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TITLE: Trends in Antibiotic Use and Nosocomial Pathogens in Hospitalized Veterans with Pneumonia at 128 Medical Centers, 2006-2010.

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ABSTRACT

Background: In 2005, pneumonia practice guidelines recommended broad-spectrum antibiotics for patients with risk factors for nosocomial pathogens. The impact of these recommendations on providers' ability to match empiric treatment with nosocomial pathogens is unknown.

Methods: Among hospitalizations with a principal diagnosis of pneumonia at 128 VA medical centers from 2006 through 2010, we measured annual trends in antibiotic selection, initial blood or respiratory cultures positive for MRSA, *Pseudomonas aeruginosa,* and *Acinetobacter* species, and alignment between antibiotic coverage and culture results for MRSA and *Pseudomonas aeruginosa* by calculating annual sensitivity, specificity, and diagnostic odds ratio [DOR] from a 2x2 contingency table.

Results:

Of 95,511 hospitalizations for pneumonia, initial use of vancomycin increased from 16% in 2006 to 31% in 2010, and piperacillin-tazobactam increased from 16% to 27%, while there was a decrease in both ceftriaxone (39% to 33%) and azithromycin (39% to 36%) ($p<0.001$ for all). The proportion of culture-positive MRSA hospitalizations decreased (2.5% to 2.0%, $p<0.001$); no change was seen for *Pseudomonas aeruginosa* (1.9% to 2.0%, $p=0.14$) or *Acinetobacter spp.* (0.2% to 0.2%, $p=0.17$). For both MRSA and *Pseudomonas aeruginosa*, sensitivity increased (46% to 65% and 54% to 63%, $p<0.001$) and specificity decreased (85% to 69% and 76% to 68%, $p<0.001$), with no significant changes in DOR (4.6 to 4.1, $p=0.57$ and 3.7 to 3.2, $p=0.95$).

Conclusions:

Between 2006 and 2010, we found a substantial increase in the use of broad-spectrum antibiotics for pneumonia despite no increase in nosocomial pathogens. Providers' ability to accurately match antibiotic coverage to nosocomial pathogens remains low.

BACKGROUND:

Pneumonia is the leading infectious cause of death in the United States and results in 1.1 million hospitalizations annually.(1,2) Optimal treatment of pneumonia involves selecting an empiric antibiotic regimen (prior to return of results of microbiological tests) that targets pathogens while avoiding drugs that extend the spectrum of coverage to include organisms not causing infection. In 2005, the Infectious Disease Society of America (IDSA) and American Thoracic Society (ATS) introduced the classification of healthcare-associated pneumonia (HCAP), recommending empiric coverage of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* in patients meeting criteria for recent prior healthcare exposure.(3) The 2007 update of the community-acquired pneumonia (CAP) guidelines further emphasized that patients with risk factors for HCAP should be treated with broad-spectrum antibiotics.(4) Efforts to improve pneumonia outcomes have reinforced this recommendation through dissemination of the practice guidelines, performance measures by Medicare, and public health initiatives.(5,6)

Since the introduction of the HCAP classification, concerns have been raised that the risk factors for HCAP put forth by the guidelines are been too broad, driving excessive antibiotic use rather than improving providers' ability to identify patients truly at risk for nosocomial pathogens.(7) It is unknown how these recommendations have impacted providers' ability to match empiric broad-spectrum antibiotic treatment to patients at risk for nosocomial pathogens.

The U.S. Veterans Affairs (VA) health system uses a comprehensive electronic health record, with standardized medication and culture data. This allows us to measure

temporal trends in initial antibiotic selection and microbiology at the patient level across a large health system. We previously measured antibiotic prescribing practices and associations between positive MRSA cultures and anti-MRSA treatment for infection-related hospitalizations.(8,9) Using the same dataset, our aims of this study were to evaluate annual trends in initial antibiotic selection and nosocomial pathogen identification over a 5-year period across the entire VA medical system, and to examine trends in the match between initial antibiotics and culture results. We tested the hypothesis that in the years following the dissemination of the guidelines, the match between broad-spectrum antibiotic use and culture results would increase.

METHODS:

Setting

This study was performed with data collected from 152 VA Medical Centers (VAMCs), between January 1, 2006 through December 31, 2010.(10) We included all facilities with ≥ 10 operational acute care beds and complete electronic medication administration records. All data were accessed and analyzed using Veterans Informatics, and Computing Infrastructure (VINCI).(11)

Subject Selection

During the study period, we selected all hospitalizations from patients ≥ 18 years of age at acute medical, surgical, or neurological wards and intensive care units. We then included hospitalizations with a principal International Classification of Disease, 9th Revision, Clinical Modification (ICD-9)(12) code consistent with pneumonia *(481-*

486), similar to other studies. (13, 14) Hospitalizations with ICD-9 codes for viral pneumonia and influenza (480.0-480.9, 487.0-488.19) were excluded.

To evaluate whether diagnostic coding for pneumonia was consistent during the study period relative to other diseases, we also identified all hospitalizations with principal ICD-9 codes consistent with sepsis (038.0, 038.11, 038.12, 038.x, 995.91, 995.92, 785.52), skin and soft tissue infections (680, 681, 682, 683, 684, 685, 686), and genito-urinary infections (590, 595.0, 597, 598.0, 599.0, 614.0, 614.1, 614.2, 614.3, 614.4, 614.5, 616.0, 616.1, 616.3, 616.4).

Measurements: Antibiotic Use

Antibiotic use was measured using bar code medication administration (BCMA), which records all medications administered to hospitalized patients.(15) As we were interested in the use of antibiotics prior to culture results availability, initial antibiotic therapy was defined as the systemic administration of one or more doses of an antibiotic within the first 2 calendar days of hospitalization. We calculated the proportion of hospitalized patients receiving antibiotics for pneumonia. Respiratory fluoroquinolones were combined into a single category (moxifloxacin, levofloxacin, and gatifloxacin used in 2006), macrolides (azithromycin, clarithromycin and erithromycin), and tetracyclines (doxycycline and tetracycline). As multiple antibiotics may be administered concurrently and we desired to detect breadth of coverage for pneumonia pathogens, we then classified antibiotics with activity against the following pathogen types: atypical organisms (respiratory fluoroquinolone, macrolide, or tetracycline); standard organisms (guideline-concordant coverage with either an anti-pneumococcal, non-anti-pseudomonal beta-lactam listed in Figure 3 plus macrolide, or a respiratory fluroquinolone); MRSA

(vancomycin or linezolid), and single coverage for *Pseudomonas aeruginosa* (piperacillin-tazobactam, ticarcillin-clavulanate, ceftazidime, cefepime, meropenem, doripenem, imipenem, aztreonam). Since guidelines call for combination therapy to ensure coverage of *Pseudomonas aeruginosa*, an additional category was created requiring the combination of single coverage with an anti-pseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside, consistent with guideline recommendations (4).

Measurements: Microbiology Data

We accessed microbiology data on all cultures drawn at any time during each hospitalization, which were standardized into Systemized Nomenclature of Medicine (SNOMED-CT) format.(16) Organism data were included if susceptibility testing was performed. Initial positive cultures for three common nosocomial pathogens associated with pneumonia – MRSA, *Pseudomonas aeruginosa,* and *Acinetobacter spp.* – were identified. We classified culture source into blood, respiratory (sputum, endotracheal aspirate, bronchiolar lavage, wash, or biopsy, or pleural fluid) or "other," which included wound and urine cultures. Since we were interested in identifying pathogens that were present upon hospital admission rather than acquired during a hospitalization, we defined a positive initial pneumonia-related culture as any positive result that had been drawn during the first 2 calendar days of the hospitalization, from either blood or respiratory sources.

Statistical Analysis

To assess providers' ability to accurately differentiate patients at risk for nosocomial pathogens, we examined trends in the alignment between the selection of initial antibiotics and recovery of organisms from microbiologic cultures. Our assessment is thus similar to the evaluation of accuracy of a diagnostic test (Table). A "True positive" was defined as the match between initial treatment and positive growth of the targeted organism in culture. A "true negative" was defined as the absence of coverage for a pathogen and lack of recovery of the corresponding organism. For example, a MRSA "true positive" was a hospitalization in which initial anti-MRSA therapy was administered and a pneumonia-related culture was positive for MRSA, while a "true negative" occurred if no anti-MRSA therapy was administered and no MRSA-positive cultures were identified. Sensitivity (Se) represented the proportion of admissions with MRSA-positive cultures that received an anti-MRSA drug, and specificity (Sp) represented the proportion of admissions without positive MRSA cultures that did not receive anti-MRSA therapy.

The diagnostic odds ratio (DOR) was calculated as a composite measure of performance to reflect both sensitivity and specificity (17). The DOR equals the positive likelihood ratio divided by the negative likelihood ratio, or (Se*Sp)/([1-Se]*[1-Sp]) – see Table). The greater the DOR, the greater the overall sensitivity and specificity, and overall matching between culture and coverage, that occurred. For example, a sensitivity and specificity of 0.50 would result in a DOR of 1, while sensitivity and specificity of 0.75 would result in a DOR of 9. To measure trends in the coverage-culture concordance for MRSA or *Pseudomonas aeruginosa*, we calculated annual sensitivity, specificity, and the diagnostic odds ratio for each year, the difference in the proportion of all true positive

cases and false positive cases from 2006 to 2010, and the ratio of the number of additional false positives per additional true positives idenitified in 2010 compared to 2006.

Temporal trends in antibiotic use, nosocomial pathogens, and alignment between coverage and culture results were analyzed using logistic generalized estimating equation (GEE) models, which took facility-level correlations into consideration. Calendar year was added as the single independent variable. All statistical analyses were performed using STATA, Version 12.0 (StataCorp, College Station, TX) and R (http://cran.r-project.org).

The study was conducted with approval from the University of Utah Institutional Review Board and the Salt Lake City VA Human Research Protection Program.

RESULTS:

Temporal Trends: diagnosis and demographics

One hundred twenty-eight facilities met inclusion criteria. Of a total of 2.4 million hospitalizations during the study period, 95,511 (3.9%) had a principal diagnosis of pneumonia. The proportion of hospitalizations for pneumonia remained stable over time, in contrast to the increase seen in sepsis diagnoses (Figure 1). Of the pneumonia hospitalizations, median patient age was 71 (mean 70, interquartile range 61-81), and median length of stay was 4 days (mean 6 days, interquartile range 3-7). Twelve percent of all pneumonia hospitalizations were initially admitted to the intensive care unit (ICU).

Antibiotic use

Antibiotic use for Veterans hospitalized with pneumonia shifted significantly during the 5-year period (Figure 2). Initial use of vancomycin increased from 16% to 31% ($p<0.001$), and piperacillin-tazobactam increased from 16% to 27% ($p<0.001$), while ceftriaxone and azithromycin decreased ($p<0.001$). Macrolides, of which 99.5% were azithromycin, decresed from 39.5% to 36.0% ($p<0.001$). Overall, anti-pseudomonal coverage and MRSA therapy increased, and a significant decline in initial therapy with standard and atypical coverage was observed (Figure 3; $p<0.001$ for all). The proportion of hospitalizations with initial double anti-pseudomonal coverage, while low, also increased significantly during the study period (5% to 11%, $p<0.001$). The proportion of hospitalizations that did not receive any guideline-concordant antibiotics was 8.1%. The most common antibiotics used in these hospitalizations were ciprofloxacin (single therapy), clindamycin, and trimethoprim/sulfamethoxazole. We found a small, nonsignificant increase in hospitalizations with discordant therapy over the study period (7.7% in 2006 to 8.3% in 2010, $p=0.055$).

Microbiology and culture-coverage concordance

Overall, 84.5% of pneumonia hospitalizations had documentation of at least one culture obtained from a blood or respiratory specimen within 2 days of admission. Respiratory cultures were less frequently collected (34.0% of hospitalization) than blood cultures (81.7% of hospitalizations). We found a small increase in blood culture collection (79.7% in 2006 to 82.1% in 2010, $p<0.001$) and no significant change in proportion of hospitalizations with respiratory cultures obtained.

The overall proportion of hospitalizations with positive initial cultures was 2.2% for MRSA, 2.0% for *Pseudomonas aeruginosa*, and 0.2% for *Acinetobacter spp.* A

significant decline in MRSA was observed, while *Pseudomonas aeruginosa* and *Acinetobacter spp.* remained stable (Figure 4). Of the positive cultures, 88% of MRSA, 96% of *Pseudomonas aeruginosa*, and 76% *Acinetobacter spp*.-positive cultures were from a respiratory source.

Figure 5 displays annual trends in sensitivity, specificity, and DORs for the alignment between antibiotic coverage and culture results for MRSA and *Pseudomonas aeruginosa*. For both pathogens, sensitivity increased and specificity decreased substantially. The resulting annual diagnostic odds ratios for both pathogens demonstrated no significant change from 2006 to 2010 (MRSA: 4.6 to 4.1, p=0.57; *Pseudomonas aeruginosa*: 3.1 to 2.8, p=0.95). The proportion of true positive cases for MRSA increased from 1.1% to 1.3%, while the proportion of false positive cases increased from 15.0% to 30.6%; for every single additional case positive for MRSA covered with anti-MRSA therapy by 2010, the additional number of negative-culture hospitalizations receiving coverage was 115. The proportion of true positive cases for *Pseudomonas aeruginosa* increased from 0.9% in 2006 to 1.2%, while the false positive cases increased from 21.0% to 33.6%; for every additional case of *Pseudomonas aeruginosa* treated with anti-pseudomonal coverage, the additional number of culture-negative hospitalizations receiving coverage was 42.

DISCUSSION:

Antibiotic selection for pneumonia is challenging, with consequences to both individual patients and the public health that are difficult to weigh. Because microbiologic tests are imperfect, whether or not a patient is given broad-spectrum

antibiotics depends upon a provider's estimation of the probability of resistant pathogens as well as his/her threshold for treatment. When a causative pathogen is uncertain, as is the case for most patients with pneumonia, providers must perform the difficult task of weighing the risks and benefits of overtreatment versus under-treatment.

Our 5-year study of over 95,000 hospitalizations for pneumonia across the VA system is the first to examine trends in antibiotic use and culture results together on a large scale. We found a substantial shift toward broad-spectrum agents. During the same time period, we found no increase in initial cultures positive for the three most common nosocomial pathogens.

The shift in antibiotic use to broad-spectrum agents for pneumonia is not unique to the VA system. Berger et al reviewed nationwide antibiotic practices in the United States and found similar trends for hospitalized non-ICU pneumonia patients.(18) The decrease seen in MRSA pneumonia has also been suggested in other studies during the same time period,(19, 20, 21, 22), in contrast to the period of 2000-2005, in which there was a rise in diagnostic coding for MRSA (23). The prevalence of *Pseudomonas aeruginosa* among hospitalized patients with pneumonia has also been previously reported to be stable.(20, 22)

By combining antibiotic administration and culture data, our study examined whether the observed trends in antibiotic use observed resulted in a change in clinicians' ability to match broad-spectrum antibiotic coverage to cultures for nosocomial pathogens. The increase in use of broad-spectrum antibiotics was comparable in patients with and without positive cultures, and the match between treatment and pathogen remained unchanged. These results suggest that the shift toward broad-spectrum antibiotics reflects

a change in criteria for decision-making rather than a response to increased prevalence or enhanced ability to identify patients at risk for resistant organisms. Increased recognition of HCAP risk factors, largely driven by dissemination of guidelines, likely modified clinicians' perception of risk. This change was not accompanied by an improvement in discrimination of which patients actually have MRSA or *Pseudomonas aeruginosa* infection. While the increase in broad-spectrum antibiotics did result in an increase in coverage of more patients with nosocomial pathogens, this came at a cost of treating a large number of patients with broad-spectrum antibiotics unnecessarily

Our study was not designed to determine whether the increase in vancomycin or piperacillin-tazobactam made a positive or negative impact on clinical outcomes. Patients meeting HCAP criteria demonstrate higher mortality risk and a higher risk of nosocomial pathogens, hence it was felt that this increase in mortality may be due to inadequate therapy.(24) However, since the adoption of the HCAP definition, the studies examining clinical outcomes have found no improvement or an increase in mortality associated with the use of therapy with broad-spectrum antibiotics for this group. (25, 26, 27, 28, 29), although one study suggested a possible benefit to broader-spectrum therapy when applying a more refined risk assessment.(31) As the proportion of patients receiving broad-spectrum antibiotics increased, those receiving standard therapies decreased, including coverage for atypical pneumonia pathogens. This raises concern that excessive use of broad-spectrum antibiotics could promote under-use of more standard therapies and failure to cover more common pneumonia pathogens.

Currently, clinicians have few tools to improve their ability to match antibiotics to likely pathogens for pneumonia. Refining and validating the clinical risk factors for

nosocomial pathogens has been a major recent focus of research, (32, 33) although accuracy in predicting resistant pathogens remains low for all risk prediction scores proposed.(33, 34) The development of new accurate rapid diagnostic tests as well as more consistent use of tests currently available may increase our yield of pathogens and include initial respiratory cultures (documented in only 32% of our patients, although the majority of positive cultures were identified from a respiratory source) and nasal MRSA surveillance testing (VA's system-wide program has demonstrated high negative predictive value when compared to cultures for pneumonia patients)(9) In lieu of rapid identification and reliable clinical risk assessment, comparative effectiveness research evaluating the consequences of conservative versus aggressive antibiotic coverage strategies (ie, withholding broad-spectrum therapy until cultures result versus tailoring of antibiotics after cultures) will also improve our ability to base our empiric antibiotic selection on actual risks.

Study limitations include the use of administrative data that relied upon principal diagnostic codes to identify cases of pneumonia, and we did not attempt to identify patient-level clinical factors. It is thus possible that our results may have been affected by unmeasured changes in clinical population or diagnostic coding practices. Broadening the study population to include all principal diagnoses for pneumonia plus those with a secondary diagnosis for pneumonia with sepsis and respiratory failure as principal would have likely provided a slightly greater number of cases of severe pneumonia in the later years, and therefore may have resulted in a slightly higher proportion of hospitalizations with broad-spectrum antibiotic use and positive cultures. However, the profound rate of increase in both piperacillin-tazobactam and vancomycin suggests that providers have

decreased their threshold of use on similar patients. Our examination of whether increases in broad-spectrum antibiotic use were associated with changes in the match between antibiotic coverage and culture results should not be construed as an individual measure of quality. We did not report trends in more typical community-acquired pneumonia pathogens or less common resistant pathogens, such as those that carry extended-spectrum beta-lactamases for which broad-spectrum antibiotics are indicated. At the individual level, it is impossible to determine the appropriateness of broad-spectrum antibiotic use for any given patient from our study. Rather, we aimed to develop a population metric that is informative about thresholds for decision-making.

Clinicians continue to be challenged by the dilemma of whether to use broad-spectrum antibiotics in the treatment of pneumonia. Unnecessary use of broad-spectrum antibiotics carries substantial risk, both to the individual patient and to public health. So does under-treatment of resistant pathogens. Given the raised awareness of antimicrobial resistance brought forth by practice guidelines, it is not surprising that providers at the VA, as in other systems, have lowered their threshold since their dissemination. Our study suggests, however, that even with an increased caliber of the shotgun, we are still missing the mark. Our study supports urgent need of research that examines the impact of this change in threshold on outcomes and better strategies to identify patients who would truly benefit from broad-spectrum antibiotics. Without better evidence that helps providers weigh the risks and benefits of broad-spectrum antibiotic use for their pneumonia patients, we are likely to see continued excessive use of this important resource.

CONCLUSIONS:

We found a substantial increase in the use of both vancomycin and piperacillin-tazobactam from the years 2006 to 2010 in a national population of 95,511 hospitalized Veterans with pneumonia, with no increase in initial positive cultures for methicillin-resistant *Staph aureus, Pseudomonas aeruginosa,* or *Acinetobacter spp.* While providers' threshold for broad-spectrum antibiotic use has decreased, the ability to accurately match antibiotic coverage to culture results for MRSA and *Pseudomonas aeruginosa* has not improved.

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management of the data and review and approval of the manuscript; M. Samore, design of the study and review and approval of the manuscript.

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REFERENCES:

1. http://www.cdc.gov/nchs/fastats/pneumonia.htm. Last accessed 9/15/14.
2. US Burden of Disease Collaborators. The State of US Health, 1990-2010: Burden of Diseases, Injuries, and Risk Factors.
3. American Thoracic Society/Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.
4. Mandell LA, Wunderink RG, Anzueto A et al. Infectious Diseases Society of America; American Thoracic Society, Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44 ((suppl 2)) S27- S72
5. Facts about ORYX for hospitals (National Hospital Quality Measures). The Joint Commission. http://www.jointcommission.org/assets/1/6/ORYX_for_Hospitals.pdf. Last accessed 9/15/2014.
6. Premier Hospital Quality Incentive Demonstration. Centers for Medicare&Medicaid Services. https://www.cms.gov/hospitalqualityinits/35_hospitalpremier.asp. Accessed 9/15/14.
7. Wunderink RG. Community-acquired pneumonia versus healthcare-associated pneumonia. The returning pendulum. *Am J Respir Crit Care Med.* 2013 Oct 15;188(8):896-8.
8. Huttner B, Jones M, Huttner A, Rubin M, Samore MH. Antibiotic prescription practices for pneumonia, skin and soft tissue infections and urinary tract infections throughout the US Veterans Affairs system. J Antimicrob Chemother. 2013 May 16.
9. Jones M, Huttner B, LEecaster M, et al. Does universal active MRSA surveillance influence anti-MRSA antibiotic use? A retrospective analysis of the treatment of patients admitted with suspicion of infection at Veterans Affairs Medical Centers between 2005 and 2010. *J. Antimicrob Chemother.* 2014 August 4.
10. Department of Veterans Affairs, Veterans Health Administration. 2010 VHA Facility Quality and Safety Report. http://www.va.gov/health/docs/HospitalReportCard2010.pdf Last accessed Aug 6 2013).
11. US Department of Veterans Affairs. VA Informatics and Computing Infrastructure (VINCI). http://hsrd.research.va.gov/for_researchers/vinci . Last accessed February 19, 2014.
12. Federal Register. 1985; 50: 31038–40.
13. Lindenauer PK, Lagu T, Shieh MS, et al. Association of diagnostic coding with trends in hospitalizations and mortality of patients with pneumonia, 2003-2009. JAMA. 2012 Apr 4;307(13):1405-13. doi: 10.1001/jama.2012.384.
14. Rhunke GW, Coca-Perraillon M, Kitch BT, Cutler DM. , Marked reduction in 30-day mortality among elderly patients with community-acquired pneumonia. Am J Med. 2011 Feb;124(2):171-178.e1. doi: 10.1016
15. Schneider R, Bagby J, Carlson R**.** Bar-code medication administration: a systems perspective. Am J Health Syst Pharm. 2008;65(23):2216, 8-9.
16. International Health Terminology Standards Development Organisation (IHTSDO). http://www.ihtsdo.org. Accessed April 29, 2014.

17. Glas AS, Lijmet JG, Prine MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a signle indicator of test performance. Journal of Clinical Epidemiology 2003; 56:11, 1129-1135.
18. Berger A, Edelsberg J, Oster G, Huang X, Weber DJ. Patterns of Initial Antibiotic Therapy for Community-Acquired Pneumonia in US Hospitals, 2000 to 2009. *Am J Med Sci.* 2014 May;347(5):347-56.
19. Kallen AJ, Mu Y, Bulens S, Reingold A, Petit S, Gershman K, Ray SM et al. Health care-associated invasive MRSA infections, 2005-2008. *JAMA*. 2010 Aug 11;304(6):641-8.
20. Jain R, Kralovic SM, Evans ME, Ambrose M, Simbarti LA, Obrosky DS et al. Veterans Affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infections. *N Engl J Med.* 2011 Apr 14;364(15):1419-30.
21. Moran. Prevalence of methicillin-resistant *Staphylococcus aureus* as an etiology of community-acquired pneumonia. *Clin Infect Dis.* 2012;54:1126-33.
22. Smith SB, Ruhnke GW, Weiss CH, Waterer GW, Wunderink RG. Trends in pathogens among patients hospitalized for pneumonia from 1993 to 2011. *JAMA Intern Med.* 2014 Nov;174(11):1837-9.
23. Zilberberg MD, Shorr AF, Kollef MH et al. Growth and Geographic Variation in Hospitals with Resistant Infections in the US, 2000-2005. *Emergence of Infections Diseases* 2008 14(11):1756-1758.
24. Ewig S1, Welte T, Torres A. Is healthcare-associated pneumonia a distinct entity needing specific therapy? Curr Opin Infect Dis. 2012 Apr;25(2):166-75. doi: 10.1097/QCO.0b013e32835023fb.
25. Grenier C1, Pépin J, Nault V, Howson J, Fournier X, Poirier MS, Cabana J, Craig C, Beaudoin M, Valiquette L. Impact of guideline-consistent therapy on outcome of patients with healthcare-associated and community-acquired pneumonia. J Antimicrob Chemother. 2011 Jul;66(7):1617-24. doi: 10.1093/jac/dkr176.
26. Rothberg MB, Zilberberg MD, Pekow PS, Priya A, Haessler S, Belforti R, Skiest D, Lagu T, Higgins TL, Lindenauer PK. J Antimicrob Chemother. 2015 Jan 3. Association of guideline-based antimicrobial therapy and outcomes in healthcare-associated pneumonia.
27. Hsu JL, Siroka AM, Smith MW et al. One-year outcomes of community-acquired and healthcare-associated pneumonia in the Veterans Affairs Healthcare System. *Int J Infect Dis.* 2011 June;15(6):e382-3287.
28. Attridge RT, Frei CR, Restrepo MI, Lawson KA, Ryan L, Pugh MJ, Anzueto A, Mortensen EM. Guideline-concordant therapy and outcomes in healthcare-associated pneumonia. Eur Respir J 2011;38:878–887.
29. Kett DH, Cano E, Quartin AA, Mangino JE, Zervos MJ, Peyrani P, Cely CM, Ford KD, Scerpella EG, Ramirez JA. Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACT-HAP) Investigators. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis 2011;11:181–189.
30. Madaras-Kelly KJ, Remington RE, Fan VS, Sloan KL. Predicting antibiotic resistance to community-acquired pneumonia antibiotics in culture-positive patients with healthcare-associated pneumonia. J Hosp Med. 2012 Mar;7(3):195-202

31. Madaras-Kelly KJ, Remington RE, Sloan KL, Fan VS. Guideline-Based Antibiotics and Mortality in Healthcare-associated Pneumonia. J Gen Intern Med. 2012 Jul;27(7):845-52. doi: 10.1007/s11606-012-2011-y. Epub 2012 Mar 7.
32. Shindo Y, Ito R, Kobayashi D, Ando M, Ichikawa M, Shiraki A, et al. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. J Respir Crit Care Med. 2013 Oct 15;188(8):985-95.
33. Prina E, Ranzani OT, Polverino E, Cillóniz C, Ferrer M, Fernandez L, et al. "Risk Factors Associated with Potentially Antibiotic-Resistant Pathogens in Community-Acquired Pneumonia", Annals of the American Thoracic Society, Vol. 12, No. 2 (2015), pp. 153-160.
34. Chalmers JD, Salih W, Eqig S. Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. Clinical Infectious Disease. 2014. 58:330-339.
35. Webb BJ, Dascomb K, Stenehjem E, Dean N. Predicting risk of drug-resistant organisms in pneumonia: moving beyond the HCAP model. Respir Med. 2015.