Published in final edited form as:

Diagn Microbiol Infect Dis. 2013 May ; 76(1): 73–79. doi:10.1016/j.diagmicrobio.2013.01.026.

Comparison of Antibigrams Developed for Inpatients and Primary Care Outpatients

Jessina C. McGregor, PhD¹, David T. Bearden, PharmD¹, John M. Townes, MD², Susan E. Sharp, PhD³, Paul N. Gorman, MD⁴, Miriam R. Elman, MPH¹, Motomi Mori, PhD⁵, and David H. Smith, RPh, PhD⁶

¹Department of Pharmacy Practice, College of Pharmacy, Oregon State University/Oregon Health & Science University, Portland, OR, USA

²Division of Infectious Diseases, Department of Medicine, School of Medicine, Oregon Health & Science University, Portland, OR, USA

³Department of Pathology, Regional Laboratory, Kaiser Permanente Northwest, Portland, OR, USA

⁴Department of Medical Informatics and Clinical Epidemiology, School of Medicine, Oregon Health & Science University, Portland, OR, USA

⁵Department of Public Health and Preventive Medicine, School of Medicine, Oregon Health & Science University, Portland, OR, USA

⁶Kaiser Permanente Northwest Center for Health Research, Portland, OR, USA

Abstract

To support antimicrobial stewardship, some healthcare systems have begun creating outpatient antibigrams. We developed inpatient and primary care outpatient antibigrams for a regional health maintenance organization (HMO) and academic healthcare system (AHS). Antimicrobial susceptibilities from 16,428 *Enterococcus*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* cultures from 2010 were summarized and compared. Methicillin susceptibility among *S. aureus* was similar in inpatients and primary care outpatients (HMO: 61.2% vs. 61.9%, $p=0.951$; AHS: 62.9% vs. 63.3%, $p>0.999$). *E. coli* susceptibility to trimethoprim/sulfamethoxazole was also similar (HMO: 81.8% vs. 83.6%, $p=0.328$; AHS: 77.2% vs. 80.9%, $p=0.192$), but ciprofloxacin susceptibility differed (HMO: 88.9% vs. 94.6%, $p<0.001$; AHS: 81.2% vs. 90.6%, $p<0.001$). In the HMO, ciprofloxacin-susceptible *P. aeruginosa* were more frequent in primary care outpatients than inpatients (91.4% vs. 79.0%, $p=0.007$). Comparison of cumulative susceptibilities across settings yielded no consistent patterns; therefore, outpatient primary care antibigrams may more accurately inform prudent empiric antibiotic prescribing.

© 2013 Elsevier Inc. All rights reserved.

Corresponding author and location work was performed: Jessina C. McGregor, PhD, OSU/OHSU College of Pharmacy, 3303 SW Bond Ave., Mail Code: CH12C, Portland, OR 97239, Telephone: 503-494-4722, Fax: 503-494-8797, mcgregoj@ohsu.edu.

Portions of these data were presented at the 51st annual Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago, IL on September 17-20, 2011.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

infectious disease; bacterial resistance; pharmacy practice; ambulatory; antimicrobial stewardship

Introduction

Antimicrobial-resistant infections are now sufficiently endemic in primary care settings that community-based physicians must consider the possibility of resistance when empirically selecting an antibiotic regimen or risk treatment failure and increased morbidity or mortality (Karlowsky et al. 2002; Jones et al. 2003; Tillotson et al. 2008; Hicks et al. 2011). Yet there is a paucity of tools designed specifically to assist community-based providers with optimizing antimicrobial prescribing. This may be due, in part, to the limited epidemiologic data available on antimicrobial resistance in these practice settings. Guidelines and recommendations for the treatment of bacterial infections are largely driven by epidemiologic data collected from hospitalized patients. Given that approximately 126 million antimicrobials are prescribed each year in the ambulatory care setting, more data are needed to support appropriate and prudent prescribing for outpatients (Yawn et al. 2000; McCaig et al. 2003; Hicks et al. 2011; Huttner et al. 2011).

Prior studies have demonstrated that unnecessary prescribing of antibiotics for viral respiratory infections is frequent and comprises up to 55% of all antibiotics prescribed for acute respiratory infections in ambulatory care settings (Gonzales et al. 2001; Hicks et al. 2011; Shapiro et al. 2011). Consequently, public health campaigns and process improvement interventions have focused on reducing unnecessary antibiotic use in these settings (Gonzales et al. 1999; CDC 2012). The use of broad-spectrum agents, such as quinolones and macrolides, are also increasing in ambulatory care settings and account for up to 48% of all adult antibiotic prescriptions and 40% of pediatric prescriptions (Steinman et al. 2003). Excessive use of these antibiotic classes further fuels the evolutionary selective pressures that contribute to the increasing prevalence of antibiotic-resistant bacteria. Yet, far less effort has been placed on improving antibiotic selection when it is warranted.

Many hospitals routinely produce antibiograms, surveillance reports that present cumulative antimicrobial susceptibilities for common bacterial pathogens (Zapantis et al. 2005). The antibiograms are intended to support clinicians in the empiric selection of antimicrobials (i.e., selection of antimicrobial therapy in the absence of microbiology culture results) (MacDougall et al. 2005). Because of differences in disease acuity and healthcare exposures between inpatients and primary care outpatients, surveillance data are unlikely to be generalizable across these two patient settings. Consequently, the use of inpatient surveillance data is unlikely to appropriately inform antimicrobial prescribing in outpatient primary care. For example, if inpatient data overestimated the degree of antimicrobial resistance found in the outpatient setting, clinicians may unnecessarily prescribe second-line agents. Our previous research has demonstrated that in the absence of specific outpatient data, physicians may overestimate the prevalence of resistance (McGregor et al. 2009). Thus, some healthcare systems are beginning to develop separate outpatient antibiograms with the hope of better informing antibiotic prescribing for this setting (Xu et al. 2012).

In this study, we compared the frequency of antimicrobial susceptibility among common bacterial pathogens between inpatients and primary care outpatients. The purpose was to identify clinically meaningful and statistically significant differences that would support the utility of antibiograms constructed explicitly for the primary care outpatient setting. Specifically, we developed and compared antibiograms for inpatients and outpatient primary care patients within the Kaiser Permanente Northwest (KPNW) healthcare system, a

regional health maintenance organization (HMO). Secondly, to assess the generalizability of the observed trends to other healthcare settings, we repeated our efforts using data from an academic healthcare system (AHS) in the same geographic region, Oregon Health & Science University (OHSU) healthcare system.

Methods

Primary patient population

The primary patient population for this study included patients in the Kaiser Permanente Northwest healthcare system. KPNW is a regional, not-for-profit health maintenance organization that serves over 485,000 members in northwest Oregon and southwest Washington. The KPNW system includes one 196-bed hospital and 27 outpatient medical offices. KPNW members may also receive inpatient care at a contracted community hospital, but data from those encounters were not available for analysis in this study. All microbiology cultures are processed centrally at the KPNW Regional Laboratory. The laboratory utilizes the automated Vitek 2 system to perform identification and susceptibility testing and supplements this with disk diffusion testing as per Clinical and Laboratory Standards Institute (CLSI) guidelines for disk diffusion testing.

Inclusion/Exclusion Criteria and Data Collection

Bacterial isolates originating from positive clinical cultures collected from patients during any inpatient or outpatient primary care encounter during 2010 were included in this study. Screening and sterility cultures were excluded, as were respiratory cultures from cystic fibrosis patients. Bronchoalveolar lavage (BAL) and urine cultures with growth less than 10,000 colonies/mL or more than 2 organisms isolated were considered non-significant and excluded from analysis. The microbiology laboratory identified quality sputum culture samples for bacterial culture and antibiotic susceptibility testing by applying the Q234 scoring system to those samples with less than 10 squamous epithelial cells per low powered field (Sharp et al. 2004). Primary care was defined as the general (i.e., non-specialty care) family medicine, internal medicine and pediatrics clinics. Isolates collected from non-primary care outpatient encounters (e.g., emergency department) were excluded. The study population was limited to represent the large, relatively homogenous, primary care population and reduce the influence of the myriad of specialty clinics (e.g., dialysis center, pulmonary clinic, ambulatory surgery centers, and hematology/oncology clinics) that, while ambulatory, include patients with distinctly different risk factor profiles. All data were collected electronically from KPNW's data warehouse and included patient demographics, encounter descriptors, and clinical microbiology records.

Antibiogram development

Separate 2010 antibiograms were created for the KPNW inpatients and primary care outpatients. The organisms selected for inclusion in the antibiograms were: *Staphylococcus aureus*, *Enterococcus* species, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. These organisms were chosen because of their clinical relevance and frequency with which they are isolated in both inpatient and outpatient primary care settings. Antimicrobial susceptibility testing results collected for these organisms were based on the standard clinical protocols for the microbiology laboratory; no additional testing was performed for this study. Disk diffusion methodologies were used as confirmatory testing for MIC/instrumentation testing, and at the time of this study, was also performed for confirmatory testing of extended-spectrum beta-lactamases. D-testing for inducible clindamycin resistance was performed for all *S. aureus* isolates. Nitrofurantoin was only tested in urine isolates; tetracycline for urinary enteric isolates, *Staphylococcus* and *Enterococcus*.

Antibiograms were developed according to the CLSI guidelines (Hindler et al. 2009). Briefly, antimicrobial susceptibility testing results were collapsed into susceptible and non-susceptible (i.e., intermediate-resistance and resistance) categories. Current guidelines recommend against using all isolates to prevent an overestimate of antimicrobial resistance due to repeat culturing of a single infection (Hindler et al. 2009). Consequently, antimicrobial susceptibility data from the first isolate of each species from a given patient in each patient setting per year were used for analysis. These data were aggregated by organism to calculate cumulative antimicrobial susceptibilities (i.e., the frequency of susceptibility) to each of the routinely tested antimicrobials. Note that cumulative susceptibilities are reported only for organisms with a minimum of 30 isolates tested (Hindler et al. 2009). For *S. aureus*, isolates susceptible to oxacillin were identified as methicillin-susceptible *S. aureus* (MSSA), while oxacillin non-susceptible isolates were identified as methicillin-resistant *S. aureus* (MRSA). Cumulative antimicrobial susceptibilities were calculated separately for MSSA and MRSA. Finally, because CLSI released new breakpoints for cephalosporins and carbapenems testing in *E. coli* and *K. pneumoniae* in mid-2010 and laboratory procedures were adapted accordingly, we retroactively applied these new cut-points to ensure interpretative categories were uniformly applied.

Statistical analysis

For each bacterial species and antimicrobial, cumulative susceptibilities were compared between inpatient and primary care outpatient settings with the Fisher's exact test. Differences with a p-value of less than 0.05 were considered significant. All data were managed and analyzed using SAS version 9.2 (SAS Institute, Cary, NC).

Assessment of generalizability of findings

To assess the generalizability of differences identified in frequencies of antimicrobial susceptibilities between inpatients and primary care outpatients at KPNW, we collected data and repeated our analyses in a second patient population from the same geographic region, the Oregon Health & Science University (OHSU) healthcare system. OHSU is an academic healthcare system that serves as a regional referral center for patients from Oregon and neighboring states. In FY2009-10, the OHSU healthcare system had over 800,000 healthcare encounters. The system includes the OHSU hospital and adjoining Doernbecher Children's Hospital, which together comprise 560 beds. OHSU outpatient clinics are located on the main campus and throughout the greater Portland, OR metropolitan area. During the study period, OHSU contracted microbiology laboratory work, including processing of bacterial cultures and antimicrobial susceptibility testing, to the KPNW Regional Laboratory. Similar antibiotic susceptibility testing protocols were applied to isolates collected from OHSU patients. However, tetracycline was tested for urinary *Staphylococcus* and *Enterococcus* isolates, but not for urinary enterics. Using the same inclusion/exclusion criteria, data collection procedures, and analytical methods described above, we compared the frequency of antimicrobial susceptibilities between inpatients and primary care outpatients at OHSU in 2010. Statistical testing was limited to comparisons made within each healthcare system (i.e., KPNW inpatients versus KPNW primary care outpatients; OHSU inpatients versus OHSU primary care outpatients).

Results

Clinical microbiology laboratory data for 13,527 isolates from 12,329 KPNW patients and for 2,901 isolates from 2,440 OHSU patients were included in the analyses. The majority of KPNW patients (92%) were seen in outpatient primary care settings whereas most OHSU patients had encounters in inpatient settings (77%). Regardless of setting, KPNW patients

were predominantly female (64% and 84% for inpatient and outpatient primary care settings, respectively) and white (76% and 59% for inpatient and outpatient primary care settings, respectively). Over 86% of KPNW patients were adults over 18 years old (96% and 86% of inpatients and primary care outpatients, respectively); the mean age of inpatients was 56 years ($SD \pm 21$ years) and of outpatients was 48 years ($SD \pm 24$ years). The demographic composition of OHSU patients was comparable to KPNW. Over half of the OHSU patients were white (89% and 87% for inpatient and outpatient primary care settings, respectively) and female (53% and 81% for inpatient and outpatient primary care settings, respectively). Approximately 83% of OHSU patients were over 18 years old (85% and 76% of inpatients and outpatients, respectively) and the mean age for patients overall was 47 years ($SD \pm 25$ years; for inpatients and outpatients, 49 $SD \pm 24$ years and 41 $SD \pm 26$ years, respectively). Table 1 presents characteristics of the isolates from each healthcare system. At KPNW, *E. coli* accounted for the majority of isolates in both patient settings; the same was true in the OHSU outpatient primary care setting, but among OHSU inpatients *S. aureus* accounted for the majority of isolates. Across all healthcare sites and settings, the majority of microbial isolates included in the analysis originated from urine cultures.

For *Enterococcus* species at KPNW (table 2), the frequency of susceptibility to ampicillin, ciprofloxacin, nitrofurantoin, and vancomycin were significantly lower in the inpatient than outpatient primary care setting ($p = 0.001$ for all). Among OHSU *Enterococcus* isolates, the frequency of susceptibility was significantly less for ampicillin ($p=0.014$), ciprofloxacin ($p=0.010$), and vancomycin ($p=0.070$) in the inpatient setting than the outpatient primary care setting (table 2). While susceptibility to nitrofurantoin was 8.5% lower in the inpatient than outpatient primary care setting, the difference did not achieve significance ($p=0.093$) in OHSU *Enterococcus* isolates (table 2).

The proportion *S. aureus* identified as MSSA was similar in both inpatient and outpatient settings at KPNW (61.2% vs. 60.9%, respectively; $p=0.951$) and at OHSU (62.9% vs. 63.3%, respectively; $p>0.999$). Among MSSA isolates collected in the KPNW system, the only statistically significant difference in antimicrobial susceptibilities identified was for trimethoprim/sulfamethoxazole ($p=0.040$; table 3); however, the difference was small (100% in inpatient setting vs. 98.0% in the outpatient primary care setting). Though it should be noted that the number of inpatient MSSA isolates was low ($n=317$; table 3). In contrast, among OHSU MSSA isolates (table 3), trimethoprim/sulfamethoxazole susceptibilities were similar in inpatient and outpatient primary care settings (98.3% vs. 97.1%, respectively; $p=0.437$) while clindamycin susceptibilities differed significantly (86.7% vs. 94.0%, respectively; $p=0.041$). Among MRSA isolates collected in the KPNW system (table 3), only clindamycin susceptibilities differed significantly between inpatient and outpatient primary care settings (58.1% vs. 89.5%, respectively; $p<0.001$). This difference was similarly observed in MRSA isolates from the OHSU system (60.3% vs. 87.5%, respectively; $p<0.001$; table 3). A statistically significant, but small magnitude, difference was also observed in OHSU MRSA isolates susceptible to trimethoprim/sulfamethoxazole (99.3% in inpatient setting vs. 93.4% in outpatient primary care setting; $p=0.012$).

Among *E. coli* isolated from patients within the KPNW health system (table 4), the frequency of susceptibility differed significantly for cefazolin ($p=0.006$), cephalothin ($p=0.022$), ciprofloxacin ($p<0.001$), and nitrofurantoin ($p<0.001$), though the differences were all within 10%. Within the OHSU system, *E. coli* isolates also differed significantly in cefazolin susceptibilities ($p<0.001$; table 4). *E. coli* isolates collected from OHSU patients were not routinely tested against cephalothin. The frequency of ciprofloxacin susceptibility differed significantly between the inpatient and outpatient primary care setting (81.2% vs. 90.6%, respectively; $p<0.001$). In both the KPNW and OHSU systems (table 4), *E. coli*

susceptibility to trimethoprim/sulfamethoxazole was similar in inpatient and outpatient settings ($p>0.05$ for both).

For *K. pneumoniae* isolates, no significant differences in cumulative susceptibilities between inpatient and outpatient primary care settings were identified for any antimicrobial at either healthcare system (table 5).

For *P. aeruginosa* isolates collected from patients in the KPNW system (table 6), the frequency of susceptibility was significantly lower in the inpatient than outpatient primary care setting for cefepime ($p=0.003$), ceftazidime ($p=0.002$), ciprofloxacin ($p=0.007$), and piperacillin/tazobactam ($p<0.001$). In the OHSU system, fewer than 30 *P. aeruginosa* isolates were isolated and tested in the outpatient setting, thus comparisons between patient settings were not performed.

Discussion

Because increased healthcare exposures and hospitalizations have repeatedly been associated with an increased risk of antimicrobial resistance among patients with bacterial infections, clinicians might surmise that primary care outpatients would have higher frequencies of antimicrobial susceptibility overall than inpatients. Yet, little data exist to support this assumption, especially in light of increasing antimicrobial resistance in the outpatient setting (Hooton et al. 2004; Mera et al. 2009; Lagace-Wiens et al. 2011; Mera et al. 2011). In hospital settings, efforts to increase prudent antimicrobial prescribing have been formalized through the development of antimicrobial stewardship teams. Typically these teams, which include physicians and pharmacists, act to evaluate and intervene upon antimicrobial prescribing to improve prudent and appropriate use (Owens 2008). Outpatient care and other community settings may benefit from similar formalized efforts to increase prudent antimicrobial prescribing. As demonstrated by this study, clinical cultures collected in the outpatient primary care setting are not universally more susceptible to antimicrobials than in the inpatient setting. Consequently, expanded stewardship efforts will require surveillance data specific to the patient population. As the majority of antimicrobial prescribing in community settings is empirical, antibiograms developed specifically for each of these settings has the potential to greatly facilitate prudent antimicrobial use.

We utilized data from two health systems to identify differences and similarities in the proportions of antimicrobial susceptibility among clinical bacterial isolates between inpatient and outpatient primary care settings. For certain organism-antimicrobial combinations, the data indicated that no significant differences existed between inpatients and primary care outpatients. Notably, the proportion of *S. aureus* isolates identified as MRSA was similar between patient settings. This held true for both healthcare systems. Clindamycin-susceptible MRSA, which are typically community-associated MRSA strains, were more frequently identified in the outpatient primary care setting, as may have been anticipated. The outpatient primary care antibiograms for MRSA and MSSA at both healthcare systems indicate that clindamycin-susceptibility is roughly 87% or greater, thus clindamycin might be considered a viable treatment option for suspected *S. aureus* infections in this setting. If only inpatient data were available, however, clindamycin would not likely be considered a reasonable treatment option to cover MRSA as susceptibility was lower than 60% among inpatients.

Overall, *E. coli* was the most frequently isolated organism in the healthcare systems studied. The large number of isolates resulted in a high degree of statistical power to detect even small differences as statistically significant, particularly in the KPNW healthcare setting. While statistical comparisons were primarily considered in this study, the clinical

significance of differences between inpatient and outpatient primary care settings should also be considered; in many scenarios, a difference of 10% may be cause for changes in the initial empiric antibiotic selection (McGregor et al. 2009). Nevertheless, clinically significant differences cannot be simply defined as they incorporate multiple factors such as the absolute values of the cumulative susceptibilities, severity of the illness in question, and the associated risks for treatment failure. For example, cumulative susceptibilities of 100% and 90%, while representing a 10% difference, will likely not impact prescribing in most scenarios. Generally, when statistically and clinically significant differences were observed, they were observed for the same organism-antimicrobial combinations in both healthcare systems. While the observed differences in susceptibilities may not be generalizable to all geographic regions or healthcare settings, these data support the potential utility of developing antibiograms specific to outpatient primary care and likely other community settings.

In this study, statistically significant differences were observed in the frequency of *E. coli* susceptibility to cefazolin, cephalothin, ciprofloxacin, and nitrofurantoin between KPNW inpatients and primary care outpatients. Susceptibility to ciprofloxacin is of particular interest, as the majority of the *E. coli* isolates were from the urinary tract (data not shown) where fluoroquinolone use is common. While statistically significant differences were not identified for trimethoprim/sulfamethoxazole-susceptibility, the differences within the OHSU system may be clinically relevant. Guidelines for the treatment of uncomplicated cystitis recommend avoiding trimethoprim/sulfamethoxazole in populations where resistance exceeds 20% (Gupta et al. 2011). While resistance exceeded 20% in the OHSU inpatient setting, among OHSU primary care outpatients resistance to trimethoprim/sulfamethoxazole had reached but not exceeded 20%. Thus, trimethoprim/sulfamethoxazole may still be considered by some providers as a potential empiric treatment option in this setting. While some may interpret this resistance level as a one in five likelihood that empiric therapy would not provide adequate coverage, it is important to recognize that antibiogram data are never used in isolation for the selection of empiric therapy. The patient's history of antibiotic use and past infections also guide antibiotic selection. Thus, direct extrapolations of the probability of treatment failure cannot be made. This highlights the need for further research aimed at supporting empiric antibiotic selection.

While similarities in susceptibility results among inpatient and primary care outpatient settings were observed, failure to use a specific outpatient antibiogram may unnecessarily limit empiric choices. For example, in the HMO setting *P. aeruginosa* exhibited significantly more favorable ciprofloxacin susceptibility in outpatients. While 79.0% ciprofloxacin susceptibility in inpatients may temper empiric ciprofloxacin selection when compared to the myriad of other options, fluoroquinolones are vitally important in outpatient settings as the only orally available option (i.e., ciprofloxacin and levofloxacin) for treatment of systemic infections with *P. aeruginosa*. Our observation of a much more acceptable 91.4% susceptibility among outpatients might allow clinicians to more comfortably empirically select of this oral option instead of the more difficult to administer intravenous-only options.

In interpreting the results of this study, it should be noted that not all infections are cultured and that the likelihood of collecting a microbiology culture specimen from a patient is dependent on multiple factors, including the clinical setting. Variation in the frequency of microbiology culture collection may lead to biased estimates of the cumulative antimicrobial susceptibilities and differences between settings; however, the magnitude and direction of this bias cannot be assessed from these data. Another limitation to this study was that the inpatient antibiograms included information on isolates from all inpatients, including intensive care unit (ICU) patients. Further work is needed to compare antibiotic

susceptibility patterns between bacterial isolates collected from specific sub-populations such as ICU patients.

The potential utility of providing clinicians with population-specific antibiograms to facilitate empiric antimicrobial selection could be further expanded if threshold values relating to patient outcomes could be better quantified. As part of an earlier study, we surveyed physicians to identify how their empiric choice of antimicrobial therapy for a pediatric outpatient presenting with skin abscess might change given varying frequencies of MRSA. In that study, the majority of clinicians altered their choice of therapy to cover MRSA after the frequency of methicillin resistance reached 30% among *S. aureus* isolates (McGregor et al. 2009). Yet this threshold value cannot be generalized to all infections and settings. A prior study by Metlay et al. surveyed prescribers to identify factors that influenced the use of a hypothetical new antimicrobial for community-associated pneumonia due to *Streptococcus pneumoniae*. In addition to the prevalence of antimicrobial resistance, the authors identified that disease severity and physician specialty impacted therapy choice (Metlay et al. 2002). While knowledge of these threshold values can inform antimicrobial stewardship teams as they work to intervene on the prescriber decision-making process, additional data is needed to relate the frequency of susceptibility to antimicrobials with empiric antimicrobial therapy selection and patient outcomes.

While significant efforts have been focused on reducing unnecessary antimicrobial prescribing in primary care, far less effort has been directed towards improving the prudent use of antimicrobials when their use is warranted. The development of antibiograms for the primary care outpatient setting may further promote prudent antimicrobial use by facilitating the implementation of antimicrobial stewardship activities beyond acute care settings by informing local order sets, prescribing policies, etc. To achieve the larger goal of limiting the emergence of antimicrobial resistance, stewardship efforts must concentrate on increasing judicious antimicrobial prescribing in both institutional and community settings. This study demonstrates that outpatient primary care antibiograms provide unique information compared to inpatient antibiograms, and the frequency of antimicrobial susceptibility cannot be expected to be uniformly higher in the primary care outpatient setting for all antimicrobials and organisms. Thus, development of outpatient primary care specific antibiograms may be a relatively important tool for enhancing prescribers' ability to prudently select empiric antimicrobial therapy for outpatients in the primary care setting.

Acknowledgments

Financial support. This project was supported by award number KL2RR024141 from the National Center for Research Resources, National Institutes of Health and by a New Investigator Program award from the American Association of Colleges of Pharmacy.

The authors would like to thank Christiane Winter and Phillip Crawford for assisting with data acquisition and Kathy Pearson for project management.

References

- Centers for Disease Control and Prevention; National Center for Immunization and Respiratory Diseases; Division of Bacterial Diseases. Get Smart: Know When Antibiotics Work. 2012. Retrieved April 5, 2012, from www.cdc.gov/getsmart
- Gonzales R, Malone DC, Maselli JH, Sande MA. Excessive antibiotic use for acute respiratory infections in the United States. *Clin Infect Dis.* 2001; 33(6):757–762. [PubMed: 11512079]
- Gonzales R, Steiner JF, Lum A, Barrett PH Jr. Decreasing antibiotic use in ambulatory practice: impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults. *Jama.* 1999; 281(16):1512–1519. [PubMed: 10227321]

- Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the infectious diseases society of america and the European society for microbiology and infectious diseases. *Clin Infect Dis*. 2011; 52(5):e103–120. [PubMed: 21292654]
- Hicks LA, Chien YW, Taylor TH Jr, Haber M, Klugman KP. Outpatient Antibiotic Prescribing and Nonsusceptible *Streptococcus pneumoniae* in the United States, 1996–2003. *Clin Infect Dis*. 2011; 53(7):631–639. [PubMed: 21890767]
- Hindler, JF.; Barton, M.; Callihan, DR.; Erdman, SM.; Evangelista, AT.; Jenkins, SG.; Johnston, J.; Master, R.; McGowan, J.; John, E.; Nimmo, G.; Stelling, J. Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data; Approved Guideline--Third Edition (M39-A3). Wayne, PA: Clinical and Laboratory Standards Institute; 2009. p. 26
- Hooton TM, Besser R, Foxman B, Fritsche TR, Nicolle LE. Acute uncomplicated cystitis in an era of increasing antibiotic resistance: a proposed approach to empirical therapy. *Clin Infect Dis*. 2004; 39(1):75–80. [PubMed: 15206056]
- Huttner B, Samore M. Outpatient antibiotic use in the United States: time to get smarter. *Clin Infect Dis*. 2011; 53(7):640–643. [PubMed: 21890768]
- Jones ME, Karlowsky JA, Draghi DC, Thornsberry C, Sahm DF, Nathwani D. Epidemiology and antibiotic susceptibility of bacteria causing skin and soft tissue infections in the USA and Europe: a guide to appropriate antimicrobial therapy. *Int J Antimicrob Agents*. 2003; 22(4):406–419. [PubMed: 14522104]
- Karlowsky JA, Kelly LJ, Thornsberry C, Jones ME, Sahm DF. Trends in antimicrobial resistance among urinary tract infection isolates of *Escherichia coli* from female outpatients in the United States. *Antimicrob Agents Chemother*. 2002; 46(8):2540–2545. [PubMed: 12121930]
- Lagace-Wiens PR, Simner PJ, Forward KR, Tailor F, Adam HJ, Decorby M, Karlowsky J, Hoban DJ, Zhanel GG. Analysis of 3789 in- and outpatient *Escherichia coli* isolates from across Canada--results of the CANWARD 2007–2009 study. *Diagn Microbiol Infect Dis*. 2011; 69(3):314–319. [PubMed: 21353959]
- MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. *Clin Microbiol Rev*. 2005; 18(4):638–656. PMC1265911. [PubMed: 16223951]
- McCaig LF, Besser RE, Hughes JM. Antimicrobial drug prescription in ambulatory care settings, United States, 1992–2000. *Emerg Infect Dis*. 2003; 9(4):432–437. [PubMed: 12702222]
- McGregor JC, Dumyati G, Casiano-Colon AE, Chang PJ, Klevens RM. Usefulness of antibiogram surveillance for methicillin-resistant *Staphylococcus aureus* in outpatient pediatric populations. *Diagn Microbiol Infect Dis*. 2009; 64(1):78–83.
- Mera RM, Miller LA, Amrine-Madsen H, Sahm DF. The impact of the pneumococcal conjugate vaccine on antimicrobial resistance in the United States since 1996: evidence for a significant rebound by 2007 in many classes of antibiotics. *Microb Drug Resist*. 2009; 15(4):261–268. [PubMed: 19857132]
- Mera RM, Suaya JA, Amrine-Madsen H, Hoge CS, Miller LA, Lu EP, Sahm DF, O'Hara P, Acosta CJ. Increasing role of *Staphylococcus aureus* and community-acquired methicillin-resistant *Staphylococcus aureus* infections in the United States: a 10-year trend of replacement and expansion. *Microb Drug Resist*. 2011; 17(2):321–328. [PubMed: 21417776]
- Metlay JP, Shea JA, Asch DA. Antibiotic prescribing decisions of generalists and infectious disease specialists: thresholds for adopting new drug therapies. *Med Decis Making*. 2002; 22(6):498–505. [PubMed: 12458980]
- Owens RC Jr. Antimicrobial stewardship: concepts and strategies in the 21st century. *Diagn Microbiol Infect Dis*. 2008; 61(1):110–128. [PubMed: 18384997]
- Shapiro DJ, Gonzales R, Cabana MD, Hersch AL. National trends in visit rates and antibiotic prescribing for children with acute sinusitis. *Pediatrics*. 2011; 127(1):28–34. PMC3010093. [PubMed: 21187311]
- Sharp, SE.; Robinson, A.; Saubolle, M.; SCM; Carroll, K.; Baselski, V. Cumitech 7B, Lower Respiratory Tract Infections. S. E. Sharp; Washington D.C: 2004.

- Steinman MA, Gonzales R, Linder JA, Landefeld CS. Changing use of antibiotics in community-based outpatient practice, 1991–1999. *Ann Intern Med.* 2003; 138(7):525–533. [PubMed: 12667022]
- Tillotson GS, Draghi DC, Sahm DF, Tomfohrde KM, Del Fabro T, Critchley IA. Susceptibility of *Staphylococcus aureus* isolated from skin and wound infections in the United States 2005–07: laboratory-based surveillance study. *J Antimicrob Chemother.* 2008; 62(1):109–115. [PubMed: 18397923]
- Xu R, Polk RE, Stencel L, Lowe DK, Guharoy R, Duggal RW, Wiest M, Putney KS, Flint NB. Antibigram compliance in University HealthSystem Consortium participating hospitals with Clinical and Laboratory Standards Institute guidelines. *Am J Health Syst Pharm.* 2012; 69(7):598–606. [PubMed: 22441793]
- Yawn BP, Wollan P, Cockerill F, Lydick E. Antibiotic bacterial resistance in ambulatory patients. *Minn Med.* 2000; 83(10):53–58. [PubMed: 11059252]
- Zapantis A, Lacy MK, Horvat RT, Grauer D, Barnes BJ, O’Neal B, Couldry R. Nationwide antibiogram analysis using NCCLS M39-A guidelines. *J Clin Microbiol.* 2005; 43(6):2629–2634. [PubMed: 15956376]

Table 1

Characteristics of microbiology isolates analyzed

	KPNW Isolates ^a		OHSU Isolates ^a	
	Inpatient (n=1087)	Outpatient Primary Care (n=12440)	Inpatient (n=2282)	Outpatient Primary Care (n=619)
Species				
<i>Enterococcus</i> spp. ^b	152 (14.0)	626 (5.0)	480 (21.0)	55 (8.9)
<i>E. faecium</i>	2 (0.2)	0 (0.0)	12 (0.5)	0 (0.0)
<i>E. faecalis</i>	21 (1.9)	8 (<0.1)	85 (3.7)	0 (0.0)
<i>Non-speciated</i>	129 (11.9)	618 (5.0)	383 (16.8)	55 (8.9)
<i>Staphylococcus aureus</i>	318 (29.3)	2171 (17.5)	739 (32.4)	167 (27.0)
<i>Escherichia coli</i>	452 (41.6)	8555 (68.8)	636 (27.9)	340 (54.9)
<i>Klebsiella pneumoniae</i>	87 (8.0)	866 (7.0)	220 (9.6)	45 (7.3)
<i>Pseudomonas aeruginosa</i>	78 (7.2)	222 (1.8)	207 (9.1)	12 (1.9)
Culture Source				
Urine	578 (53.2)	10212 (82.1)	964 (42.2)	445 (71.9)
Wound	235 (21.6)	2135 (17.2)	466 (20.4)	154 (24.9)
Blood	53 (4.9)	19 (0.2)	268 (11.7)	1 (0.2)
Respiratory	88 (8.1)	11 (0.1)	303 (13.3)	0 (0.0)
Sputum	8 (0.7)	11 (0.1)	299 (13.1)	0 (0.0)
BAL	4 (0.4)	0 (0.0)	3 (0.1)	0 (0.0)
Other respiratory cultures	76 (7.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Tissue	98 (9.0)	0 (0.0)	182 (8.0)	0 (0.0)
Other ^c	35 (3.2)	63 (0.5)	99 (4.3)	19 (3.1)

KPNW = Kaiser Permanente Northwest; OHSU = Oregon Health & Sciences University; BAL = bronchoalveolar lavage.

^aData are no. (%) of isolates analyzed for each setting and institution.^b*Enterococcus* isolates were only routinely speciated if isolated from a sterile source or vancomycin resistant.^cOther includes cultures from body fluid, catheter tip, ear, eye, joint fluid, nasal, sinus, cerebrospinal fluid, and continuous ambulatory peritoneal dialysis.

Table 2

Frequency of susceptibility to antimicrobials for *Enterococcus* species, 2010

Antimicrobial	KPNW Antibiogram ^{a,b}				OHSU Antibiogram ^{b,c}			
	Inpatient (%)	Outpatient (%)	No. tested	p-value ^d	Inpatient (%)	Outpatient (%)	No. tested	p-value ^d
Ampicillin	84.9	97.3	777	<0.001	84.6	96.4	535	0.014
Ciprofloxacin	60.6	84.5	711	<0.001	67.9	85.2	356	0.010
Nitrofurantoin	86.3	95.4	709	0.001	87.7	96.2	354	0.093
Tetracycline	20.6	19.3	709	0.787	22.9	25.9	355	0.605
Vancomycin	87.5	98.9	778	<0.001	87.9	96.4	535	0.070

KPNW = Kaiser Permanente Northwest; OHSU = Oregon Health & Sciences University.

^a A total of 152 inpatient and 626 outpatient isolates were tested for susceptibilities for KPNW.^b Percentages are those isolates susceptible to the specified antimicrobial.^c A total of 480 inpatient and 55 outpatient isolates were tested for susceptibilities for OHSU.^d P-values are for comparisons between inpatient and outpatient settings within each institution.

Table 3

Frequency of susceptibility to antimicrobials for *Staphylococcus aureus*, 2010

Antimicrobial	KPNW Antibigram ^{a,b}				OHSU Antibigram ^{b,c}			
	Inpatient (%)	Outpatient (%)	No. tested	p-value ^d	Inpatient (%)	Outpatient (%)	No. tested	p-value ^d
<i>All Staphylococcus aureus</i>								
Oxacillin	61.2	60.9	2474	0.951	62.9	63.3	899	>0.999
Methicillin-Susceptible <i>Staphylococcus aureus</i> (MSSA)								
Cefazolin	100.0	100.0	1515	NA	100.0	100.0	561	NA
Clindamycin ^e	84.7	88.6	1427	0.118	86.7	94.0	543	0.041
Erythromycin	71.4	70.4	1426	0.798	74.7	67.0	543	0.133
Tetracycline	96.9	96.1	1506	0.691	96.5	97.1	565	>0.999
Trimethoprim/Sulfamethoxazole	100.0	98.0	1516	0.040	98.3	97.1	566	0.437
Vancomycin	100.0	100.0	1515	NA	100.0	100.0	565	NA
Methicillin-Resistant <i>Staphylococcus aureus</i> (MRSA)								
Cefazolin	0.0	0.0	972	NA	0.0	0.0	330	NA
Clindamycin ^e	58.1	89.5	926	<0.001	60.3	87.5	318	<0.001
Erythromycin	7.7	9.6	927	0.612	8.4	12.5	318	0.315
Tetracycline	92.7	95.6	966	0.171	97.8	98.4	332	>0.999
Trimethoprim/Sulfamethoxazole	100.0	98.1	971	0.246	99.3	93.4	333	0.012
Vancomycin	100.0	100.0	971	NA	100.0	100.0	333	NA

KPNW = Kaiser Permanente Northwest; OHSU = Oregon Health & Sciences University; NA = not applicable.

^a A total of 317 inpatient and 2157 outpatient isolates were tested for susceptibilities for KPNW.^b Percentages are those isolates susceptible to the specified antimicrobial.^c A total of 733 inpatient and 166 outpatient isolates were tested for susceptibilities for OHSU.^d P-values are for comparisons between inpatient and outpatient settings within each institution.^e D-test for inducible clindamycin resistance performed for all *S. aureus*

Table 4

Frequency of susceptibility to antimicrobials for *Escherichia coli*, 2010

Antimicrobial	KPNW Antibiogram ^{a,b}				OHSU Antibiogram ^{b,c}			
	Inpatient (%)	Outpatient (%)	No. tested	p-value ^d	Inpatient (%)	Outpatient (%)	No. tested	p-value ^d
Ampicillin	63.8	66.3	8993	0.283	55.4	67.1	976	<0.001
Amoxicillin/Clavulanate ^e	61.3	61.6	3056	>0.999	-	-	-	-
Cefazolin	87.3	91.3	8916	0.006	80.6	92.9	973	<0.001
Cephalothin ^e	65.2	70.9	8820	0.022	-	-	-	-
Ciprofloxacin	88.9	94.6	9006	<0.001	81.2	90.6	973	<0.001
Gentamicin	95.8	96.9	9005	0.212	93.7	94.1	976	0.889
Nitrofurantoin	93.8	97.7	8854	<0.001	96.3	96.1	792	>0.999
Tetracycline ^e	78.7	82.4	8828	0.081	-	-	-	-
Tobramycin	95.6	97.1	9006	0.063	93.4	94.7	976	0.485
Trimethoprim/Sulfamethoxazole	81.8	83.6	8981	0.328	77.2	80.9	976	0.192

KPNW = Kaiser Permanente Northwest; OHSU = Oregon Health & Sciences University.

^a A total of 452 inpatient and 8555 outpatient isolates were tested for susceptibilities for KPNW.^b Percentages are those isolates susceptible to the specified antimicrobial.^c A total of 636 inpatient and 340 outpatient isolates were tested for susceptibilities for OHSU.^d P-values are for comparisons between inpatient and outpatient settings within each institution.^e Numbers not shown where less than 30 specimens received susceptibility testing.

Table 5

Frequency of susceptibility to antimicrobials for *Klebsiella pneumoniae*, 2010

Antimicrobial	KPNW Antibigram ^{a,b}				OHSU Antibigram ^{b,c}			
	Inpatient (%)	Outpatient (%)	No. tested	p-value ^d	Inpatient (%)	Outpatient (%)	No. tested	p-value ^d
Amoxicillin/Clavulanate ^e	96.5	98.9	900	0.150	-	-	-	-
Cefazolin	97.7	97.6	949	>0.999	93.6	95.6	265	>0.999
Cephalothin ^e	96.5	95.8	898	>0.999	-	-	-	-
Ciprofloxacin	97.7	98.6	952	0.371	95.9	95.5	264	>0.999
Gentamicin	100.0	99.3	953	>0.999	98.2	100.0	264	>0.999
Nitrofurantoin	32.8	28.6	902	0.549	21.0	23.3	167	0.830
Tetracycline ^e	86.0	89.1	899	0.511	-	-	-	-
Tobramycin	98.9	98.9	953	>0.999	98.2	100.0	264	>0.999
Trimethoprim/Sulfamethoxazole	96.6	92.8	952	0.264	94.1	93.3	265	0.740

KPNW = Kaiser Permanente Northwest; OHSU = Oregon Health & Sciences University.

^a A total of 87 inpatient and 866 outpatient isolates were tested for susceptibilities for KPNW.^b Percentages are those isolates susceptible to the specified antimicrobial.^c A total of 220 inpatient and 45 outpatient isolates were tested for susceptibilities for OHSU.^d P-values are for comparisons between inpatient and outpatient settings within each institution.^e Numbers not shown where less than 30 specimens received susceptibility testing.

Table 6Frequency of susceptibility to antimicrobials for *Pseudomonas aeruginosa*, 2010^a

Antimicrobial	KPNW Antibigram ^{b,c,d}			p-value ^e
	Inpatient (%)	Outpatient (%)	No. tested	
Cefepime	87.0	96.8	298	0.003
Ceftazidime	85.9	96.4	300	0.002
Ciprofloxacin	79.0	91.4	297	0.007
Gentamicin	87.0	90.9	296	0.380
Imipenem	93.4	96.8	293	0.310
Meropenem	95.6	98.5	270	0.170
Piperacillin/Tazobactam	85.7	97.3	297	<0.001
Tobramycin	97.4	98.2	300	0.652
Trimethoprim/Sulfamethoxazole	1.3	0.0	298	0.262

KPNW = Kaiser Permanente Northwest; OHSU = Oregon Health & Sciences University.

^aNumbers are not shown for OHSU as less than 30 outpatient primary care specimens were received for susceptibility testing^bPercentages are those isolates susceptible to the specified antimicrobial.^dA total of 78 inpatient and 222 outpatient isolates were tested for susceptibilities for KPNW.^eP-values are for comparisons between inpatient and outpatient settings within the institution.