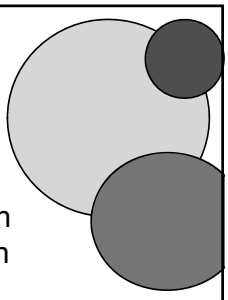
Antimicrobial Stewardship



Reducing Antibiotic use in Hospitalized Patients with Pneumonia

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Disclosure Statement

1. List of potential conflicts of interest, including relevant financial relationship(s): None

Objectives

- Describe risk factors that are more likely to predispose a patient to infection with a multidrug resistant organism (MDRO)
- Identify situations in which HCAP "double coverage" may not be necessary
- Describe use of MRSA surveillance cultures to aid in the de-escalation of empiric HCAP therapy
- Explain the potential applications of procalcitonin in limiting duration of therapy in pneumonia

HCAP Treatment

1. Selecting Empiric HCAP Therapy
2. De-escalating Empiric HCAP Therapy
3. Duration of Therapy

Patient Case

- 79 M to ED with recurrent fever, productive cough, SOB, weakness
- Discharged 24 hrs prior after a 3 day admit for COPD exacerbation
  - Received Azithromycin & Steroids
- PMH: COPD, sleep apnea, h/o bladder CA w/urostomy, GERD, AF, seizure disorder, h/o Lung CA s/p lung resection and remote chemoradiation > 1 year ago
- NKDA

Patient Case

- Lives at home, had a prior admission 4 months ago (x 5 days for GIB)
- PTA Meds: Depakote, Prilosec, Qvar, albuterol, warfarin, Azithromycin & Prednisone taper both x 2 more days
- WBC 14.6 (12 at d/c) HR 98 RR 24 T 100.8
- Lungs: decreased BS, BL crackles, no wheezing
- CXR: New focal area of consolidation in right lower lobe, consistent with bibasilar pneumonia

⇨ What empiric therapy would you prescribe?

What is HCAP?

- A **new** category of PNA created in 2005 by the ATS/IDSA to address patients living in the community who are at greater risk of colonization and infection with MDR pathogens
  - *P. aeruginosa*
  - MRSA
  - Highly resistant Enterobacteriaceae
  - Acinetobacter sp.

HCAP Criteria & Treatment

TABLE 2. RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS CAUSING HOSPITAL-ACQUIRED PNEUMONIA, HEALTHCARE-ASSOCIATED PNEUMONIA, AND VENTILATOR-ASSOCIATED PNEUMONIA

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

Why HCAP?

The Evidence for HCAP

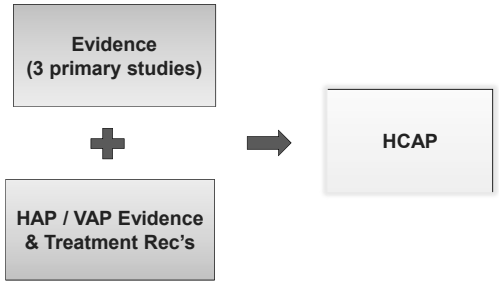
Patients with Blood Stream Infection *(1 study)*

- Home IV therapy or wound care in past 30 days
- HD clinic or hospitalized for IV chemo in past 30 days
- Hospitalized > 2 days in past 90 days
- Nursing home

Patients with Severe PNA requiring ventilation *(2 studies)*

- Nursing home
- Immunosuppression
- Prior antibiotic exposure

The HCAP Concept



HCAP Treatment Recommendations

Antipseudomonal β-lactam	+	Antipseudomonal Fluoroquinolone OR Aminoglycoside	+/-	MRSA Agent
Piperacillin/tazobactam Carbapenem (meropenem or imipenem) Cephalosporin (Cefepime or Ceftazidime)		Ciprofloxacin Levofloxacin Tobramycin Gentamicin Amikacin		Vancomycin Linezolid

The HCAP Concept

Question: Do the HCAP criteria accurately predict if pneumonia in a non-hospitalized patient will be due to a MDRO?

HCAP Evidence

Study	Design	Location	MRSA		Pseudomonas	
			CAP	HCAP	CAP	HCAP
Carratala 2007	Prospective	Spain	0% (n=601)	0.8% (n=126)	0.5%	1.6%
Park 2011	Retrospective	Korea	0.6% (n=163)	2.7% (n=182)	1.2%	5%
Shindo 2011	Retrospective	Japan	0.9% (n=230)	3.5% (n=141)	1.7%	5.7%
Garcia - Vidal 2011	Prospective	Europe	0.05% (n=1,668)	0.17% (n=577)	1.1%	2.4%
Micek 2007	Retrospective ***Culture positive cases only***	USA	**12%** (n=208)	**30.6%** (n=431)	**4.8%**	**25.5%**
Kollef 2005	Retrospective ***Culture positive cases only***	USA	**34.8%** (n=2,221)	**56.8%** (n=988)	**17%**	**25.3%**

HCAP Evidence

- More questions…
- Are all HCAP risk factors consistently associated with isolation of MDROs?
- Are there significant risk factors missing from the criteria?

MDRO Risk Factors

	Immune Suppressed	Recent Admit	SNF/ LTCF	Prior ABX	COPD	PPI	ICU Admit	HD	NG / TF	ADL Score
Shorr 2008	NS	Y	Y				Y	Y		
Schreiber 2010	Y	NS	Y	Y	Y			NS		
Shindo 2011	NS			Y	NS				Y	NS
Park 2012	NS	Y	NS	Y				NS	Y	
Aliberti 2013	Y (MRSA)	Y	Y	Y (PSA)			Y	NS		
Shindo 2013	Y	Y		Y	NS	Y			Y	Y

HCAP Evidence

Limitations

- Culture negative vs. Culture positive
- Retrospective vs. Prospective
- Location
- Definitions
- Inclusion / Exclusion criteria

HCAP Scoring Tools

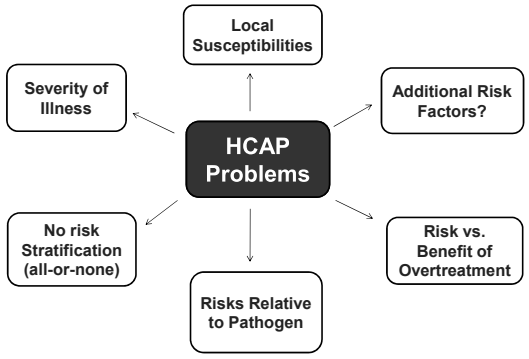
Risk Factor *(Schreiber et al, 2010)*	**Points**
Immunosuppression	3
From SNF / ECF	2
Prior Abx	1

Risk Factor *(Park et al, 2012)*	**Points**
NG tube	5
Recent Admit	3
IV Abx w/in 30 days	2
From SNF/ECF, chemotherapy or wound care w/in 30 d, or Chronic HD	1

HCAP Scoring Tools

Risk Factor *(Shorr et al, 2008)*	**Points**
Recent admit	4
From SNF/ECF	3
Chronic HD	2
ICU care w/in 24 hrs	1

Risk Factor *(Aliberti et al, 2013)*	**Points**
Chronic renal failure	5
Recent admit	4
From SNF/ECF	3
Comorbidities, *prior Abx*, home infusion therapy immunosuppression, home wound care	0.5



The HCAP Problem

Guideline-concordant HCAP therapy results in *excessive an unnecessary antimicrobial exposure* for a significant number of patients

HCAP is a heterogeneous disease of patients with varying severity of illness. True risk for MDRO infection differs significantly among populations.

Not all patients need a broad-spectrum, multidrug regimen that covers complex nosocomial PNA

HCAP – A New Approach

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

Takuya Maruyama,[1] Takao Fujisawa,[1] Masataka Okuno,[2] Hirokazu Toyoshima,[3] Kiyoyuki Tsutsui,[1] Hikaru Maeda,[4] Hisamichi Yuda,[4] Masamichi Yoshida,[4] Hiroyasu Kobayashi,[5] Osamu Taguchi,[5] Esteban C. Gabazza,[6] Yoshiyuki Takei,[7] Naoyuki Miyashita,[8] Toshiaki Ihara,[1] Veronica Brito,[9] and Michael S. Niederman[9]

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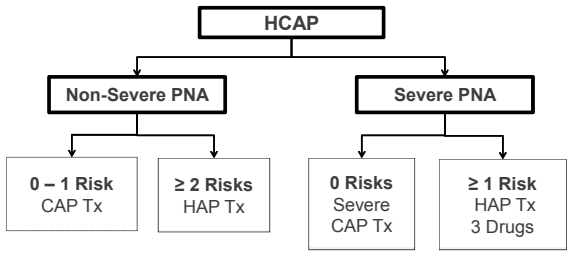


Clin Infect Dis. 2013 Nov;57(10):1373-83

HCAP – A New Approach

- Low risk HCAP patients received inappropriate therapy with a CAP regimen 3.2% of the time
- HCAP patients with ≥2 MDRO risks received inappropriate therapy with a HAP regimen 10.1% of the time
- 30-day mortality rate increased as the number of HCAP risk factors increased

Stewardship Approach to HCAP

Design empiric HCAP treatment guidelines that:

1. Prompt an evaluation of the overall likelihood of a MDRO
2. Account for different sub-populations of HCAP patients
3. Ensures patients receive appropriate empiric therapy without exposure to risks associated with unnecessary antibiotic use

HCAP Guideline

Considerations

- MDRO risk factors
- Gram negative double coverage
- Atypical coverage
- Severity of illness

MDRO Risks

Risk Factors

- Hospitalized > 2 days in past 90 days
- Broad spectrum antibiotics in past 90 days
- SNF / LTCF residence
- Dependency / Need for assistance
- Immunosuppression

Other Considerations

- h/o MDRO colonization or infection
- Colonization pressure
- Conditions that predispose to colonization
  (i.e. chronic wounds, indwelling devices, structural lung disease)
- Severity of illness

Why Double Cover?

1. Synergy

- The activity of a combination regimen is greater compared to either agent alone
- Demonstrated in laboratory conditions for certain combinations, *but not all*
  - *B-lactam + aminoglycosides*
  - *Meropenem + Cipro (67% of strains even when concentrations were sub-MIC)*
  - *Zosyn + Levaquin (synergy only apparent when strains were resistant to one or both of the agents)*
- *No clear impact on microbiologic outcome, clinical outcome, or mortality in practice*

Why Double Cover?

2. Ensure adequate initial activity

- Inappropriate empiric therapy in gram negative sepsis is associated with worse outcomes
- Combination therapy increases the likelihood that at least one agent will cover the causative pathogen

Why Double Cover?

2014 GNR Antimicrobial Susceptibilities

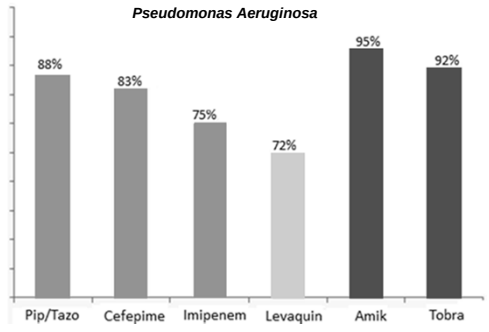
	Cefepime				Zosyn				Imipenem*			
	A	B	C	D	A	B	C	D	A	B	C	D
Pseudomonas	**83**	**87**	**91**	**85**	**88**	**76**	**100**	**98**	**63**	**82**	**92**	**82**
E. coli	90	91	95	100	94	94	100	93	99	100	100	100
K. pneumoniae	100	100	100	100	97/3	93	100	90	100	100	100	100
Kleb. oxytoca	100	100			100	89			100	100		
E.cloacae	100	100	100		58/6	72	85		100	100	100	
E. aerogenes	100	100			89	67			100	100		
P. mirabilis	90	100		100	100	98		100	NT	100		NT
S. marcescens	100				100				100			
Acinetobacter	73	22			NT	NT				44		

* Resistance rates for *Pseudomonas* and imipenem cannot be extrapolated to meropenem

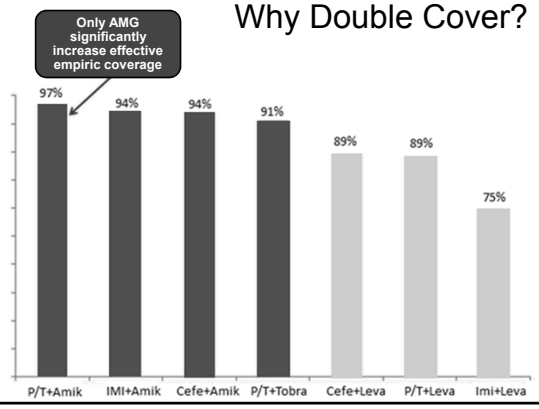
Why Double Cover?

- Current “standard” of care = Zosyn, cefepime, ceftazidime, or meropenem + Ciprofloxacin or Levofloxacin
  - **QUESTION**: Does the addition of Levaquin or Cipro to a strong backbone increase the likelihood of providing adequate empiric coverage?
  - ANSWER: probably not

Why Double Cover?



Why Double Cover?



Antibiotic Risk v. Benefit

Beneficial Effects
- Reduced mortality from infection
- Reduced morbidity from infection
- Reduced cost of hospitalization

Give Antibiotics:
- **If benefit is certain and significant**
- **If magnitude of uncertain benefit is great**

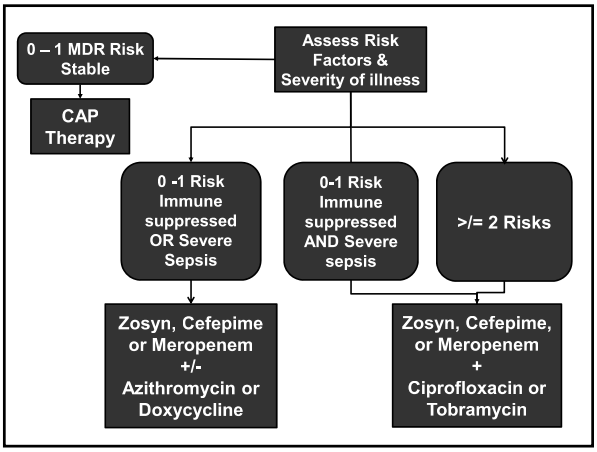
The fewer, the narrower and briefer the better

Adverse Effects
- ↑ mortality from ADRs
- ↑ morbidity from ADRs
- Allergic reactions
- Toxicity
- Side effects
- Drug interactions
- Reduced normal flora and decreased colonization resistance against MDRO strain acquisition
- Superinfection with MDRO
- Diarrhea and dissemination of MDRO to patients, HCWs, or the environment
- Contribution to antimicrobial shortages
- ↑ fungal infection
- ↑ *C. difficile* infection and dissemination
- Cost of antimicrobials
- ↑ cost of hospitalization
- Complications of IV infusion devices

Double Cover?

- Not all "HCAP" patients require broad, double coverage for MDR Gram negative pathogens
- Quinolones do not consistently increase the likelihood of delivering adequate empiric therapy
- Quinolones DO put patients at risk for serious adverse effects

  ➢They should be avoided unless the benefit clearly outweighs the risk



MRSA Risks

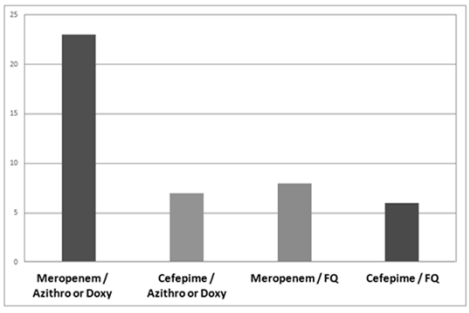
- Implanted device or line
- HD in past 30 days
- IVDA
- Severe PNA (i.e. fever >39C, leukopenia)
- Empyema or suspected lung abscess
- h/o MRSA infection or colonization
- Recent influenza-like illness during flu season
- Broad spectrum antibiotic therapy w/in 90 days

HCAP Treatment MUE

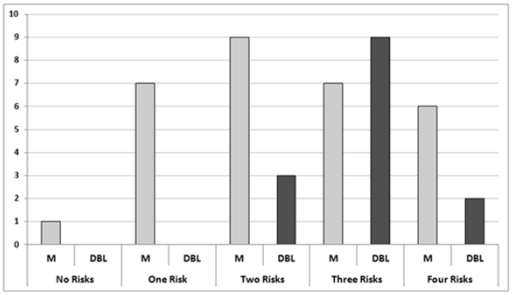
- Search Criteria
  - Zosyn, cefepime, ceftazidime, meropenem

  AND
  - An order for: Ciprofloxacin, levofloxacin, azithromycin, or doxycycline
  - *Excluded* –> antibiotic therapy started > 48 hrs after admission, non-PNA diagnosis, therapy discontinued early with documentation of PNA ruled out, cases with multiple potential sources of infection

HCAP MUE Results – Empiric Therapy



HCAP MUE Results – Risk Factors



MUE Findings - Atypical Coverage

- Significant number of patients are getting atypical coverage (almost all of them)
  - Is this coverage necessary in HCAP?
  - Risk v. Benefit of Azithromycin
    - Cardiovascular disease

Patient Case – Part 2

- 79 M to ED with recurrent fever, productive cough, SOB, weakness
- Hospital day 3, feeling better
- WBC 13 HR 88 RR 18 (2L NC, SpO2 >96%) T AF
- Sputum culture collected < 24 hours after admission

  "moderate number of mixed organisms typical of the upper respiratory tract"

⇨ Can we de-escalate therapy?
⇨ What would you de-escalate to?

Problems with HCAP & Cultures

- Guidelines recommend lower respiratory tract (LRT) for all patients
- Recommend de-escalation only for culture positive cases
  - No direction for culture negative PNA other than "consider stopping"
- Provides no guidance on expectorated sputum cultures or how to interpret them

Culture Negative De-escalation Evidence

- Schlueter et al, 2010
  - Retrospective review of HCAP over 2-years
  - 72% (73/102) culture negative
    - 75% deescalated
      - 70% moxifloxacin (Avelox)
  - No significant increase in readmit rates or mortality
- Experience from other stewardship teams

Culture Negative De-escalation

What do we know?

- Absence of a MDRO from a LRT specimen is strong evidence they are *not* the causative pathogen
  - Time course of clearance of MDROs is usually slow
  - True even with recent / current antibiotics
- Tracheal aspirates almost always contain the same pathogen(s) found in LRT cultures

HCAP MUE – Future Directions

Broaden scope to evaluate:

- HCAP patients who receive CAP therapy
- β-lactam monotherapy regimens
- Atypical agent use & cardiac risks

Culture Negative De-escalation

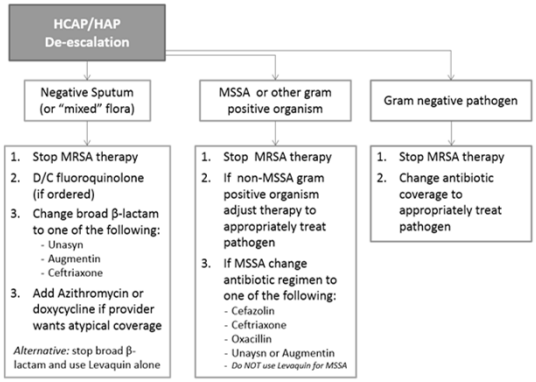
Consider de-escalating therapy when:

- Sputum collected within ~ 48 hours of starting broad spectrum antibiotics
- Patient is clinically improved
  1. Discontinue MRSA coverage
  2. De-escalate Gram negative coverage
     - Ceftriaxone / Cefdinir
     - Unasyn / Augmentin
     - Levofloxacin or Moxifloxacin

Culture Negative De-escalation

Caution with de-escalation:

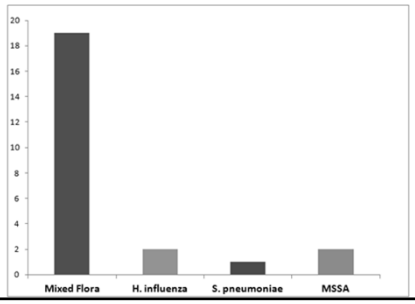
- Neutropenia or profound immunosuppression
- Delay in sputum culture collection ≥ 72 hrs
- Deteriorating clinical status
- Critically ill patients



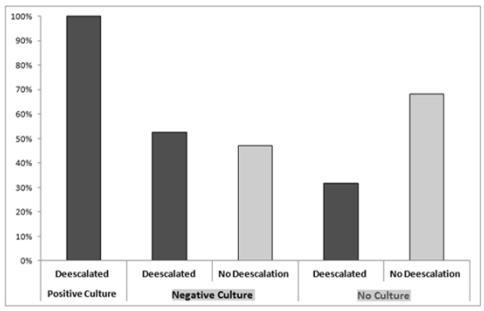
HCAP MUE: Culture Results

23/44 patients had a respiratory culture obtained

20 expectorated sputum; 3 bronchoalveolar lavage (4 had both)



HCAP MUE: GN Therapy De-escalation



HCAP MUE: MRSA Agent De-escalation

	Total	Respiratory Culture	No Respiratory Culture
Empiric Coverage?	38.6%	52%	28.5%
MRSA PCR Screen?	41%	39%	38%
MRSA Screen Positive?	1	1	None
MRSA Agent D/C'd (per micro results)*?	87.5%	92% (11/12)	75% (3/4)
Avg DOT (with micro), D	2.2	2.3	2
Avg DOT (no micro, n = 2), D	4.5	NA	NA

* Micro results includes both respiratory cultures and MRSA PCR screen

Patient Case

- 75 F brought to ED for SOB, productive cough, weakness, and feeling chilled
- PMH: COPD on 2-3 L O2 continuously PTA, CKD stg 3, AF, h/o TIA, HTN, CHF
- SH: From assisted living facility, no recent admissions. Received Levaquin x 5 days one month ago for UTI
- WBC 15 HR 90 T AF
- RR 30 (BiPAP 40% to maintain SpO2 >90%)
- CXR: slight interval increase in bilateral interstitial airspace opacity suggesting edema with possible superimposed pneumonia

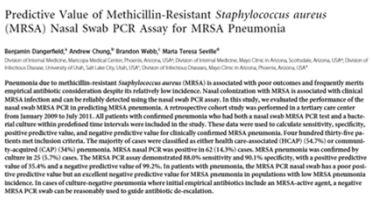
Patient Case

- PTA Meds: prednisone 10 mg/d, Lasix, Lisinopril, metoprolol, simvastatin, aspirin, Symbicort, albuterol, Spiriva, loratadine
- Patient is admitted with dx of HCAP & CHF exacerbation
- Empiric therapy -> Zosyn + Cipro + Vancomycin
- Sputum culture cannot be collected

➡ What can we do to facilitate therapy de-escalation?

MRSA Nasal PCR Assay

- Use when respiratory culture unavailable to de-escalate MRSA coverage in PNA
- Negative predictive value -> 99.2%
- Positive predictive value -> 35.4%



Predictive Value of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nasal Swab PCR Assay for MRSA Pneumonia

Benjamin Dangerfield,[a] Andrew Chung,[b] Brandon Webb,[c] Maria Teresa Seville[d]

Division of Internal Medicine, Maricopa Medical Center, Phoenix, Arizona, USA[a]; Division of Internal Medicine, Mayo Clinic in Arizona, Scottsdale, Arizona, USA[b]; Division of Infectious Disease, University of Utah, Salt Lake City, Utah, USA[c]; Division of Infectious Diseases, Mayo Clinic in Arizona, Phoenix, Arizona, USA[d]

Pneumonia due to methicillin-resistant *Staphylococcus aureus* (MRSA) is associated with poor outcomes and frequently merits empirical antibiotic consideration despite its relatively low incidence. Nasal colonization with MRSA is associated with clinical MRSA infection and can be reliably detected using the nasal swab PCR assay. In this study, we evaluated the performance of the nasal swab MRSA PCR in predicting MRSA pneumonia. A retrospective cohort study was performed in a tertiary care center from January 2009 to July 2011. All patients with confirmed pneumonia who had both a nasal swab MRSA PCR test and a bacterial culture within predefined time intervals were included in the study. These data were used to calculate sensitivity, specificity, positive predictive value, and negative predictive value for clinically confirmed MRSA pneumonia. Four hundred thirty-five patients met inclusion criteria. The majority of cases were classified as either health care-associated (HCAP) (54.7%) or community-acquired (CAP) (34%) pneumonia. MRSA nasal PCR was positive in 62 (14.3%) cases. MRSA pneumonia was confirmed by culture in 25 (5.7%) cases. The MRSA PCR assay demonstrated 88.0% sensitivity and 90.1% specificity, with a positive predictive value of 35.4% and a negative predictive value of 99.2%. In patients with pneumonia, the MRSA PCR nasal swab has a poor positive predictive value but an excellent negative predictive value for MRSA pneumonia in populations with low MRSA pneumonia incidence. In cases of culture-negative pneumonia where initial empirical antibiotics include an MRSA-active agent, a negative MRSA PCR swab can be reasonably used to guide antibiotic de-escalation.

Patient Case

- 68 F found confused by family and brought to ED
- HPI: worsening SOB for a week, with new productive cough and fatigue, wheezing and chest tightness
- SH: no recent admits or antibiotics, + smoking
- PMH: COPD, AF, HTN
- WBC 21 HR 106 RR 28 T 98.1
- *Procalcitonin* 6.9
- CXR: New patchy left basilar opacities could represent atelectasis or pneumonia
- Dx: CAP + COPD exacerbation

Patient Case

- Treatment
  - Ceftriaxone (day 6) +
  - Azithromycin (5 days total - complete)
- Hospital Day 6
  - WBC 11 HR < 90 AF
  - Weaned to 2L NC, however still with DOE
- Repeat PCT -> 0.21

➡ Can you make any recommendations regarding her CAP therapy?

Procalcitonin

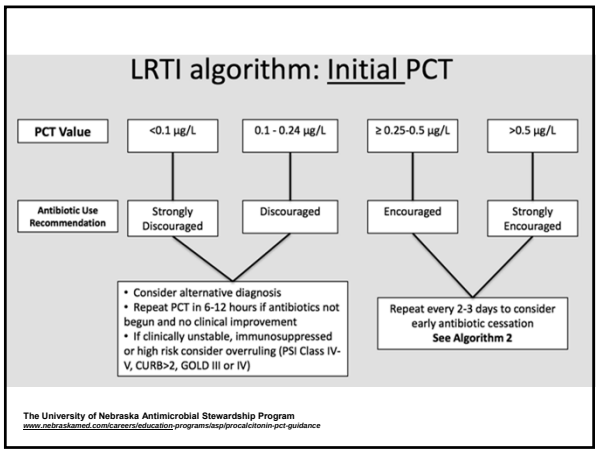
- Precursor pro-hormone of calcitonin released from many tissues in response to bacterial infection
- Production up-regulated by bacterial infection & down-regulated by viral infection
- Rapid induction (T ½ ~ 24 h)
  - Rapid decline with adequate antimicrobial Rx
- Mortality correlates with peak level & a rising level
- False positives (i.e. ESRD, SCLC, thyroid tumors, acutely following major surgery)

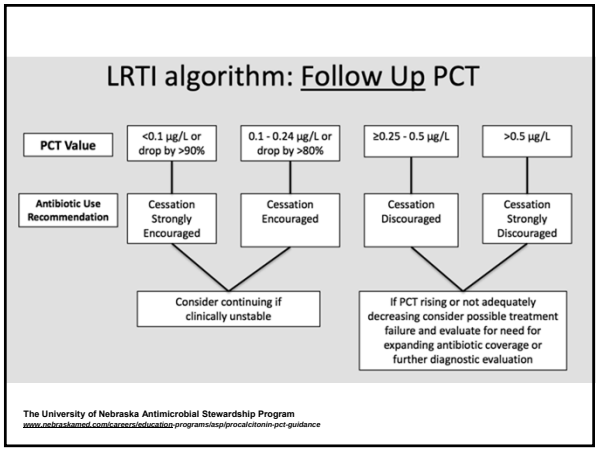
Procalcitonin

- Can help distinguish bacterial infection from viral infection or non-infectious conditions
  - Utility shown for:
    - Respiratory infection
    - Sepsis
  - Not for localized bacterial infection, endocarditis, SSTI, etc...
  - Cannot be used as the sole determinant of therapy

Procalcitonin Uses

- To limit effective antibiotic duration of therapy in patients with probable bacterial pneumonia
- Withdraw antibiotics at an early point in patients whose clinical course does not suggest bacterial pneumonia





Procalcitonin Evaluation

- Using PCT to limit DOT in Pneumonia if:
  - Responded to initial treatment regimen
  - Clinically improved
  - Reached "typical" DOT

Condition	Duration of Rx
CAP	5 – 7 days
HAP/VAP/HCAP	7 – 8 days (no MDRO isolated)
Aspiration PNA	7 – 10 days ?

  - Diagnostic uncertainty

Patient Case

- 63 M presented to ED with SOB
- PMH:
  - Paranoid Schiz, HTN, DM II, COPD
  - Recent admit two weeks prior x 4 days:
    - New Dx CHF w/ EF 20%
    - Improved with diuresis
    - Rx Moxifloxacin for bronchitis due to bronchospasm
- PE / Labs:
  - T 36^{7} HR 92 R 24 BP 120/84
  - Mild-Mod resp distress w/ accessory muscle use
  - + JVD ++ Pitting Edema Wt up ~ 9 lbs from DC
  - WBC 12.9 BNP 1700

Patient Case

- Stewardship Team Recommendations:
  - Check PCT
    - Rationale: diagnostic uncertainty
    - PCT < 0.05 on the morning after admission
    - *Action*: antibiotics continued per provider preference
  - Hospital Day 3
    - Repeat CXR -> Improvement in interstitial opacities
    - Repeat PCT <0.05
    - *Action*: stop antibiotics

References

- Handout Provided


Q
&
A