Improving Empirical Antibiotic Therapy with a Healthcare-Associated UTI Combination Antibiogram

A Senior Honors Thesis for the Department of Biology

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Abstract

One in 25 patients in acute care hospitals develops a healthcare-associated infection (HAI), and one of the most prevalent HAIs is urinary tract infection (HA-UTI). Initial treatment before the pathogen is identified, called empirical therapy, frequently consists of ineffective or sub-optimal antibiotics. Antibiotic resistance makes effective empirical therapy challenging, and misused empirical antibiotics can contribute to the crisis. Antimicrobial stewardship is the practice of ensuring optimal antibiotic usage to improve clinical outcomes and decrease adverse effects. One tool of antimicrobial stewardship is the use of an antibiogram—a table of antibiotic resistance at the hospital—for guiding adequate and appropriate empirical therapy.

We created an antibiogram for 2013 HA-UTI bacterial isolates for single and dual antibiotic combinations (n=235), and refined it to create antibiograms specific for isolates collected from patients with urinary catheters (n=83), and with documented symptoms (n=74). All antibiograms had similar organism distributions and resistance patterns, and differed considerably from the traditional antibiogram. The novel antibiograms indicated the optimal regimen was a combination of cefepime and vancomycin, which had a substantially higher percentage of susceptible isolates than the current recommendation for HA-UTI, cefepime alone. We confirmed these results by analyzing 2014 patients with empirical HA-UTI therapy (n=108). In this sample, the percent of isolates susceptible to cefepime with vancomycin was significantly greater than that of cefepime alone ($p \leq 0.001$), and that of prescribed empirical antibiotics ($p \leq 0.001$). These results indicate that the use of this novel antibiogram could increase effective empirical therapy of HA-UTI, and potentially other infections.

Introduction

Healthcare-Associated Infections

A healthcare-associated infection (HAI) is an infection occurring during hospitalization, without any indication of existence or incubation at the time of admission.[1] HAIs are the foremost complication of hospitalization,[2] posing troublesome and even life-threatening consequences for the patient, and immense challenges for healthcare facilities, and the nation.[3]

Certain device and procedure-associated HAIs are reported by over 13,000 hospitals to the National Healthcare Safety Network (NHSN), the HAI surveillance system of the Centers for Disease Control and Prevention (CDC).[4] However, since most types of infection are not tracked, the true magnitude of HAIs in the U.S. is unknown. To estimate the total number of national HAIs, the CDC conducted a point-prevalence survey in 2011 with 183 acute care hospitals in 10 states.[5] The survey revealed that one out of 25 patients developed an infection as a result of hospitalization, indicating an annual rate of 721,800 HAIs in the U.S.[5] The survey also found a high case fatality rate of 11.5%, indicating a considerable national HAI mortality.[5]

The two most frequent types of infection in the study were pneumonia and surgical site infection, each comprising 21.8% of all HAIs, followed by gastrointestinal infection at 17.1% and UTI at 12.9%.[5] However, other evaluations have found that UTIs comprise at least one third of HAIs.[6,7] To update the estimates of these principal infections, in 2013 the CDC published a progress report of HAIs in acute care hospitals. Six infection types were tracked: central-line associated bloodstream infection, surgical site infection, hospital-onset *C. difficile* infection,

hospital-onset methicillin resistant *Staphylococcus aureus* bloodstream infection, and catheter-associated UTI (CA-UTI).[4] There was a significant reduction on a national level of each infection type except CA-UTI, which increased 6% between 2009 and 2013.[4] Indwelling urinary catheters—tubes inserted through the urethra to the bladder for draining urine—increase a patient's risk of infection, and 75% of HA-UTIs are estimated to be CA-UTIs.[8]

Urinary Tract Infections and Asymptomatic Bacteriuria

A UTI is defined as an inflammatory reaction of the urothelium in response to microorganisms in the urinary tract,[11] which is comprised of the urethra, bladder, ureters, and kidney.[12] UTI is classified by anatomical location, and by the severity of the infection as either uncomplicated or complicated.[13] Lower UTI affects the bladder (cystitis), urethra (urethritis), and/or ureters, and upper UTI affects the renal parenchyma of the kidney (pyelonephritis).[13] Complicated UTI is characterized by presence of 1) anatomical, structural or functional alterations of the urinary tract, 2) diminished renal function, or 3) diseases that compromise the patient's immune system.[14] Ultimately, a complicated UTI occurs when there is an underlying condition increasing the chance the patient will fail treatment, and thus all HA-UTIs are considered complicated.[15]

UTIs are primarily caused by bowel bacteria that ascend through the urethra to the bladder and in some cases to the kidney.[13] Consequently, the majority of bacterial species causing UTI are fecal flora, primarily gram-negative bacteria, often in the Enterobacteriaceae family, such as *Escherichia coli,* the most prevalent UTI pathogen.[13] Certain factors, including age, diabetes, spinal cord injury, or catheterization, increase a patient's risk of infection from a less virulent bacterial species. Accordingly, there is a greater diversity of pathogens responsible for complicated UTI, and a greater prevalence of *Pseudomonas, Serratia, Providencia,*

Staphylococcus and *Enterococcus* species.[15] Additional pathogens common in diabetic patients include *Klebsiella* species and Group B *Streptococcus*, and in patients with spinal cord injuries typical organisms also include *Proteus mirabilis* and *Enterobacter* species.[16]

In 2000, the SENTRY program, an international antimicrobial surveillance program, produced a report of UTI pathogen occurrence and resistance profiles for North America, Europe and Latin America.[17] In North America, the seven most prevalent organisms were *E. coli* (43.3%), *Enterococcus* species (15.8%), *Klebsiella* species (12.0%), *P. aeruginosa* (7.2%), *P. mirabilis* (4.2%), *Citrobacter* species (3.5%) and *Enterobacter* species (3.0%).[17] The other two regions had similar pathogen frequency, except for a lower rate of *Enterococcus* species in Latin America.[17]

Bacteriuria, the presence of bacteria in the urinary tract, can occur in the absence of symptoms and is therefore called asymptomatic bacteriuria (ASB).[13] ASB represents colonization of the urinary tract rather than true infection. ASB is rare in young and healthy individuals, but prevalence increases with age, and it occurs in 25-50% of elderly women in long-term care facilities.[18] A high prevalence of ASB is also found with certain conditions, including diabetes and spinal cord injuries, and it appears in virtually 100% of patients with long-term (over a month) indwelling urinary catheters.[19] Pregnant women should be screened for ASB, as well as patients undergoing a few specified traumatic urological procedures, where the potential consequences warrant management.[20] Conversely, screening is not recommended for all other individuals because treatment will not reduce the chance of acquiring a symptomatic infection, or improve other clinical outcomes.[20] Of equal importance, unnecessary antimicrobial treatment poses unwarranted risks of adverse effects, including hypersensitivity reactions, nephrotoxicity, neurotoxicity, drug-interactions,[21] gastrointestinal symptoms, bacterial colonization or infection

by a resistant organism, and infection by *C. difficile*.[22] *C. difficile*, a spore-forming gram-positive bacteria, causes severe diarrheal infection, and is almost exclusively associated with antimicrobial use.[23,24] *C. difficile* infection has become a tremendous burden for patients and healthcare facilities; each year in the United States, 250,000 patients receive hospital care for *C. difficile*, and more than 14,000 of these patients die as a result of the infection.[25]

Patients afflicted with UTIs experience one or more symptoms of fever, urgency, frequency, dysuria (painful urination), suprapubic tenderness, or costovertebral angle pain (flank pain).[26] A UTI diagnosis also requires a positive urinalysis and quantitative urine culture. A urinalysis positive for UTI has the presence of pyuria (white blood cells in the urine), leukocyte esterase (detection of lysed neutrophils and a surrogate marker of pyuria), and nitrite (indication of Enterobacteriaceae species that reduce nitrate to nitrite).[27] If the urine culture contains fewer than 10,000 colony-forming units (CFU)/mL, it is not considered an infection; a culture containing more than 100,000 CFU/mL is indicative of UTI, and cultures with CFU/mL counts between 10,000-100,000 indicate that other clinical factors should be considered before making a diagnosis.[27] When the patient experiences symptoms indicating a true UTI, antibiotic treatment is recommended.

Antibiotics

Antibiotics are categorized by their mode of action into major classes, including beta-lactam, glycopeptide, aminoglycoside, and quinolone. The beta-lactam class of antibiotics—characterized by a four-membered beta-lactam ring—attacks bacteria by inhibiting cell wall synthesis.[28] Bacterial cell walls are composed of peptidoglycan, a backbone of polysaccharide chains cross-linked to peptides. Peptidoglycan is formed by penicillin-binding proteins that catalyze a cross-linking reaction between the dipeptide, D-alanyl-D-alanine, and the budding

peptidoglycan chain within the growing cell wall.[28] In beta-lactam antibiotics, the structural similarity of the beta-lactam ring to the D-alanyl-D-alanine dipeptide allows the antibiotic to bind to the penicillin-binding protein, preventing the transpeptidation reaction, which destabilizes the cell wall, and results in bacteriolysis.[28] Penicillins (including ampicillin and ampicillin/sulbactam), carbapenems (including meropenem and ertapenem) and cephapholosporins (including cefazolin, cefoxitin, ceftazidime, ceftriaxone, and cefepime) all belong to the beta-lactam class. Cephalosporins are categorized into five major generations based on antibacterial activity.[29] Cefepime, a fourth-generation cephalosporin, has a broad spectrum with activity against the Enterobacteriaceae family, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*, but is not clinically effective against *Enterococcus* species[30] or methicillin-resistant *Staphylococcus aureus*.[31]

Antibiotics of the glycopeptide class also inhibit the transpeptidation reaction and cause cell lysis, but instead of binding to the penicillin-binding protein, these antibiotics bind to the D-alanyl-D-alanine dipeptide.[32] Glycopeptides are only active against gram-positive bacteria because, as large molecules, they are unable to penetrate the outer membrane of gram-negative bacteria.[33] The glycopeptide vancomycin is typically active against methicillin-susceptible and resistant S*taphylococcus aureus*, *Enterococcus faecalis* and *Enterococcus faecium*, although resistant strains have emerged.[34]

Quinolones are a synthetic class of antibiotics that act by inhibiting bacterial DNA replication.[35] The fluoroquinolone sub-class, including ciprofloxacin, has the addition of 6-fluoro and 5-piperdine groups, which increase the antibiotic's efficacy at lower doses.[35] Ciprofloxacin has extensive antibacterial activity against the majority of clinically important pathogens, but it is among the most widely used agents in the world,[35] and, consequently, pathogens are now

frequently resistant.[17,35,36]

The same antibiotic is not suitable for every case of an infection, and which antibiotic to prescribe at what dose and duration must be considered for each patient. The treatment course for a UTI is determined by the classification of infection. Uncomplicated UTIs can be treated with antibiotics that obtain a sufficient concentration in the urine, whereas complicated infections require antibiotics that achieve a high systemic concentration, such as higher generation cephalosporins, to treat the possibility of bacteria in the kidneys or bloodstream.[13]

Empirical Therapy

When a patient exhibits symptoms of an infection, a body site sample is collected to culture for the presence of a pathogen, and to perform antimicrobial susceptibility testing (AST).[21] In AST, the ability of the organism to grow in the presence of various antimicrobials is measured, and the microorganism is categorized as "susceptible," "intermediate," or "resistant" to each agent tested, which is a predictor of the clinical efficacy of each drug for the organism.[21] However, AST results are not available until 24-72 hours after the sample is collected; therefore, empirical antimicrobial treatment—before the species or the susceptibility are known—is common.[21]

Empirical therapy typically consists of an antimicrobial that has a broad spectrum of activity, to cover the wide range of potential pathogens,[21] and may be a combination of two drugs, which increases the likelihood that the organism will be susceptible to the treatment. Selection of the empirical regimen should consider the 1) infection site, and the organisms common to the site, 2) previous known species of bacteria in the patient, 3) whether the infection was acquired in the community or in a healthcare setting and 4) resistance patterns in the

community or healthcare institution.[21] Empirical therapy for UTI should be active against gram-negative species, especially in the Enterobacteriaceae family.[13] A complicated UTI requires early management, with particular attention to the patient's previous antimicrobial use and the local resistance data.[15]

Selection of an empirical antibiotic that is ineffective against the pathogen, enabling the infection to progress, may have problematic or even fatal consequences. A serious complication of UTI is bacteremia, the presence of bacteria in the blood stream, which in turn can lead to sepsis. Sepsis is a result of extreme immune activation in response to microorganisms, and involves systemic inflammation and extensive tissue injury.[37] Severe sepsis can cause organ dysfunction, and septic shock results in acute circulatory collapse.[37] The most common sites of infection causing sepsis are the respiratory and urinary tracts.[37] A 2012 study in Spain found 63.6% of the 66 patients with HA-UTIs had urinary sepsis, and there was a 30-day case fatality rate of 9.1%.[38] Elderly individuals have a considerably higher risk, and a study of geriatric patients in 2005 showed a bacteremic HA-UTI case fatality rate of 39.5%.[39]

Many studies have shown that inadequate empirical antibiotic therapy (IEAT) in critically ill, hospitalized patients is associated with a longer hospital stay and greater morbidity and mortality.[21,40,41] However, there is also evidence that IEAT causes severe adverse effects in patients who are not critically ill. Esparcia et al. (2014) researched the efficacy of empirical treatment for UTI in elderly patients in a non-intensive care unit university hospital.[42] In the study, 67% of the 53 patients with HA-UTI received IEAT.[42] A considerable proportion of these regimens were cephalosporins and quinolones, and there was a significant association between IEAT and infection by *E. faecalis*.[42] Of the 24 deaths in the study, 62.5% were from HA-UTI, which had a case fatality rate of 11.9%, indicating high mortality is associated with IEAT even

when the percentage of severe sepsis and septic shock is low.[42] These results provide compelling evidence to improve empirical UTI treatment, but this study is among the few researching the consequences of ineffective initial treatment for UTI. Further research and larger studies are needed to confirm these findings, and to assess additional adverse effects resulting from IEAT, including antimicrobial resistance.

Antimicrobial Resistance

Antimicrobial resistance can arise within the microorganism, through chromosomal mutations, or a resistance gene can be transferred from another microorganism through modes of gene transfer such as bacteriophage-mediated transduction, uptake of naked DNA through transformation, and conjugation through cell-to-cell contact.[43] Resistance is achieved through mechanisms of decreased cell membrane permeability, detoxification enzymes, drug efflux pumps, and modification of drug targets.[13,43] Although antimicrobial resistance emerged before human existence, the current widespread use of antibiotics in agriculture and medicine has placed intense selection pressure on bacteria, resulting in an unprecedented magnitude of resistance.[13,43]

A report by the CDC, *Antibiotic Resistance Threats in the United States, 2013*, highlights the troubling statistics and the dangers posed by antibiotic resistance. In the U.S., bacteria resistant to one or more typically used antibiotics infect two million people each year, with fatal consequences for some patients.[25] At least 23,000 patients die as a direct outcome of the antibiotic-resistant infection, and an even greater number die as a result of other conditions that were complicated by the infection.[25] The magnitude of resistant cases also takes an extreme toll on the healthcare system. The majority of patients with antibiotic-resistant infections require extended and/or more expensive treatment, longer hospital stays, and additional physician visits

and use of healthcare services.[25] Roberts et al. (2009) estimated that antimicrobial-resistant infections cost $18,588 to $29,069 for each patient, and lengthen hospital stay by 6.4 to 12.7 days.[44] For the nation, the annual cost of antibiotic resistance has been estimated to be as high as $20 billion in increased healthcare costs, and $35 billion in the burden to society resulting from decreased productivity.[25]

In 2000, results from the SENTRY UTI antimicrobial susceptibility report raised concerns of fluoroquinolone resistance across North America, Europe and Latin America.[17] Of the most prevalent pathogens in North America, only *E. coli* had high rate of susceptibility (96.0%) to ciprofloxacin. The other organisms—*Klebsiella* species (72.7%), *P. aeruginosa* (69.5%), and *Enterococcus* species (45.1%)—were all considerably lower.[17] In another report to assess uropathogen resistance, the Study for Monitoring Antimicrobial Resistance Trends (SMART) tracked the prevalence and resistance profiles of gram-negative UTI pathogens from hospitalized patients between 2009 to 2011, and found that resistance to beta-lactams, beta-lactamase inhibitors, and fluoroquinolones is an escalating and frightening problem.[36] In the healthcare-associated isolates, there were particularly low susceptibility rates to ciprofloxacin: *E. coli* (59.3%), *K. pneumonia* (84.6%), *P. mirabilis* (75.0%), and *P. aeruginosa* (57.1%).[36]

Antimicrobial resistance is a critical issue for HAIs, which are more likely to be caused by a resistant pathogen than infections acquired in the community.[45] In addition, HA-UTIs are a significant reservoir of antibiotic-resistant bacteria in healthcare facilities.[7] Antimicrobial resistance is introduced to and transmitted throughout hospitals through multiple mechanisms, but numerous studies have shown antibiotic use to be the most significant cause of the persistence and amplification of resistance.[43,45-47] In addition to creating selection pressures for bacteria to develop survival mechanisms, antibiotics contribute to the spread of resistance

through the eradication of normal bacterial flora.[22] This enables the overgrowth of pathogenic organisms, and a higher density of resistant pathogens increases the probability of contamination on hospital surfaces and transmission to other patients.[22] The use of broad-spectrum rather than narrow-spectrum antibiotics increases these risks because these antibiotics have a greater impact on normal bacterial flora.[43]

The CDC recommends four principal activities to combat antibiotic resistance: preventing infections and the spread of resistance, promoting the development of new antibiotics and of new tests for diagnosing resistant bacterial strains, monitoring resistant bacteria, and improving antibiotic usage.[25] Our study focuses on two of these actions by tracking resistant bacteria in order to improve the prescription of antibiotics. Inadequate and inappropriate antimicrobial use is rampant in the U.S; an estimated one-third of hospitalized patients receive antibiotics, and half of these prescriptions are either unnecessary or not optimally effective.[47] The excessive unnecessary use of antimicrobials has a high financial cost,[22] but of even greater concern, the patient is exposed to unjustifiable risks of side effects, *C. difficile* infection, and antimicrobial resistance.[21,22]

Programs to improve the practice of antimicrobial treatment, called antimicrobial stewardship programs, have significant potential to reduce antibiotic-resistance, improve patient outcomes, and decrease healthcare costs.[25] Unfortunately, however, such programs have not yet been widely implemented in the U.S.[25,48]

Antimicrobial Stewardship

Antimicrobial stewardship is defined as "the optimal selection, dosage and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of

infection, with minimal toxicity to the patient and minimal impact on subsequent resistance."[49]

The first objective of antimicrobial stewardship is to assist practitioners in providing optimal treatment for the patient, which includes prescribing an adequate and appropriate antibiotic in the accurate dose with the lowest chance of adverse effects.[50] An "adequate" antibiotic is one that is effective against the bacteria. An "appropriate" antibiotic is one that considers all available clinical, pharmacological, and microbiological data, and that is narrowed or changed in dosage if necessary.[41]

The second objective is to stop the current overuse, abuse and misuse of antimicrobials. Ending overuse involves preventing the prescription of antimicrobials when they are unwarranted, as in viral infections, non-infectious illnesses, and bacterial infections that can be resolved without the use of antibiotics.[50] Misuse can be reduced by prescribing antimicrobials with the narrowest spectrum for the infection, and modifying the antibiotics if necessary once the susceptibilities of the organism are known.[50] Antibiotic abuse can be avoided by ensuring that antibiotics are not favored for reasons other than evidence-supported efficacy.[50]

The third objective is to reduce the emergence of resistant microorganisms for both the patient and the population. By using antimicrobials with greater efficacy, and decreasing overall usage, the risk of resistant bacteria developing within the patient, and spreading throughout the community, is greatly diminished.[50]

Tufts Medical Center has a well-established antimicrobial stewardship program directed by an infectious diseases physician and a specially-trained clinical pharmacist. The program was recently recognized for a 20% reduction in antibiotic use at the hospital compared to hospitals nationwide, and over the past 10 years the program has saved the hospital an estimated $5-10

million. The program's strategies to improve antibiotic use include antibiotic restrictions requiring authorization from a member of the stewardship team, daily review of patients on antibiotics with feedback to clinicians, and education. Every year, the antimicrobial stewardship team publishes an updated treatment and dosing guide that is distributed to every medical practitioner. This guide includes recommended antibiotics for common infections, dosing information, and an annual antibiogram.

Antibiograms

A cumulative antibiogram report, or antibiogram, is an annual summary of antimicrobial susceptibility rates at a healthcare facility.[51] An antibiogram presents the percentage of bacterial isolates of a predominant species that are susceptible to a selection of antimicrobials commonly used at the institution. Antibiograms can be used to analyze and monitor resistance trends at the healthcare facility, and to guide empirical antimicrobial therapy.[51] A traditional antibiogram combines bacterial isolates of one species collected from all body sites of all patients admitted to the hospital, and shows the percentage of these that are sensitive to individual antibiotics. The Clinical and Laboratory Standards Institute produces specific guidelines for the collection, analysis and presentation of antibiograms, and the recently updated recommendations suggest presenting susceptibility rates based on patient types, body sites and two antibiotics used in combination.[52]

Fox et al. (2008) produced an antibiogram that calculated the susceptibilities of isolates to two antibiotics for bloodstream and lower respiratory isolates of Enterobacteriaceae and *P. aeruginosa*.[53] The antibiogram included isolates from a university hospital over a two-year period, and was analyzed to assess its effectiveness for guiding empirical treatment of these gram-negative rod infections.[53] The results indicated two new combinations that had a

statistically higher percentage susceptible than the popular combination at the hospital.[53]

Rabs et al. (2014) made an antibiogram specific for urinary isolates of the four most prevalent gram-negative pathogens from both inpatient and outpatient settings combined over one year.[54] There was an overall increase in susceptibility in the urinary-specific antibiogram compared to the standard antibiogram, which is thought to be a result of including only the four most common urinary pathogens, rather than all pathogens responsible for UTI.[54] Despite the overall increase, the main antibiotics prescribed for UTI (ciprofloxacin, ampicillin, ampicillin-sulbactam, and piperacillin-tazobactam) were consistent with the susceptibility of *E. coli* and *P. mirabilis* in the standard antibiogram.[54] The study also analyzed isolates for hospital units separately and found slight or no impact, but recognized this may have been caused by a deficient number of isolates from the intensive care unit.[54] Elderly patients were found to be at a heightened risk for an antimicrobial-resistant infection, and patients were significantly more likely be infected specifically by a fluoroquinolone-resistant pathogen if they were elderly or living in a healthcare facility (i.e. a nursing home or long-term care facility).[54]

Hebert et al. (2012) created a weighted-incidence syndromic combination antibiogram (WISCA), which presented the probability that different antibiotic regimens would be effective for a specific infection.[55] All bacterial species causing an infection type were combined to show the percent susceptible to both single and dual antibiotic combinations.[55] The study included isolates from patients with either a final diagnosis code of abdominal-biliary tract infection (ABI) or UTI that were acquired in the community, but required hospitalization, and were collected over a four-year period in a four-hospital academic health system.[55] In both the ABI and UTI WISCAs, there were considerable differences in the susceptibilities compared to the susceptibilities of typical pathogens in the standard antibiogram. For example, 84% of *E. coli*

were susceptible to ciprofloxacin in the traditional antibiogram, compared to only 62% of isolates in the UTI WISCA.[55] Additionally, there were significant differences in efficacy between the ABI and UTI WISCAs for eight of the antibiotic regimens.[55] Patients stratified by potential risk factors, including over 65 years of age, a recent ER or inpatient visit, and those who had recently been treated with a fluoroquinolone, consistently had considerably lower susceptibilities than otherwise healthy patients.[55] These results indicate the importance of customizing antibiograms by disease and risk factors to evaluate reliable resistance rates, and provide adequate and appropriate treatment.

Antibiograms are a crucial guide for empirical antibiotic therapy, and they are an untapped resource with data that could be extracted to make them even more valuable. Experts are now recommending the customization of antibiograms, and Fox et al. (2008), Rabs et al. (2014), and Hebert et al. have demonstrated the new information that can be obtained from dual regimen and/or UTI-specific antibiograms.[53-55] Esparcia et al. has shown the rate of IEAT is strikingly high for HA-UTI, and that its consequences are severe,[42] indicating the need to improve HA-UTI empirical antibiotic therapy that could potentially be achieved through a novel antibiogram.

Study Aims

The goal of this study was to develop a method of presenting antimicrobial resistance data that would be a better guide for the selection of empirical antibiotic therapy. Specifically, we aimed to:

1. Create a UTI-specific antibiogram with single and dual antibiotic regimens. We hypothesized that resistance to antimicrobials of bacterial urine isolates will be distinct from resistance of bacterial isolates from all body site sources, and that dual regimens will have a higher percentage of susceptible isolates.

2. Create an HA-UTI-specific antibiogram with single and dual antibiotic regimens. We hypothesized that resistance rates will be higher in the HA-UTI isolates than those of community-acquired UTI, and dual antibiotic regimens will still show benefit over single agents.

3. Create a symptomatic HA-UTI antibiogram with single and dual antibiotic regimens. We hypothesized that the gram-positive isolates in the HA-UTI antibiogram were not primarily colonizing bacteria, and the symptomatic HA-UTI antibiogram will still show low susceptibility to antibiotics only active against gram-negative bacteria.

4. Confirm the efficacy of the antibiogram-determined regimen in a new cohort by comparing the antibiogram-determined regimen to the current empirical recommended regimen for HA-UTI, and to the empirical antibiotics patients actually received. We hypothesized that the antibiogram-determined regimen will have the greatest likelihood of efficacy.

Methods

Setting

The study occurred at Tufts Medical Center, a 415-bed, level I trauma and tertiary care center in the major metropolitan center of Boston, Massachusetts.

Creation of UTI-Specific Combination Antibiograms

A SafetySurveillor (a data mining software system) Real-time Report was generated for all urine cultures from adult inpatients in 2013. All isolates containing fungus and mixed bacterial flora were excluded. Antimicrobial susceptibilities of the isolates were obtained from SIEMENS Soarian (the electronic medical record system used at Tufts Medical Center). Antimicrobial susceptibility testing was performed at the Tufts Medical Center clinical microbiology laboratory using VITEK-2®**.** For the purpose of this study, intermediate resistance was considered resistance (M39-A2 guidelines), and only the first isolate of a given species was included for each patient (M39-A2 guidelines).[51] Except for β-hemolytic *Streptococcus* group B, an organism without susceptibility data was excluded, either because of insufficient colony count or because it was a non-relevant organism, and unlikely to be a urinary pathogen. Only cultures with greater than 10^3 CFU/ml were included. "Probable" and "morphology consistent with" isolates of β-hemolytic *Streptococcus* group B were considered positive UTI cultures and included in the data.

Assumptions of antibiotic susceptibility for certain isolates were necessary in this type of antibiogram because antibiotics with known inactivity are not tested, and if these were not included in the antibiogram the total percent susceptible would be overestimated. In other cases

antibiotics are not tested because they are not commonly used for the species, but the efficacy can be presumed. We used assumptions from Hebert et al. (2012), which were determined by expert opinion and literature review[55] (Supplement 1). Our study included additional assumptions determined by Dr. Doron and Dr. Beaulac (Supplement 2). Ten antibiotic combinations commonly used at Tufts Medical Center were chosen to study the effects of two antibiotics used in conjunction: vancomycin with piperacillin-tazobactam, vancomycin with meropenem, vancomycin with ertapenem, vancomycin with ceftriaxone, vancomycin with cefepime, tobramycin with piperacillin-tazobactam, tobramycin with meropenem, tobramycin with ertapenem, tobramycin with cefepime, ciprofloxacin with trimethoprim-sulfamethoxazole. Antibiotic combinations were considered effective if the organism was susceptible to at least one of the two antibiotics. Antibiotic combinations required additional assumptions for isolates in which only one of the antibiotics had been tested, and these were again determined by Dr. Doron and Dr. Beaulac (Supplement 3).

Creation of HA-UTI, Community-Acquired UTI and Catheter-Related HA-UTI Antibiograms

HA-UTI and community-acquired organisms were separated into two antibiograms. Urine specimens collected on the third hospital day and later (with admission as day one) were HA-UTI by CDC/NHSN criteria (Supplement 4). HAI isolates of patients with indwelling urinary catheters were further categorized into a specific catheter-related HA-UTI antibiogram. Antibiotics tested for fewer than 30 isolates were excluded from the antibiogram (M39-A2 guidelines).[51]

Creation of Symptomatic HA-UTI Combination Antibiogram

The HA-UTI antibiogram was further refined by omitting all isolates of ASB. Electronic and paper medical records were searched to identify isolates that caused a symptomatic UTI, which was defined using CDC criteria 2a and 2b, modified based on available data and to reflect clinical significance (Supplement 5). A symptomatic UTI was defined as urinalysis positive for UTI *and* a documented UTI symptom in the patient's medical record. A urinalysis positive for UTI had at least *one* of the following: leukocyte esterase, nitrite, or pyuria. A symptomatic UTI included at least *one* of the following documented in the patient's medical record: fever, urgency, frequency, dysuria, suprapubic tenderness, or costovertebral angle pain. The distribution of organisms was analyzed for these patients, and a new antibiogram was created with only the susceptibilities of these patients.

Comparison of Regimens

The next phase of the project was to assess if the regimen determined from the HA-UTI combination antibiogram was more effective than the current recommended regimen for HA-UTI (cefepime) and the actual regimens given as empirical treatment. The sample of isolates was obtained from a SafetySurveillor Real-time Report for all urine cultures from adult inpatients in 2014. The same methods of determining susceptibilities and exclusion of isolates for the HA-UTI combination antibiogram were used. The antibiotics prescribed were found using SIEMENS Soarian. An antibiotic was considered empirical if it was administered within 24 hours before or after collection of the urine specimen. Electronic patient discharge summaries were searched to determine if an antibiotic was prescribed for a reason other than presumed infection, and these

isolates were excluded. The same assumptions for the HA-UTI combination antibiogram were used, and two additional assumptions were included (Supplement 6). The percentages of isolates that would have been covered for the prescribed antibiotic, cefepime alone, and cefepime with vancomycin were calculated. A prescribed regimen was considered appropriate if it included one of the antibiotics designated for treatment of HA-UTI in the Tufts Medical Center treatment and dosing guide: cefepime, meropenem, aztreonam, and tobramycin.

Statistical Analysis

Statistical analysis was performed using statistical pack SPSS version 22.0 (IBM, Armonk, NY). The relationship between the presence of UTI symptoms and an indwelling urinary catheter was determined with a Pearson Chi-square test (Supplement 7). A Mann-Whitney U test was used to compare the presence of symptoms and the length of hospital stay (Supplement 8). A Pearson Chi-square was used to determine if there was a correlation between the adequacy of empirical treatment and gender (Supplement 9) or an indwelling urinary catheter (Supplement 10). The associations between the three regimens' efficacies were tested with McNemar tests (Supplement 11). A p value <0.05 was considered statistically significant.

Results

Organism Distributions of Traditional and UTI-Specific Combination Antibiograms

The HA-UTI combination antibiogram was comprised of 235 bacterial isolates (200 unique patients). The distribution of organisms was consistent with the known UTI pathogens, predominately gram-negatives of the Enterobacteriaceae family, as well as *P. aeruginosa*, *Enterococcus*, *Staphylococcus* and *Streptococcus* species (Table 1, Figure 1). The most prevalent species was *E. coli* (31.9%), followed by *E. faecalis* (14.0%), *K. pneumonia* (8.5%), *P. mirabilis* (6.8%), and *P. aeruginosa* (6.4%). Compared to the traditional 2013 Tufts Medical Center antibiogram there was a greater percentage of *E. coli* and *E. faecalis*, and lower percentage of *S. aureus*, *P. aeruginosa,* and *K. pneumonia* (Table 2, Figure 1).

The community-acquired UTI combination antibiogram contained 273 bacterial isolates (237 unique patients). The proportions of species were similar to those in the HA-UTI combination antibiogram, but contained a higher percentage of *E. coli* (38.5%) and Group B β-hemolytic *Streptococcus* (6.2%), and a lower percentage of *E. faecalis* (11.7%) (Table 3, Figure 1). Additionally, there were more species with only one isolate.

The catheter-related HA-UTI combination antibiogram had 83 bacterial isolates (72 unique patients). Again, the trend of organisms was comparable to that of the HA-UTI combination antibiogram, but with higher proportions of *E. faecalis* (18.1%) and *S. aureus* (9.6%) (Table 4, Figure 1).

Organism	Number of Isolates	Percentage of Isolates
Escherichia coli	75	31.9%
Enterococcus faecalis	33	14.0%
Klebsiella pneumoniae	20	8.5%
Proteus mirabilis	16	6.8%
Pseudomonas aeruginosa	15	6.4%
Staphylococcus aureus	11	4.7%
Enterobacter cloacae	10	4.3%
Enterococcus faecium	9	3.8%
Serratia marcescens	7	3.0%
Enterococcus (undifferentiated)	7	3.0%
Enterobacter aerogenes	6	2.6%
Citrobacter freundii	6	2.6%
β-hemolytic *Streptococcus* B	6	2.6%
Klebsiella oxytoca	4	1.7%
Proteus vulgaris	3	1.3%
Morganella morganii	2	0.9%
Staphylococcus epidermidis	1	0.4%
Citrobacter species	1	0.4%
Citrobacter braakii	1	0.4%
Citrobacter koseri	1	0.4%
Citrobacter amalonaticus	1	0.4%
Total	235	

Table 1.

Organism distribution of HA-UTI combination antibiogram 2013

n=235 adult inpatient HA-UTI urine isolates.

Organism	Number of Isolates	Percentage of Isolates
Escherichia coli	489	21.2%
Staphylococcus aureus	598	25.9%
Pseudomonas aeruginosa	331	14.3%
Klebsiella pneumoniae	197	8.5%
Enterococcus faecalis	140	6.1%
Enterococcus faecium	86	3.7%
Serratia marcescens	79	3.4%
Staphylococcus epidermidis	77	3.3%
Proteus mirabilis	69	3.0%
Enterobacter cloacae	69	3.0%
Stenotrophomonas maltophilia	55	2.4%
Enterobacter aerogenes	36	1.6%
Acinetobacter baumannii	32	1.4%
Klebsiella oxytoca	28	1.2%
Streptococcus viridans	23	1.0%
Total	2095	

Table 2.

Organism distribution of Tufts Medical Center 2013 Antibiogram

n=2095 adult and pediatric inpatient isolates from all body site sources.

Organism	Number of Isolates	Percentage of Isolates
Escherichia coli	105	38.5%
Klebsiella pneumoniae	43	15.8%
Enterococcus faecalis	32	11.7%
Pseudomonas aeruginosa	18	6.6%
β-Hemolytic *Streptococcus* B	17	6.2%
Staphylococcus aureus	10	3.7%
Proteus mirabilis	9	3.3%
Enterococcus faecium	9	3.3%
Enterococcus (undifferentiated)	7	2.6%
Enterobacter cloacae	4	1.5%
Citrobacter freundii	4	1.5%
Klebsiella oxytoca	4	1.5%
Enterobacter aerogenes	3	1.1%
Serratia marcescens	1	0.4%
Proteus vulgaris	1	0.4%
Staphylococcus epidermidis	1	0.4%
Morganella morganii	1	0.4%
Citrobacter species	1	0.4%
Acinetobacter lwoffii	1	0.4%
Citrobacter koseri	1	0.4%
Providencia rettgeri	1	0.4%
Total	273	

Table. 3

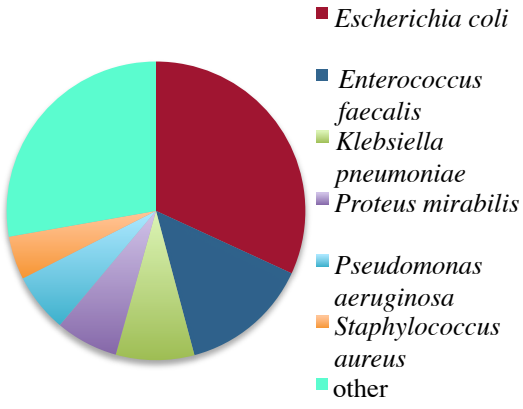
Organism distribution of community-acquired UTI combination antibiogram 2013

n=273 adult inpatient community-acquired UTI urine isolates.

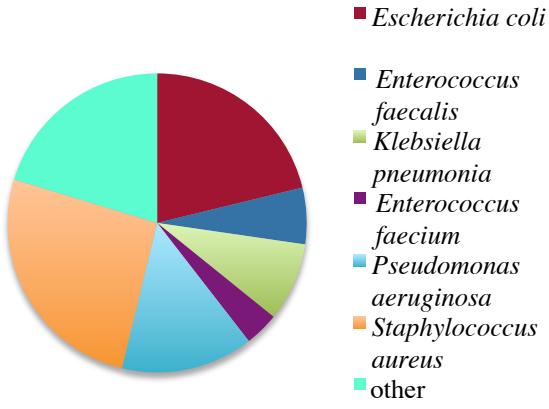
Organism	Number of Isolates	Percentage of Isolates
Escherichia coli	25	30.1%
Enterococcus faecalis	15	18.1%
Klebsiella pneumoniae	9	10.8%
Pseudomonas aeruginosa	8	9.6%
Staphylococcus aureus	8	9.6%
Enterococcus faecium	3	3.6%
Proteus mirabilis	3	3.6%
Citrobacter freundii	3	3.6%
Enterobacter cloacae	2	2.4%
Klebsiella oxytoca	2	2.4%
Enterobacter aerogenes	1	1.2%
Serratia marcescens	1	1.2%
Citrobacter braakii	1	1.2%
Citrobacter species	1	1.2%
Enterococcus (undifferentiated)	1	1.2%
Total	83	

Table 4.

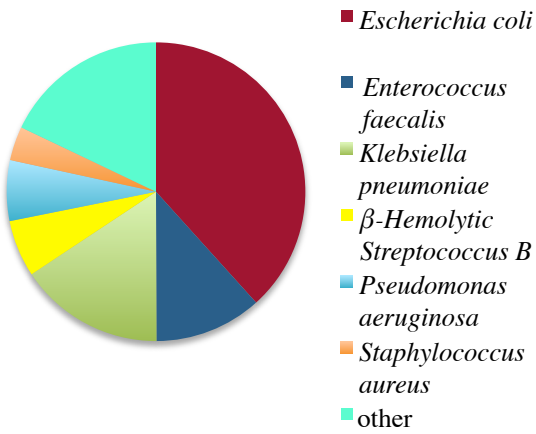
Organism distribution of catheter-related HA-UTI combination antibiogram 2013
n=83 adult inpatient HA-UTI urine isolates collected from an indwelling urinary catheter.



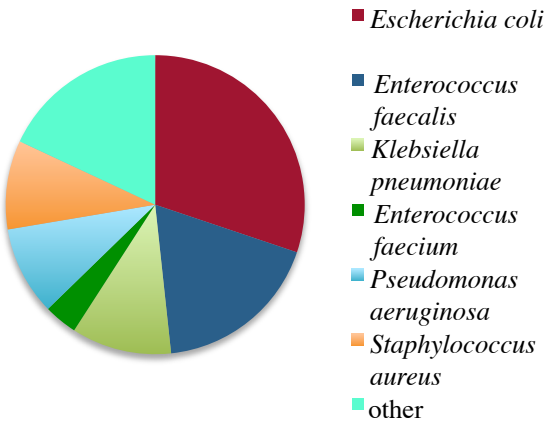
HA-UTI combination antibiogram



Tufts Medical Center 2013 antibiogram



community-acquired UTI combination antibiogram



HA-UTI catheter-related combination antibiogram

Figure 1.
Comparison of organism distributions in UTI combination and traditional antibiograms
Proportion of six most prevalent organisms and remaining organisms combined of each antibiogram. HA-UTI combination antibiogram: n=235 adult inpatient HA-UTI urine isolates. Tufts Medical Center 2013 antibiogram: n=2095 adult and pediatric inpatient isolates from all body site sources. Community-acquired combination antibiogram: n=273 adult inpatient

community-acquired urine isolates. Catheter-related HA-UTI combination antibiogram: n=83 adult inpatient HA-UTI urine isolates collected from an indwelling urinary catheter.

Traditional and UTI-Specific Combination Antibiograms

All antibiotics had a high proportion of isolates for which they were tested, producing fairly large and comparable sample sizes for each agent. The HA-UTI combination antibiogram indicated that overall, single antibiotics have a low likelihood of efficacy (Table 5). Only one antibiotic, piperacillin-tazobactam, exceeded 80%, the standard limit for empirical use designated by the CDC. The current recommended regimen for HA-UTI (cefepime) would be effective for 75% of the isolates, and 64% of isolates were susceptible to ciprofloxacin.

As expected, the isolates had higher susceptibilities to the antibiotic combinations, and six out of the ten combinations had over 80%. The two regimens with the highest percentage of susceptible isolates were vancomycin with meropenem (95%) and vancomycin with cefepime (93%). Vancomycin with cefepime was determined to be the optimal regimen, because of meropenem's broader spectrum of activity, and thus greater possibility of adverse effects, including antimicrobial resistance. Although neither cefepime nor vancomycin had a sufficient percent susceptibility used alone, there was a significant increase when combined because vancomycin is active against organisms that cefepime is not, primarily *E. faecalis* and methicillin-resistant *S. aureus*, whereas cefepime has the gram-negative coverage that vancomycin lacks.

The current traditional Tufts Medical Center antibiogram showed a high susceptibility to cefepime for many of the prevalent species of the HA-UTI combination antibiogram: *E. coli* (95%), *K. pneumonia* (95%), and *P. mirabilis* (97%), although it is lower for *P. aeruginosa* (81%) (Table 6). Cefepime was not tested for *Enterococcus* species because it is known to be

inactive. Ciprofloxacin had generally low susceptibilities in the traditional antibiogram: *E. coli* (69%), and *P. mirabilis* (66%), *P. aeruginosa* (78%) and S. aureus (65%), except for *K. pneumonia* (91%) (Table 6).

The community-acquired UTI isolates were generally the same or fairly more susceptible than the HA-UTI isolates (Table 7). Ampicillin-sulbactam, cefazolin, cefoxitin, and nitrofurantoin had a higher percentage of susceptible isolates in community-acquired infections, but ciprofloxacin had a lower percentage. The antibiotic combinations had a similar proportion of susceptible isolates compared to the HA-UTI antibiogram.

Overall, the isolates from the catheter-related HA-UTI combination antibiogram had decreased sensitivity compared to all isolates from the HA-UTI combination antibiogram (Table 8), as has been seen in other studies.[56,57] The combination of cefepime with vancomycin retained a high proportion of susceptible isolates (91%), indicating this regimen was also an adequate empirical choice for patients with indwelling urinary catheters.

Percent Susceptible																	
IN-PATIENT, Urine adult	**Penicillins & Related Antibiotics**					**Cephalosporins 1st 3rd 4th generation**					**Aminoglycosides**			**Quinolone**	**Other**		**UTI Agent**
	AMPICILLIN (187)	**AMPICILLIN /SULBACTAM (202)**	**PIPERACILLIN /TAZOBACTAM (219)**	**MEROPENEM (223)**	**ERTAPENEM (231)**	**CEFAZOLIN (229)**	**CEFOXITIN (194)**	**CEFTAZIDIME (209)**	**CEFTRIAXONE (224)**	**CEFEPIME (232)**	**GENTAMICIN (232)**	**TOBRAMYCIN (230)**	**AMIKACIN (235)**	**CIPROFLOXACIN (229)**	**TRIMETHOPRIM/SULFA (219)**	**VANCOMYCIN (217)**	**NITROFURANTOIN (221)**
	50	60	83	75	68	37	53	67	62	75	67	66	71	64	58	18	57

Percent Susceptible										
IN-PATIENT, Urine adult	**Antibiotic Combinations**									
	VANCOMYCIN + PIPERACILLIN/TAZOBACTAM (222)	**VANCOMYCIN + MEROPENEM (207)**	**VANCOMYCIN + ERTAPENEM (243)**	**VANCOMYCIN + CEFTRIAXONE (209)**	**VANCOMYCIN + CEFEPIME (214)**	**TOBRAMYCIN + PIPERACILLIN/TAZOBACTAM (230)**	**TOBRAMYCIN + MEROPENEM (229)**	**TOBRAMYCIN + ERTAPENEM (233)**	**TOBRAMYCIN + CEFEPIME (233)**	**CIPROFLOXACIN + TRIMETHOPRIM/SULFA (225)**
	87	95	87	81	93	90	76	75	76	71

Table 5.
HA-UTI combination antibiogram January-December 2013
n=235 adult inpatient HA-UTI urine isolates. Data are expressed as n(%) susceptible.

Gram Negative Organisms	Percent Susceptible															
IN-PATIENT, all sources (adult and pediatric combined)	**Penicillins & Related Antibiotics**					**Cephalosporins 1st 3rd 4th generation**					**Aminoglycosides**			**Quinolone**		**UTI Agent**
ORGANISM	**AMPICILLIN**	**AMPICILLIN / SULBACTAM**	**PIPERACILLIN/ TAZOBACTAM**	**MEROPENEM**	**ERTAPENEM**	**CEFAZOLIN**	**CEFOXITIN**	**CEFTAZIDIME**	**CEFTRIAXONE**	**CEFEPIME**	**GENTAMICIN**	**TOBRAMYCIN**	**AMIKACIN**	**CIPROFLOXACIN**	**TRIMETHOPRIM/ SULFA**	**NITRO-FURANTOIN**
Acinetobacter baumannii (32)	NA	93	90	93	NA	NA	ND	82	3	68	87	90	ND	90	93	ND
Enterobacter aerogenes (36)	ND	ND	57	86	91	0	0	63	58	88	100	100	100	91	94	ND
Enterobacter cloacae (69)	ND	ND	64	94	85	0	0	66	55	91	81	75	100	81	71	ND
E. coli (489)	42	52	92	99	99	64	83	89	85	95	90	89	99	69	71	89
Klebsiella oxytoca (28)	0	67	85	100	100	39	90	85	85	92	92	100	100	92	78	ND
Klebsiella pneumoniae (197)	0	80	89	99	97	84	92	90	90	95	93	92	98	91	87	15
Proteus mirabilis (69)	55	73	100	100	97	49	86	100	95	97	66	69	98	66	59	NA
Pseudomonas aeruginosa (288)	NA	NA	81	78	NA	NA	NA	81	NA	81	85	91	97	78	NA	NA
Pseudomonas aeruginosa (43) (Cystic Fibrosis sputum Kirby-Bauer method) Doripenem %S = 98%	NA	NA	95	93	NA	NA		98	NA	88	57	98	44	57	NA	NA
Serratia marcescens (79)	ND	ND	ND	98	98	0	27	98	83	98	96	82	97	94	100	ND
S. maltophilia (55)															87	
Emergency Department Urines (adult and pediatric)																
E. coli (290)	45	60				90								78	68	90
GMA Outpatient Urines																
E. coli (408)	60	66				93								85	80	94

Table 6.

Tufts Medical Center antibiogram January-December 2013

n=2095 adult and pediatric inpatient isolates from all body site sources. Data are expressed as n(%) susceptible.

Gram Positive Organisms		**Percent Susceptible**															
IN-PATIENT, all sources		Penicillins				Amino-glycosides			Other								
ORGANIISM (# of Isolates)		**AMPICILLIN**	**PENICILLIN**	**OXACILLIN**	**CEFTRIAXONE**	**GENTAMICIN**	**STREPTOMYCIN**	**ERYTHROMYCIN**	**CLINDAMYCIN**	**DAPTOMYCIN[5]**	**CIPROFLOXACIN**	**MOXIFLOXIN**	**RIFAMPIN[4]**	**TETRACYCLINE**	**TRIMETHOPRIM/ SULFA**	**VANCOMYCIN**	**LINEZOLID**	**NITROFURANTOIN (UTI agent)**
Enterococcus faecalis	(140)	99	ND	NA	NA	77 syn[1]	84 syn[1]	NA	NA	NA	NA	NA	NA	ND	NA	89	100	99
Enterococcus faecium	(86)	6	ND	NA	NA	86 syn[1]	77 syn[1]	NA	NA	ND	NA	NA	NA	ND	NA	28[2]	98	10
Staph. aureus combined	(598)	ND	0	57	ND	98	NA	21	64	100	65	73	99	91	97	100	100	100
for oxacillin: adults	(384)			55[2]														
pediatrics	(66)			79[2]														
Staph. Epidermidis	(77)	ND	0	24	ND	63	NA	27	45	ND	27	24	93	88	38	100	100	91
Streptococcus viridans grp[3]	(23)		65		90													

Table 6. (Cont.)

Tufts Medical Center antibiogram January-December 2013

n=2095 adult and pediatric inpatient isolates from all body site sources. Data are expressed as n(%) susceptible.

Percent Susceptible																
IN-PATIENT, Urine adult	**Penicillins & Related Antibiotics**					**Cephalosporins 1st 3rd 4th generation**					**Aminoglycosides**			**Quinolone**	**Other**		**UTI Agent**
	AMPICILLIN (239)	**AMPICILLIN / SULBACTAM (258)**	**PIPERACILLIN /TAZOBACTAM (259)**	**MEROPENEM (259)**	**ERTAPENEM (262)**	**CEFAZOLIN (261)**	**CEFOXITIN (223)**	**CEFTAZIDIME (242)**	**CEFTRIAXONE (266)**	**CEFEPIME (269)**	**GENTAMICIN (261)**	**TOBRAMYCIN (260)**	**AMIKACIN (273)**	**CIPROFLOXACIN (260)**	**TRIMETHOPRIM/SULFA (241)**	**VANCOMYCIN (239)**	**NITROFURANTOIN (244)**
	48	66	88	77	72	49	62	71	64	77	66	64	72	58	60	14	63

Percent Susceptible										
IN-PATIENT, Urine adult	**Antibiotic Combinations**									
	VANCOMYCIN + PIPERACILLIN /TAZOBACTAM (258)	**VANCOMYCIN + MEROPENEM (226)**	**VANCOMYCIN + ERTAPENEM (229)**	**VANCOMYCIN + CEFTRIAXONE (233)**	**VANCOMYCIN + CEFEPIME (236)**	**TOBRAMYCIN + PIPERACILLIN /TAZOBACTAM (265)**	**TOBRAMYCIN + MEROPENEM (266)**	**TOBRAMYCIN + ERTAPENEM (262)**	**TOBRAMYCIN + CEFEPIME (270)**	**CIPROFLOXACIN + TRIMETHOPRIM/SULFA (244)**
	92	94	87	78	92	92	80	79	79	73

Table 7.

Community-acquired UTI combination antibiogram January-December 2013

n=273 adult inpatient community-acquired UTI urine isolates. Data are expressed as n(%) susceptible.

Percent Susceptible																	
IN-PATIENT, Urine adult	**Penicillins & Related Antibiotics**					**Cephalosporins 1st 3rd 4th generation**					**Aminoglycosides**			**Quinolone**	**Other**		**UTI Agent**
	AMPICILLIN (68)	**AMPICILLIN / SULBACTAM (76)**	**PIPERACILLIN /TAZOBACTAM (80)**	**MEROPENEM (78)**	**ERTAPENEM (82)**	**CEFAZOLIN (83)**	**CEFOXITIN (62)**	**CEFTAZIDIME (70)**	**CEFTRIAXONE (81)**	**CEFEPIME (81)**	**GENTAMICIN (83)**	**TOBRAMYCIN (83)**	**AMIKACIN (83)**	**CIPROFLOXACIN (80)**	**TRIMETHOPRIM/SULFA (82)**	**VANCOMYCIN (78)**	**NITROFURANTOIN (81)**
	49	57	78	67	57	33	48	60	51	67	65	63	66	59	52	22	60

Percent Susceptible										
IN-PATIENT, Urine adult	**Antibiotic Combinations**									
	VANCOMYCIN + PIPERACILLIN /TAZOBACTAM (80)	**VANCOMYCIN + MEROPENEM (74)**	**VANCOMYCIN + ERTAPENEM (77)**	**VANCOMYCIN + CEFTRIAXONE (77)**	**VANCOMYCIN + CEFEPIME (76)**	**TOBRAMYCIN + PIPERACILLIN /TAZOBACTAM (83)**	**TOBRAMYCIN + MEROPENEM (82)**	**TOBRAMYCIN + ERTAPENEM (83)**	**TOBRAMYCIN + CEFEPIME (82)**	**CIPROFLOXACIN + TRIMETHOPRIM/SULFA (83)**
	86	92	81	74	91	84	68	67	68	67

Table 8.

Catheter-related HA-UTI combination antibiogram January-December 2013

n=83 adult inpatient HA-UTI urine isolates collected from indwelling urinary catheters. Data are expressed as n(%) susceptible.

Symptomatic HA-UTI Combination Antibiogram

Of the 235 total isolates included in the HA-UTI combination antibiogram, 174 had a urinalysis positive for UTI, and of these, 74 were from patients with a documented symptom (68 unique patients) (Table 9). Thus, nearly two-thirds of the isolates were ASB. Fever was the most common symptom, occurring in patients from whom 44 of the isolates were obtained (Table 9). Potential risk factors of UTI were found (Table 10) and symptomatic patients were significantly more likely to have an indwelling urinary catheter (n=235, df=1, X^2=4.068, p=0.044) and a longer hospital stay (n=235, df=1, U=4489, p=0.002). The organism distribution of the symptomatic antibiogram was very similar to that of the HA-UTI combination antibiogram, with the same four most prevalent organisms, but with a slightly higher percentage of *E. coli*: 37.8% compared to 31.9% in the HA-UTI combination antibiogram (Table 11, Figure 2). The susceptibilities of the isolates in the symptomatic antibiogram were comparable to those of the HA-UTI combination antibiogram, and cefepime was still effective for 75% of isolates (Table 12). Cefepime with vancomycin only decreased to 91% of isolates susceptible, as compared with 93% in the HA-UTI combination antibiogram, and remained the antibiogram-determined recommended regimen.

Isolates in HA-UTI antibiogram	235	
Isolates with negative urinalysis	52 (22%)	
Isolates without urinalysis	9 (4%)	
Isolates with positive urinalysis	174 (74%)	
Isolates without symptoms	98 (56%)	
Isolates without charts	2 (1%)	
Isolates with symptoms	74 (43%)	
Isolates fever		44
Isolates dysuria		13
Isolates frequency		11
Isolates urgency		8
Isolates suprapubic tenderness		7
Isolates with flank pain		3

Table 9.

Symptomatic isolates from HA-UTI combination antibiogram

n=235 adult inpatient HA-UTI urine isolates with positive culture. n=174 adult inpatient HA-UTI urine isolates with positive culture and urinalysis. n=74 adult inpatient HA-UTI urine isolates with positive culture, positive urinalysis, and documented symptom.

	Number Urinary Catheters	Average Age	Median Age	Number Female	Average Length of Stay (days)	Median Length of Stay (days)
Symptomatic 74	33 (44.6%)	63.4	65	53 (71.6%)	22.8	14.5
Not Symptomatic 161	50 (31.0%)	66.3	70	118 (73.3%)	15.7	10
All Isolates 235	83 (35.3%)	65.4	67	171 (72.8 %)	17.9	11

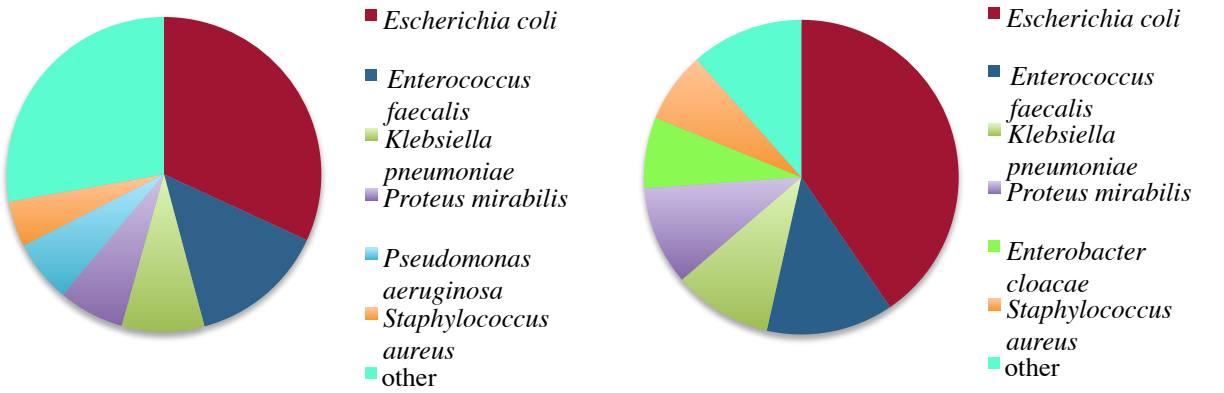
Table 10.

Patient characteristics of isolates from HA-UTI antibiogram

n=235 adult inpatient HA-UTI urine isolates with positive culture. n=74 adult inpatient HA-UTI urine isolates with positive culture, positive urinalysis, and documented symptom. n=161 adult inpatient HA-UTI urine isolates with positive culture and without positive urinalysis *or* documented symptom. Statistical differences were found between symptomatic and asymptomatic patients with urinary catheters (n=235, df=1, X^2=4.068, p=0.044) and a longer hospital stay (n=235, df=1, U=4489, p=0.002).

Organism	Number of Isolates	Percentage of Isolates
Escherichia coli	28	37.8%
Enterococcus faecalis	9	12.2%
Klebsiella pneumoniae	7	9.5%
Proteus mirabilis	7	9.5%
Enterobacter cloacae	5	6.8%
Staphylococcus aureus	5	6.8%
Pseudomonas aeruginosa	4	5.4%
Serratia marcescens	4	5.4%
Enterococcus faecium	1	1.4%
Enterobacter aerogenes	1	1.4%
Citrobacter freundii	1	1.4%
Enterococcus (undifferentiated)	1	1.4%
Klebsiella oxytoca	1	1.4%
Total	74	

Table 11.
Organism distribution of symptomatic HA-UTI combination antibiogram
n=74 adult inpatient HA-UTI urine isolates with positive culture, positive urinalysis, and documented symptom.



HA-UTI combination antibiogram

symptomatic HA-UTI combination antibiogram

Figure 2.
Organism distributions in HA-UTI and symptomatic HA-UTI combination antibiograms
Proportion of six most prevalent organisms and remaining organisms combined of each antibiogram. HA-UTI combination antibiogram: n=235 adult inpatient HA-UTI urine isolates. Symptomatic HA-UTI combination antibiogram: 74 adult inpatient HA-UTI urine isolates with positive culture, positive urinalysis, and documented symptom.

Percent Susceptible																
IN-PATIENT, Urine adult	**Penicillins & Related Antibiotics**					**Cephalosporins 1st 3rd 4th generation**					**Aminoglycosides**			**Quinolone**	**Other**		**UTI Agent**
	AMPICILLIN (59)	**AMPICILLIN / SULBACTAM (63)**	**PIPERACILLIN /TAZOBACTAM (68)**	**MEROPENEM (70)**	**ERTAPENEM (74)**	**CEFAZOLIN (72)**	**CEFOXITIN (61)**	**CEFTAZIDIME (65)**	**CEFTRIAXONE (73)**	**CEFEPIME (73)**	**GENTAMICIN (74)**	**TOBRAMYCIN (73)**	**AMIKACIN (74)**	**CIPROFLOXACIN (73)**	**TRIMETHOPRIM/SULFA (72)**	**VANCOMYCIN (70)**	**NITROFURANTOIN (71)**
	49	60	81	77	70	40	56	71	63	75	68	67	77	64	58	13	56

Percent Susceptible										
IN-PATIENT, Urine adult	**Antibiotic Combinations**									
	VANCOMYCIN + PIPERACILLIN /TAZOBACTAM (70)	**VANCOMYCIN + MEROPENEM (66)**	**VANCOMYCIN + ERTAPENEM (70)**	**VANCOMYCIN + CEFTRIAXONE (69)**	**VANCOMYCIN + CEFEPIME (69)**	**TOBRAMYCIN + PIPERACILLIN /TAZOBACTAM (73)**	**TOBRAMYCIN + MEROPENEM (72)**	**TOBRAMYCIN + ERTAPENEM (74)**	**TOBRAMYCIN + CEFEPIME (73)**	**CIPROFLOXACIN + TRIMETHOPRIM/SULFA (72)**
	86	94	86	78	91	85	78	76	77	74

Table 12.

Symptomatic HA-UTI combination antibiogram January-December 2013

N=74 adult inpatient HA-UTI urine isolates with positive culture, positive urinalysis, and documented symptom. Data are expressed as n(%) susceptible.

Comparison of Regimens

Within the 2014 HA-UTI bacterial isolates, there were 108 isolates from patients who were given an empirical antibiotic (93 unique patients). Potential risk factors were analyzed (Table 13), but IEAT was not significantly more likely in either patients with an indwelling urinary catheter (n=108, df=1, X^2=0.323, p=0.570), or male patients (n=108, df=1, X^2=1.053, p=0.305). The distribution of organisms was very similar to the symptomatic HA-UTI and HA-UTI combination antibiograms, except for an increase in the proportion of *P. aeruginosa* isolates: 12.0% compared to 6.4% and 5.4% in the HA-UTI and symptomatic HA-UTI combination antibiograms respectively (Table 14).

Thirty-one (31) of these isolates were treated with inadequate empirical antibiotics. *E. faecalis* was the species most likely to be treated with an inadequate antibiotic, accounting for 35.5% of all inadequate prescriptions (Table 15, Figure 3). Ciprofloxacin was the most frequently given regimen, comprising nearly a third of all prescriptions, and was adequate in 77.1% of cases (Table 16, Figure 4). Cefepime with vancomycin was the third most commonly prescribed regimen, and adequate in 93.3% of isolates. Cefepime alone was adequate in 100% of isolates, but was only prescribed twice. In total, the empirically-given antibiotics were adequate for 71.3% of the isolates, and appropriate (according to the treatment and dosing guide) for 19.4% of isolates (Table 17). Cefepime would have been adequate for 77.8% of isolates, and cefepime with vancomycin would have been adequate for 92.6% of isolates (Table 17).

The increase in percentage of isolates susceptible to cefepime was not statistically significant compared to the percentage of isolates susceptible to the empirical regimens (n=108, df=1, p=0.092285). In contrast, there was a statistically significant increase in the percentage

susceptible to cefepime with vancomycin compared to both cefepime alone (n=108, df=1, p=0.0000305176) and to the empirical regimens (n=108, df=1, p=0.00000155).

	Number Urinary Catheter	Average Age	Median Age	Female	Average Length of Stay (days)	Median Length of Stay (days)
Adequate (77)	23 (29.9%)	67.05	70	55 (71.4%)	18	16
Inadequate (31)	11 (35.5%)	70.58	73	19 (61.3%)	15.7	15
All Isolates (108)	34 (31.5%)	68.0	71	74 (68.5%)	17.8	15

Table 13.

Patient characteristics of 2014 HA-UTI empirical antibiotic therapy

n=108 adult inpatient HA-UTI urine isolates treated with empirical antibiotic therapy. n=77 adult inpatient HA-UTI urine isolates treated with adequate empirical antibiotic therapy. n=31 adult inpatient HA-UTI urine isolates treated with inadequate empirical antibiotic therapy.

Organism	Number of Isolates	Percent of Isolates
Escherichia coli	38	35.2%
Pseudomonas aeruginosa	13	12.0%
Enterococcus faecalis	13	12.0%
Klebsiella pneumoniae	10	9.3%
Proteus mirabilis	6	5.6%
Staphylococcus aureus	6	5.6%
Enterococcus faecium	5	4.6%
Enterobacter cloacae	4	3.7%
Morganella morganii	3	2.8%
Citrobacter koseri	2	1.9%
β-hemolytic Streptococcus B	2	1.9%
Klebsiella oxytoca	2	1.9%
Enterobacter aerogenes	1	0.9%
Proteus vulgaris	1	0.9%
Enterococcus (undifferentiated)	1	0.9%
Citrobacter (undifferentiated)	1	0.9%
Total	108	

Table 14.

Organism distribution of 2014 HA-UTI empirical antibiotic therapy

n=108 adult inpatient HA-UTI urine isolates treated with empirical antibiotic therapy.

Species	Number of Isolates	Percent of all Inadequate Prescriptions
Enterococcus faecalis	11	35.5%
Escherichia coli	5	16.1%
Pseudomonas aeruginosa	4	12.9%
Enterococcus faecium	4	12.9%
Klebsiella pneumoniae	2	6.5%
Proteus mirabilis	1	3.2%
Staphylococcus aureus	1	3.2%
Klebsiella oxytoca	1	3.2%
Enterobacter cloacae	1	3.2%
Enterococcus (undifferentiated)	1	3.2%
Total	31	

Table 15.

Organisms treated with IEAT in 2014 HA-UTI empirical antibiotic therapy

n=31 adult inpatient HA-UTI urine isolates treated with inadequate empirical antibiotic therapy.

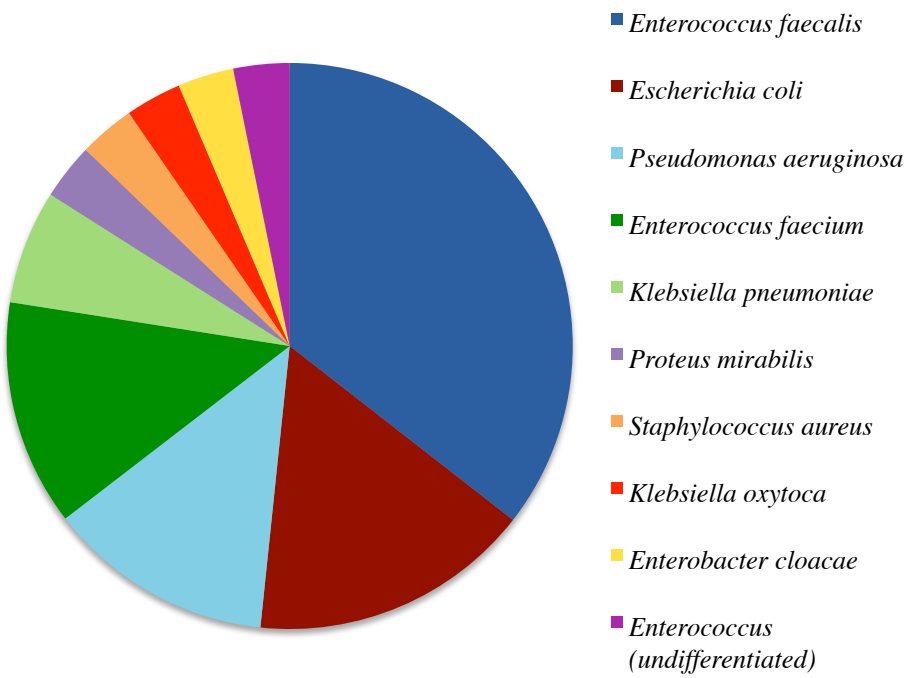


Figure 3.
Proportion of organisms treated with IEAT in 2014 HA-UTI empirical antibiotic therapy
n=31 adult inpatient HA-UTI urine isolates treated with inadequate empirical antibiotic therapy

Antibiotic Regimen	Prescribed	Adequate
Ciprofloxacin	35 (32.4%)	27 (77.1%)
Ceftriaxone	19 (17.6%)	12 (63.2%)
Cefepime & Vancomycin	15 (13.9%)	14 (93.3%)
Trimethoprim/Sulfa	9 (8.3%)	6 (66.7%)
Nitrofurantoin	7 (6.5%)	4 (57.1%)
Cefazolin	4 (3.7%)	2 (50.0%)
Vancomycin	3 (2.8%)	1 (33.3%)
Linezolid	3 (2.8%)	3 (100.0%)
Cefepime	2 (1.9%)	2 (100.0%)
Meropenem	2 (1.9%)	2 (100.0%)
Ertapenem	2 (1.9%)	1 (50.0%)
Pipieracillin/Tazobactam &Vancomycin	2 (1.9%)	1 (50.0%)
Ciprofloxacin & Trimethoprim/Sulfa	2 (1.9%)	1 (50.0%)
Ciprofloxacin & Cefazolin	1 (0.9%)	0 (0%)
Amikacin and Meropenem	1 (0.9%)	0 (0%)
Aztreonam	1 (0.9%)	1 (100%)
Total 108		77 (71.3%)

Table 16.
Regimens of 2014 HA-UTI empirical antibiotic therapy
n=108 adult inpatient HA-UTI urine isolates treated with empirical antibiotic therapy.

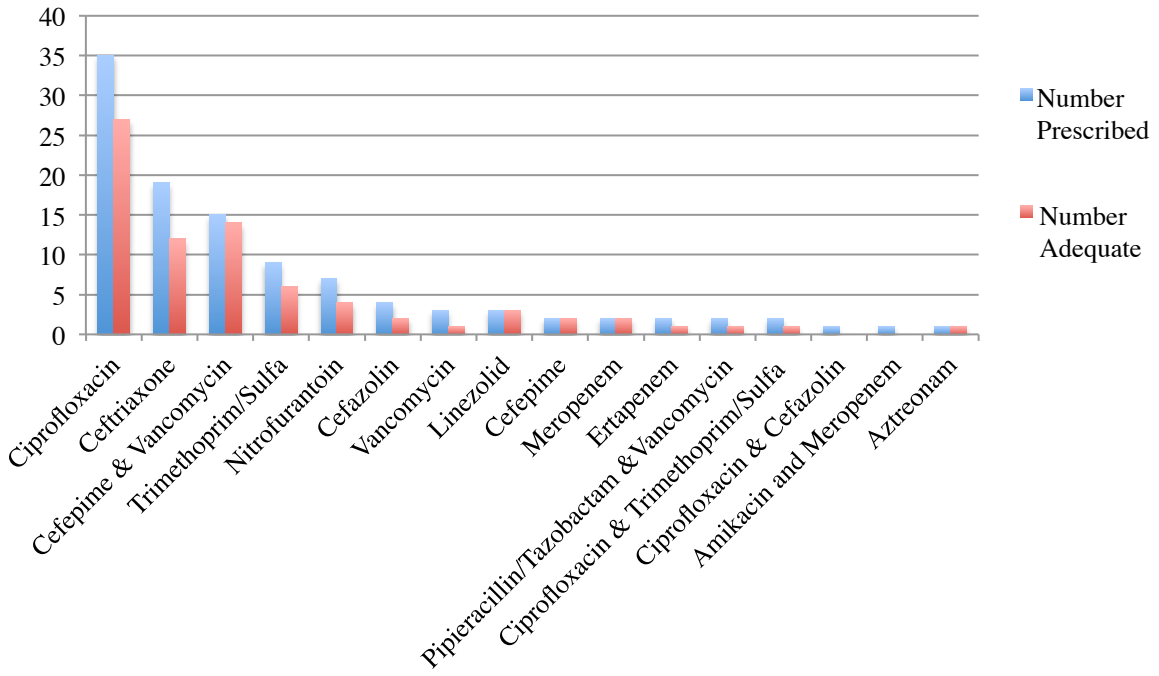


Figure 4.
Regimens of 2014 HA-UTI empirical antibiotic therapy
n=108 adult inpatient HA-UTI urine isolates treated with empirical antibiotic therapy

Regimen	Percent Adequate	Percent Appropriate
Actual Prescriptions	71.3%	19.4%
Cefepime	77.8%	
Cefepime & Vancomycin	92.6%	

Table 17.
Comparison of regimens for 2014 HA-UTI empirical antibiotic therapy
n=108 adult inpatient HA-UTI urine isolates treated with empirical antibiotic therapy. Cefepime with vancomycin had significantly higher percentage of isolates susceptible than cefepime alone (n=108, df=1, p=0.0000305176) and to the empirical regimens (n=108, df=1, p=0.00000155).

Discussion

Contributions to Previous Research

The discrepancy between the susceptibilities of prevalent pathogens in the traditional 2013 Tufts Medical Center antibiogram and the susceptibilities in the UTI combination antibiograms highlights distinct uropathogen resistance, and the utility of disease-specific antibiograms. Additionally, the low efficacies of single antibiotics in the UTI-combination antibiograms emphasize the advantage of including dual regimens.

A unique antibiogram for HAIs provides users with a better understanding of the resistance patterns of pathogens transmitted within the hospital, which infect the most vulnerable patients, and thus require early effective treatment. The community-acquired UTI combination antibiogram represents a diverse patient population, which did not acquire the infection within the hospital, but their severity of illness that required hospitalization distinguishes the resistance trends from those of the general community. These infections are distinct from HAIs, and have different recommendations for empirical antibiotic therapy. Although there was a high degree of similarity between the HA-UTI and community-acquired combination antibiograms, the inherent variability of pathogens that are acquired anywhere outside of the hospital warrants the creation of separate antibiograms to regularly assess resistance trends for both groups.

The prevalence of all *Enterococcus* species was slightly higher in the HA-UTI combination antibiogram (20.8%) than in the symptomatic HA-UTI combination antibiogram (15.0%), but both were greater than that in the Hebert et al. WISCA (10%).[55] This is expected, since the WISCA included only community-acquired isolates, but interestingly, our community-acquired UTI combination antibiogram also had a higher proportion of *Enterococcus* species (17.6%). The SENTRY surveillance report of combined community-acquired and HA-UTI rate

of *Enterococcus* isolates in North America (15.8%) was within the range of the prevalence in our antibiograms.[17]

Our study supports other findings that urinary catheters are a risk factor for symptomatic UTI,[8] and we also found an association between a longer hospital stay and a symptomatic UTI. In the urinary antibiogram created by Rabs et al., 66% were identified as true infections based on a final diagnosis of UTI.[54] However, this high rate was likely impacted by the inclusion of only the four most prevalent gram-negative UTI pathogens, and perhaps also misdiagnosis. Our study found that the majority of isolates in the HA-UTI combination antibiogram were not true infections, with only 31.5% of isolates collected from patients with a positive urinalysis and documented symptoms. Despite the high prevalence of isolates of ASB, the similarity between the HA-UTI and symptomatic HA-UTI combination antibiograms confirms the necessity of a regimen with activity against gram-positive bacteria, and that cefepime with vancomycin is still the optimal recommendation.

It is alarming that over two thirds of isolates in the HA-UTI combination antibiogram did not have a positive urinalysis and recorded symptom. In some cases it may be a lack of examination or documentation of urinary symptoms, but many are likely asymptomatic patients whose specimens were cultured because the ramifications are not fully understood. To be an optimal guide for treatment, antibiograms must be representative of pathogenic organisms, and thus include only isolates from symptomatic patients. When colonizing bacteria are included, the hospital does not have an accurate view of pathogenic organisms or trends in resistance to assess current practices and provide recommendations. Additionally, the presence of colonization may sway physicians to elect for treatment, subjecting the patient to unnecessary antibiotics with potential adverse effects. Furthermore, because certain infections must be reported to national

organizations, these cases of colonization inflate the true prevalence of infection, which has a significant impact on healthcare reimbursement, and it may be a determining factor for a patient choosing where to receive care. Although our study showed comparable resistance patterns between organisms causing symptomatic infections and ASB, this may not always be the case, and if the evidently non-infectious episodes are not cultured, the utility of the antibiogram, and the benefits for the patients and institution, will be greatly increased.

The rate of inadequate empirical antibiotic therapy (IEAT) of HA-UTI found in this study (29.4%) is strikingly similar to the results of Esparcia et al. (29.3%) for both community-acquired and HA-UTI isolates.[42] However, in Esparcia et al., the rate of IEAT for HA-UTI isolates alone was significantly higher (67%).[42] This may be because the study only included geriatric patients, who are infected by non-typical pathogens with greater resistance.[58] In our study, the indication that infection by *E. faecalis* is a risk factor for IEAT, evidenced by comprising 35.5% of isolates with IEAT, is supported by Esparcia et al., which found a statistically significant correlation.[42]

Ciprofloxacin, the most frequently prescribed regimen, comprised nearly a third of all empirical therapy, and was inadequate in 22.9% of isolates. This is troubling considering both the overall low sensitivity in the traditional 2013 Tufts Medical Center antibiogram, and the well-documented escalation of fluoroquinolone resistance in urinary pathogens.[17,36] Cefepime with vancomycin was the third most common regimen, but it is unlikely this regimen was chosen solely for presumed UTI. These cases are likely treating for the potential of pneumonia as well, since this is the recommended regimen for healthcare-associated pneumonia, and it is common to collect and culture all body fluids when there is an infection at an unknown site.

It is unclear why the recommended regimen (cefepime) was only prescribed in 1.9% of the isolates, and only 19.4% of regimens contained one of the appropriate antibiotics listed in the Tufts Medical Center treatment and dosing guide. Possible explanations could be that practitioners are unaware of the recommendations; there was a high rate of patients with special circumstances (i.e. allergies and drug interactions); or the antibiotic selection was based on personal preferences of the practitioners. It would be useful to conduct a survey of physician antimicrobial selection to understand the rationale for their choices, and gauge their awareness of the recommendations.

The HA-UTI, catheter-related HA-UTI, and symptomatic HA-UTI combination antibiograms determined a regimen with a significantly higher susceptibility than that of both the current recommended regimen, and that of the empirically prescribed regimens. This agrees with the findings of Fox et al., in which the dual cross-table antibiogram-determined regimen had statistically higher percentage susceptible than the popular combination at the hospital.[53] Cefepime with vancomycin had a significantly higher efficacy than both cefepime alone and the prescribed regimens because it was active against most *Enterococcus* isolates, which accounted for the majority of cases not covered by the other two regimens.

Study Implications

HAIs and antimicrobial resistance are two of the greatest threats in modern healthcare, and this study is valuable because our new method of presenting antibiotic resistance data addresses the two-fold challenge of adequately treating infections while minimizing the emergence of resistance. The HA-UTI combination antibiogram has the potential to be applied to additional infections, but the infection must have a high prevalence in order to have a sufficient

sample size. We have demonstrated the feasibility of producing customized antibiograms, and have shown their utility for patient care. The significantly higher susceptibility of the HA-UTI combination antibiogram-determined regimen compared to both the current recommendation and actual prescriptions shows the ability of this novel antibiogram to guide effective empirical treatment.

The results of this study indicate that the recommended empirical regimen for HA-UTI at Tufts Medical Center should be changed from cefepime alone to cefepime combined with vancomycin. If practitioners follow this suggestion, there should be an increase in patients with HA-UTIs who are successfully treated with empirical antibiotics. If there were to be a switch in the recommendation, information should be disseminated to ensure that physicians are aware of the change, and the rationale behind it. If this antibiogram were to be distributed, there would need to be an explanation of the novel aspects and its implications, so it is not inadvertently used as the traditional antibiogram. There should be data collection prior to and following the switch to assess if there is a change in clinical practice, and if so, if there is an increase in the prescription of adequate empirical antibiotics. Additionally, it would be beneficial to collect data on patient outcomes—including length of hospital stay, spread of infection, and case fatality rate—to further assess the impact of utilizing this novel antibiogram.

If there is hesitancy to change to a recommended regimen with extended antibacterial coverage, further research could assess the effects of IEAT for HA-UTI, which may demonstrate the necessity of additional antimicrobial use. Another option would be to evaluate patient characteristics that may be risk factors for IEAT—including urinary catheter, recurrent UTI, prior antibiotic use, and recent hospitalization—with the goal of identifying these patients and giving them broader treatment, without recommending this regimen for all patients. This study

did not find statistical associations between IEAT and a few selected patient characteristics (urinary catheter, age, gender, length of hospital stay), but different risk factors or study designs may reveal trends. However, since the selection of appropriate empirical therapy requires consideration of many of the risk factors for IEAT, in theory most of these patients should already be identified.

Study Limitations

Limitations to this research primarily resulted from retrospective data collection. Determining the acquisition of infection could be complicated; in some cases, the medical record documented that the patient experienced symptoms on the first or second day after hospital admission, but the urine specimen was not collected until the third day or later. These isolates were removed from the HA-UTI combination antibiogram and added to the community-acquired combination antibiogram, but it is possible that there were others that went undetected.

An additional challenge was the identification of symptomatic cases. Many patients' medical records did not include documented UTI symptoms, but also did not record why the sample was cultured. Patients determined to be non-symptomatic may have had symptoms that were not recorded. Another potential reason for a lack of recorded symptoms could be that patients with altered mental status or in critical condition may have been unable to communicate symptoms, and thus could only be identified as symptomatic if they developed a fever. Conversely, other isolates that were included may not be from true symptomatic UTI, such as isolates with fever as the only symptom, which may be indicative of another infection site. Additionally, if a urine culture is growing more than two species it is considered contaminated with bacterial flora, but if only two species are present both are considered pathogens. There is

no way to determine if both organisms are responsible for the symptoms, and thus some of these cases may have resulted in the inclusion of a colonization isolate in the antibiogram. However, there were only six cultures with two organisms within the symptomatic antibiogram, so it is unlikely that this significantly affected the results.

Defining the criteria of an empirical antibiotic for this study was also complicated. To be empirical it must be prescribed without any knowledge of which microbe will grow, but the clinical microbiology lab relays information about the culture to the practitioner as it is discovered. The results are typically updated at each stage: if an organism is growing, if bacteria are gram-positive or negative, which species, and lastly the final report with antibiotic susceptibility testing. It was impossible to know when the physician became aware of each of these results, and thus antibiotics were defined as empirical based on a universal time cutoff. This approach cannot account for the particular circumstances in each episode, but overall will reflect the majority of empirical prescriptions. There is also the potential that some of the antibiotics were not intended for a suspected UTI. Isolates were excluded if there was documentation in the electronic discharge summary that the antibiotic was prescribed for another purpose, or if expert opinion considered them non-relevant. However, in many cases the practitioner may not know the source of infection, or the presumed site may not be documented in the discharge summary.

Conclusions

Empirical therapy is challenging, especially for HAIs, and ineffective choices are being made at an unacceptable rate. The consequences of inadequate use of antibiotics pose serious challenges amidst the current high incidence of HAIs and escalating antibiotic resistance. Antibiograms are a valuable resource to understand the specific pathogens and resistance trends at a healthcare facility. With this knowledge, the patterns in antibiotic resistance can be monitored, and unknown organisms can be treated with a better chance of accuracy. This study has demonstrated that a customized antibiogram is a better reflection of antibiotic susceptibility, and thus increases the likelihood of successful empirical treatment. Antibiograms with greater precision will be instrumental in the optimal selection of empirical antibiotics, benefiting the patient, hospital and community.

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Supplements

Supplement 1. Assumptions from Hebert et al.

Antibiotic	Organisms Covered	Organisms Not Covered
Ampicillin	β-hemolytic *streptococcus*	*Staphylococcus aureus***
Ampicillin-sulbactam	β-hemolytic *streptococcus* Gram positives excluding *enterococcus**** *Enterobacteriaceae* ***	*Pseudomonas aeruginosa* *Staphylococcus aureus***
Piperacillin-tazobactam	β-hemolytic *streptococcus* *Gram positives excluding enterococcus**** *Enterobacteriaceae excluding Acinetobacter*****	*Staphylococcus aureus***
Meropenem	β-hemolytic *streptococcus* *Gram positive excluding enterococcus**** *Enterobacteriaceae* *****	*Staphylococcus aureus***
Ertapenem	β-hemolytic *streptococcus*	*Enterococcus* species *Pseudomonas aeruginosa* *Staphylococcus aureus***
Cefazolin	β-hemolytic *streptococcus*	*Enterococcus* species *Pseudomonas aeruginosa* *Staphylococcus aureus***
Cefoxitin	β-hemolytic *streptococcus*	*Enterococcus* species *Staphylococcus aureus***
Ceftazidime	β-hemolytic *streptococcus*	*Enterococcus* species *Staphylococcus aureus***
Ceftriaxone	β-hemolytic *streptococcus*	*Enterococcus* species *Pseudomonas aeruginosa* *Staphylococcus aureus***
Cefepime	*Streptococcus species*	*Enterococcus species* *Staphylococcus aureus***
Ciprofloxacin		*Enterococcus species** *Streptococcus species**
Trimethoprim-sulfamethoxazole		*Pseudomonas aeruginosa*

*Unless tested and found to be susceptible
**If resistant to Methicillin/Oxacillin
***If sensitive to Ampicillin
****If sensitive to Ampicillin-sulbactam
*****If sensitive to Piperacillin-tazobactam

Supplement 2. Additional Assumptions for this Study

Antibiotic	Organisms Covered	Organisms Not Covered
Ampicillin	*Staphylococcus epidermidis ****	*Staphylococcus aureus****
Ampicillin-sulbactam	*Enterococcus***	*Enterococcus**

	Staphylococcus epidermidis ***	*Staphylococcus aureus****
Piperacillin-tazobactam	*Enterococcus*** *Staphylococcus epidermidis ***	*Enterococcus** *Staphylococcus aureus****
Meropenem	*Staphylococcus epidermidis ***	*Enterococcus* *Staphylococcus aureus****
Ertapenem	*Staphylococcus epidermidis ***	*Staphylococcus aureus****
Cefazolin	*Staphylococcus epidermidis ***	*Staphylococcus aureus****
Cefoxitin	*Staphylococcus epidermidis ***	*Staphylococcus aureus****
Ceftazidime	*Staphylococcus epidermidis ***	*Staphylococcus aureus****
Ceftriaxone	*Staphylococcus epidermidis ***	*Staphylococcus aureus****
Cefepime	*Staphylococcus epidermidis ***	*Staphylococcus aureus****
Gentamicin		*Enterococcus* *Staphylococcus* *Streptococcus*
Tobramycin		*Enterococcus* *Staphylococcus* *Streptococcus*
Amikacin		*Enterococcus* *Staphylococcus* *Streptococcus*
Trimethoprim-sulfamethoxazole		*Enterococcus*
Vancomycin	*Staphylococcus* *Streptococcus*	Gram negatives
Nitrofurantoin		*Pseudomonas aeruginosa*

*If resistant to Ampicillin
**If sensitive to Ampicillin
***If sensitive to Oxacillin
****If resistant to Oxacillin

Supplement 3. Assumptions for Antibiotic Combinations

Antibiotics	**Organisms Not Covered**	**Organisms Excluded**
	No vancomycin Data and resistant to second antibiotic	Resistant to vancomycin and without data for second antibiotic
Vancomycin and Piperacillin-tazobactam	*Serratia marcescens* *Enterococcus species*	*Citrobacter freundii* *Enterobacter cloacae* *Enterobacter aerogenes* *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Morganella morganii* *Serratia marcescens*
Vancomycin and Meropenem	*Enterococcus species*	*Enterobacter cloacae* *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Morganella morganii* *Pseudomonas aeruginosa* *Serratia marcescens*
Vancomycin and Ertapenem	*Enterococcus species*	*Acinetobacter lwoffii* *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Morganella morganii*
Vancomycin and Ceftriaxone	*Enterococcus species*	*Citrobacter amalonaticus* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli*
Vancomycin and Cefepime	*Enterococcus species*	*Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae*
	No tobramycin data and resistant to second antibiotic	Resistant to tobramycin and without data for second antibiotic
Tobramycin and Piperacillin-tazobactam	*Escherichia coli*	*Staphylococcus epidermidis*
Tobramycin and Meropenem		*Escherichia coli* *Klebsiella oxytoca* *Staphylococcus epidermidis*
Tobramycin and Ertapenem		*Staphylococcus epidermidis*
Tobramycin and Cefepime		*Enterobacter cloacae* *Escherichia coli* *Staphylococcus epidermidis*
		Resistant to Trimethoprim-sulfamethoxazole and without data for Ciprofloxacin
Ciprofloxacin and Trimethoprim-sulfamethoxazole		Pseudomonas aeruginosa
		Resistant to Ciprofloxacin and without data for Trimethoprim-sulfamethoxazole
Ciprofloxacin and Trimethoprim- sulfamethoxazole		*Enterobacter cloacae* *Escherichia coli*

Supplement 4. CDC/NHSN HAI Definition

Date of Event (Event Date):

The Date of Event is the date the first element used to meet an NHSN site-specific infection criterion occurs for the first time within the seven-day infection window period.

> An infection is considered **Present on Admission (POA)** if the date of event of the NHSN site-specific infection criterion occurs during the POA time period, which is defined as the day of admission to an inpatient location (calendar day 1), the 2 days before admission, and the calendar day after admission. For purposes of NHSN surveillance and determination of the Repeat Infection Timeframe (as defined below) if the date of event is determined to be either of the two days prior to inpatient admission, then the date of event will be hospital day 1.
>
> An infection is considered a **Healthcare-associated Infection (HAI)** if the date of event of the NHSN site-specific infection criterion occurs on or after the 3rd calendar day of admission to an inpatient location where day of admission is calendar day 1.

Table 3: Date of Event and Classification Determination

Hospital Day	Date of Event Assignment for RIT	Classification
2 days before admit	Hospital Day 1	POA
1 day before admit	Hospital Day 1	
1	Hospital Day 1	
2	Hospital Day 2	
3	Hospital Day 3	HAI
4	Hospital Day 4	
5	Hospital Day 5	

http://www.cdc.gov/nhsn/PDFs/pscManual/2PSC_IdentifyingHAIs_NHSNcurrent.pdf

Supplement 5. CDC Symptomatic UTI Criteria and Modifications

Criterion 2a Patient had an indwelling catheter in place for >2 calendar days*, with the day of device placement being Day 1, and catheter was in place on the date of the event *and* at least one of the following symptoms: fever (>38°C)**; suprapubic tenderness; costovertebral angle pain or tenderness doesn't include dysuria, frequency, urgency *and* at least 1 of the following findings: leukoesterase, or nitrite, or pyuria (>5 WBC/high power field of spun urine), or microorganisms seen on a Gram's stain of unspun urine*** *and* a positive urine culture of $\geq 10^3$ and $\leq 10^5$ CFU/ml**** and with no more than 2 species of microorganisms*****. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements*****.
Criterion 2b Patient did <u>not</u> have an indwelling urinary catheter that had been in place for >2 calendar days* and in place at the time of, or the day before the day of the event *and* has at least one of the following signs or symptoms: fever (>38°C)** in a patient that is ≤65 years of age; urgency; frequency; dysuria; suprapubic tenderness; costovertebral angle pain or tenderness *and* at least 1 of the following findings: leukoesterase, or nitrite, or pyuria (>5 WBC/high power field of spun urine), or microorganisms seen on a Gram's stain of unspun urine*** *and* a positive urine culture of $\geq 10^3$ and $\leq 10^5$ CFU/ml**** and with no more than 2 species of microorganisms. Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day between two adjacent elements*****.
*Catheter insertion date not noted **38 (considered fever if noted by healthcare practitioner) *** didn't check gram stain **** Tufts Medical Center microbiology lab doesn't cap CFU/ml ***** Mixed bacterial flora noted with some isolates ****** ±2 calendar days for UA and UCx, symptoms associated with culture

Supplement 6. Assumptions for Prescribed Regimens

Antibiotic	**Organisms Covered**
Aztreonam	*P. aeruginosa*
Linezolid	*S. aureus* *E. faecalis*

Supplement 7. Chi-square test: presence of symptoms and indwelling urinary catheter

group * foley Crosstabulation

			foley		
			yes	no	Total
group	No_Sx	Count	50	111	161
		% within group	31.1%	68.9%	100.0%
		% within foley	60.2%	73.0%	68.5%
		% of Total	21.3%	47.2%	68.5%
	Sx	Count	33	41	74
		% within group	44.6%	55.4%	100.0%
		% within foley	39.8%	27.0%	31.5%
		% of Total	14.0%	17.4%	31.5%
Total		Count	83	152	235
		% within group	35.3%	64.7%	100.0%
		% within foley	100.0%	100.0%	100.0%
		% of Total	35.3%	64.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.068[a]	1	.044		
Continuity Correction[b]	3.497	1	.061		
Likelihood Ratio	4.005	1	.045		
Fisher's Exact Test				.056	.031
N of Valid Cases	235				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 26.14.

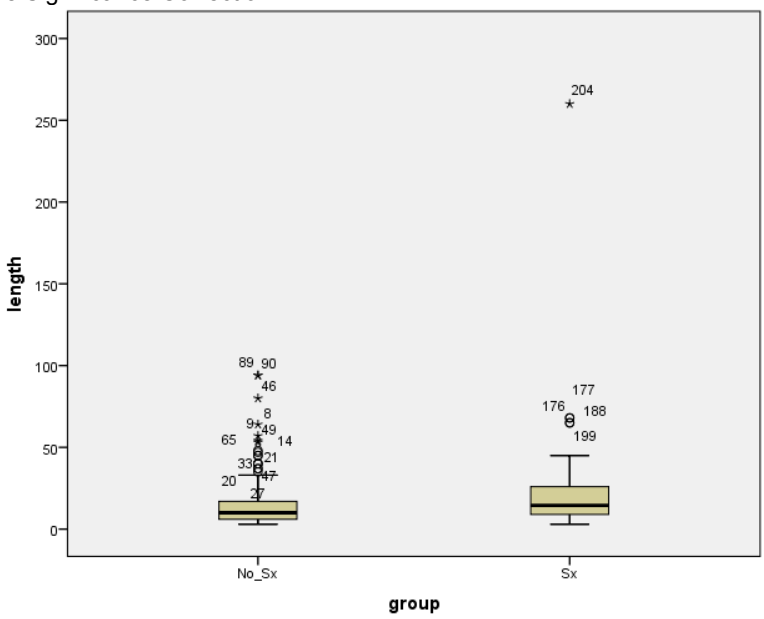
b. Computed only for a 2x2 table

Supplement 8. Mann-Whitney U test: presence of symptoms and length of hospital stay

Tests of Normality

	group	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
length	No_Sx	.244	161	.000	.693	161	.000
	Sx	.276	74	.000	.459	74	.000

a. Lilliefors Significance Correction



Mann-Whitney Test

Ranks

	group	N	Mean Rank	Sum of Ranks
length	No_Sx	161	108.88	17530.00
	Sx	74	137.84	10200.00
	Total	235		

Test Statistics[a]

	length
Mann-Whitney U	4489.000
Wilcoxon W	17530.000
Z	-3.037
Asymp. Sig. (2-tailed)	.002

a. Grouping Variable: group

Supplement 9. Chi-square test: adequacy of empirical therapy and gender

Group * Gender Crosstabulation

			Gender		
			female	male	Total
Group	adequate	Count	55	22	77
		% within Group	71.4%	28.6%	100.0%
		% within Gender	74.3%	64.7%	71.3%
		% of Total	50.9%	20.4%	71.3%
	inadequa	Count	19	12	31
		% within Group	61.3%	38.7%	100.0%
		% within Gender	25.7%	35.3%	28.7%
		% of Total	17.6%	11.1%	28.7%
Total		Count	74	34	108
		% within Group	68.5%	31.5%	100.0%
		% within Gender	100.0%	100.0%	100.0%
		% of Total	68.5%	31.5%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.053[a]	1	.305		
Continuity Correction[b]	.636	1	.425		
Likelihood Ratio	1.032	1	.310		
Fisher's Exact Test				.362	.211
N of Valid Cases	108				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 9.76.
b. Computed only for a 2x2 table

Supplement 10. Chi-square test: adequacy of empirical therapy and indwelling urinary catheter

group * foley Crosstabulation

			foley		
			yes	no	Total
group	adequate	Count	23	54	77
		% within group	29.9%	70.1%	100.0%
		% within foley	67.6%	73.0%	71.3%
		% of Total	21.3%	50.0%	71.3%
	inadequa	Count	11	20	31
		% within group	35.5%	64.5%	100.0%
		% within foley	32.4%	27.0%	28.7%
		% of Total	10.2%	18.5%	28.7%
Total		Count	34	74	108
		% within group	31.5%	68.5%	100.0%
		% within foley	100.0%	100.0%	100.0%
		% of Total	31.5%	68.5%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.323[a]	1	.570		
Continuity Correction[b]	.115	1	.734		
Likelihood Ratio	.319	1	.572		
Fisher's Exact Test				.649	.363
N of Valid Cases	108				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 9.76.
b. Computed only for a 2x2 table

Supplement 11. McNemar Test: comparison of regimens

McNemar Test

Crosstabs

Rx_covered & Cefe_covered

Rx_covered	Cefe_covered	
	yes	no
yes	74	3
no	10	21

Test Statistics[a]

	Rx_covered & Cefe_covered
N	108
Exact Sig. (2-tailed)	.092[b]

a. McNemar Test

b. Binomial distribution used.

McNemar Test

Crosstabs

Cefe_covered & CefeVanco_covered

Cefe_covered	CefeVanco_covered	
	yes	no
yes	84	0
no	16	8

Test Statistics[a]

	Cefe_covered & CefeVanco_covered
N	108
Exact Sig. (2-tailed)	.0000305176[b]

a. McNemar Test

b. Binomial distribution used.

McNemar Test

Crosstabs

Rx_covered & CefeVanco_covered

Rx_covered	CefeVanco_covered	
	yes	no
yes	76	1
no	24	7

Test Statistics[a]

	Rx_covered & CefeVanco_covered
N	108
Exact Sig. (2-tailed)	.000001550[b]

a. McNemar Test

b. Binomial distribution used.