ASSOCIATIONS BETWEEN CLINICAL AND LABORATORY PARAMETERS IN PNEUMOCOCCAL PNEUMONIA FROM THE UNIVERSITY OF KANSAS HOSPITAL DURING THE YEARS 1996 TO 2005

By

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Date Defended: 08 July 2011

The Dissertation Committee for Natalie A. Reed
certifies that this is the approved version of the following dissertation:

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Abstract:

Pneumococcal pneumonia is a significant disease that requires rapid treatment with effective antibiotics. This study attempts to identify associations with clinical and laboratory parameters from pneumococcal pneumonia cases from the University of Kansas Hospital during the years 1996 to 2005 that can be used to identify appropriate antibiotic therapies. Antibiotic resistance profiles together with retrospective chart reviews were used to identify associations. This study found no association between multi-drug non-susceptibility and mortality and no association between classification of pneumonia acquisition in individual groups (CAP, HCAP, HAP, VAP) and mortality. This study did find an association between multi-antibiotic non-susceptibility in isolates from patients who acquired pneumonia in a healthcare setting (HCAP, HAP, VAP). These results suggest the possibility that patients who frequently need healthcare may be more likely to have empiric antibiotic therapy. This may then be associated with carriage of more antibiotic resistant SPN isolates. The empiric antibiotic therapy should be reviewed frequently to provide the best therapy for patients while reserving the other antibiotics for the more acute cases of resistant pneumococcal disease.

Acknowledgments:

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Introduction:

Streptococcus pneumoniae is a major cause of community-acquired pneumonia (CAP). [File 2003, File 2004] There are approximately 135,000 hospitalizations due to pneumococcal pneumonia each year and 14% of these patients die from this infection. [CDC 2006] Pneumonia is a very serious disease and rapid initial antibiotic therapy can be life saving. However, it is difficult to determine appropriate antibiotic therapy for serious, life threatening cases of *S. pneumoniae* (SPN) since this bacteria has developed antibiotic resistance to several first line antibiotics [Skalet 2010, Van Eldere 2007, Croucher 2011]. Antibiotic resistance and mortality associations have been studied in pneumococcal pneumonia for single antibiotics [Pallares 1995, Feilkin 2000], and 2 or more antibiotics [Arredondo-Garcia 2011, Aspa 2004, Bonnard 2005, Valles 2006] but no study has analyzed mortality associations with antibiotic resistance of pneumococcal pneumonia by the 2 multi-drug non-susceptibility groups of penicillin and macrolide; penicillin, macrolide and sulfonamide or the non-susceptibility rates for these 2 multi-drug non-susceptibility groups by category of pneumococcal pneumonia categories.

Mortality rates have been compared between pneumococcal pneumonia categories of CAP and HCAP [Micek 2007], between pneumococcal pneumonia categories of CAP and HAP [Feilkin 2000], between all cause HAP and VAP [Esperatti 2010] as well as mortality between all pneumonia categories including all causative agents [Kollef 2005]. However, the assessment of mortality rates of pneumococcal pneumonia by all categories (CAP, HCAP, HAP and VAP) has not been reported.

The current study analyzes SPN isolates from hospitalized adult patients with SPN pneumonia. The antibiotic non-susceptibility rate was analyzed in association with mortality

as well as the category of pneumococcal pneumonia acquisition. Additionally the category of pneumococcal pneumonia acquisition was analyzed for association with mortality.

Background:

S. pneumoniae is a bacterium that commonly colonizes the oral-pharyngeal area of several mammals including humans [Austrian 1986, Hendley 1975]. It can be transmitted person to person by airborne droplets. However, this bacterium can also cause a serious pneumonia in humans. Pneumonia due to SPN can occur either in the community and become serious enough to result in the hospitalization of patients. These pneumonias are classified as either community acquired pneumonia (CAP). The definition of CAP is the development of pneumonia in a patient that has not been hospitalized in the last 6 months and does not have a chronic disease.

A separate group of patient may have serious underlying health problems and acquire SPN pneumonia outside of the hospital. These patients are considered to have health care associated pneumonia (HCAP) with SPN. HCAP is defined as the development of pneumonia outside the hospital but satisfying one or more of the following conditions: previously hospitalized within 90 days of developing pneumonia; residence in a nursing home or long-term care facility; receipt of intravenous antibiotic therapy, chemotherapy or wound care within 30 days and/or attended a hospital or hemodialysis clinic. [ATS 2005]

In addition patient hospitalized for non-pneumonia reasons can develop SPN pneumonia while in the hospital. This study analyzes SPN pneumonia acquired both outside or after hospitalization. The data from the various categories of SPN pneumonias will be compared to hospital-acquired pneumonia (HAP) in which the patient was hospitalized for a medical

reason that was not pneumonia and developed SPn pneumonia 48 hours or more after admission to the hospital. A subset of HAP is ventilator-associated pneumonia (VAP), which is the development of pneumonia 48 to 72 hours after intubation. Patients with SPN pneumonias meeting this criterion were analyzed as a separate subset than those patients with HAP. These categories allow for a valuable comparison of adult patients with SPN pneumonia that required hospitalization. [ATS 2005, Kollef 2008]

This study evaluated the association of antibiotic resistance, mortality, and the category of pneumonia (CAP, HCAP, HAP and VAP). Specifically, this study evaluated whether multi drug non-susceptibility is associated with mortality in patients with pneumococcal pneumonia. Additionally it will be determined if the category of pneumonia is associated with an increase in mortality in pneumococcal pneumonia patients and if the category of pneumonia is associated with multi-drug non-susceptibility in SPN.

Methods:

Study Design:

This study was conducted at the University of Kansas Medical Center Department of Pathology and Laboratory Medicine between 2002 and 2005. A retrospective chart review was conducted for all SPN isolates in storage. The data from the retrospective chart review was entered into the research database and linked to the SPN isolate in freezer storage. The data was de-identified after matching to the isolate in storage.

Definition of pneumonia:

Subjects were classified as having pneumonia if the chart review of the episode when the sample was collected indicated: fever, tachypnea (respiration rate of 24-30 breaths/minute),

Tachycardia (heart rate > 100 beats / minute), rales, thick and purulent sputum that was described as rust colored and had a Gram stain showing Polymorphic Neutrophils and bacteria, a white blood cell count of 15,000 – 30,000/mm^3, abnormal chest x-ray, moderate hypoxia due to ventilation/perfusion abnormalities.

Identification and characterization of Bacterial isolates:

Strains of SPN isolated from patients at the University of Kansas Hospital from 1996 through 2005 were collected and frozen at -70ºC. These isolates were later tested for antibiotic resistance using e-Strips (Remel) in five classes of antibiotics: penicillin, cephalosporin, macrolide, sulfonamide, quinolone. The minimum inhibitory concentrations (MIC) for each strain were classified into susceptible, intermediate, and resistant based on the 1999 National Committee on Clinical Laboratory Standards (NCCLS) MIC breakpoints.

Identification of Clinical Inclusion and Exclusion Criteria:

Retrospective chart review was performed and clinical data was collected related to each patient infected with SPN such as age of patient at the time of SPN isolation, radiographic and/or clinical signs or symptoms of pneumonia, whether or not a positive blood culture was also present at the time of SPN isolation, mortality, length of stay, and using the information in the medical chart, each case of pneumonia was categorized as to the location of acquisition of the disease.

Only those SPN isolates obtained from patients who were age 18 or greater at the time of collection of the specimen positive for SPN and who were determined to have a case of pneumonia at the time of specimen collection and who were hospitalized were included in the analysis (see Figure 1 and Table 1).

Calculations:

For the purposes of calculating drug resistance percentages, if a particular strain had not been challenged in the laboratory by a particular class of antibiotics the strain was not counted in the total number of strains. All antibiotic analysis of percentage of non-susceptible strains used the following formula:

$$100\% * \left[\frac{\#\text{ of intermediate} + \#\text{ of resistant}}{\#\text{ of susceptible} + \#\text{ of intermediate} + \#\text{ of resistant}} \right]$$

Also in the case of multiple drug resistance calculations if a strain was not challenged by all of the antibiotic classes in question it was not included in the numerator nor in the denominator of the equation.

Isolates were classified into susceptible and non-susceptible categories by collapsing intermediately susceptible isolates into the non-susceptible category.

Chi Square analysis and Fisher's Exact Test were done using statistical analysis software SAS (see appendix 1).

Results:

Patient Population:

After chart review 424 SPN isolates met the inclusion criteria. Of these isolates, 174 (41.04%) came from patients who acquired the pneumonia from the community (CAP), 98 (23.11%) were from health care associated pneumonia (HCAP), 64 (15.09%) were from hospital-acquired pneumonia (HAP), 88 (20.75%) were from ventilator-associated pneumonia (VAP). (See Table 1)

Mortality by Multi-Drug Non-Susceptibility:

420 isolates were tested with penicillin and macrolide drugs in vitro for susceptibility. Only 238 isolates were tested with penicillin, macrolide and sulfonamide drugs in vitro.

Of the 420 isolates that were challenged by both penicillin and macrolide drugs 93 were non-susceptible to both. Of those 93 that were non-susceptible, 10 isolates came from patients who died during hospitalization giving a mortality rate of 10.8% associated with SPN isolates non-susceptible to both penicillin and macrolide drugs. The mortality rate for all isolates that were challenged by penicillin and macrolide drugs was 12.1%. It appears that resistance to penicillin and macrolide drugs in vitro is not associated with an increase in mortality rate.

Of the 238 isolates that were challenged by penicillin, macrolide and sulfonamide drugs 47 were non-susceptible (19.8%). Of the 47 SPN that were non-susceptible to these drugs, 6 isolates came from patients who died during hospitalization giving a mortality rate of 12.8%. The mortality rate of all isolates that were challenged by penicillin, macrolide and sulfonamide drugs was 13.4% (see table 2). It appears that resistance to penicillin, macrolide and sulfonamide drugs in vitro is not associated with an increase in mortality rate.

Mortality by category of Pneumonia:

The total population of 424 isolates used in this analysis included 51 isolates that came from patients who died during hospitalization giving an overall mortality rate of 12.0% (Table 3). Individually no particular category (CAP, HCAP, HAP, VAP) showed a statistically significant higher mortality rates. (χ^2 analysis p-value = 0.436)

When the health care associated categories are collapsed (Table 4) there is a no significant difference in mortality rates between the two categories (Fisher's Exact Test p-value 0.1716).

Drug Non-Susceptibility by category of Pneumonia:

The data shown in Table 5 show the raw number of isolates considered non-susceptible to each drug with the percentage of non-susceptibility to each of 5 classes of antibiotics as well as two multi-drug categories. The raw data show that those categories associated with health care (HAP and VAP) have higher rates of antibiotic non-susceptibility. It may be that previous therapies for the current incident and for co-morbidities make it valuable to collapse data between true community-acquired pneumonia and that associated with some form of health care. Table 6 shows the two multi-drug classes and the non-susceptibility as collapsed into 2 categories of disease. The Fisher's Exact test shows that HCAP/HAP/VAP group (which generally includes patients with higher co morbidities) and the CAP group have a statistically significant difference in having SPN isolates with 2 different drug non-susceptibility (Fisher's Exact test p-value 0.0027) and with 3 antibiotic non-susceptibility markers (Fisher's Exact test p-value 0.0029).

Discussion:

Mortality by Multi-Drug Non-Susceptibility:

In this study, antibiotic resistance to any one specific drug was not associated with a change in mortality rate. Multi-drug categories were created based on antibiotic therapies considered to be commonly found in SPN. These multiresistant SPN have increased in the last 10 years. The mortality rates among patients infected with SPN strains susceptible to penicillin and macrolides showed no significant difference in mortality rates when compared to patients infected with isolates non-susceptible to penicillin and macrolides. The mortality rates of patients infected with SPN that are susceptible to penicillin, macrolides and sulfonamides

were not significantly different than that of isolates that were non-susceptible to penicillin, macrolides and sulfonamides. The limitation of this study may be due to the number of isolates challenged by sulfonamides, which could result in insufficient data to assess the 3-drug non-susceptibility category for an increase in mortality rate. However, researchers in Mexico also found a "slightly higher" mortality rates among multi-drug resistant SPN [Arredondo-Garcia 2011]. Other studies have found that there is mortality rates were not increased in patients infected with multi-drug non-susceptibility SPN isolates [Aspa 2004, Bonnard 2005, Valles 2006].

A possible explanation for the lack of an association between mortality and multi-drug resistance in this study may be that 59% of the subjects included in the current study were under medical treatment on presentation or had received medical treatment within the last 3 months before the pneumococcal pneumonia diagnosis. It is possible that attending physicians were aware of current or recent antibiotic therapies and begin treatment with alternative antibiotic therapies sooner thereby preventing mortality in these patients.

Mortality by category of Pneumonia:

No statistically significant difference in mortality was noted among patients in individual categories of pneumonia (CAP, HCAP, HAP, VAP) nor the collapsed groups of CAP vs HCAP/HAP/VAP. This may be due to the fact that people with CAP may wait until the disease has progressed significantly before seeking medical care however this analysis has no data to assess this possibility. Pneumococcal CAP and HCAP rates published by Micek in 2007 showed a higher pneumococcal CAP mortality than that of pneumococcal HCAP. However, Micek did not present any statistical analysis to determine whether or not the difference was significant. The comparison of HAP and CAP published by Feikin in 2000

did show a significantly different rate of mortality between pneumococcal CAP and pneumococcal HAP. The definitions of category of pneumococcal disease only included the time from admission to the time of collection of a specimen positive with SPN. This may indicate that cases in the current study defined as VAP could be included in HAP. This would account for more severe cases included in Feikin's HAP leading to a higher mortality rate which appears to be more significant. This would therefore not truly be comparable to the analysis of all 4 categories found in this study.

Drug Non-Susceptibility by category of Pneumonia:

When non-susceptibility SPN were analyzed and evaluated in each separate category of pneumonia no antibiotic had a statistical significantly difference in the rate of multi drug non-susceptibility (including isolates with only 2 multi-drug non-susceptibility rates). When the HCAP, HAP and VAP categories were combined into one category and the drug-non-susceptibility was compared to patients in the CAP category, the results showed that the HCAP/HAP/VAP had significantly higher rates of multi-drug non-susceptibilities (2-drug resistance Fisher's Exact test p-value 0.0027 and 3-drug resistance Fisher's Exact test p-value 0.0029). This may be explained by the SPN having encountered multiple classes of antibiotics in the course of treatment and that these patients had more co-morbidities including chronic disease that exposed them to multiple courses of antibiotic therapy. No published research could be found that assessed all 4 classes of pneumococcal pneumonia and compared the rates of non-susceptibility in SPN. Several researchers published resistance rates among hospitalized patients but did not provide an evaluation of outcomes by the category of pneumonia. A recent study from Mexico indicated that SPN isolates from hospitalized children collected between 2002 and 2005 noted that 41% of these children were

infected with SPN resistant to Penicillin, while 43% of the SPN had resistance to macrolides while 58% were resistant to sulfonamides [Arredondo-Garcia 2011]. Another report from Japan found that for patients in their nationwide surveillance with respiratory tract infections between January 2008 and April 2008 47.4% of SPN isolates were non-susceptibility to penicillin and that there was a "high frequencies of resistance to macrolides." [Niki 2011] Research from Taiwan showed that among all hospitalized patients including patients seen in the emergency services and outpatient clinics from 1999 to 2005 that 39.4% of SPN isolates were non-susceptibility to penicillin, while 92% of isolates were non-susceptibility to macrolides. . The Taiwan isolates include SPN collected from any body sites and was not restricted to respiratory infections. [Lo 2011] It is likely that the differences in resistance rates between our research and the others listed above (Arrendondo-Garcia, Niki and Lo) reflects the differences in the use of certain antibiotics as empiric therapy. Additional studies would be useful if they included the antibiotic recommendations for use in CAP versus the antibiotics that are recommended in the institution for hospital/healthcare associated pneumonias. Antibiotic algorithms can vary between countries as well as types of institutions. This variability in therapy choices will affect the amount and type of antibiotic exposure that circulating SPN encounter.

Conclusion:

At the University of Kansas Hospital from 1996-2005 SPN isolates from patients with healthcare associated, hospital acquired and ventilator associated pneumonia cases show a significantly higher rate of multiple drug non-susceptibility than isolates from patients infected outside the health care system (Community Acquired pneumonia).

The healthcare community continues to struggle to strike a balance between the use an antibiotic therapy that is sufficient to treat the pneumonia yet still reserves the most powerful antibiotic therapy for the more resistant bacterial strains. Many researchers, healthcare providers and government institutions (CDC) have called for a judicious use of antibiotics to curb the multi-drug resistance that is prevalent in SPN worldwide [Harboe 2010, Lo 2011, Niki 2011, Matsumoto 2010, Welte 2010]. Our healthcare facilities must continue to carefully monitor infection control procedures which will reduce the transmission of bacterial strains. Additional research should be conducted to find other ways to rapidly identify the isolates that are multiply resistant and determine which patients are most at risk of carrying multiply resistant isolates. When designing future studies it may be beneficial to include post hospitalization mortality data when available. Other studies have indicated that mortality post hospitalization may be an important consideration [Kaplan 2003, Koivula 1999, Niederman 2007] when reviewing the true affects of pneumonia on patients. Some researchers have indicated that c-reactive protein [Almirall 2004] and procalcitonin [Bousskey 2006, Masia 2005] may also be important markers in the severity and progress of pneumonia. These markers should be included in future research. Furthermore, empiric therapy should be re-assessed frequently to capture current trends in the disease state as well as the resistance of microbes currently circulating in the population.

Figures and Tables:

Figure 1

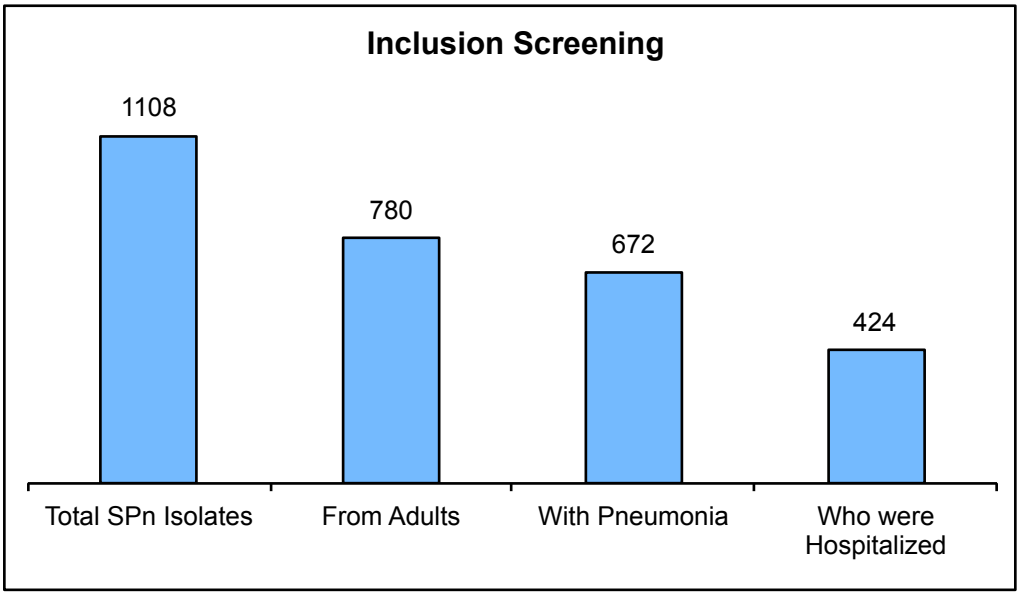

Table 1

S. pneumoniae Pneumonia Classification					
	CAP	HCAP	HAP	VAP	Total
# of Cases	174	98	64	88	424
% of Whole	41.04%	23.11%	15.09%	20.75%	100.00%

Table 2

Multi Drug Non-Susceptibility and Mortality Rates			
	Non-Susceptible	Susceptible	All
Penicillin + Macrolide	10 deaths /93 non-susceptible Mortality Rate (10.8%)	41 deaths /327 susceptible Mortality Rate (12.5%)	51 deaths /420 challenged Mortality Rate (12.1%)
Penicillin + Macrolide + Sulfonamide	6 deaths/47 non-susceptible Mortality Rate (12.8%)	26 deaths /191 susceptible Mortality Rate (13.6%)	32 deaths /238 challenged Mortality Rate (13.4%)

Table 3

S. pneumoniae Pneumonia Mortality by Pneumonia Category					
	CAP	HCAP	HAP	VAP	Total
# of Cases	174	98	64	88	424
Mortality	16/174 (9.2%)	13/98 (13.3%)	8/64 (12.5%)	14/88 (15.9%)	51/424 (12.0%)

Table 4

S. pneumoniae Pneumonia Mortality using collapsed HCAP/HAP/VAP categories versus CAP			
	CAP	HCAP/HAP/VAP	Total
# of Cases	174	250	424
Mortality	16/174 (9.2%)	35/250 (14 %)	51/424 (12.0%)

Table 5

Non-Susceptible *S. pneumoniae* Pneumonia by Pneumonia Category					
	CAP	HCAP	HAP	VAP	Total
Penicillin	49/172 (28.5%)	32/98 (32.7%)	31/64 (48.4%)	39/88 (44.3%)	151/422 (35.8%)
Cefalosporin	4/172 (2.3%)	1/98 (1%)	2/64 (3.1%)	6/88 (6.8%)	13/422 (3.1%)
Macrolide	33/171 (19.3%)	28/97 (28.9%)	22/64 (34.4%)	33/88 (37.5%)	116/420 (27.6%)
Quinilone	4/171 (2.3%)	4/98 (4.1%)	3/64 (4.7%)	1/88 (1.1%)	12/421 (2.9%)
Sulfonamide	25/102 (24.5%)	17/58 (29.3%)	9/31 (29%)	28/47 (59.6%)	79/238 (33.2%)
Penicillin + Macrolide	25/171 (14.6%)	19/97 (19.6%)	22/64 (34.4%)	27/88 (30.7%)	93/420 (22.1%)
Penicillin + Macrolide + Sulfonamide	11/102 (10.8%)	9/58 (15.5%)	8/31 (25.8%)	19/47 (40.4%)	47/238 (19.8%)

Not all isolates were challenged by all antibiotic classes. The cells contain the raw number of non-susceptible isolates / the raw number of isolates challenged by the drug(s) followed by the (calculated percentage of non-susceptibility).

Table 6

Multi-Drug Non-Susceptable *S. pneumoniae* Using collapsed HCAP/HAP/VAP categories versus CAP			
	CAP	HCAP/HAP/VAP	Total
Penicillins + Macrolides	25/171 (14.6%)	68/249 (27.3%)	93/420 (22.1%)
Penicillins + Macrolides + Sulfonomide	11/102 (10.8%)	36/136 (26.5%)	47/238 (19.7%)

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Appendix 1:

```
dm 'log;clear;output;clear';

PROC IMPORT OUT= WORK.nat
        DATAFILE= "C:\Documents and Settings\autologon\My Documents\

Downloads\Thesis Files\Thesis Files\Adult Pneumo Natalie Thesis.csv"
          DBMS=CSV REPLACE;
     GETNAMES=YES;
     DATAROW=2;
RUN;

data nat;
          length locacq2 $15 Location_of_Spn_Aquisition $4 pms $3.;
          format Location_of_Spn_Aquisition $4.;
          set nat;
          where collection_date ^= . and box_number ^= '';
          Location_of_Spn_Aquisition = tranwrd(Location_of_Spn_Aquisition,'HCA','HCAP');
          if Location_of_Spn_Aquisition in('HAP','HCAP','VAP') then locacq2 =
'HCAP/HAP/VAP';
          else if Location_of_Spn_Aquisition = 'CAP' then locacq2 = 'CAP';
          if pen_macro ^='N' and not_p_m_tested = '' then pm = 'Y';
          else pm = pen_macro;
          if pen_macro_sulfa ^= 'N' and not_pm_s_tested = '' then pms = 'Y';
          else pms=pen_macro_sulfa;
run;

proc freq;
          tables locacq2*Location_of_Spn_Aquisition;run;
*table 3;
proc freq data=nat;
          tables patient_expired*Location_of_Spn_Aquisition /chisq;
run;
*table 4;
proc freq data=nat;
          tables patient_expired*locacq2 /fisher;
run;
*table 6;
proc freq data=nat;
          tables pm*locacq2 /fisher;
run;
proc freq data=nat;
          tables pms*locacq2 /fisher;
run;
```