Medscape
EDUCATION

Emerging Therapies for Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia

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HAP and VAP Are Among the Deadliest of Hospital-Acquired Infections

- Bacterial HAP and VAP combined are the leading cause of death among hospital-acquired infections, with mortality ranging from 20% to 50%
- 75% of healthcare-associated infections are resistant to first-line antibiotics

Magill SS, et al. *N Engl J Med*. 2014;370:1198-1208; Restrepo MI, et al. *Infect Control Hosp Epidemiol*. 2010;31:509-515.

Defining HAP and VAP*

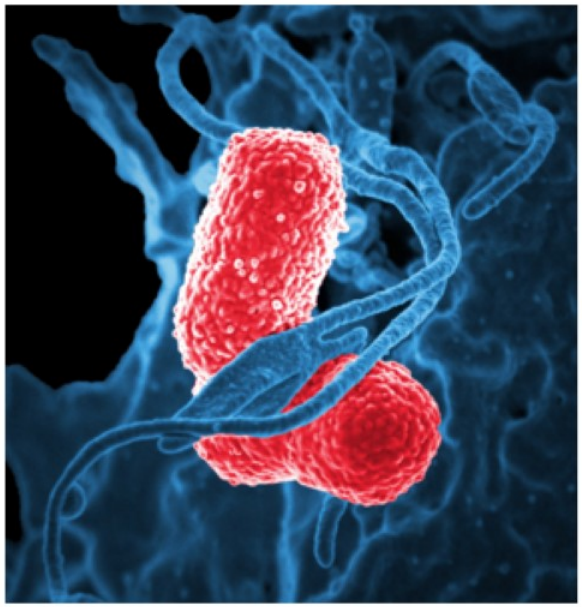
- HAP occurs 48 hours or more after admission, and was not incubating at the time of admission
- VAP, a subset of HAP, occurs more than 48 to 72 hours after endotracheal intubation

*Bacterial in origin.

American Thoracic Society; Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2005;171:388-416.

Pathogens Most Commonly Associated With HAP and VAP

- Monomicrobial or polymicrobial
- Gram-negative bacilli
  - *Enterobacteriaceae*
    - *Escherichia coli*
    - *Klebsiella pneumoniae*
    - *Enterobacter* species
  - Nonfermenting organisms
    - *Pseudomonas aeruginosa*
    - *Acinetobacter baumannii*
- Gram-positive cocci: MRSA, *Streptococcus* species
  - ~50% of *S aureus* organisms are MRSA



Multidrug-resistant
K pneumoniae bacteria

Magill SS, et al. *N Engl J Med*. 2014;370:1198-1208; Photo Credit: David Dorward; PhD; National Institute of Allergy and Infectious Diseases (NIAID).

When Should You Suspect Pneumonia?

- Diagnosis cannot be made on clinical features alone
- Suspect pneumonia when there is:
  - A new lung infiltrate
  - Clinical evidence that the infiltrate is infectious
    - New onset of fever
    - Purulent sputum
    - Leukocytosis
    - Decline in oxygenation
- Obtain specimens for microbiology

Rapid Diagnostic Methods for Nosocomial Pneumonia

- MALDI-TOF: rapid diagnostic test for pneumonia
  - Identifies bacteria, fungi, and mycobacteria isolated from cultures of sputum or BAL specimens in clinical microbiology laboratories
  - Fast, accurate, and helps to rule out infection
  - Does not identify resistance genes
  - Facilitates antimicrobial stewardship by allowing clinicians to target the precise pathogen, and in some cases narrow the spectrum of antimicrobial coverage
    - Shorter duration of therapy
    - Reduced resistance by de-escalating antibiotic therapy for gram-positive organisms

Singhal N, et al. *Front Microbiol*. 2015;6:1-16.

Novel Cephalosporins Coupled With a Beta-Lactamase Inhibitor*

- Current SOC: Combination therapy for a specific pathogen should be used judiciously in HAP, with consideration of short-duration aminoglycoside therapy, when used in combination with a β-lactam to treat *P aeruginosa*. Linezolid is an alternative to vancomycin. Colistin should be considered as therapy for patients with VAP due to a carbapenem-resistant *Acinetobacter* species[a]
- Few agents are available with activity against resistant gram-negative organisms
- Overuse of carbapenems to treat resistant pathogens has contributed to the rise in carbapenemase-producing bacteria, especially *Klebsiella pneumoniae*, and prompted the development of novel agents with extended activity against ESBL-producing microorganisms
- Ceftazidime/avibactam
  - Carbapenemase producers and carbapenem-resistant *Enterobacteriaceae* (*E coli*, *Klebsiella*, and *Enterobacter)*
- Ceftolozane/tazobactam
  - MDR and extensively resistant *Pseudomonas* in critically-ill patients
  - ESBL-carrying organisms

*Not approved by the FDA for the treatment of HAP or VAP.

a. American Thoracic Society; Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2005;171:388-416.

Ceftolozane/Tazobactam

- Ceftolozane/tazobactam
  - Tazobactam: (non-β-lactam β-lactamase inhibitor), especially against those belonging to the SHV-1 and TEM-1 groups
  - Combined with ceftolozane, is active against MDR *Pseudomonas aeruginosa* and ESBL-producing *Enterobacteriaceae*

Multidrug-resistant
Pseudomonas aeruginosa

Photo credit: US Centers for Disease Control and Prevention -- Medical Illustrator.

Ceftazidime/Avibactam

- Ceftazidime/avibactam
  - Avibactam (non-β-lactam β-lactamase inhibitor): restores in vitro activity of ceftazidime against class A, class C, and some class D β-lactamase-producing pathogens
  - In vitro activity against Ambler classes A and C β-lactamases, including KPC and some class D enzymes
  - Combined with ceftazidime, restores in vitro activity against ESBL-producing *Enterobacteriaceae* and MDR *Pseudomonas aeruginosa*

Carbapenem-resistant *Enterobacteriaceae*

Photo credit: US Centers for Disease Control and Prevention -- Medical Illustrator.

Case 1

59-Year-Old Man With Chronic Bronchiectasis Admitted for CHF

- Green sputum
- New onset fever
- Pulmonary infiltrate on hospital day 4
- Multiple courses of antibiotic therapy within past year, some in past month
  - Piperacillin/tazobactam
  - Meropenem
  - Inhaled colistin

Case 1 (cont)
Basic Principles of Treatment and Management

- Recognize the variability in bacteriology from unit to unit in the hospital
  - Know the local microbiology and susceptibility patterns
- Effective initial treatment is critical
  - Avoid undertreatment or inadequate treatment
  - Do not delay treatment
  - Avoid overuse of antibiotics; dose for shorter duration
  - Tailor the therapy to the culture results
    - In some cases, de-escalating therapy may be necessary

Case 1 (cont)
Deciding on Antimicrobial Therapy

- Multiple risk factors for MDROs: multiple courses of broad-spectrum antibiotics and multiple hospital admissions
- Consider prominent local pathogens and susceptibility patterns and prior sputum culture results and susceptibility
  - With history of bronchiectasis, patient may have a relapse of prior infection
- Assess Gram stain
- Target MDROs
  - MRSA → vancomycin, linezolid, or telavancin if either 1 of the initial agents was unsuitable
  - Gram-negative bacilli → antipseudomonal β-lactam + aminoglycoside or fluoroquinolone
  - Panresistant organisms → consider colistin, polymyxin, or new combination agent

Case 1 (cont)
Options for Treatment of Pneumonia Due to Panresistant Pseudomonas Aeruginosa

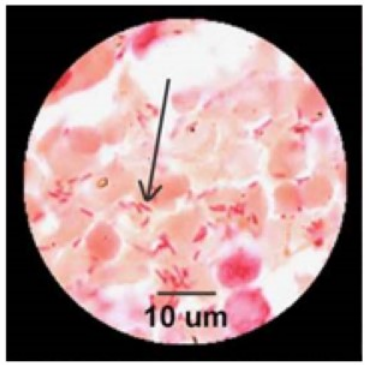
- Patient was initiated on meropenem 2 g q8h and colistin + linezolid to cover suspected MRSA
- Sputum culture grew a MDR -- *Pseudomonas aeruginosa and* MRSA
  - No other antimicrobial options available
  - Administered high-dose ceftolozane/tazobactam to cover MDRO + colistin

Soliman R, et al. *JMM Case Rep*. 2015. DOI 10.1099/jmmcr.0.000025.

Case 2

52-Year-Old Man in the ICU on Mechanical Ventilation

- Postoperative day 5: ruptured diverticular abscess
- On piperacillin/tazobactam
- Prior admission 2 months ago for an acute exacerbation of COPD
- Developed new-onset fever, new pulmonary infiltrates, new leukocytosis (WBC = 18,000 mcL)
- ET aspirate: new purulent secretions; Gram stain shows gram-negative bacilli
- Treated with meropenem and an aminoglycoside
- Culture revealed carbapenem-resistant *Klebsiella pneumoniae*



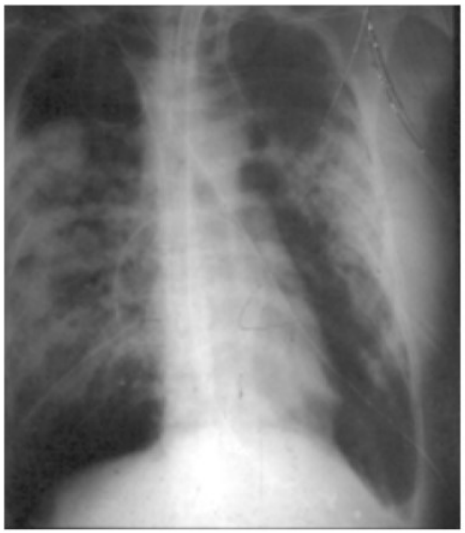


Photo credit: Thomas M. File, Jr, MD, MSc.

Case 2 (cont)
The Challenge of Carbapenem-Resistant Klebsiella Pneumoniae

- Switch to ceftazidime/avibactam* to provide coverage against KPCs/CREs
  - Monotherapy vs in combination with aminoglycoside or colistin?
  - Difficult case due to heterogeneity of patient population
    - No guidance available from RCTs
- Applying genetic mechanisms and rapid testing may help guide future therapy

*Not approved by the FDA for the treatment of HAP or VAP.

Measuring the Success of Antimicrobial Stewardship Programs

- Emphasize protecting antibiotics vs restricting them
- The high cost of resistance
  - Patients infected with MDROs have longer hospital LOS and higher cost of care
- Antimicrobial stewardship teams have been effective in interpreting rapid diagnostic tests appropriately and applying swift intervention to ensure better patient outcomes
- Track metrics for cost of resistance
  - Ventilator days
  - Overall hospital LOS, infection-related hospital LOS
  - ICU LOS: decreasing ICU LOS by 1 to 2 days can almost justify the cost of any new antimicrobial
  - Infection-related mortality
  - Clinical and microbiologic cure rates

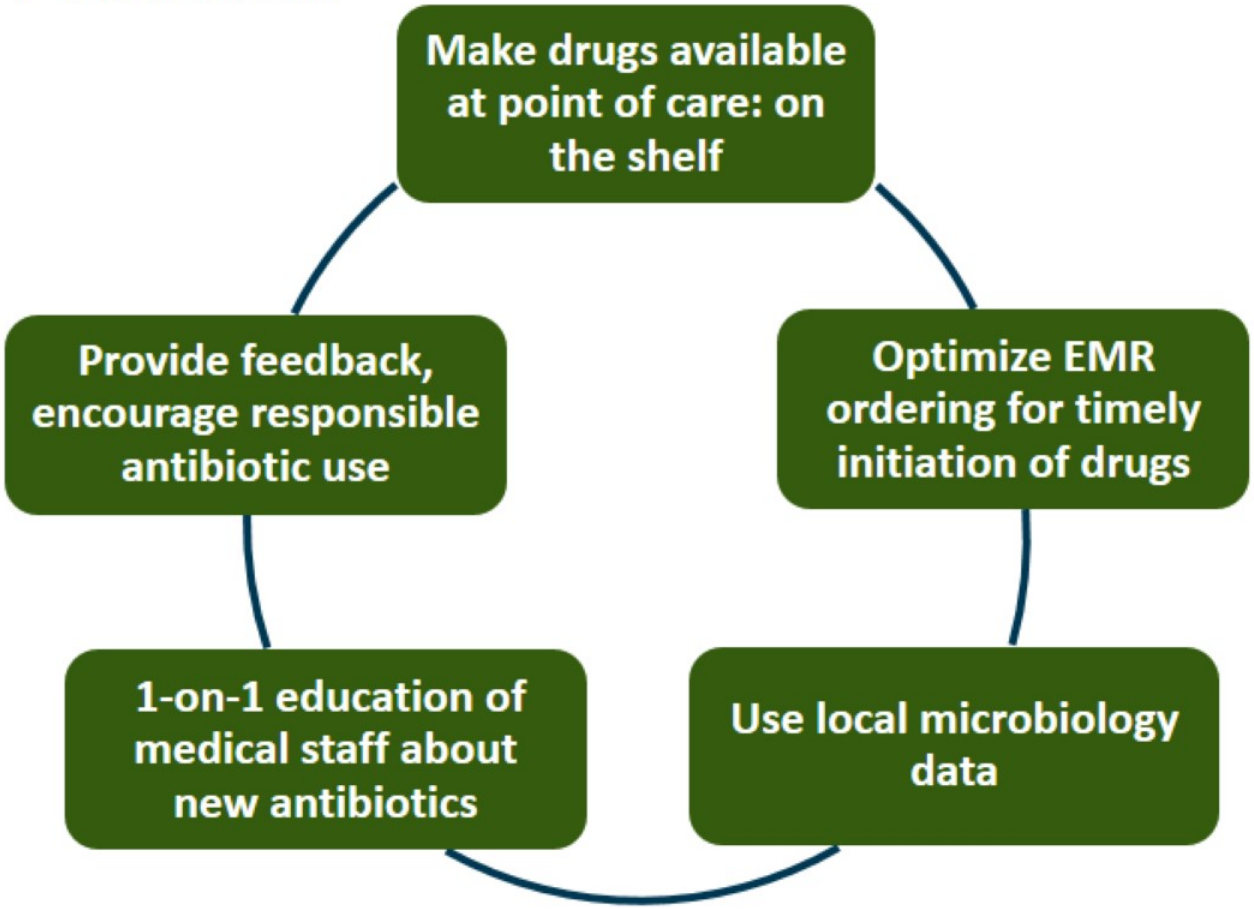
The Role of Rapid Diagnostic Tests in Antimicrobial Stewardship

A Key Success Factor

- Rapid identification and appropriate interpretation of diagnostic tests → more appropriate and timely therapy → improved outcomes

Adding a New Antibiotic to the Hospital Formulary

Hospital Process Should Not Be Part of the Problem



De-escalation
A Critical Component of Antimicrobial Stewardship

- Narrowing the antimicrobial spectrum by changing from a broad-spectrum agent to a narrow-spectrum agent or eliminating a drug from combination therapy
- Should ideally occur as soon as possible after availability of culture results
- Benefits
  - Reduced bacterial resistance
  - Decreased incidence of bacterial, viral, and fungal superinfections
  - Limited exposure to unnecessary drug therapy and the associated risks, eg -- *Clostridium difficile* infection
  - Decreased costs

Duration of Antibiotic Therapy

- Even for serious infections (ie, HABP or VABP) the ideal duration of therapy is 7 to 8 days
- If patients are stabilized, treating them longer than necessary may increase the selection of pressure for resistance and adverse events such as *Clostridium difficile* infection

Use of Procalcitonin in Reducing Duration of Antibiotic Therapy

- Observational, historical control study to assess the impact of using PCT levels
  - Procalcitonin correlates with bacterial load and responds very quickly to reduction in bacterial load
  - Increased confidence in decision to stop antibiotics when level decreases significantly
- Findings
  - Duration of antibiotic use decreased by 3.3 days (*P* =.0238)
  - Hospital LOS decreased by 4.3 days (*P* =.029)
  - Rate of readmission to hospital decreased by 16% (*P* =.055)
  - 30-day readmission for infection to hospital decreased by 24% (P = .001)

Bishop BM, et al. *Ann Pharmacother*. 2014;48:577-583.

Other Treatment Options for HAP and VAP Due to MRDOs

- Optimize PK/PD
  - Extended infusion; continuous infusion; higher doses for β-lactams (eg, cefepime, ampicillin/sulbactam)[a-d]
- Consider using older drugs (colistin IV) pathogens are susceptible to
- Reserve new drugs to meet the challenge of MDROs
  - Ceftolozane/tazobactam
  - Ceftazidime/avibactam
- Combination therapy
  - Colistin, carbapenems
- Alternative administration
  - Aerosolized drugs
  - Aminoglycosides, colistin

a. Courter JD, et al. *Pediatr Blood Cancer*. 2009;53:379-385; b. Bauer KA, et al. *Antimicrob Agents Chemother*. 2013;57:2907-2912; c. Chastre J, et al. *Crit Care Med*. 2008;36:1089-1096; d. Betrosian AP, et al. *Scand J Infect Dis*. 2007;39:38-43.

Extended-Infusion Antibiotic Therapy for Gram-Negative Infections

- Clinical and economic outcomes for patients with *P aeruginosa* bacteremia and/or pneumonia who received cefepime via intermittent vs extended infusion

Clinical or economic outcome	Intermittent infusion, % (n = 54)	Extended infusion, % (n = 33)	*P* Value
Mortality	20	3	.03
ICU LOS, days	18.5	8	.04
Total hospital costs, $	51,231	28,048	.13
Infection-related hospital costs, $	15,322	13,736	.78

Bauer KA, et al. *Antimicrob Agents Chemother*. 2013;57:2907-2912.

Summary

- Timely, effective empiric therapy for HABP and VABP is critical, but providers must know which agents are available and the susceptibilities of the pathogens they need to target
- Rapid diagnostic testing can identify pathogens in a timely fashion to deliver effective, targeted therapy
- Optimizing antibiotic therapy (appropriate agent, duration, dose, de-escalation, and timing) may help to reduce the development of MDROs
- Antimicrobial stewardship encourages the protection of vs the restriction of new antibiotics