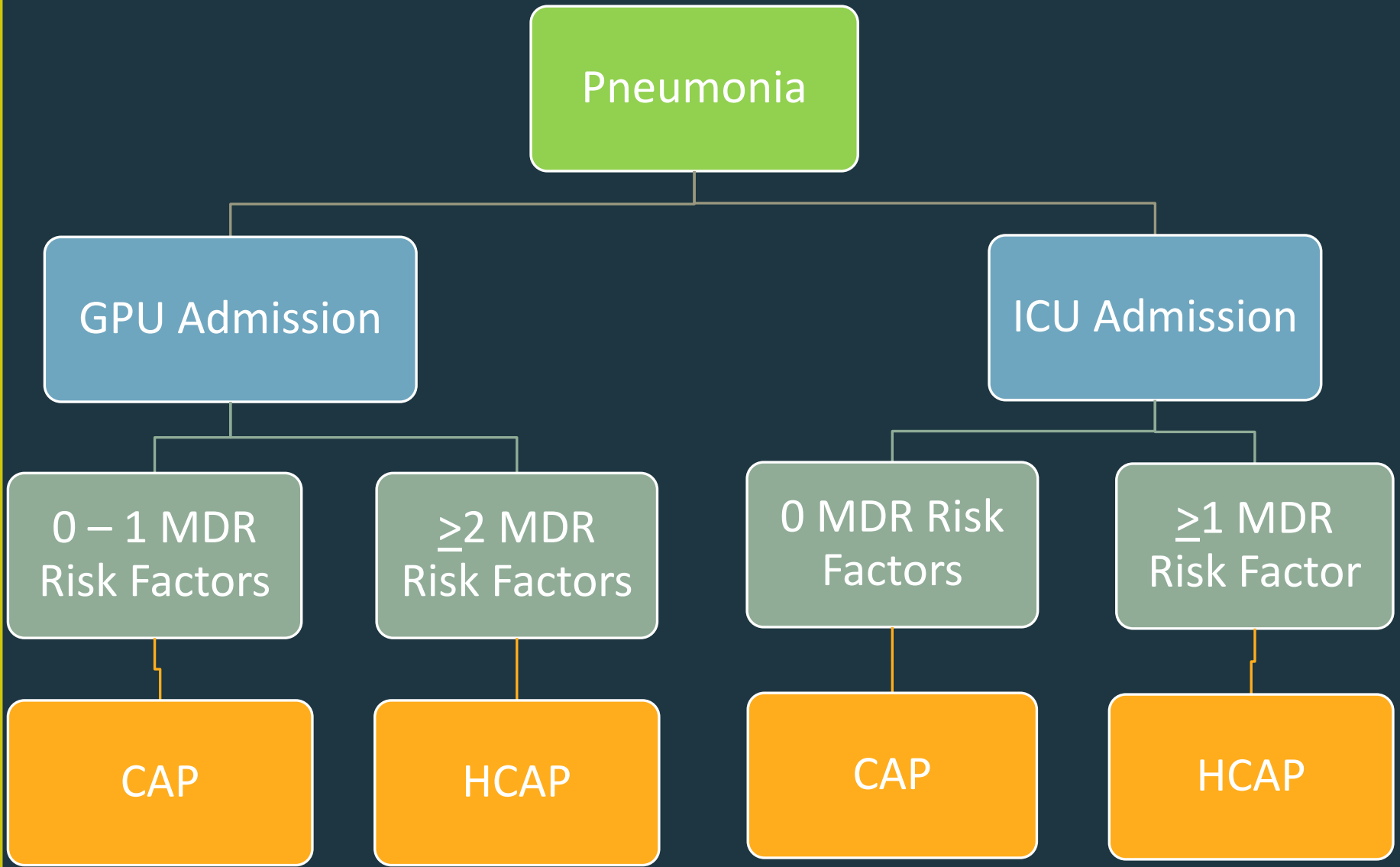
Randomized patients into CAP or HCAP therapy based on severity of illness:

1. Need for mechanical ventilation
2. Admission to ICU

and the number of the following risk factors:

1. Recent antibiotics
2. Recent hospitalization
3. Poor functional status
4. Immunosuppression

Mayumara T, et al. Clin Infect Dis 2013. 57(10):1373-83.



Mayumara T, et al. Clin Infect Dis 2013. 57(10):1373-83.

Stay tuned for the updated CAP guidelines in the summer of 2017!

Practical Strategies for Guideline Implementation

- Empiric and definitive treatment resources
- Order sets with antibiotic choices
  - Adaptive selections
- Order sentences with indication and duration
- Antibiotic “Time Out”
  - Renewal requirement with rationale
- Education! Education! Education!

Case 48 hours later….

- The WBC is down slightly to 14.6, ventilator requirements are cut in half. PCT is 4.2. Sputum cultures from before antibiotics started came back with *Klebsiella pneumoniae* with the following resistance pattern. What is your next step?

	Klebsiella pneumoniae	
Drug	MIC Interp	MIC Dilutn
Ampicillin	R	>=32
Ampicillin/Sulbactam	I	16
Cefazolin	S	<=4
Ceftriaxone	S	<=1
Ciprofloxacin	S	<=0.25
Gentamicin	S	<=1
Piperacillin/Tazobactam	S	8
Trimethoprim/Sulfa	S	<=20

Case 48 hours later…

A. Continue cefepime, discontinue vancomycin
B. Continue cefepime and vancomycin
C. Continue cefepime, add tobramycin and discontinue vancomycin
D. Discontinue all antibiotics and switch to ceftriaxone
E. Discontinue all antibiotics and switch to cefaozlin

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