Over-prescribing of Antibiotics for Veterans with Acute Respiratory Illness in an Outpatient Setting

by

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CERTIFICATE OF APPROVAL

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ABSTRACT

Background

Patients with acute respiratory tract infections (RTIs) frequently present to primary care clinics. Most of these infections are caused by viruses and are not treatable with antibiotics. Their overuse can result in adverse patient health effects and increase community antibiotic resistance. Antibiotic over-prescribing was suggested by a preliminary study of three Portland Veteran Administration Medical Center (PVAMC) community based outpatient clinics (CBOCs). This retrospective study of the same time period (July 1, 2008 to June 30, 2009), augments that study with the addition of patients who presented with acute (RTIs) at the remaining four PVAMC CBOCs.

Methods

Electronic medical records (EMR) were assembled using the International Statistical Classification of Diseases (ICD-9) codes to include subjects with non-specific RTIs, sinusitis, bronchitis, pharyngitis, and pneumonia. Excluded ICD-9 codes were for chronic lung diseases, heart failure, and mental illnesses. Excluded also were patients who had initially presented to another healthcare facility or had symptoms lasting longer than 14 days. Eligible EMRs were abstracted for clinical signs and symptoms, pertinent laboratory results and chest x-ray findings, and antibiotic treatment. In addition to using the preliminary study data, additional details of all subject records were extracted for provider type and clinic location. All respiratory antibiotics are currently ordered via computer order entry (CPOE) in the EMR, where treatment guidelines are displayed. Abstracted clinical findings were used to derive a determination of antibiotic prescribing adherence to these guidelines.

Descriptive statistics, univariate and multivariate analysis, and logistic regression (MLR) modeling characterized the predictors of antibiotic prescribing; the dependent variable of interest. The outcomes of both "over-prescribing" and "non-adherence to guidelines" were analyzed.

Results

This study identified 485 subjects with acute, uncomplicated RTIs having a mean age of 54.9 years and were 87% males. A diagnosis of either Sinusitis, Bronchitis, Pharyngitis, or Acute RTI, was recorded in 93% of patients. Antibiotics were prescribed for 49% of all subjects. Antibiotics were "overprescribed" (antibiotics prescribed when not recommended) for 44% of patients while overall "non-adherence to guidelines" occurred in 40% of subjects. MLR modeling with 95% Confidence Intervals (CI) for these two outcomes (over-prescribing; non-adherence) determined their respective risk factors as, advancing *age* (OR 1.02, CI 1.00-1.03; OR 1.02, CI 1.01-1.04), *physician* provider (OR 2.04, CI .883-4.72; OR 2.01, CI .885-4.56), *Port/Dist*...CBOC location (OR 3.56, CI 1.59-8.00; OR 2.84, CI 1.30-6.23), in addition to specific diagnoses of statistical significance. For "over-prescribing" the risk factor diagnoses were *Sinusitis* (OR 6.63, CI 1.77-24.8) and *Bronchitis* (OR 4.49, CI 1.51-13.3) while for "non-adherence" these were *Bronchitis* (OR 7.72, CI 3.02-19.8) and *Pharyngitis* (OR 3.32, CI 1.29-8.51).

Inter-observer variability was analyzed using a kappa statistic (k=.236, 95% CI .000-.626) for concordance of guideline recommendation derivation. This evaluation proved insightful as to systemic issues which may be contributing to inappropriate antibiotic prescribing.

Conclusions

When presenting with acute respiratory infections, Veterans often receive antibiotics not indicated per guidelines. Over-prescribing and non-adherence continues despite CPOE directed guidelines according to this study. Characterizing the determinants of this inappropriate treatment should inform interventions to optimize antibiotic use in caring for area Veterans.

BACKGROUND

Inappropriate antibiotic use for the treatment of patients with common infections is a major problem worldwide (Werner & Deasy, 2009). An upper-respiratory-tract infection is the third most common reason for a doctor's consultation in the USA. About a third of these consultations are diagnosed as acute rhinosinusitis, and 80% of patients with this diagnosis are prescribed an antibiotic. In Europe, similar antibiotic prescription rates in primary care range from 72% to 92% for patients with acute Rhinosinusitis types 3-5. This individual patient data from the U.S. and Europe was reported in a meta-analysis of antibiotic use in adults with viral rhinosinusitis, the "common cold" (Young et al., 2008). Acute respiratory complaints resulted in 84 million visits to their primary care providers in the US in 1998 (Gonzales, Malone, Maselli, & Sande, 2001; Steinman, Landefeld, & Gonzales, 2003). This data was reported from the 1998 National Ambulatory Medical Care Survey (NAMCS), a sample survey of United States ambulatory physician practices, and was used to estimate primary care office visits and antibiotic prescription rates for acute respiratory infections (Gonzales et al., 2001). The (NAMCS) Survey conducted annually by the National Center for Health Statistics, provides national estimates of reasons people seek medical attention, and the diagnoses and prescriptions they receive from a representative sample of United States ambulatory physician practices. Using this survey data, Gonzales, et al, were able to calculate antibiotic use for all office visits that yielded a principal diagnosis of one of the following acute respiratory infections (ARIs), among others, based on the codes of the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM):* sinusitis, bronchitis, pharyngitis and upper respiratory infections (URIs).

Cough, congestion, fever, chills, nasal discharge and sputum production are common symptoms of respiratory infections, the majority of which are self-limited. Most rapid-onset respiratory infections (sinusitis, pharyngitis, and bronchitis) are caused by viruses, which cannot be treated by antibiotics. However, many outpatient visits for acute respiratory symptoms result in antibiotic prescriptions. In the above 1998 survey, nearly 54% of these visits resulted in such a prescription (Gonzales et al., 2001). The reasons for overuse of antibiotics are complex and are influenced by patient anxieties and expectations, provider non-evidence based clinical beliefs, clinic patient load and the frequency of return visits (Ladd, 2005).

Although diagnostic criteria and prescribing guidelines exist for the use of anti-bacterials in sinusitis, (Hickner et al., 2001), pharyngitis, (Cooper et al., 2001), bronchitis (Gonzales et al., 2001; Smucny, Fahey, Becker, & Glazier, 2004), and acute RTIs (Gonzales et al., 2001; Little et al., 2005), health providers may prescribe antibiotics even when diagnostic criteria are not met. It has been estimated that up to 55% of antibiotics prescribed are given to patients without bacterial infections.(Gonzales et al., 2001)

Adverse health effects due to antibiotic use for viral infections may outweigh the benefits of over-treatment in healthy adults with acute respiratory tract infections. Common adverse effects such as gastrointestinal upset, as well as serious anaphylactic reactions and drug-drug interactions, combined with increased medical costs of treatment, support the judicious prescribing of antibiotics (Thomas, 2005).

Community antibiotic drug-resistance is increasing at an alarming rate across the US (Shehab, Patel, Srinivasan, & Budnitz, 2008).The excessive use of antibiotics in ambulatory practice has contributed to the emergence and spread of antibiotic resistance

and has resulted in a vigorous educational campaign to combat this trend by the CDC (Werner & Deasy, 2009). The appropriate use of antimicrobial agents for respiratory infections could potentially reduce the emergence of antibiotic resistance (Gonzales et al., 2005). In the 1990's, drug resistance to both erythromycin and penicillin was wide-spread, and complicated the treatment of community-acquired pneumonia (Gonzales et al., 2004). Educational interventions were introduced, targeting healthcare providers. The subsequent success of controlling erythromycin resistance among group A streptococci, and of controlling penicillin resistance among pneumococci, should encourage health organizations to adopt intervention strategies, aimed at decreasing the inappropriate use of antibiotics (Linder et al., 2009). Although antibiotic prescribing for acute respiratory infections has been studied in Veterans presenting to the Veterans' Administration emergency departments (Tobia, Aspinall, Good, Fine, & Hanlon, 2008), it is necessary to understand prescribing practices in the outpatient clinic setting, where the majority of acute respiratory infections are evaluated. Additionally, previous studies of healthy outpatient populations may not yield findings that are directly applicable to Veteran populations, which may be older on average, with a higher frequency of heart and lung co-morbidities (Dosh, Hickner, Mainous, & Ebell, 2000).

STUDY RATIONALE

Antibiotics are often inappropriately prescribed for acute, uncomplicated Respiratory Tract Infection (RTI) in the U.S. This can lead to serious adverse health effects in patients, increased drug resistance in communities, and increase the costs of medical care. A recent study conducted at Portland area Veteran outpatient clinics

suggested that antibiotics were prescribed to treat such illnesses in this population against the accepted guideline recommendations. Investigating the determinants of this non-adherence to antibiotic prescribing practices, should inform future interventions and promote their judicious use. To further evaluate this issue, a retrospective cohort study was conducted evaluating the use of antibiotics in a cohort of Veterans presenting to the Portland VA Medical Center (PVAMC) and its associated community based outpatient clinics (CBOCs) over a one year time period.

Specific Aims

1. Assemble the Electronic Medical Records (EMRs), selected using the International Statistical Classification of Diseases 9th revision (ICD-9) codes for inclusion/exclusion criteria, of all Veterans who presented with acute, uncomplicated respiratory illness to these PVAMV CBOCs in the Oregon and southwestern Washington area from July 1, 2008 to June 30, 2009.
2. Abstract data from these encounters to include demographic and clinical information.
3. Determine guideline recommendations for antibiotic usage using the identical information prompts, Computerized Order Entry (CPOE), that the provider would use in the CBOC encounter.
4. Quantify non-adherence to guidelines by comparing the actual to the recommended antibiotic prescribing via the CPOE system.
5. Describe interactions of antibiotic prescribing as noted in the strata of provider types and clinic locations.

Study Objectives

1. Estimate the extent of and the determinants of provider non-adherence when guidelines do not recommend antibiotics (i.e. "over-prescribing").
2. Estimate the extent of and the determinants of overall adherence to antibiotic prescribing guidelines.

METHODS

Preliminary Study

A previous retrospective study conducted by Jennifer Logan MD MPH, strongly suggested that inappropriate prescribing of antibiotics was indeed occurring in the PVAMC CBOCs. That study of the treatment of uncomplicated RTI, however, did not provide statistically significant information due to its small sample size. The three CBOC sites closest to the PVAMC hospital were selected for that study. Located within the Portland metroplex, these sites are Portland (Primary Care Clinic at PVAMC), Portland West (Hillsboro), and Portland East (NE Portland). These facilities will collectively be referred to as Port/Prox to indicate their proximity to the PVAMC main hospital. The design and methods used in that preliminary study, to include the identical time span, were replicated and are described in detail below.

Study Design

This study is a retrospective cohort study involving all patients who presented with an acute, uncomplicated respiratory infection to any of the seven PVAMC catchment area CBOCs between July 1, 2008 and June 30, 2009. This time period was

thought to be reflective of recent CBOC activity without including the potential confounding influence of the H1N1 epidemic which began in the Fall of 2009.

The records of this cohort of patients, were selected for review from the PVAMC Computerized Patient Record System (CPRS). In addition to using that study's protocols and data, additional abstraction of clinic site and provider type details from those records allowed for the evaluation of these factors as potential determinants of antibiotic prescribing. The expanded (seven clinic) study added four additional clinic populations comprised of the remaining outlying CBOCs in the PVAMC catchment area. These sites, located outside of the Portland metroplex, are Bend, Salem, Vancouver (Washington), and North Coast (Warrenton). They collectively will be referred to as Port/Dist to indicate their remote location from the PVAMC main hospital.

Selection Criteria

This cohort was assembled by VA Informatics staff, who queried the VA's Electronic Medical Record (EMR) system for all patients presenting with non-specific respiratory tract infection (RTI) including, sinusitis, bronchitis, pharyngitis, and pneumonia as identified using the codes from the International Statistical Classification of Diseases, 9th revision (ICD-9), (Appendix A). Eligible patient encounters were those occurring at all seven of the PVAMC CBOCs from July 1, 2008 to June 30, 2009.

Exclusion criteria

After identifying patients with acute respiratory infections during the period of interest, patient records were reviewed to further determine inclusion into the cohort. The study was limited to acute illness by including only patients who reported less than 14 days of symptoms at initial presentation. Each patient could contribute only one illness

episode to the study. Excluded were patients who initially presented at other venues (e.g. emergency department, hospital, or other healthcare facility). Follow-up visits occurring within 30 days of initial presentation were treated as a single illness episode (i.e. >14 days duration) and were thus excluded. To facilitate comparisons with previous studies of low-risk populations (Gill et al., 2006), patients with the following chronic diseases were excluded using ICD-9 codes: chronic bronchitis, emphysema, asthma, brochiectasis, and the severe mental illnesses of dementia, schizophrenic disorders, and mental retardation (Appendix A).

Recruitment Identification

The VA informatics section (Jianji Yang PhD, Program Analyst, Portland Center for the Evaluation of Clinical Services) was responsible for assembling the patients' electronic records . This included developing lists of subject records to be evaluated by the examiners based on the above inclusion/exclusion criteria. Encounters for patients who had any of the exclusion (chronic disease) diagnoses within five years prior to the encounter were excluded from the list. Additions to the list included information regarding eligible patients' smoking status, antibiotic prescriptions, laboratory and imaging orders issued on the day of encounter. The eligible patient records were uploaded from the VA region1 data warehouse server. These eligible subject EMRs were listed and transmitted via secure VISTA email to the examiners for data abstraction.

Data Management

Data was entered into an Excel spreadsheet and stored on the secure (password-protected) drive at the PVAMC. All subject information was de-identified in the collection instruments, and during the analysis and aggregate reporting of the data.

Data Abstraction

Unique identifier keys were created to anonymously abstract and record data from the eligible CPRS records. Once a subject's record was located, the selected outpatient visit was examined. Many subjects had several entries on the selected date. The entry with the complete history and physical examination was chosen for abstraction. On rare occasions, there was more than one examiner identified with the selected encounter. In those instances, the provider type recorded was the most senior medical person noted.

1. The independent variables were abstracted and recorded on an Excel worksheet. These included patients' signs and symptoms, laboratory tests, imaging studies, smoking status, patient demographic information, and diagnosis.
2. Based on the patient's clinical symptoms and signs as recorded in the EMR, a determination was recorded as to whether the patient's condition met or did not meet the guidelines for prescribing an antibiotic . The examiner who made this determination (KG) was blinded to the antibiotic usage for the encounter (detailed method below).
3. The dependent variable of whether or not an antibiotic was prescribed was abstracted and recorded.
4. Continuous and categorical variables that were candidates for predictors of antibiotic use were abstracted and codified on an Excel collection worksheet using a variable key (Appendix B). These included data on patients symptoms, signs, laboratory data, chest x-ray results, clinic location and provider type (physician vs non-physician).

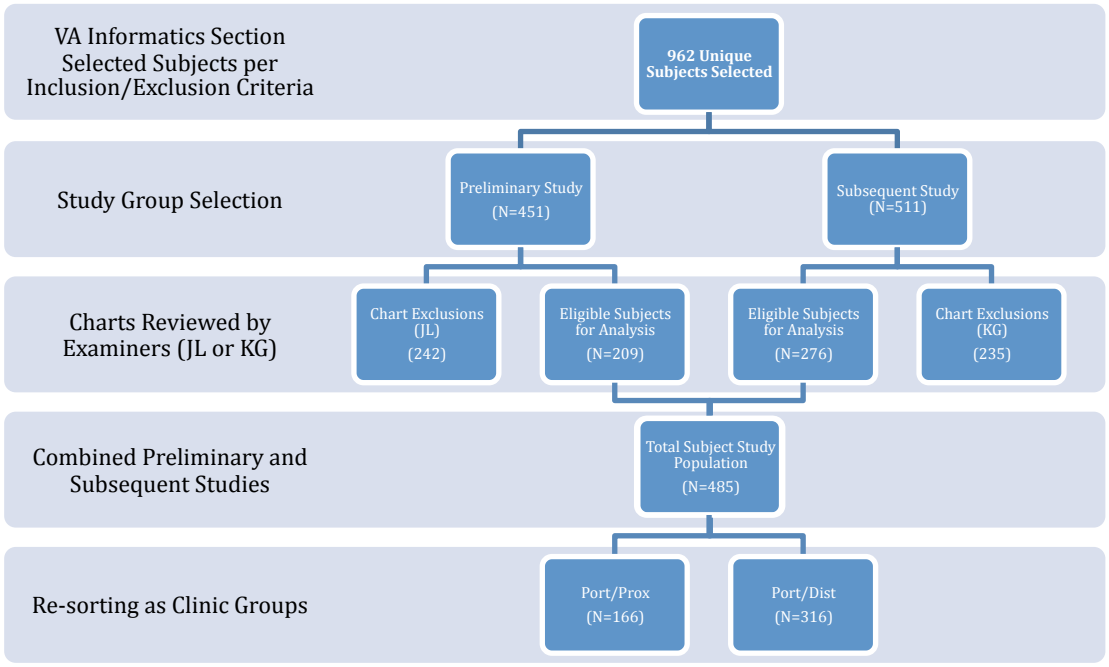
5. Subjects who met the criteria for abstraction were excluded during chart review for a variety of reasons. (See Table 2)
    a. Follow-up visits within 30 days
    b. Duplicate visits (same day, multiple providers)
    c. No RTI noted (i.e. ICD-9 coded for inclusion for past tonsillitis, etc.)
    d. Initial presentation at another facility
    e. Symptoms >2 weeks upon presentation
    f. Co-morbidities not noted by Informatics electronic scan
    g. Vaccine injection visit only
    h. Telephone contact only
6. In addition to all of the above abstracted information, all 485 eligible encounters were abstracted and coded for the following two new variables of interest that had not been initially collected in the preliminary study:
    a. Provider type (physician or non-physician)
    b. Clinic (CBOC) site categorized by:
        i. Port/Prox
        ii. Port/Dist
7. The Excel data collection worksheet was designed to blind the examiner from knowing whether an antibiotic was prescribed for the selected visit. This was accomplished by placing the antibiotic usage information from the encounter on a second worksheet identified only by the Study ID number. The examiner collected the remaining independent variables for each patient from the first sheet and then used the second sheet to record the antibiotic information.

8. Once abstractions of the independent variables were complete for all of the patients, the examiner reviewed the first sheet for the first patient and recorded a determination on that sheet as to whether or not that patient met the guidelines recommended for antibiotic use.
9. The examiner repeated this procedure for the entire subject list en masse.
10. In this way, the examiner was blinded from knowing the antibiotic usage status, recorded on the second worksheet, when determining whether the patient's care followed the EMR point of care guidelines for prescribing antibiotics based on data recorded for each patient encounter.

The following hierarchical diagram illustrates how patients were brought into the study. The initial and subsequent studies were combined and extra details regarding provider type and clinic site added to the initial study with additional chart abstraction (KG). The combined study was then stratified by clinic proximity to the main PVAMC.

It is not unusual, according to Informatics and clinicians at PVAMC, to find patients who, though primarily assigned to a certain CBOC, travel to another to receive care. Conversely, 2 patients from the expanded study designated to be distal CBOC patients, were found to have received their care for the encounter of interest at one of the three Portland CBOCs in that original study.

Figure 1. Patient Selection Diagram



In summary, there were "cross-over" patients that were seen at locations that did not "respect" the original and subsequent group designations. Nevertheless, the interest of this study was clearly to analyze the patient encounter as to what provider type treated the subjects and at which location. So the subjects were "re-sorted" by the actual clinic site of service. This is illustrated in Table 1.

Table 1. Redistribution of Study Group to Clinic Group (due to patient "cross-over")

Study Group	Clinic Group		Total
	Port/Prox	Port/Dist	
Pilot	164	45	**209**
Present	2	274	**276**
Total	**166**	**319**	**485**

Therefore in this study (N=485), subjects were stratified by clinic group (Port/Prox=166; Port/Dist=319) in relation to their proximity to the main PVAMC hospital.

The chart review examiner exclusions represented many categories as noted in Table 2.

Table 2. Chart Review Exclusion Categories

Study Group Selection	**Preliminary Study 451**	**Subsequent Study 511**
Exclusion Categories		
Follow up visits	5	56
No acute RTI present	62	19
1st presented elsewhere	31	16
Symptoms >14 days	75	91
Co-morbidities	16	47
Vaccine shot visit only	50	5
Tel con only	3	1
Total Exclusions	**-242**	**-235**
Eligible Subjects Remaining	**209**	**276**
	Total N=485	

Internal Validity

1. Inter-observer variability was assessed by having a second reviewer abstract data from fifty subject records randomly selected from the list of study candidates (962) that was provided by the Informatics section

2. The second reviewer (GF) determined whether the selected subject met the inclusion/exclusion criteria for the study. This was compared with the first reviewer's (KG) determination of whether the patient met the study inclusion/exclusion criteria.
3. This second reviewer (GF) was given the same Excel data collection sheet noted above, blank except for 50 chart ID numbers from the unique identifier keys.
4. The chart numbers were selected by a random number generator (Excel…RANDBETWEEN) and identified subjects who, after chart review, had been both included and excluded by the previous examiners (JL and KG).
5. The second examiner (GF) was blinded in the same fashion as described above so that the guideline recommendation was not influenced by antibiotic usage. He was also blinded to any determinations/abstracting performed by the previous reviewers.
6. The data collection sheet from the internal validity study was used to generate a Kappa statistic of concordance compared to the original examiners with respect to several key variables based on chart review:
    a. Inclusion/Exclusion of subjects
    b. Diagnosis recorded on encounter of interest
    c. Guideline recommendation for antibiotic usage using the CPOE protocols (Appendix C)
    d. Antibiotic usage

STATISTICAL ANALYSIS

Dependent/Outcome Variables

The dependent variable for this study was Antibiotic Prescribed (Yes/No) as noted in Table 3. The primary outcome variable of interest was the proportion of subjects who had been prescribed antibiotics when not recommended by guidelines (i.e. "Over-prescribed") . A secondary outcome variable of interest was the proportion of subjects whose providers were non-adherent to guidelines, overall (i.e. "total non-adherence"). A third outcome variable of interest was the proportion of subjects who had not been prescribed antibiotics when they were recommended by guidelines (i.e. "Under-prescribed").

These outcomes were derived from the dependent variable, Antibiotic Prescribed, and one of the independent variables, Guidelines Met/Not Met. They may be summarized as follows:

1. Over-prescribed
2. Total non-adherence to guidelines (patients who received antibiotics when they were not recommended in addition to patients not receiving antibiotics when they were recommended based on the point of care guidelines)
3. Under-prescribed

Independent/Predictor Variables

The dependent and independent variables were abstracted from the subjects' medical record. Several of these variables were re-coded for analysis:

1. The seven clinic sites were dichotomized into Port/Prox and Port/Dist. These will be referred to as the *clinic groups*.

2. The *provider types* were dichotomized to Physician and non-Physician. The category of Resident was collapsed into the Physician category as there were too few entries for analysis.
3. The eleven diagnosis categories were collapsed into 5 categories (*Sinusitis, Bronchitis, Pharyngitis, Acute RTI,* and *Other*). This corresponds to their relative frequencies and to conventions in the current literature (Linder et al., 2009).

Table 3. Variable Characteristics

Variable Name	Variable Type	Variable Measurement	
Dependent Outcome Variable			
Antibiotic prescribed	Dependent = categorical	0=No 1=Yes	
Primary Outcomes of Interest			
Over-prescribed	Outcome = categorical	0=No 1=Yes	Antibiotic prescribed when not recommended by guidelines
Non-adherence	Outcome = Categorical	0=No 1=Yes	Antibiotic prescribed when not recommended or not prescribed when recommended
Under-prescribed	Outcome = Categorical	0=No 1=Yes	Antibiotic not prescribed when recommended
Independent Predictor Variables			
Age	Predictor = continuous	Years	
Gender	Predictor = categorical	0 = Female 1 = Male	
Smoking Status	Predictor = categorical	0 = No 1 = Yes	
Provider type	Predictor = categorical	0=Non-physician 1=Physician	
Clinic group	Predictor = categorical	0=Port/Prox 1=Port/Dist	
Guidelines recommend antibiotics	Predictor = categorical	0=Not recommended 1=Recommended	
Diagnoses	Predictor = categorical	0=Other 1=Sinusitis 2=Bronchitis 3=Pharyngitis 4=Acute RTI	

Variable Selection for Logistic Regression Modeling

Selection methods identified the independent variables that were likely to be most predictive of the outcome of interest. Each outcome was dichotomized; e.g., over-prescribed, Yes=1; No=0. Univariate associations between the dichotomized outcomes

and the independent variables were determined depending upon the variables' characteristics (Table 3).

Continuous variables were each evaluated using histograms for range and distribution, and T-tests for statistical significance. Categorical variables were each evaluated using Pearson Chi-square contingency tables for statistical significance.

All independent variables with univariate associations and p-values <0.25 were considered for inclusion in the logistic model. Collinearity was considered for each univariate for possible elimination of correlated independent variables. Possible interaction terms were considered on the basis of clinical relevance. As a result, the variables, *provider type* and *clinic group* were considered for use as an interaction term and later evaluated for inclusion in the final model.

Data Analysis

STATA version 11.2 (StataCorp, College Station) was used for data analysis. White blood cell count result (*wbcrslt*), a continuous variable, had only 85 observations it could not be used for analysis. Logistic regression modeling of the following outcomes was attempted :

1. Outcome: "Over-prescribing"

   In testing the univariates for their associations with the outcome, "over-prescribing" (N=430), for the remaining continuous variable *age*, histograms evaluated range and displayed a normal distribution. This was followed by a t-test which was significant (p<.25) and *age* was selected for inclusion in the model. Chi square tests for the categorical variables, *clinic group, sinusitis, bronchitis,* and *acute RTI,* were found to be significant (p<.25) and these variables were included in the

model. The categorical variable, *provider type*, was not significant (p>.25), however, because it was to be considered for use in an interaction term, it was retained in the model.

2. Outcome: "Non-adherence to guidelines"

Similarly, univariate testing for associations with the outcome, "non-adherence to guidelines" (N=485). A t-test was significant (p<.25) for the variable *age*, as were Chi square tests for the variables, *clinic group, bronchitis, acute RTI,* and *pharyngitis*. Again, *provider type* was not significant (p>.25) but was kept in the model for consideration of the above interaction term.

3. Outcome: "Under-prescribing"

The final outcome of interest, "under-prescribing" (N=55), was evaluated for univariate associations in a similar fashion. This outcome was not amenable to modeling because of the small sample size.

Following univariate selection for the two outcomes of interest, each selected variable was included in a Multiple Logistic Regression (MLR) model. The Wald statistics for each of the above selected univariates' coefficients were checked for statistical significance (<0.25) as were the overall models using the Likelihood Ratio Test (LRT) (p<0.0001). This yielded a *Preliminary Main Effects Model* for each of the two outcomes. The above interaction term, *provider type*clinic group* was inserted and tested in both models and found to improved the significance of both models.

The two MLR models were each built to assess predictors of the outcomes "over-prescribing" and "non-adherence" respectively using the above variable selection methods. Each variable's Wald statistic was evaluated for significance at a level of p-

value >0.05. This significance level excluded *pharyngitis* from the model of "over-prescribing". This diagnosis term was still significant and included in the model of "non-adherence" outcome (p=0.04). The "canned" backward and forward variable selection procedures were assessed to compare with the manual methods above. Since these procedures do not take the requisite interaction into account, the manual product was be used in both final models.

Reflecting the effect modification evident with the presence of the interaction term in both models, the outcome measures were stratified by clinic group. The final models were checked with the Hosmer-Lemeshow Goodness of Fit test statistic (Hosmer & Lemeshow, 1989), calculated with a value of >0.05 in support of the models, due to presence of the continuous variable *age* in the models.

Final results are presented as both Odds Ratios, with 95% Confidence Intervals, and p-values. In addition, Predictive Probabilities were calculated and are presented for sample subjects using each model.

RESULTS

Demographic Characteristics

This study included 485 patients whose mean age was 54.9 years and were 87% male. As was noted in Table 1, a resorting of subjects into clinic site group by proximity to the main PVAMC (Port/Prox vs Port/Dist) was an important distinction made in this study. There were statistically significant differences between these clinic groups including provider types (66% vs 50% physicians), proportion of antibiotics prescribed (37% vs 56%), and diagnosis distribution respectively, as noted in table 4.

Table 4. Subject Characteristics by Clinic Group

	CLINIC GROUP			
	Port/Prox	**Port/Dist**	**p-value***	**Overall**
N	166	319		485
Age (mean)	52.5	56.2	0.013	54.9
Gender (male)	85%	88%	0.382	87%
Provider type (physician)	66%	50%	<0.001	55%
Smoker	36%	20%	<0.001	25%
Sinusitis	9.6%	16.0%	0.05	13.8%
Bronchitis	18.1%	16.0%	0.56	16.7%
Pharyngitis	12.0%	13.2%	0.73	13.8%
Acute RTI	56.0%	47.0%	0.06	50.1%
Other	4.2%	7.8%	0.13	6.6%
Guidelines recommend antibiotics	5%	14%	0.003	11%
Antibiotics prescribed	37%	56%	<0.001	49%
Outcomes of Interest				
**Over-prescribing	34%	50%	0.001	44%
***Overall Non-adherence	33%	44%	0.013	40%
****Under-prescribing	11%	9%	0.818	9%

*p-value refers to differences between Clinic Groups when appropriate

** Over-prescribing means prescribing when guidelines recommend no antibiotics

***Overall Non-adherence includes both over- and under-prescribing

****Under-prescribing means not prescribing antibiotics when guidelines recommend them

The overall study noted over-prescribing 44% of patients; overall non-adherence to guidelines in 40%; under-prescribing in 9%. There were 25% of subjects who reported being current smokers. The following 2x2 tables illustrate the combined followed by the clinic site location as it relates to the correlation or antibiotic use and guideline recommendations (Table 5-7).

Table 5. Antibiotics vs Guidelines; Combined Clinic Groups

	Guidelines Recommending Antibiotics	Guidelines Not Recommending Antibiotics	
Antibiotics Prescribed	50 (10%)	190 (39%)	**240**
Antibiotics Not Prescribed	5 (1%)	240 (49%)	**245**
	55	**430**	**285**

Table 6. Antibiotics vs Guidelines; Port/Prox Clinic Group

	Guidelines Recommending Antibiotics	Guidelines Not Recommending Antibiotics	
Antibiotics Prescribed	8 (0%)	53 (32%)	**61**
Antibiotics Not Prescribed	1 (0%)	104 (63%)	**105**
	9	**157**	**166**

Table 7. Antibiotics vs Guidelines; Port/Dist Clinic Group

	Guidelines Recommending Antibiotics	Guidelines Not Recommending Antibiotics	
Antibiotics Prescribed	42 (13%)	137 (43%)	179
Antibiotics Not Prescribed	4 (0%)	136 (43%)	140
	46	**273**	**319**

A further order to the presentation will be in terms of the three outcomes of interest:

1. Over-prescribing of antibiotics per guidelines
2. Non-adherence to guidelines overall
3. Under-prescribing of antibiotics per guidelines

Sample Size

The sample size of this study was fixed. Confidence intervals (95%) were calculated for each of the proportions of the three outcomes of interest (Table 8).

Table 8. Confidence intervals for outcomes of interest with fixed sample sizes.

Outcome of Interest	Sample Size	Outcome Proportion	95% Confidence Intervals
Over-prescribed	430	.44	.395 - .489
Non-Adherent to Guidelines	485	.40	.358 - .446
Under-prescribed	55	.09	.015 - .167

For each of the three outcomes of interest, there is 95% confidence that the proportion of subjects for that outcome lies between the tabulated confidence intervals.

Outcome Measures

Over-prescribing

The MLR model identified the independent predictors of the outcome, over-prescribing (N=430), as *age, provider type, clinic group, sinusitis, bronchitis, acute RTI,* and the interaction term of *provider type*clinic group.* The Hosmer-Lemeshow Goodness of Fit test was run on the final model(Hosmer & Lemeshow, 1989). The Chi square value (df=8) was 7.28, (p-value=0.5065). Since the null hypothesis implies that the model fits well, we cannot reject the null hypothesis here and can conclude that the model fits well. The characteristics of the final models are presented in Table 9**.** All of the diagnoses, except "other", have been put into the model even if not statistically significant so that a subject with any diagnosis may be modeled. The diagnosis "other" is omitted due to collinearity and represents less than 7% of all diagnoses.

Non-adherence

Similarly, the MLR model identified the independent predictors of the outcome, non-adherence (N=485), as *age, provider type, clinic group, bronchitis, acute RTI, pharyngitis* and the interaction term of *provider type*clinic group.* The Hosmer-Lemeshow Goodness of Fit test was run on the final model. The Chi square value (df=8) was 2.65, (p-value=0.9543). Again, since the null hypothesis implies that the model fits well, we cannot reject the null hypothesis here and can conclude that the model fits well. The characteristics of the final models are presented in Table 9.

Under-prescribing

There were only a total of 5 subjects out of 55 subjects in the overall (Table 5) study who had guidelines recommend antibiotics and did not have them prescribed. This was an inadequate sample size for modeling antibiotic "under-prescribing".

Table 9. Characteristics of the Final MLR Models

Outcome	Variable	OR's	95% CI (OR)	p-value
Over-prescribing				
	Age	1.02	1.00, 1.03	.011
	Provider type	2.04	.883, 4.72	.095
	Clinic group	3.56	1.59, 8.00	.002
	Prov*Clinic	.373	.138, 1.01	.052
	Sinusitis	6.63	1.77, 24.8	.005
	Bronchitis	4.49	1.51, 13.3	.007
	Pharyngitis	1.91	.636, 5.71	.249
	Acute RTI	.582	.214, 1.58	.289
Non-adherence				
	Age	1.02	1.01, 1.04	.001
	Provider type	2.01	.885, 4.56	.095
	Clinic group	2.84	1.30, 6.23	.009
	Prov*Clinic	.446	.172, 1.16	.096
	Sinusitis	2.01	.795, 5.07	.140
	Bronchitis	7.72	3.02, 19.8	<.001
	Pharyngitis	3.32	1.29, 8.51	.013
	Acute RTI	.991	.431, 2.28	<.001

***Note: Inclusive of all diagnoses except "other" due to collinearity.**

Predictive Probabilities

Predictive probabilities (PP) are simply another way of presenting data other that odds ratios. In MLR, odds ratios can be difficult to interpret and there are many ways in which a sample "average" patient may be presented. However, this is a hypothetical patient who may not exist, e.g. a patient who is 0.357 female and .0175 black, etc. With PPs it is possible to take a complex MLR model and describe an actual patient for which you can predict the probability of an outcome, e.g. over-prescribing or non-adherence in this study. This can be presented graphically but with a complex model, the graphs can be difficult to discern. Therefore, Tables 10 & 11 are matrices of sample "actual" patients with values assigned to each predictor in the models which yields a PP for that actual subject. Subjects may be compared in this way as a relative risk estimate which makes

intuitive sense. The illustration in the tables uses color to illustrate how changing one variable can yield a different PP. These tables can be used to "operationalize" the MLR models.

Table 10. Predictive Probabilities; Over-prescribing

OUTCOME	VARIABLES						
	Age	***Provider type; Phys/Non-Phys***	***Clinic group; Prox/Dist***	***Sinusitis; Yes/No***	***Bronchitis; Yes/No***	***Acute RTI; Yes/No***	**PREDICTIVE PROBABILITIES (SE)**
OVER-PRESCRIBING	55	**Phys**	Prox	Yes	No	No	.606 (.109)
	55	**Non-Phys**	Prox	Yes	No	No	.460 (.102)
	55	Phys	Dist	No	No	No	.812 (.090)
	55	Non-Phys	Dist	No	No	No	.699 (.073)
	55	Phys	**Dist**	Yes	No	No	.822 (.076)
	55	Phys	**Prox**	Yes	No	No	.606 (.109)
	30	Non-Phys	Dist	Yes	No	No	.625 (.117)
	55	Non-Phys	Dist	Yes	No	No	.713 (.098)
	85	Non-Phys	Dist	Yes	No	No	.802 (.084)

Note: Prov*Clinic interaction term entered into each calculation at its mean value=.373

Table 11. Predictive Probabilities; Non-adherence

OUTCOME	VARIABLES						
	Age	***Provider type; Phys/Non-Phys***	***Clinic group; Prox/Dist***	***Pharyngitis; Yes/No***	***Bronchitis; Yes/No***	***Acute RTI; Yes/No***	**PREDICTIVE PROBABILITIES** (SE)
NON-ADHERENCE	55	**Phys**	Prox	Yes	No	No	.452 (.073)
	55	**Non-Phys**	Prox	Yes	No	No	.310 (.970)
	55	Phys	Dist	Yes	No	No	.750 (.088)
	55	Non-Phys	Dist	Yes	No	No	.614 (.096)
	55	Phys	**Dist**	Yes	No	No	.671 (.087)
	55	Phys	**Prox**	Yes	No	No	.452 (.073)
	30	Non-Phys	Dist	Yes	No	No	.400 (.078)
	55	Non-Phys	Dist	Yes	No	No	.522 (.075)
	85	Non-Phys	Dist	Yes	No	No	.666 (.083)

Note: Prov*Clinic interaction term entered into each calculation at its mean value=.446

Univariate/Multivariate Analysis Results

Clinicians are often interested in how the univariate association with an outcome is adjusted by the multivariate analysis. This allows one to see the effect that adjusting with multiple variables (MLR OR's) has on the crude Odds' Ratios of a single variable's association with an outcome. These comparisons are illustrated with both over-

prescribing and non-adherence outcomes and stratified by clinic group in Tables 12 and 13.

Table 12. Univariate/Multivariate Predictors of Antibiotic Over-prescribing

Clinic site	Variable	Univariate OR's	Univariate 95% CI	Multivariate OR's	Multivariate 95% CI
Port/Prox					
	Age	1.04	1.01, 1.06	1.04	1.01, 1.07
	Male	*1.00	-	n/a	-
	Female	.837	.321, 2.18	n/a	-
	Non-physician	*1.00	-	*1.00	
	Physician	2.31	1.09, 4.91	2.00	.793, 4.92
	Non-Smoker	*1.00	-	n/a	-
	Smoker	1.06	.529, 2.11	n/a	-
	Other diagnosis	*1.00	-	n/a	-
	Sinusitis	3.51	.805, 15.3	.847	.092, 7.77
	Bronchitis	10.6	4.15, 27.2	1.64	.255, 10.6
	Pharyngitis	1.50	.565, 4.00	.446	.067, 2.99
	Acute RTI	.097	.045, .211	.088	.015, .516
Port/Dist					
	Age	1.01	.994, 1.03	1.01	.996, 1.03
	Male	*1.00	-	n/a	
	Female	1.40	.673, 2.93	n/a	
	Non-physician	*1.00	-	*1.00	
	Physician	.802	.498, 1.29	.733	.434, 1.24
	Non-Smoker	*1.00	-	n/a	
	Smoker	1.35	.752, 2.43	n/a	
	Other diagnosis	*1.00	-	n/a	
	Sinusitis	8.03	2.33, 27.6	17.9	3.17, 100.9
	Bronchitis	3.22	1.65, 6.30	6.59	1.66, 26.2
	Pharyngitis	1.41	.717, 2.78	3.61	.895, 14.5
	Acute RTI	.273	.166, .451	1.35	.433, 1.24

n/a indicates variable not present in MLR model
*** indicates referent category**

For the outcome of over-prescribing, the most dramatic adjustment effect on the OR's is for the diagnoses categories. Another notable finding is the differences in OR's with regard to the physician provider type between near and distant CBOCs.

Table 13. Univariate/Multivariate Predictors of Non-adherence to guidelines for antibiotic usage

Clinic site	Variable	Univariate OR's	Univariate 95% CI	Multivariate OR's	Multivariate 95% CI
Port/Prox					
	Age	1.04	1.01, 1.06	1.04	1.01, 1.07
	Male	*1.00	-	n/a	-
	Female	.778	.034, 1.99	n/a	-
	Non-physician	*1.00	-	*1.00	
	Physician	2.26	1.07, 4.77	1.96	.798, 4.79
	Non-Smoker	*1.00	-	n/a	-
	Smoker	.940	.477, 1.85	n/a	-
	Other diagnosis	*1.00	-	n/a	-
	Sinusitis	.937	.309, 2.84	.221	.030, 1.60
	Bronchitis	11.1	4.36, 28.4	1.62	.251, 10.4
	Pharyngitis	1.84	.711, 4.84	.484	.073, 3.21
	Acute RTI	1.27	.060, 2.78	.087	.015, .511
Port/Dist					
	Age	1.01	1.00, 1.03	1.02	1.00, 1.04
	Male	*1.00	-	n/a	-
	Female	.707	.707, 2.71	n/a	-
	Non-physician	*1.00	-	*1.00	
	Physician	.958	.616, 1.49	.861	.535, 1.39
	Non-Smoker	*1.00	-	n/a	-
	Smoker	1.39	.801, 2.42	n/a	-
	Other diagnosis	*1.00	-	n/a	-
	Sinusitis	1.04	.572, 1.91	3.49	1.15, 10.6
	Bronchitis	4.17	2.15, 8.08	9.91	3.18, 30.9
	Pharyngitis	1.63	.849, 3.13	5.27	1.68, 16.5
	Acute RTI	.477	.304, .749	1.96	.719, 5.33

n/a indicates variable not present in MLR model
*** indicates referent category**

Similarly, for the outcome of non-adherence, the OR's of the diagnoses categories showed a marked effect after adjustment. Again, the differences in OR's with regard to the physician provider type between near and distant CBOCs is apparent.

Internal Validity

An internal validity study of 50 randomly selected study subjects was conducted to measure the concordance of agreement between the original examiner (KG) and the validating examiner (GF) with regard to the determination of guideline recommendations for antibiotic prescribing. The proportion of agreement and the correlation coefficient are both measures that can be used. However, the correct statistic is kappa which corrects the proportion of agreement due to chance (Landis & Koch, 1977).

Excluded, after chart review were 26 subjects. Even if one examiner excluded a subject, that subject could not be analyzed as there needed to be two examiners per subject in order to compare the outcome results. One additional subject was excluded due to an error in the subject identification number which left 23 subjects eligible for analysis.

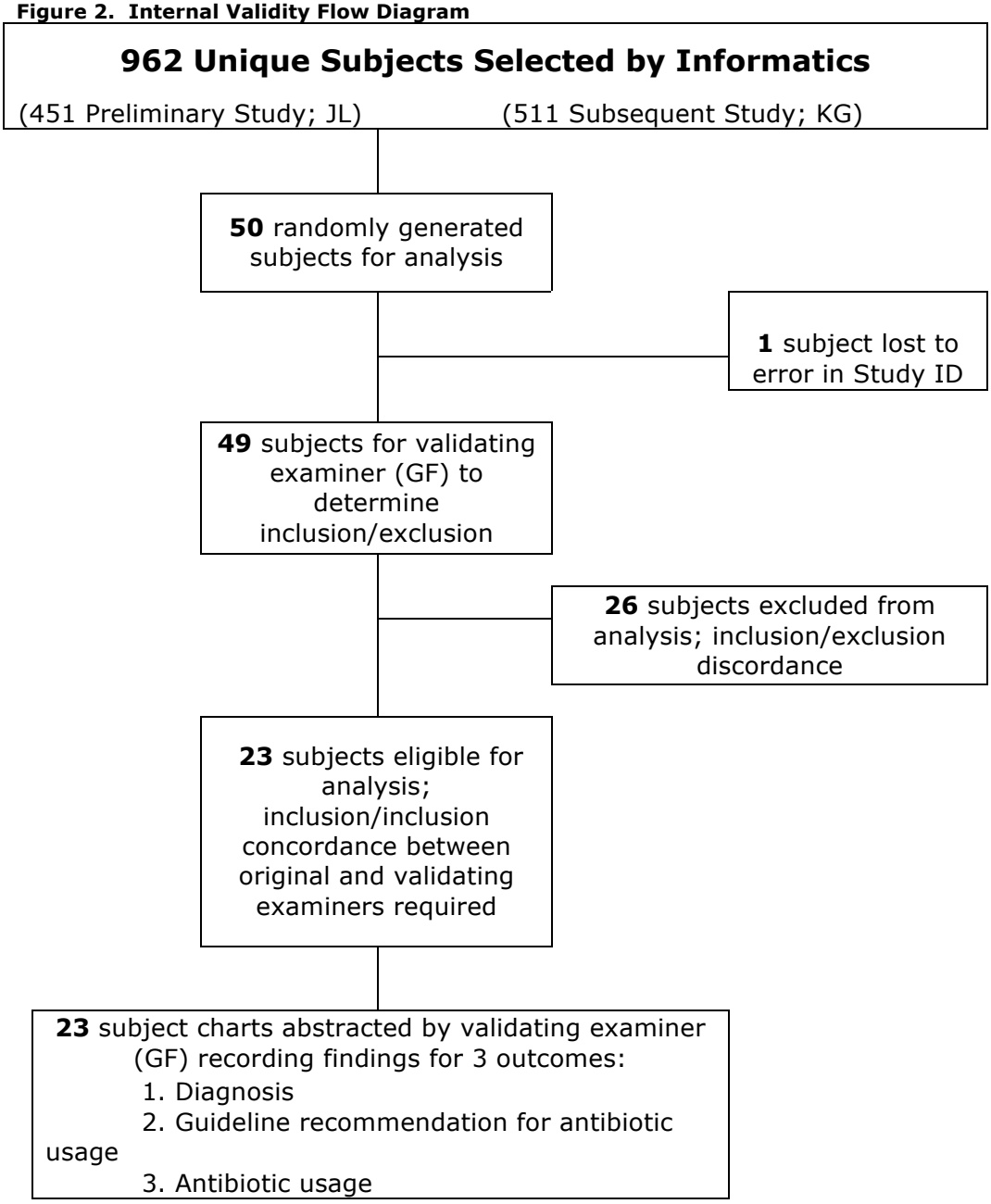
Table 14. Inclusion/Exclusion concordance at chart review

		Validating Examiner		
		Inclusion Yes	**Inclusion No**	
Original Examiner	**Inclusion Yes**	23	5	**28**
	Inclusion No	6	15	**21**
		29	**20**	**49**

Kappa=.5389; SE=.1427

It is important to emphasize that the abstracted information from the first examiner was by KG only, using the CPOE guidelines to determine the original guideline recommendation. This emphasizes a study aim which is to determine the effectiveness of the CPOE prompted guideline recommendations, therefore, the examiners (KG and GF) each used these as a basis for their determinations. Figure 2 illustrates the flow of subjects through the internal validity testing.

Figure 2. Internal Validity Flow Diagram



The Internal Validity study illustrates a salient point going forward in this analysis. That is, chart abstracting is fraught with ambiguity which was highlighted in the blinded comparison of the 2 examiners, each including or excluding participants in the study. That is one of many system weaknesses that are apparent from this study. An

analysis of the 23 subjects with regard to concordance with guidelines for antibiotic prescribing is presented in Table 15.

Table 15. Guideline recommendation for antibiotic usage

		Validating Examiner		
		Guidelines recommend	**Guidelines do not recommend**	
Original Examiner	**Guidelines recommend**	4	1	**5**
	Guidelines do not recommend	8	10	**18**
		12	**11**	**23**

Kappa=.2362; SE=.1986 95% CI (-.153 to .625)

The concordance is poor, with a wide CI between observers, when comparing their determination of the guideline recommendations for antibiotics. This is an anticipated finding in light of the similar discord in comparing who was included or excluded in the study. There are chart abstracting issues here that are difficult to determine with certitude. This seems amplified by every step in the process, culminating in the decision as to whether to prescribe antibiotics or not.

DISCUSSION

This retrospective cohort study of Veterans with acute upper respiratory infections documents the continued prescribing of antibiotics despite the CPOE directed guidelines. These findings reflect the literature supporting inappropriate antibiotic use in the general U.S. population. In a large survey study conducted of over 52,000 URI episodes treated in the primary care, outpatient setting, 65% of these patients received antibiotics when they should not have (Gill et al., 2006). This study was interesting as it also uses EMRs to abstract patient encounter information similar to the present study. While they did not

estimate the total proportion of patients who should have received antibiotics, per guidelines (using the identical protocols as does PVAMC), they did report that 46% of those with nonspecific URIs (corresponding with this study's acute RTI diagnostic category) and 60% of those with Bronchitis received antibiotics. Neither of these conditions meet recommendations for such treatment so frequent over-prescribing may be inferred.

This study did allow identification of the significant predictors of both of the outcomes of interest; overprescribing and general non-adherence to guideline recommendations. From the public health risk standpoint, these are the most clinically relevant of the outcomes as they affect the largest segment of the at risk population. The small number of patients in this and literature studies who are under-prescribed typically have self-limited conditions that are not life-threatening. For instance, not treating strep throat (*pharyngitis*), even when positively identified as group A beta-hemolytic streptococcus (GABHS), is not a serious life-threatening condition and most will resolve without therapy. On a population basis, treating 50% of patients with antibiotics of whom 90% are likely to have a viral infection has a more profound effect on risk to the patient for adverse reactions such as allergy or C. difficile infections related to drug resistance. The risks extend to the population at large as well with antibiotic resistance on the rise. The latter issue does not apply to the few cases of under-prescribing, another reason to be less concerned clinically about this small at risk population.

Both of the outcomes of interest in this study had very similar independent predictors that were present in their final respective MLR models. This is not surprising as over-prescribing is a subset of the more global non-adherence to guidelines. In fact the

only variation in the predictive factors were in which diagnoses were statistically significant enough to be included in the final MLR model. Antibiotics are more likely to be prescribed for older Veterans, treated by a physician, at a CBOC in close proximity to PVAMC, and with a specific diagnosis, (Sinusitis for the outcome, "over-prescribing"; Bronchitis for the outcome, "non-adherence"). The introduction of the interaction term between provider type and clinic site highlighted the effect modification of CBOC location as illustrated by stratifying the study results by Port/Prox and Port/Dist.

Both of the outcomes showed this interesting relationship with regard to provider type and clinic location. As noted in both Tables 12 and 13, a patient's risk of being treated with antibiotics is increased when seen at a proximal CBOC and being treated by a physician provider.

This study provided no insights into the root causes of these disparities in treatment. One possible hypothesis would be that there is a different training and culture in the outlying CBOCs regarding treatment regimens. What may be routine in rural areas may not be found in closer proximity to an academic teaching hospital. That there were differences demonstrated indicates that this an area that warrants intervention consideration.

Inappropriate antibiotic use has been common for many years ever since they were introduced as a panacea. There have been interventional successes such as in the 1990's when wide-spread drug resistance to both erythromycin and penicillin complicated the treatment of community-acquired pneumonia (CAP). Educating providers helped to control erythromycin resistance among group A streptococci, and penicillin resistance among pneumococci (Bartlett et al., 2000) These successes should be

encouraging but, even though today's guidelines have been widely publicized since their development in 2001, the problem of overuse of antibiotics is again a common public health issue.

The internal validity analysis that was a prominent finding in this study highlights some interesting issues that relate to the use of medical records to identify and characterize clinical patient encounters. First, it is important to realize that a retrospective review of a patient record is quite different than actually caring for the patient presenting in a clinical encounter. The abstractor has only the data recorded in the EMR. The internal validity ancillary findings highlight the ambiguities inherent in this process such that there were even differences in the patients that would have been included in the cohort as well as differences in determination as to whether antibiotics were appropriate or not.

Consider the exclusion criteria disparities which were present in 11 of 49 subject records. This discordance illustrates the ambiguities in retrospective chart reviews. Co-morbidities are a good example of this source of a difference between providers and abstractors. If a chronic lung disease like asthma is not stated anywhere in the record, and it may be recorded in several places, but the patient reports a cough "like I get all the time ever since I was diagnosed as a teenager with asthma"…does the patient get excluded from this analysis because of an unrecorded co-morbidity? Similar areas of this potential discordance abound. Another common exclusion criterion, used to define an acute illness, is the limitation of symptoms to 2 weeks or less. The patient record that states, "smokers cough chronic, new sputum production and sinus tenderness for 1 week". This patient could reasonably be thought to have an acute URI, should this record be excluded?

The next area of discordance was whether or not antibiotics were prescribed, which was this study's dependent variable of interest. This was problematic as, if one is reading the provider's chart note and the treatment plan states "Amoxicillin", but there is no record of this prescription being written or filled, how is this coded? There is not one definitive way of determining whether or not a prescription was issued. Conversely, the chart note may make no mention of antibiotics but the "Meds" chart tab can contain this prescription. Depending on where the abstractor looks, the outcome can be recorded differently. Of course, it is beyond the scope of this study to deal with the issue of whether or not a prescription issued is filled, or used for that matter. The abstractors were only given a symptom, sign, laboratory test, or another concrete variable to abstract. There were no guidelines to indicate where this information should or could come from in the EMR. The implication with much of the abstraction discord is that this is one of the significant areas of information disagreement. Standardizing this process is critical. The protocols for the method of abstraction were set up in the preliminary study and followed subsequently.

Lastly, and most emblematic of the systemic issues that are being raised by these discordances, is the issue of diagnosis. The guidelines are keyed to the clinical diagnosis. This is recorded in the chart in a number of locations starting with the chart note. If the patient's diagnosis is recorded as Sinusitis, for instance, then one would look for the guideline clinical indications for treatment of that condition, such as unilateral facial pain or sinus tenderness. Consider the chart that records, "head congestion, cheek sore, sinus tender to touch" but the coded diagnosis in the chart is acute RTI (the guidelines for which do not recommend antibiotics). Is this a missed Sinusitis condition which should

have had antibiotics recommended? There may be a diagnosis in the chart record that is different from the computer coded entry in the diagnostic field, which one does the abstractor record? Recall, the guideline recommendation starts with a diagnosis, so the abstractor might be making the recommendation based on a best guess as to what the provider intended. Of course, some of these issues are common to retrospective chart reviews. On the other hand, the EMR has been promoted as a way of standardizing charting and making abstracting and searching records much more accurate. Another diagnostic issue that is not specific to coding in the EMR (as it is a problem in the paper chart as well), is the issue of the inadequate chart note. As an example, the entire note that reads, "head congestion, cough, fever, (no temperature recorded in chart); Z-pack", and the diagnosis coded is Sinusitis. This is a multiple of our discordant issues. Should this chart be included as an acute illness of <2 weeks duration…it is not specified? Sinusitis may be indicated for focal signs and symptoms of even short duration but there is no chart note support for this here. Does "head congestion" qualify as unilateral facial pain per the Sinusitis guideline and should antibiotics be recommended?

Limitations

As noted in the above discussion, data abstraction needs to be further standardized in a detailed fashion. This will hopefully eliminate some but not all of the inherent ambiguities of extracting clinical information that is placed in written form in the clinical record. Furthermore, the inherent problem of retrospectively abstracting a clinical note in contrast to actually treating the patient does not allow the abstractor to divine what the provider was thinking, seeing, or feeling about the patient in the clinical context. Some of this important information cannot be recorded no matter how excellent the charting.

There is not a place in the clinical record where a provider records why he or she is deviating from the guidelines. This limits this study's ability to compare treatment intentions with guideline adherence.

Generalizablity of the results presented here, to the greater VA hospital system outpatient population is a potential limitation of this study. This study was limited to low-risk Veterans in an outpatient setting in one region of the U.S. Approximately one-third of our sample was excluded from analysis due to preexisting co-morbidities that would place patients at higher risk of complications. Therefore, our findings may not be applicable to Veterans or others with chronic respiratory and cardiac co-morbidities. Information on comparative demographics may allow adjustment of these results and extrapolation to other populations. This potential weakness is potentially testable as comparative studies can be designed elsewhere to test the reproducibility of our results.

A notable limitation of this study is that involving the internal validity testing. It was considered a point of interesting information as to whether a second examiner would exclude subjects from the study in concordance with the original determination. This unfortunately limited the sample size by excluding over 50% of the validation study subjects. This small sample size resulted in wide confidence intervals which make the Kappa statistics generated unreliable. If the guidelines concordance Kappa=0.238 is a true reflection of low inter-rater reliability of the study outcomes, then reasons for this are numerous. As mentioned above, non-standardized chart abstraction is a leading contender. Poor charting is another prominent reason that leaves much open to the interpretation of the examiners and with this would flow discordance of abstraction as well. Increasing the sample size and limiting the population to the subjects included in

the study would have likely produced a more precise Kappa estimate as would have standardizing abstraction methods. However, realizing the inherent ambiguities in the charting and the retrospective nature of the study leads one to speculate as to whether poor concordance is not a surrogate for a systemic difficulty in using the guidelines as a way to direct appropriate antibiotic usage.

Strengths

This is a broadened retrospective study based on the methods developed in the previous study. More than doubling the number of clinic sites, yielded a sample size suitable for determining predictors of provider antibiotic prescribing for acute respiratory infections in Veterans occurring during this time period. This allowed an analysis of over-prescribing as well as the overall non-adherence to antibiotic prescribing guidelines. The enhanced details of provider-type and clinic-site allowed stratification of this interaction. Observer bias was addressed rigorously by the blinding technique which was use for the primary abstractor and the validation examiner. Selection bias has been minimized by design as inclusion and exclusion criteria are based on ICD-9 coding and managed by VA informatics personnel who were not otherwise associated with this study. A major source of confounding was eliminated with the exclusion of chronic diseases.

CONCLUSIONS

Misclassification bias, potentially present in the measurement or assessment of the areas of discord was revealed by the internal validity evaluation. Rather than presenting this as a strength or limitation of this study, it needs to be a part of its conclusion. This was illustrated in ample fashion with the inter-observer variability test. This analysis brought to light what may have been the most salient findings of this study; the systemic charting issues which can misdirect and complicate the adherence to antibiotic prescribing guidelines. The effect on the outcomes is selective in the sense that the providers seemed to recommend antibiotics much more than did the retrospective examiner. This would suggest bias away from the null, with the null being no difference between the provider and observer in interpreting the guidelines and using antibiotics judiciously.

The VA has the largest and arguably the most sophisticated EMR system in the U.S. This EMR system prompts the provider with the CPOE system at the appropriate time in the clinical encounter. Despite this mechanism in place to assist providers, antibiotic over-prescribing and non-adherence to prescribing guidelines is occurring in the PVAMC CBOCs according to this study. The determinants of these outcomes should help to target provider types, clinic locations, and certain diagnoses for interventions.

As has been shown, charting properly and recording a diagnosis correctly, is key to using the guidelines long established. The guidelines are simple and straight-forward. They each use a very few clinical details in order to make antibiotic recommendations. Hopefully, this study can be useful to inform such educational intervention and technological prompting features which will optimize this system. Of course, there are

many human factors which this study has not addressed, including the patient demand for treatments, the provider's psychological desire to "do something" for an ill patient, follow up of prescription filling and medication compliance issues, among many others. There is also the issue of ancillary measures that are part of the guidelines which were not addressed in this study that are amenable to further evaluation. Such as, if a patient has a cough illness and auscultatory findings, did they get a chest x-ray which is called for in the guideline? Similarly for rapid strep test for pharyngitis.

Future Studies

In addition to the above interventional studies, the present study can be improved by meticulously improving the technique of chart abstraction. It is possible to be more specific as to what information sources are acceptable. Perhaps a group of frequent users of CPRS can be formed and help to provide a detailed abstraction method which can minimize ambiguity. Unfortunately, the weak chart note is a flaw which will be more difficult to remedy. Performance standards may be helpful but difficult to enforce.

The goal of more judicious use of antibiotics is of major public health import which has implications to the individual patient and to the community. This study has been instructive in underscoring the problem and hopefully will be helpful in developing its solutions.

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APPENDIX A

PVAMC Informatics Section Inclusion and Exclusion Diagnoses

ICD9 codes (http://icd9cm.chrisendres.com/index.php?action=contents)

INCLUSION DIAGNOSES (for visit between July 1, 2008 and June 30, 2009)

460-466 Acute respiratory infections
- 460 Acute nasopharyngitis [common cold]
- 461 Acute sinusitis
  - 461.0 Maxillary
  - 461.1 Frontal
  - 461.2 Ethmoidal
  - 461.3 Sphenoidal
  - 461.8 Other acute sinusitis
  - 461.9 Acute sinusitis, unspecified
- 462 Acute pharyngitis
- 463 Acute tonsillitis
- 464.0 Acute laryngitis
  - 464.1 Acute tracheitis
  - 464.2 Acute laryngotracheitis
  - 464.3 Acute epiglottitis
  - 464.4 Croup
  - 464.5 Supraglottitis, unspecified
  - 465 Acute upper respiratory infections of multiple or unspecified sites
- 465.0 Acute laryngopharyngitis
  - 465.8 Other multiple sites
  - 465.9 Unspecified site

480 Viral pneumonia (I guess we can include this in case someone writes viral pneumonia with bacterial superinfection)

485 Bronchopneumonia, organism unspecified

486 Pneumonia, organism unspecified

487 Influenza
- 487.0 Influenza with pneumonia
- 487.1 Influenza with other respiratory manifestations
- 487.8 Influenza with other manifestations

490 Bronchitis, not specified as acute or chronic

APPENDIX A (Continued)

EXCLUSION DIAGNOSES (for any diagnosis in past 5 years)

290 Dementias
295 Schizophrenic disorders
317-319 Mental retardation

428 Heart failure

491 Chronic bronchitis
492 Emphysema
493 Asthma
494 Bronchiectasis

APPENDIX B

VARIABLE KEY

Were any exclusion criteria met (has problem been occurring longer than 14 days, based on note in CPRS related to that visit)? ***exc***
0 for no
1 for yes

1. Patient identification number (not medical record number): ***id***

2a. Which medication was/were prescribed? ***abx***

1	Moxifloxacin
2	Azithromycin
3	Moxifloxacin & Azithromycin
4	Moxifloxacin & another antibiotic
5	Azithromycin & another antibiotic
6	Another antibiotic
7	No antibiotics were prescribed
8	sulfamethoxazole/trimethorpim
9	penicillin
10	amoxicillin
11	doxycycline
12	clindamycin
13	erythromycin
14	cefpodoxiome
15	amoxicillin/clavulanate
16	ciprofloxacin
17	cephalexin

2b. Specify which antibiotic prescribed (only if 2a response is D or E or F) ***abxspe***
(Only enter text if abx = 4 or 5 or 6)

3. Prescribed length of antibiotic therapy: _____ days ***abxleng***

4. Does the patient have a documented drug allergy to the following antibiotics?
a. **0 (no) or 1 (yes)** Penicillins (penicillin, amoxicillin, amoxicillin-clavulonic acid) ***allpen***
b. **0 (no) or 1 (yes)** Cephalosporins (cephalexin, cefuroxime, ceftazidime, ceftriaxone) ***allcef***
c. **0 (no) or 1 (yes)** Sulfonamides (sulfamethoxazole, trimethorpim) ***allsulf***
d. **0 (no) or 1 (yes)** Macrolides (azithromycin, clarithromycin, erythromycin ***allmac***
e. **0 (no) or 1 (yes)** Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin) ***allquin***
f. **0 (no) or 1 (yes)** Tetracyclines (doxycycline, tetracycline) ***alltet***
g. **0 (no) or 1 (yes)** Other ***alloth***
0 (no) or 1 (yes) Clindamycin ***allclind***
0 (no) or 1 (yes) Ophthalmic ***alloph***

4b. Specify antibiotics to which patient is allergic (only if 4a response is G) ***allspe***
(Only enter text if alloth = 1)

APPENDIX B (Continued)

VARIABLE KEY

5. Is the patient a current smoker? ***smok***
Appendix B

0 (no) or 1 (yes)

6a. Which of the following was the patient's clinical diagnosis? ***diag***

1	Sinusitis
2	Bronchitis
3	Pharyngitis
4	Pneumonia
5	Acute respiratory tract infection
6	Unspecified
9	Other
7	Tonsillitis
8	Influenza
10	Epiglottitis
11	Laryngitis

6b. Please specify other diagnosis (only if 6a response is G) ***diagspe***
(Only enter text if diag = 9)

7. Symptoms

7a.	**0 (no) or 1 (yes)**	Cough	***sxcough***
7b.	**0 (no) or 1 (yes)**	Sputum production	***sxsput***
7c.	**0 (no) or 1 (yes)**	Congestion	***sxcong***
7d.	**0 (no) or 1 (yes)**	Nasal discharge	***sxnas***
7e.	**0 (no) or 1 (yes)**	Subjective fever	***sxfever***
7f.	**0 (no) or 1 (yes)**	Subjective chills	***sxchill***
7g.	**0 (no) or 1 (yes)**	Unilateral facial pain	***sxface***
7h.	**0 (no) or 1 (yes)**	Malaise	***sxmal***
7i.	**0 (no) or 1 (yes)**	Myalgia and/or arthralgia	***sxmyarth***
7j.	**0 (no) or 1 (yes)**	Thoracic pain	***sxthor***
7k.	**0 (no) or 1 (yes)**	Dyspnea	***sxdysp***
7l.	**0 (no) or 1 (yes)**	Vomiting	***sxvom***
7m.	**0 (no) or 1 (yes)**	Diarrhea	***sxdiar***

8. Signs

8a.	**0 (no) or 1 (yes)**	Fever ≥ 101.5	***snfever***
8b.	**0 (no) or 1 (yes)**	General impression of "ill-appearing"	***snill***
8c.	**0 (no) or 1 (yes)**	Purulent nasal drainage	***snnas***
8d.	**0 (no) or 1 (yes)**	Maxillary/frontal sinus tender percussion or palpation	***snsinus***
8e.	**0 (no) or 1 (yes)**	Focal auscultatory abnormality on chest exam	***snausc***

VARIABLE KEY

8f. **0 (no) or 1 (yes)** Focus percussion abnormality on chest exam ***snperc***

9a. Was a chest x-ray (CXR) ordered? ***cxr***
0 (no) or 1 (yes)

9b. If a CXR was performed, were focal radiographic signs present? ***cxrfoc***
Appendix B

0 (no) or 1 (yes)
(Only enter number if cxr = 1)

10a. Was a White blood count (WBC) performed? ***wbc***
0 (no) or 1 (yes)

10b. If a WBC was performed, what was the result? _____ ***wbcrslt***
(Only enter decimal (to tenths) if wbc = 1)

11a. Was a culture performed? ***cx***
0 (no) or 1 (yes)

11b. If a culture was performed, from what site was the sample taken? _____ ***cxsite***
(Only enter text if cx = 1)

11c. If a culture was performed, what was the result? _____ ***cxrslt***
(Only enter text if cx = 1)

12. Were inhalational steroids prescribed? ***rxinster***
0 (no) or 1 (yes)

13. Was guanefesin prescribed? ***rxguan***
0 (no) or 1 (yes)

14. Was pseudoephedrine prescribed? ***rxpseud***
0 (no) or 1 (yes)

15. Was albuterol or ipratropium inhaler prescribed? ***rxalbipr***
0 (no) or 1 (yes)

16. Was an antihistamine prescribed? ***rxanti***
0 (no) or 1 (yes)

17. Was an oral/pharyngeal anesthetic prescribed? ***rxanes***

APPENDIX B (Continued)

VARIABLE KEY

0 (no) or 1 (yes)

18. Was nasal saline prescribed? ***rxsal***
0 (no) or 1 (yes)

19. Was a systemic steroid prescribed? ***rxsysster***
0 (no) or 1 (yes)

20. Were eye drops prescribed? ***rxeye***
0 (no) or 1 (yes)

21. Did the patient return for this problem within 14 days? ***ltrworse***
0 (no) or 1 (yes)

22. Was the patient admitted within 14 days with pneumonia? ***ltrpneu***
0 (no) or 1 (yes)

23. Did the patient die within 30 days of initial visit? ***ltrdie***
0 (no) or 1 (yes)

24. Did the patient require antibiotics within the next 14 days? ***ltrabx***
0 (no) or 1 (yes)

25. Did the patient have any further documented problems related to this visit? ***ltrfurth***
0 (no) or 1 (yes)

26. Rapid strep test ordered Y/N

APPENDIX C

Practice Guidelines

Practice Guidance for Judicious Use of Antibiotics

Acute Sinusitis / Rhinosinusitis -- Adults

URI symptoms with mucopurulent discharge

<10 DAYS DURATION (UNLESS SEVERE SYMPTOMS)

Purulent nasal secretions or sputum do not predict bacterial infection.

Most cases of acute rhinosinusitis seen as outpatients are caused by uncomplicated viral upper respiratory infection.

Antibiotic treatment of adults with non-specific URI does not improve symptoms or prevent complications.

Management

Symptomatic measures include:

- Avoid cigarette smoke
- Drink plenty of liquids
- Steam (e.g., showers or baths) to loosen secretions
- Warm facial packs for 5-10 minutes 3-4 times a day to promote drainage
- Saline nasal spray or drops may provide some relief
- Acetaminophen or ibuprofen as needed for fever or pain
- Adequate rest
- Elevate head of bed to promote sinus drainage

SPECIFIC SYMPTOMS OF SINUSITIS OF ANY DURATION OR SYMPTOMS >10 DAYS WITHOUT IMPROVEMENT

Purulent nasal discharge for 3-4 days
Unilateral facial pressure/pain
Maxillary toothache
Worsening of symptoms after initial improvement

Management

Mild disease, no recent antibiotic use*: amoxicillin (1.5 - 4 gm/day**); amoxicillin-clavulanate (1.75 - 4 gm/day**); cefdinir, cefpodoxime or cefuroxime.

Moderate disease or mild disease with recent antibiotic use*:** amoxicillin-clavulanate (4 gm/day); ceftriaxone; gatifloxacin, levofloxacin, or moxifloxacin.

For Type 1 pen-allergic patients (hives or anaphylaxis): TMP/SMX, doxycycline, erythromycin, azithromycin, clarithromycin, or telithromycin.

* For patients with no improvement after 72 hours, consider drugs listed under moderate disease.

** Use higher dose when patient has risk factors for DRSP or in geographic areas where prevalence of DRSP is known to be high.

***For patients with no improvement after 72 hours, consider imaging studies, sinus aspirate or ENT consultation.

These guidelines were produced in collaboration with the Infectious Diseases Society of Oregon.

Oregon Alliance Working for Antibiotic Resistance Education
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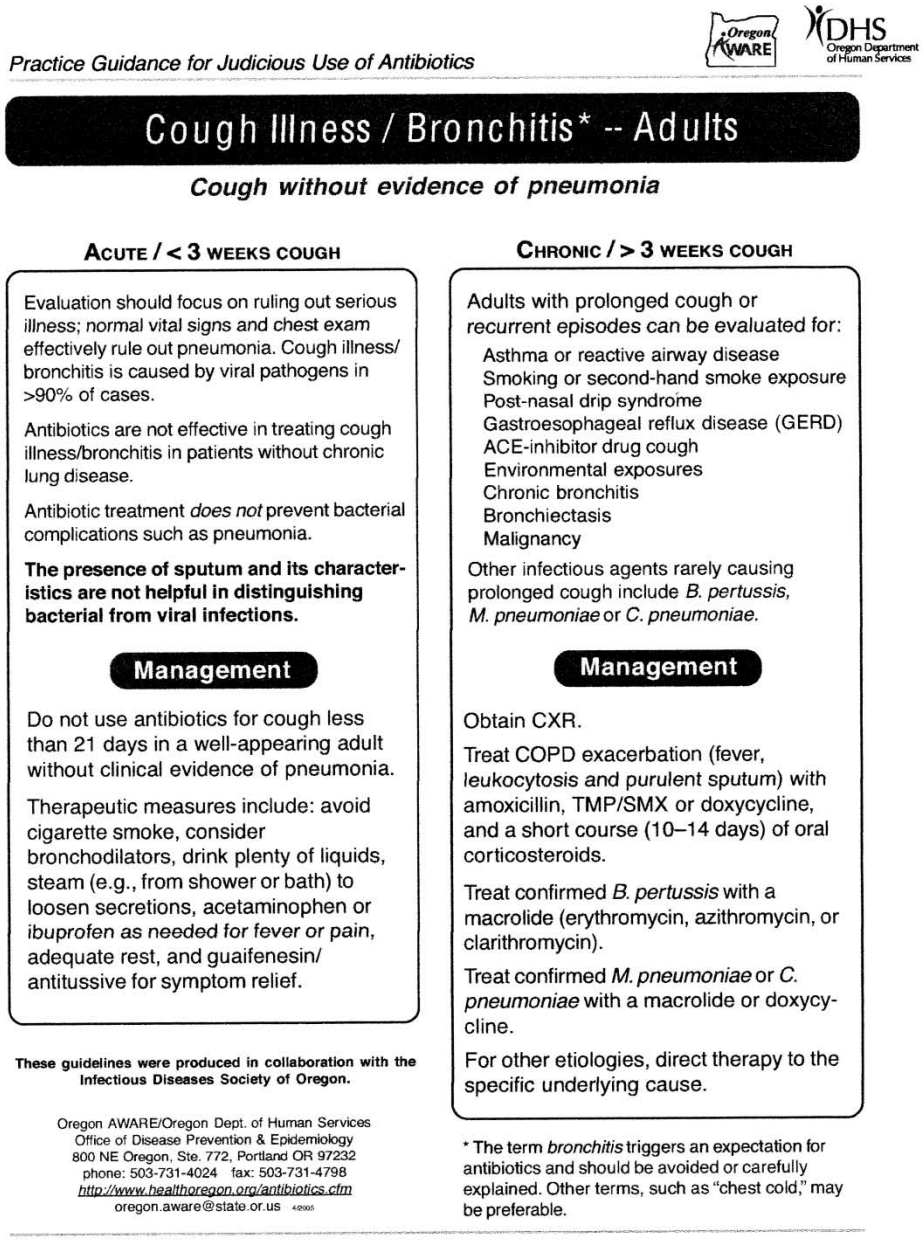
http://www.healthoregon.org/antibiotics.cfm
oregon.aware@state.or.us 4/2005

APPENDIX C (Continued)

Practice Guidelines



Practice Guidance for Judicious Use of Antibiotics

Cough Illness / Bronchitis* -- Adults

Cough without evidence of pneumonia

ACUTE / < 3 WEEKS COUGH

Evaluation should focus on ruling out serious illness; normal vital signs and chest exam effectively rule out pneumonia. Cough illness/ bronchitis is caused by viral pathogens in >90% of cases.

Antibiotics are not effective in treating cough illness/bronchitis in patients without chronic lung disease.

Antibiotic treatment *does not* prevent bacterial complications such as pneumonia.

The presence of sputum and its characteristics are not helpful in distinguishing bacterial from viral infections.

Management

Do not use antibiotics for cough less than 21 days in a well-appearing adult without clinical evidence of pneumonia.

Therapeutic measures include: avoid cigarette smoke, consider bronchodilators, drink plenty of liquids, steam (e.g., from shower or bath) to loosen secretions, acetaminophen or ibuprofen as needed for fever or pain, adequate rest, and guaifenesin/ antitussive for symptom relief.

CHRONIC / > 3 WEEKS COUGH

Adults with prolonged cough or recurrent episodes can be evaluated for:

- Asthma or reactive airway disease
- Smoking or second-hand smoke exposure
- Post-nasal drip syndrome
- Gastroesophageal reflux disease (GERD)
- ACE-inhibitor drug cough
- Environmental exposures
- Chronic bronchitis
- Bronchiectasis
- Malignancy

Other infectious agents rarely causing prolonged cough include *B. pertussis, M. pneumoniae* or *C. pneumoniae.*

Management

Obtain CXR.

Treat COPD exacerbation (fever, leukocytosis and purulent sputum) with amoxicillin, TMP/SMX or doxycycline, and a short course (10–14 days) of oral corticosteroids.

Treat confirmed *B. pertussis* with a macrolide (erythromycin, azithromycin, or clarithromycin).

Treat confirmed *M. pneumoniae* or *C. pneumoniae* with a macrolide or doxycycline.

For other etiologies, direct therapy to the specific underlying cause.

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* The term *bronchitis* triggers an expectation for antibiotics and should be avoided or carefully explained. Other terms, such as "chest cold," may be preferable.

APPENDIX C (Continued)

Practice Guidelines

Practice Guidance for Judicious Use of Antibiotics

Pharyngitis in Children & Adults

Signs and symptoms:

1. Tonsillar exudate 2. Tender anterior cervical lymph nodes 3. Absence of cough 4. Fever

2-4 CRITERIA PRESENT

OBTAIN RAPID STREPTOCOCCAL ANTIGEN TEST

POSITIVE

Group A Streptococcal Pharyngitis Management

Adults: single-dose benzathine penicillin 1.2 m.u. IM *or* penicillin V 500 mg po bid x 10 days.
Pen-allergic adults: erythromycin.

Children <12 years: single-dose benzathine penicillin 25,000 units/kg IM (max. dose 1.2 million units) *or* amoxicillin or penicillin V 45 mg/kg/day po divided bid or tid x 10 days.
Pen-allergic children: erythromycin.

Macrolide use should be discouraged for initial therapy in patients that can tolerate beta-lactams.

Children with streptococcal pharyngitis should not return to school or child care during the first 24 hours after beginning antimicrobial therapy. Follow-up throat culture is not recommended.

NEGATIVE

< 2 CRITERIA PRESENT

DO NOT TEST

Viral Pharyngitis Management

90% of pharyngitis is viral in origin.

Antibiotics benefit only the 10% of cases caused by Group A beta-hemolytic streptococcus.

Symptomatic treatments:
- Avoid cigarette smoke
- Gargle with dilute salt water
- Acetaminophen or ibuprofen as needed for fever or pain
- Throat lozenges (age-appropriate)
- Hydration—drink plenty of liquids
- Adequate rest

*For children, a negative rapid antigen test should be confirmed with a throat culture. Due to the lower incidence of strep infection and acute rheumatic fever in adults, a negative rapid test alone is sufficient to rule out Group A strep infection in adults.**

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*According to Clinical Laboratory Improvement Amendments (CLIA) guidelines, throat culture should be performed if required by the manufacturer.

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