OVERUSE OF ANTIBIOTICS FOR ASYMPTOMATIC BACTERIURIA IN A UNIVERSITY TEACHING HOSPITAL

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ABSTRACT

Public Health Significance: Antibiotic resistance is an increasingly important public health issue. Antibiotic resistance emerges from antibiotic use, and unnecessary and incorrect usage of these drugs is accelerating the increasing prevalence and severity of resistant organisms. Misdiagnosis of a urinary tract infection is one of the main causes of unnecessary antibiotic use.

Problem Statement: Antibiotic overuse can lead to adverse patient outcomes, and antibiotics should be used judiciously and according to published treatment guidelines. Many clinicians at healthcare facilities do not adhere to treatment guidelines for asymptomatic bacteriuria; often clinicians incorrectly give asymptomatic patients a diagnosis of a urinary tract infection which has been shown to yield high rates of unnecessary antibiotic use.

Objective: To determine whether the University Teaching Hospital adheres to IDSA treatment guidelines for UTI and ABU for this cohort of patients and explore the relationship between failure to adhere to IDSA guidelines of treatment of ABU and excess pharmaceutical costs.

Setting: A public acute care teaching hospital affiliated with a local state university in central Texas.

Participants: Patients included in the cohort were at least 18 years of age and admitted to the hospital for >2 days between the dates of September 2011 and February 2012 and diagnosed with a UTI.

Main outcome measures: Frequency of patients who were incorrectly diagnosed with a UTI who were asymptomatic and treated inappropriately, total number of antibiotics used for these patients, and the costs of these unnecessary antibiotics.

Results: Of the 88 included patients, 26 patients (29.5%) had no documentation of any symptoms of a UTI but were diagnosed and treated inappropriately. There were a total of 353 doses given to these patients for a total excess cost of $512.45. Eleven patients (12.5%) were classified as a "questionable" diagnosis of a UTI because documentation was not clear enough to indicate if the patient had a UTI or ABU. There were a total of 234 doses given to these patients for a total excess cost of $271.76.

Conclusion: Based upon this sample, clinicians in this facility do not strictly adhere to IDSA treatment guidelines. The clinicians could benefit from an antibiotic stewardship program or an educational intervention to improve adherence to the current IDSA guidelines.

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1.0 INTRODUCTION

Globally, healthcare professionals are concerned about the increasing prevalence and incidence of antibiotic resistant organisms and their facility's relationship with the emergence of resistance. Since antibiotic resistance is a product of antibiotic use, hospital systems need to be especially diligent in the monitoring of their rates of antibiotic use. One way of slowing the development of resistant organisms is to limit the amount of unnecessary antimicrobial prescriptions for patients who many not need treatment. Throughout the country, studies are finding high rates of asymptomatic bacteriuria (ABU) that is being improperly diagnosed as a urinary tract infection (UTI) and inappropriately treated with antibiotics. Recommendations for screening and treatment for ABU have been published by the Infectious Diseases Society of America (IDSA) guidelines.

This project will review why inappropriate antibiotic use is an increasingly important public health problem that affects healthcare systems universally, and will analyze the existing literature of the overuse of antibiotics overall and also for patients with ABU. This project will also highlight the resulting harmful effects of overuse of antibiotic with a focus on increased adverse reactions, the emergence of antibiotic resistance, increased healthcare costs, and increased length of hospitalization.

This study will assess one particular hospital's adherence to treatment guidelines for ABU to determine their baseline rate of antibiotic prescription for patients who were asymptomatic and improperly diagnosed and treated with antibiotics for a UTI when no

treatment was recommended by IDSA. As a stewardship effort, a true assessment is needed of the rates of ABU and this University Teaching Hospital (UTH)'s compliance with the IDSA's treatment guidelines in order to ensure the highest quality of care for all patients. This project will assess the need for future education of hospital staff at the UTH. Discussion of different types of antibiotic stewardship programs (ASP) that have been developed to combat antimicrobial overuse and its subsequent problems will be addressed, and recommendations will be suggested for the best intervention based on successes seen in other healthcare facilities for ABU overtreatment interventions.

Based on recent findings in the literature and observations made by the clinical pharmacy specialists, our hypothesis is that clinicians at this hospital are not strictly adhering to the IDSA treatment guidelines and are treating asymptomatic patients unnecessarily.

2.0 BACKGROUND

2.1 ANTIBIOTICS AND THE RISE OF ANTIBIOTIC RESISTANCE

The increasing prevalence of antibiotic resistance is considered by the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and many scientists to be one of today's most pressing public health problems. Resistance to almost every type of antimicrobial is increasing globally, and the emergence of pan-drug-resistant and extremely drug-resistant organisms is becoming more and more frequent.[1] Common infections are becoming more difficult to treat, and resistant infections are becoming time-consuming and expensive to cure. Current antibiotics are becoming less effective, and the lack of antibiotic agents in development that could combat resistant organisms is even more problematic.

When a patient uses antibiotics it applies selective pressures on internal bacteria and drives the emergence of resistant organisms. When a new antibiotic is introduced in a clinical setting, initially the targeted organism will be susceptible to the drug, and it will be prohibited from replicating or be killed. As the antibiotic is used more frequently, bacteria develop ways to resist the drug's effects and reduce their susceptibility. New strains have emerged and will continue to emerge with resistance to a drug or a whole drug class.[2]

Since resistance arises with antibiotic use, it is important to use antibiotics as judiciously as possible. Antibiotic use is especially common in healthcare facilities. Antibiotics are the most

frequently used types of medications in the United States,[3] and primary care is responsible for the majority of antibiotic prescriptions.[4] Approximately 200 to 300 million prescriptions are written for antibiotics each year; 45% of these are for outpatient use, and around 25% of all hospitalized patients receive antibiotics.[2] Inappropriate use of antibiotics, including inappropriate dosages and durations, or treating a patient with antibiotics when they should not have been treated is unnecessarily contributing to the problem. Studies have shown that "antibiotic use is unnecessary or inappropriate in as many as 50% of cases in the United States."[2]

Antibiotics used in one patient can have a tremendous impact on other patients in a healthcare facility and the larger society, unlike other medicines. As a result of antibiotics, resistant organisms can emerge and then spread to others; "thus, the use and misuse of these resources have 'societal' consequences' that underscore the importance of stewardship in the hospital, community, and in long-term care facility populations."[1]

The rise of antibiotic resistance is an especially alarming public health problem because of the lagging development of new antibiotics. The problem is best summarized by Goff et al.: "Antibiotic resistance has exploded at the same time large pharmaceutical companies have reduced their research and development programs for newer agents with different mechanisms of action that might be useful in combating the emergence of resistance. Some investigators have described this as a 'perfect storm' for healthcare in the United States and other countries."[5] There isn't any evidence that the immense need for new drugs against resistant organisms will be met anytime soon, reports that describe the future of the development of antibiotics provide little hope.[6] It is increasingly important to use the antibiotics in existence as carefully as possible as to slow the development of resistant organisms.

A variety of antimicrobial agents are being tested in preclinical studies, but it is estimated that it will take at least 10 to 15 years before any will be available for routine because the pharmaceutical industry, both in the United States and globally, has slowed, and has not put forth as many resources to the development of drugs targeting the organisms that are causing the most problems. No agents that are targeting resistant gram-negative bacteria have entered the clinical development phase.[2]

One of the reasons why development of antibiotics has slowed globally is "because all of the so-called easily exploitable bacterial binding sites have been exploited."[1] Gram-negative organisms are particularly complex. This makes development of a new antibiotic with a novel target or mechanism especially difficult because they have several ways to protect themselves from the toxic effects of antibiotic drugs. A new drug would have to overcome several of these mechanisms in order to kill a bacterium or restrict its growth and replication.[6]

Other factors impact the development of new antibiotics on the institutional level. Regulations strictly define the structure of clinical trials, which makes it difficult to test the efficacy of antibiotics that target gram-negative organisms in human trials, especially against rare and multi-drug resistant pathogens such as *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species. These are the gram-negative members of the so-called ESKAPE / ESCAPE pathogens."[6] The acronym ESKAPE or ESCAPE refers to the organisms that some scientists believe should be receiving the most focus, due to their increasing prevalence in healthcare facilities and their increasing resistance to the current antibiotics.[5]

Table 1: ESKAPE vs. ESCAPE Organisms

	Organism		Organism
E	*E. faecium*	E	*E. faecium*
S	*S. aureus*	S	*S. aureus*
K	*K. pneumoniae*	C	*C. difficile*
A	*A. baumannii*	A	*A. baumannii*
P	*P. aeruginosa*	P	*P. aeruginosa*
E	*Enterbacter spp.*	E	*Enterobacteriaceae (includes K. pneumoniae, different species of Enterobacter, and E. coli)*

Although there are many factors that have been hindering the development of new pharmaceutical agents and progress is slow, there is still movement towards achieving a future with novel antibiotics. The pharmaceutical industry has recognized the intensity of the problem and is rising to meet the needs created by the "changing epidemiological landscape."[6] The American government has also recognized the severity of the antibiotic resistance and development problem, and is taking action to build a "sustainable research and development infrastructure to ensure the pipeline of new antibacterial agents."[6] In November 2009, President Barack Obama met with Swedish Prime Minister Fredrick Reinfeldt to establish a transatlantic task force with the European Union to address the issue of antibiotic resistance and develop strategies to improve the progress toward the development of new antimicrobial drugs.[6]

2.2 EFFECTS OF INAPPROPRIATE ANTIBIOTIC USE

There are risks associated with antibiotic use, but the high rates of inappropriate use increase these risks unnecessarily. The risks associated with antibiotic use are adverse reactions,

development of *C. difficile* infections, and the emergence of resistant organisms, which can lead to longer lengths of hospital stay, higher risks of mortality, and higher hospital costs.

2.2.1 Adverse Reactions to Antibiotics

Antibiotic use, whether appropriate or inappropriate, can potentially cause harmful reactions to an individual patient. Although antibiotics infrequently cause adverse effects, they are the second most common class of drugs to cause adverse drug reactions, second only to analgesics. Because they are some of the most commonly given drugs at healthcare facilities, the result is high numbers of antibiotic-associated adverse events,[5] although they are usually considered to be mild.[3]

The CDC reports that antibiotics cause over 140,000 emergency visits for patients with adverse reactions to their treatment.[7] Studies using national databases estimated that antibiotics cause around "19% of ambulatory care visits and 18% of emergency department visits for drug-related adverse events."[3] In a study of antibiotic related adverse events in emergency departments by Shehab et al., they found that the overall rate of emergency department visits for antibiotic-related adverse events was 10.5 visits per 10,000 outpatient prescription visits, which is half the rate of adverse events related to "high risk" medications like warfarin and insulin, but over 3 times higher than adverse events related to anticoagulant and antiplatelet drugs, oral hypoglycemic drugs, and "some narrow therapeutic index agents."[3]

Shehab et al. characterized the different types of antibiotic-associated adverse events into five different categories: adverse effects (diarrhea, headache, or dizziness), allergic reactions (immune responses such as rash or anaphylaxis), unintentional overdoses, unintentional exposures, and other effects (such as choking or injection site reactions).[3] Of their study

population, almost 80% of drug-related adverse events were attributed to allergic reactions" and 6.1% of drug-related adverse events led to hospitalization.[3]

Unnecessary exposure to antibiotics increases the patient's opportunities for harmful antibiotic-related adverse events. A study of antibiotic use in hospitals by Hecker et al., showed that 25% of unnecessary antimicrobial treatment regimens were associated with adverse effects or complications that were possibly attributable to the therapy.[8] Most patients complained of gastrointestinal problems like nausea and diarrhea, but other patients developed UTIs, bacteremia with multi-drug resistant organisms, and *C. difficile* colitis after inappropriate antibiotic treatment regimens.[8] The most effective way to reduce the majority of allergic reactions, other types of events, and emergency department visits is to minimize unnecessary or excessive exposures to antibiotics.[3]

2.2.2 *Clostridium difficile* Infections

Antibiotic use is one of the top risk factors for *C. difficile* infection in healthcare facilities.[9] In fact, *C. difficile* causes 20-30% of antibiotic-associated diarrhea in hospitals, and is the primary cause for antibiotic-associated colitis.[9] Antibiotics disrupt the normal flora in the colon, which renders the colon unprotected, leaving *C. difficile* with a new "niche" to flourish in.[9] Longer treatment regimens, higher numbers of doses, and higher number of antibiotics used are all associated with a greater risk of *C. difficile* infection, although any exposure to antibiotics, short or long term, can increase a patient's risk of infection.[9]

C. difficile is a gram-positive, anaerobic organism that is commonly found in the natural environment,[10] and it creates spores which can infect humans and be subsequently propagated through infected patients who shed the spores fecally.[9,10] *C. difficile* can be isolated from 1-3%

of healthy adults[10] but can be isolated from 7-26% of adult inpatients, and 20-50% of inpatients in facilities where there are endemic levels of *C. difficile*.[9] The typical presentation of a symptomatic *C. difficile* is a mild diarrhea, but it can also cause a colitis which is potentially fatal. Although about 2% of cases result in death,[9] according to the CDC, these infections cause around 14,000 deaths in the U.S. each year, which is at a historically high level.[11] *C. difficile* spores are extremely difficult to kill because they are resistant to heat, acids, and many cleaning disinfectants, and can survive for months in the environment.[10] The infection is spread via fomites shared between inpatients such as electronic rectal thermometers, toilets, and bedpans,[9] or through the hands of healthcare workers.[10]

Studies reviewed by Cohen et al. show that 85%-96% of patients with symptomatic *C. difficile* infections had received antibiotics 14-28 days before the onset of symptoms.[9] In another study of community-acquired pneumonia, 1 in 5 patients who were admitted to the ICU with a *C. difficile* infection were receiving antibiotics for pneumonia without any evidence of infection.[1] In another ICU, 50% of patients who received antibiotics for community-acquired pneumonia that developed a *C. difficile* infection were determined later to not actually have pneumonia and were treated unnecessarily. One-third of these patients died from their *C. difficile* infection.[1]

With high rates of inappropriate or indiscriminate use of antibiotics, it can be extrapolated that over-prescription behaviors will lead to higher rates of *C. difficile* infections, mortality, and healthcare costs.

2.2.3 Mortality

Since inappropriate use of antibiotics leads to resistance, it is important to look at adverse events associated with resistance, although these effects are less immediate than poor drug reactions and *C. difficile* infections.

Patients who are infected with an antibiotic resistant strain have higher rates of mortality compared to patients with susceptible strains. Cosgrove et al. have published a review detailing studies that have investigated mortality rates of resistant versus susceptible organisms involved in different types of infections. Significant findings are summarized in the table below.

Table 2: Mortality for Resistant Organisms compared to Susceptible and Uninfected Patients

Resistant organism	**Comparison organism**	**Infection site**	**Mortality indicator**	**Value**
MRSA	MSSA	Bacteremia	Odds ratio	1.93
	MSSA	Surgical wound	90 day post-operative mortality risk	3.4
	Uninfected	Surgical wound	90 day post-operative mortality risk	11.4
VRE	Uninfected	Multiple sites	Adjusted attributable mortality rate	6%
			Adjusted relative risk	2.1
P. aeruginosa	Susceptible *P. aeruginosa*	Multiple sites	Relative Risk of mortality	3
***Enterobacter* spp.**	Susceptible *Enterobacter* spp.	Multiple sites	Relative risk of mortality	5.02

Since the different authors cited in the review used different methods and mortality indicators, so it is difficult to compare the mortality associated with different organisms, but all indicators show that resistant organisms are related to higher risks and rates of mortality when compared to susceptible infections and uninfected patients.[12] Results of a study by Roberts et al. echoes Cosgrove's analysis: when comparing patients with antibiotic resistant infections to those without, 19.1% of patients with resistant infections died, compared with 3% of uninfected patients. This yields an adjusted mortality odds ratio of 2.16 and an attributable mortality rate of 6.5%.[13] Increases in mortality could be explained by a variety of factors, including increased need of surgery and other procedures, include increased odds of being sent to the ICU, a delay in treatment due to lack of effective antibiotics, and improper dosages, increased toxicity, and decreased effectiveness of drugs available for resistant organisms.[12]

2.2.4 Length of Stay

Antibiotic resistant infections are associated with increased length of hospitalization. A study by Goff et al. shows that patients with an antibiotic resistant infection have an average length of stay of 24.2 days, which is remarkable compared to the average length of stay for patients without a resistant infection, which is 8.0 days.[5] A review of studies of the effects of antibiotic resistant infections demonstrates that many types of resistant infections are related to increased risks and longer hospital stays. [12, 13]

Table 3: Increased length of hospital stay due to antibiotic resistant infections

Resistant organism	Comparison	Attributable excess hospitalization days	Risk of increased length of hospitalization
MRSA bacteremia	MSSA bacteremia	2	1.3
VRE	Uninfected	6.2 days	n/a
P. aeruginosa	*P. aeruginosa*	5.7 days	1.7
Enterobacter spp.	*Enterobacter* spp.	9	1.5
All resistant infections	Uninfected	12.7 +/- 1.2 days	n/a

These studies depict a distinct longer length of stays for patients with resistant infections, ranging from 2 to 13 days of excess hospitalization time. This difference is most notable when compared with patients without any infection. Longer lengths of hospital stay attributed to resistant infections could be explained by the increased need for surgical interventions required in order to control infections.[12]

2.2.5 Costs

Healthcare in the United States is already very expensive. In 2013, it is estimated that 18.4% of the US gross domestic product will be spent on healthcare,[5] and the overuse of antibiotics is only adding unnecessary costs to an already heavily burdened health system. The excess costs of antibiotics include the pharmaceutical costs, costs of hospitalizations attributed to resistant infections, and costs associated with treatment of *C. difficile.*

2.2.5.1 Costs of antibiotics

Prices of the individual antibiotics add up to substantial pharmaceutical costs to healthcare facilities. The CDC reports that $1.1 billion dollars is spent every year on unnecessary antibiotics for adult upper respiratory infections alone.[14] In a study of unnecessary antibiotic use by Hecker et al., researchers found the total average wholesale price of unnecessary antibiotics for study patients was almost $15,000, or an estimated yearly total of over $350,000.[8] The antibiotic costs considered are relatively little compared to the total cost of care.[1]

2.2.5.2 Hospitalization Costs

It is important to consider the downstream costs of unnecessary antibiotic use. As previously described, antibiotic use leads to antibiotic resistance, which is directly linked to increased adverse effects, increased rates of *C. difficile* infections and colitis, and lengths of hospitalization. These result in higher costs incurred by patients at healthcare facilities. No data could be found to assess the costs of allergic reactions and other adverse antibiotic-associated drug events.

Overall, it is estimated that the United States spends $5 billion each year for antibiotic resistant infections.[5] Patients with antibiotic-resistant infections cost more per day to stay in the hospital compared to those without antibiotic-resistant infection ($2,098 vs. $1,581 per day).[5] The total cost of care for those with antibiotic resistant strains was higher compared to those without an antibiotic resistant strain ($58,029 vs. $13,210).[5]

Several published reviews have investigated the differences in costs between patients that are infected with different types of resistant organisms compared with susceptible infections and patients without infections. The table below summarizes some of the notable findings of these reviews. [12, 13]

Table 4: Mean Attributable Hospital Costs due to Resistant Infections

Infection	Comparison	Mean Attributable cost to resistant infection
MRSA	MSSA	$13,901
MRSA	Uninfected	$41,274
VRE	Uninfected	$12,766
***Enterobacter* spp.**	Susceptible *Enterobacter* spp.	$29,379
All ARI	Uninfected	$27,715

This table clearly demonstrates that patients with antibiotic resistant infections are more expensive to treat than susceptible organisms; these differences are especially striking when comparing the costs to uninfected patients. Costs could be higher due to longer lengths of stay in the hospital, increased need for surgeries, increased risk of hospital-acquired infections, and adverse reactions to treatments. Urinary tract infections will be the main focus of this project later, and according to Stone et al., the mean attributable cost of a hospital acquired urinary tract infection is $1006.[15]

Although these numbers only reflect hospital costs, it is important to consider societal costs that are much more difficult to measure, such as loss of productivity, time spent away from the workplace, time spent away from family and friends, and stress.

2.2.5.3 Costs of *C. difficile* infections

C. difficile infections are very costly to the individual patient's health, but it also costs the hospital a substantial amount to treat and care for the infected patient. An estimated $3.2 billion dollars is spent each year to treat *C. difficile* infections in the United States alone.[9, 10] In a study

done in Massachusetts, $55.2 million was used to manage *C. difficile* infections in 55,380 inpatient-days at the study hospital.[9]

2.2.5.4 Medicare Retaliates

The cost of antibiotic overuse has recently become more expensive for healthcare facilities. Hospital-acquired infections cost around $6.5 billion a year to treat, and much of this money is reimbursed to hospitals by Medicare and Medicaid.[5] Beginning in October of 2008, the Centers for Medicare and Medicaid Services announced that it was no longer reimbursing hospitals for hospital-acquired infections in order to incentivize their reduction. The rationale behind this decision is that hospital-acquired infections are considered to be preventable, especially because there are a variety of evidence-based treatment guidelines to direct physicians and hospital staff on the proper ways to treat patients and protect them from nosocomial infections.[5] Since antibiotics are improperly administered and often result in further infections and with resistant strains, hospitals now have an incentive to reduce the amount of patients who receive antibiotics unnecessarily because, should they develop a hospital acquired infection, they will not receive money for those patients who were covered with Medicare, which would be detrimental to the facility.[5]

2.2.6 Urinary Tract Infections and Asymptomatic Bacteriuria

Urinary tract infections (UTIs) are one of the most common infections that receive prescriptions for antibiotics each year.[16] The IDSA's definition of an acute uncomplicated UTI is a "symptomatic bladder infection characterized by frequency, urgency, dysuria, or suprapubic pain in a person with a normal genitourinary tract, and is associated with both genetic and behavioral

determinants."[17] A more complete and comprehensive definition of a UTI by the CDC and the National Healthcare Safety Network (NHSN) is provided in appendix A. UTIs are responsible for 35-40% of all nosocomial infections in North America, most commonly from a urinary catheter.[18] Catheter-associated urinary tract infections (CAUTI) are the most common nosocomial infections. Approximately 560,000 CAUTIs are reported to the CDC each year,[19] but it estimated that there are around 1 million cases in US hospitals and nursing homes each year.[20]

A patient can be colonized with bacteria in their urinary tract but lack any symptoms of a UTI, which is known as asymptomatic bacteriuria (ABU). The IDSA definition of ABU is the "isolation of a specified quantitative count of bacteria in an appropriately collected urine specimen obtained from a person without symptoms or signs referable to urinary infection."[17] For ABU, different organisms are more common depending on gender and age. *E. coli* is the most common organism found in women with ABU, and the strains of E. coli found in women with ABU have fewer virulence factors than strains typically isolated from women with a symptomatic UTI.[17] *Proteus mirabilis* is more commonly found in men. Other strains commonly found in patients include *Enterobacteriaceae* (like *K. pneumoniae*), *P. aeruginosa*, *Enterococcus* species, and *group B streptococci*, many of these are previously listed in the ESCAPE/ESKAPE pathogens.[17] ABU is common in many demographics, but its prevalence is different depending on a patient's age, sex, sexual activity, the presence of genitourinary abnormalities, use of indwelling Foley catheters, and diabetes status. This prevalence data will be discussed in more detail.[21] Catheter-associated bacteriuria is the most common hospital acquired infection worldwide.[22]

Inaccurate diagnosis of UTIs is one of the leading causes of unnecessary antimicrobial exposure.[18] In response, the IDSA has developed guidelines for the screening and treatment of

patients with ABU in order to help physicians make informed decisions for treatment based on evidence. Screening for ABU is only recommended if there are adverse outcomes (such as a development of a symptomatic UTI, bacteremia, sepsis, worsening functional status, progression to chronic kidney disease or hypertension, urinary tract cancer, or increased risk of mortality) that could be prevented by antibiotic treatment.[17] The IDSA treatment guidelines are listed in the table below. [17]

Table 5: IDSA recommendations for diagnosis and treatment of ABU in adults

1.	The diagnosis of asymptomatic bacteriuria should be based on results of culture of a urine specimen collected in a manner that minimizes contamination.
	• For asymptomatic women, bacteriuria is defined as 2 consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts 10^5 cfu/mL. • A single, clean-catch voided urine specimen with 1 bacterial species isolated in a quantitative count 10^5 cfu/mL identifies bacteriuria in men. • A single catheterized urine specimen with 1 bacterial species isolated in a quantitative count 10^2 cfu/mL identifies bacteriuria in women or men.
2.	Pyuria accompanying asymptomatic bacteriuria is not an indication for antimicrobial treatment.
3.	Pregnant women should be screened for bacteriuria by urine culture at least once in early pregnancy, and they should be treated if the results are positive.
	• The duration of antimicrobial therapy should be 3–7 days. • Periodic screening for recurrent bacteriuria should be undertaken following therapy. • No recommendation can be made for or against repeated screening of culture-negative women in later pregnancy.
4.	Screening for and treatment of asymptomatic bacteriuria before transurethral resection of the prostate is recommended.
	• An assessment for the presence of bacteriuria should be obtained, so that results will be available to direct antimicrobial therapy prior to the procedure. • Antimicrobial therapy should be initiated shortly before the procedure. • Antimicrobial therapy should not be continued after the procedure, unless an indwelling catheter remains in place.
5.	Screening for and treatment of asymptomatic bacteriuria is recommended before other urologic procedures for which mucosal bleeding is anticipated.
6.	Screening for or treatment of asymptomatic bacteriuria is not recommended for the following persons.
	• Premenopausal, nonpregnant women. • Diabetic women. • Older persons living in the community. • Elderly, institutionalized subjects. • Persons with spinal cord injury. • Catheterized patients while the catheter remains in situ.
7.	Antimicrobial treatment of asymptomatic women with catheter-acquired bacteriuria that persists 48 h after indwelling catheter removal may be considered
8.	No recommendation can be made for screening for or treatment of asymptomatic bacteriuria in renal transplant or other solid organ transplant recipients.

The table below summarizes prevalence of ABU in different populations, and IDSA treatment recommendations. [17] Each group will be discussed more in depth.

Table 6: A summary of prevalence of ABU in different populations

Population	Prevalence, %
Healthy, premenopausal women	1.0-5.0
Pregnant women	1.9-9.5
Healthy, young men	0-1.5
Diabetic patients	
Women	9.0-27
Men	0.7-11
Elderly persons in the community	
Women	10.8-16
Men	3.6-19
Elderly persons in a long-term care facility	
Women	25-50
Men	15-40
Patients with spinal cord injuries	23-89
Patients with indwelling catheter use	
Short-term	9-23
Long-term	100
Patients undergoing urologic procedure	n/a

Premenopausal, non-pregnant women have been found to have a prevalence of ABU between 1% and 5%.[17] In this population, a urinary bacterial infection will usually resolve on its own. Although ABU is not associated with any long-term adverse outcomes, some data suggests that up to 30% of these women with ABU may develop a symptomatic UTI in the year following infection.[21] However, treatment of ABU in this population does not decrease the frequency of subsequent UTIs.[16] In fact, treatment of ABU in these women is "difficult, time consuming, costly, and potentially hazardous."[21] For these reasons, IDSA does not recommend the screening or treatment of ABU in non-pregnant, premenopausal women.[17]

ABU prevalence in pregnant women ranges between 1.9% and 9.5%.[17] Pregnant women with ABU are 20-30 times more likely to develop pyelonephritis during pregnancy compared to

pregnant women without ABU[16] because "dilatation of the ureters and rental pelvis allow bacteria in the bladder to reach the kidneys."[21] Pyelonephritis can lead to premature delivery and babies with low birth weight.[16] Treatment with antibiotics is associated with a 90% risk reduction of these poor fetal outcomes,[21] so the IDSA recommends that all pregnant women should be screened and treated for ABU.[17]

Women with diabetes have an ABU prevalence of 9% to 27%, more than 3 times higher than women without diabetes.[17] Women with diabetes and ABU show no difference in the incidence of a subsequent UTI, mortality, or progression to diabetic complications when compared with women without ABU,[16] so IDSA does not recommend the screening or treatment for ABU in diabetic women.[17]

UTIs rarely occur in men,[17] and the prevalence of ABU in young, healthy men ranges from 0% to 1.5% for both heterosexual men and men who have sex with men.[21] Because of the rarity of these events, the IDSA does not consider ABU to be a relevant clinical issue and does not recommend screening or treatment for this population.[17]

ABU in men with diabetes has a prevalence of 0.7% to 11%,[17] although other sources say that men with diabetes show no differences in prevalence than men without diabetes.[21] As with healthy young men, events are rare and screening and treatment for ABU is considered inappropriate.[17]

The prevalence of ABU increases with age. Elderly patients have very high rates of ABU, and this prevalence differs depending on residence. The prevalence of ABU in elderly populations not in nursing homes or long term care facilities range between 10.8% to 16% in women, and 3.6 to 19% in men, and these rates increase with age.[17] The prevalence is higher in "institutionalized" elderly patients living in long-term care facilities, which is between 25% and

50% in women, and between 15% and 40% in men.[17] Studies did not see any difference in symptomatic episodes, morbidity, or mortality in elderly patients who were treated for ABU; in fact, elderly patients treated showed higher reinfection rates with antibiotic-resistant organisms and showed higher incidence of adverse drug reactions and side effects.[21] Therefore, IDSA does not recommend screening or treating any elderly patients for ABU.[17]

ABU is found in 23-89% of patients with spinal cord injuries.[17] After treatment, almost all patients had recurrent bacteriuria with bacterial strains with increased antibiotic resistance,[16] so the IDSA does not recommend treatment for patients with spinal cord injuries.[17]

Patients using catheters have high rates of ABU. In patients with short term catheterization (less than 30 days), the prevalence of ABU ranges between 9 and 23%[17]and increases daily by 2% to 7%.[21] For patients with chronic indwelling catheters (longer than 30 days), "bacteriuria is universal."[21] IDSA does not recommend for the screening or treatment of "catheterized patients while the catheter remains in situ,"[17] but treatment should be considered for patients who have persistent ABU 48 hours after an indwelling catheter has been removed.[17]

ABU in patients who undergo traumatic genitourinary procedures leads to bacteremia in 60% of patients.[23] Due to these findings, the IDSA recommends screening and treatment of patients before they undergo a "transurethral resection of the prostate" as well as before "other urologic procedures for which mucosal bleeding is anticipated."[17]

Although the IDSA guidelines clearly identify patients who should be treated and why, many ABU infections are treated as if they were UTIs or for completely inappropriate reasons. Pyuria is a common reason why physicians may treat ABU. The IDSA defines pyuria as "the presence of increased numbers of polymorphonuclear leukocytes in the urine and is evidence of an inflammatory response in the urinary tract."[17] However, 30% of healthy young women, 70%

of diabetic women, 90% of the institutionalized elderly, 90% of hemodialysis patients, and 30-70% of pregnant women with ABU present with pyuria, so it is impossible to differentiate symptomatic from asymptomatic urinary tract infections based on pyuria alone.[23] IDSA does not recommend treating any patient because they have pyuria.[17] Physicians also commonly treat an asymptomatic patient for a UTI because they have cloudy or foul-smelling urine although "cloudy or foul smelling urine is not an indication for urinalysis, culture, or antimicrobial treatment."[16]

Why is overtreatment of ABU so common in healthcare facilities, especially if there are clear and specific treatment screening and treatment guidelines available? Evidence shows that guidelines are not followed very often and their creation and dissemination do not often result in a change in attitudes or practice.[1] What are possible influences for this trend?

First, it is important to look at factors influencing physicians to prescribe antibiotics. In a survey of physicians at the University of Miami Miller School of Medicine, Abbo et al. examined attitudes and reasons for antibiotic use.[24] Almost all of the faculty and residents who responded acknowledged that antibiotics are misused locally and nationally, and recognized that misuse causes antibiotic resistance and was harmful to patients. They both noted that they were concerned about resistance in their hospital and society when they prescribed antibiotics.[24] The survey found that the factors that most often influenced antibiotic use "were the risk of missing an infection and whether a patient is critically ill or immunocompromised."[24] When considering the prescription of an antibiotic, faculty members were concerned about the costs that the hospital would incur, and residents were "significantly more likely to be reassured when using an antibiotic even if it might be the wrong one."[24] More than one third of both faculty and residents rarely or did not consider the potential for a *C. difficile* infection when prescribing."[24] The most

interesting result of the study was that 62% of the physicians and residents who responded to the survey agreed that other doctors overprescribe antibiotics. However, only 13% of the same respondents "agreed that they themselves overprescribe antibiotics."[24] The survey did reveal that physicians and residents both wanted to receive "more education about antibiotics and feedback about their antibiotic selections."[24]

Communication with patients can influence antibiotic prescribing behaviors. It is well-known that patients can pressure physicians to give antibiotics when it is often unnecessary. Studies show that patients do not usually think of resistance when considering the harmful consequences of antibiotic use, and many patients do not understand when antibiotics are biologically necessary (i.e. thinking antibiotics are effective against viral infections).[3] Physicians have "reported difficulty with communicating information on antibiotic effectiveness and resistance" and sometimes feel that they do not have enough time with a patient to explain the risks associated with resistance and antibiotic overuse.[3]

When specifically investigating prescribing practices for UTIs, some physicians reported that they prescribed antibiotics based on the information provided by the nursing staff and without ever assessing the patient's symptoms themselves.[25] Many physicians were unaware of IDSA guidelines for screening and treatment of ABU and thought that patients with ABU would benefit from therapy.[25] Physicians were also concerned that "that their clinical decision making might be questioned if patients with ABU were not treated and then developed a symptomatic UTI."[25]

Changing definitions of UTIs as a HAI are affecting the prevalence rates seen in healthcare facilities. In March of 2012, the CDC/NHSN sent out a newsletter that said that because fever can be attributed to many different HAIs, like CAUTIs and pneumonia, it is

impossible to distinguish which infection is the root cause, it must be attributed to both causes.[26] This change in definition attempts to prevent healthcare facilities from "gaming" the system and selectively choosing which type of HAI to attribute the fever to so that it is not included in public reporting.[26] This definition change will cause more physicians to diagnose and treat patients for a UTI although that patient may have ABU and the fever is due to another reason; in turn, this will lead to artificial inflation in the number of CAUTIs diagnosed and treated, leading to unnecessary exposures to antibiotics.

In summary, antibiotic use has the potential to lead to adverse health events for patients in healthcare facilities, including the emergence of antibiotic resistance, which is an increasingly important public health issue. Unnecessary antibiotic use accelerates this process, so it is necessary to examine antibiotic prescription practices as the key determinant of this problem. Because the realm of infections is so broad, urinary tract infections and asymptomatic bacteriuria will be examined more closely. Reasons for choosing UTIs and ABU are that UTIs comprise a majority of all healthcare associated infections and because inaccurate diagnosis of UTIs is one of the leading causes of unnecessary antimicrobial exposure because ABU is often misdiagnosed as a UTI. Since treatment guidelines exist for patients with ABU, an investigation of the extent that a facility adheres to these guidelines could help a facility direct attention and resources to this issue to help reduce unnecessary antibiotic use.

3.0 METHODS

3.1.1 Study Objectives

The primary objective of this study was to determine the frequency of people that were diagnosed with and received antibiotic treatment for a UTI who lacked documentation of UTI signs and symptoms. For this study, these patients without documentation of UTI symptoms are considered to have ABU, and this study examined how many of these ABU patients received antibiotics inappropriately. A secondary outcome of this study was to determine the excess pharmaceutical costs that this hospital spent on antibiotics that were administered inappropriately.

3.1.2 Study Design

This study is a retrospective chart review of all patients admitted to the University Teaching Hospital (UTH) with a hospital stay of longer than 2 days for which a urine culture was obtained and a diagnosis of a UTI was made between September 2011 and February 2012.

3.1.3 Study Area

The UTH, at which this data was collected, will be kept anonymous on request of the principal investigator. This study was developed as a quality improvement measure, and, based on local requirements, was exempt from formal submission to the network's Institutional Review Board (IRB). It is important to note that although formal IRB approval was not necessary for data collection, the study was approved by both the infection control staff and the department of pharmacy. Data collection and analysis protocols were overseen and approved by the hospital's clinical pharmacy infectious diseases specialists. The data was analyzed at both the UTH and at the University of Pittsburgh. Because this data set contained information collected from human subjects, the analysis of this data has been approved as an exempt study by the University of Pittsburgh IRB (IRB# PRO12100220).

Though the hospital name will remain anonymous, it is important to note several features of the facility. The UTH is part of a large network of hospitals, but this particular facility is a 250-bed public acute care teaching hospital that is affiliated with a local state university in central Texas with a case mix index of 1.7279. The hospital also serves as a Level I Trauma Center.

3.1.4 Study Population

3.1.4.1 Eligibility Criteria

To be included in the analysis, the patient had to be at least 18 years of age and admitted to the hospital for >2 days between the dates of September 2011 and February 2012. To be

eligible, the subject needed a discharge code of one of the following International Classification of Diseases, Ninth Revision (ICD-9) codes:

Table 7: ICD-9 Codes Eligible for Study

Code	Definition
595.0	Acute cystitis
595.2*	Other chronic cystitis
595.4*	Cystitis in diseases classified elsewhere
595.89*	Other specified types of cystitis
595.9	Cystitis unspecified
599.0	Urinary tract infection, site not specified (majority)
599.9*	Unspecified disorder of urethra and urinary tract
601.0	Acute prostatitis
601.1*	Chronic prostatitis
601.2	Abscess of prostate
601.3*	Prostatocystitis
601.4*	Prostatitis in diseases classified elsewhere
601.8*	Other specified inflammatory diseases of prostate
601.9*	Prostatitis unspecified
602.9*	Unspecified disorder of prostate
603.1*	Infected hydrocele
603.8*	Other specified types of hydrocele
603.9	Hydrocele unspecified
604.0	Orchitis epididymitis and epididymo-orchitis with abscess
604.99	Other orchitis epididymitis and epididymo-orchitis without abscess
607.1*	Balanoposthitis
607.2*	Other inflammatory disorders of penis
607.8*	Various Disorders of penis
607.9*	Unspecified disorder of penis
608.0*	Seminal vesiculitis
608.4	Other inflammatory disorders of male genital organs
608.8*	Other specified disorders of male genital organs
608.9*	Unspecified disorder of male genital organs
616*	Cervicitis, endocervicitis, vaginitis, vulvovaginitis

Code definitions are from the Centers of Medicare and Medicaid.[27] These codes encompass the full spectrum of cases that could be presenting with symptoms similar to those of

a UTI. After the search was done, no records were found for several of the ICD-9 codes, which are indicated with an asterisk.

3.1.4.2 Inclusion Criteria

To be included in this study, the eligible patients must have had a diagnosis of a UTI according to progress notes and discharge reports, in order to eliminate patients whose discharge ICD-9 codes were miscoded.

3.1.4.3 Exclusion Criteria

There are several groups of patients who should receive treatment for ABU according to IDSA guidelines. These patients were excluded in order to evaluate how many people with ABU were receiving inappropriate treatment. These groups included pregnant women, and patients admitted for a urologic procedure. Immunocompromised patients, indicated by moderate to severe levels of neutropenia, were also excluded because of special issues regarding treatment. Patients who were taking antibiotics upon admission or were diagnosed with a concomitant infection that required antibiotics were also excluded. Patients who had urine cultures taken during a stay in the ICU were excluded because the clinical pharmacy specialists felt the documentation of ICU patients was too complex to determine the appropriateness of a UTI diagnosis and treatment.

3.1.4.4 The Population

Figure 1 below depicts the breakdown of patients who were eligible, included, and excluded from the study. There were a total number of 237 eligible patients based on age, length of stay, and ICD-9 code requirements. Of these, 7 patients were deemed to be miscoded. Of the

230 included patients, 142 patients were excluded from analysis, leaving 88 patients in the analysis. The patients' charts were then classified into four different categories: the excluded patients, patients with UTIs, patients with ABU, and patients with a questionable UTI diagnosis. Patients whose records that were not clearly indicative of a UTI were reviewed carefully by an infectious disease specialist. The clinical infectious disease specialists made the final decision if the more vague symptoms, like fever, altered mental status, and abdominal pain, listed were explained by other causes or if the patient was asymptomatic. There were several cases in which there were listed symptoms that could be indicative of a UTI but could also be explained by other illness or circumstances, and the charts did not give a clear picture the patient truly had a UTI or not. These were labeled as "questionable."

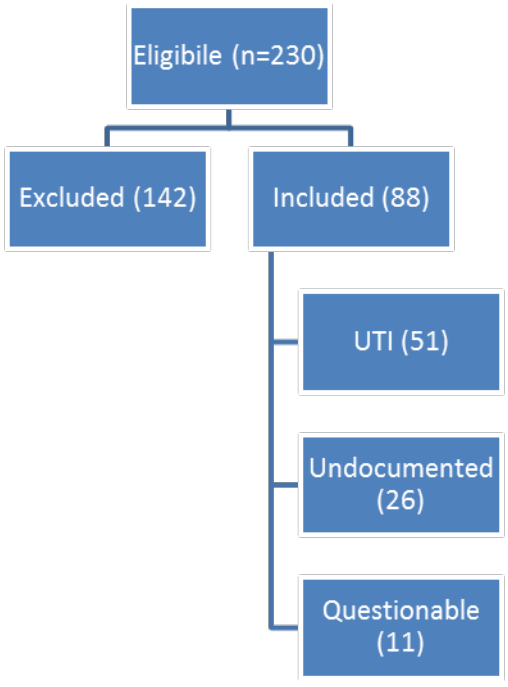

Figure 1: Summary of Study Participants

3.1.5 Data Collection

Patient information was accessed via the UTH's electronic record system, which presented all of the nurses' observation notes, admission notes, progress notes, consultation notes, and discharge notes and summary for each patient encounter. Information was documented on a data collection sheet found in appendix B. The charts were reviewed to examine different elements: demographics, signs and symptoms of a UTI, lab values, and patient response variables. The variables chosen for collection were based on a compilation of variables that were collected in similar published studies.[18-19, 28-32]

Demographic variables collected included age, sex, comorbidities, and catheter use, including catheter type and duration of use. The signs and symptom variables that were collected included the highest temperature during the length of stay, dysuria (burning during urination), increased frequency of urination, urgency of urination, costovertebral angle tenderness, suprapubic pain or tenderness, flank pain, and altered mental status. The lab values collected included serum white blood cell count, the type of organism found from the urine culture, the amount of bacteria found (cfu/ul), and the results of the urinalysis (UA), specifically the white blood cell count in the urine. The WBC count noted was the one done closest to the time that the urine culture was taken. The patient response variables collected include the dosage and duration of treatment, and the antibiotics prescribed for the UTI. A price list of the antibiotics was obtained from the hospital's pharmacy and is included in appendix C.

3.1.6 Data analysis

Most of the analysis was calculated using Microsoft Excel. Information collected from all the groups was the frequency of the organisms isolated from urine cultures, symptoms found in patients, reasons for culture and treatment, and these will also be calculated as percentages. The dates of hospital admission and discharge were recorded to calculate length of stay, and the date of urine culture and date of treatment initiation were collected to calculate the length of time between culture and treatment. Dates of hospitalization, culture, catheter insertion and removal were collected to speculate whether colonization was catheter-acquired. Over 2 days of hospitalization or catheter use prior to culture was presumed to be a case of hospital-acquired or catheter-acquired bacteriuria, respectively. The total number of doses of antibiotics was added for the ABU and questionable groups, and when multiplied by the price of the antibiotic, the total costs of excess pharmaceuticals will be obtained. Defined Daily Doses per 1000 patient days was calculated as well as antibiotic days per 1000 patient days.

4.0 RESULTS

4.1 EXCLUDED GROUP

Of the 230 eligible patients, 142 patients were excluded from the study. The most common reasons for exclusion were diagnosis with a concomitant infection that required an antibiotic treatment, having a urine culture taken while admitted in the ICU, and taking antibiotics at the time of admittance. Exclusion information is summarized in Table 8.

Table 8: Reasons for Exclusion from Study

Reason for Exclusion	**No. Patients (%)**
Concomitant infections requiring antibiotics	79 (55.6%)
ICU at time of urine culture	29 (20.4%)
Taking antibiotics on admittance	21 (14.8%)
Pregnant	7 (4.9%)
Planned urological procedure	5 (3.5%)
Neutropenia	1 (0.7%)

4.2 INCLUDED PATIENTS

The included patients were categorized into 3 groups: patients with clear and documented symptoms of a UTI, those with undocumented symptoms of a UTI and considered to have ABU, and those whose diagnosis of UTI was questionable. The groups were very similar in terms of demographics. The mean age of all groups was in the 60s, although the patients were on average older in the ABU group than in the UTI group, and oldest in the questionable categories. All 3 groups had higher numbers of women than men, which is expected since women have ABU and UTIs more often than men in the literature. Most patients in the ABU group appear to have acquired bacteria from the community prior to entering the hospital, but several members of the ABU and questionable group appear to have acquired their bacteriuria during their hospital stay (9 and 7 respectively), and some from catheters (4 and 5 respectively) during their stay at the UTH.

Table 9: Summary of demographics of included patients

	UTI	**ABU**	**Questionable**
Average age	60.8	65.7	68.4
% Female	66.7%	76.9%	63.6%
Hospital-acquired	n/a	9 (34.6%)	7 (63.6%)
Catheter-acquired	n/a	4 (15.4%)	5 (45.5%)

4.2.1 UTI Group

Of the 88 included patients, 51 patients (58%) had clear, documented symptoms of a UTI. *E. coli* was isolated in almost half (47%) of patients, which was expected based on the literature. The other most common organisms isolated from patients were *E. faecalis* and *P. mirabilis.* A complete list of isolated organisms can be found below.

Table 10: Organisms Isolated from Patients with UTIs

Organisms in Urine Culture	**No. Patients**
Escherichia coli	24
Enterococcus faecalis	6
Proteus mirabilis	3
Citrobacter koseri	2
Enterobacter aerogenes	2
Klebsiella pneumoniae	2
Streptococcus viridans	2
Enterobacter clocae	1
Enterococcus faecium	1
Pseudomonas aeruginosa	1
Salmonella enterica	1
Staphylococcus haemolyticus	1
Staphylococcus epidermidis	1
No culture taken	1
Mixed growth (probable contamination)	10

The most common symptom seen in these patients was burning during urination (51%), followed by urinary frequency (33%). 24 patients had at least 2 concurrent symptoms (47%), and 8 patients had at least 3 symptoms (16%).

Table 11: Symptoms seen in patients with UTIs

Symptom	No. Patients (%)
Burning during urination	26 (50.9%)
Urinary frequency	17 (33.3%)
Flank pain	8 (15.7%)
Suprapubic pain/tenderness	8 (15.7%)
Altered Mental Status	8 (15.7%)
Urinary urgency	7 (13.7%)
Fever >100˚F	5 (9.8%)
Costovertebral Angle Tenderness	4 (7.8%)
2+ Symptoms	24 (47.1%)
3+ Symptoms	8 (15.7%)

4.2.2 ABU Group

Of the 88 included patients, 26 patients (29.5%) had no documentation of any symptoms of a UTI but were diagnosed and treated for one according to progress notes, discharge summary, and the pharmacy logs. These patients were considered to have ABU and not a UTI in this analysis.

The most common organisms isolated from urine cultures from these patients was E. coli (42%), which was similar to patients who had clear UTIs. The other most common organisms isolated were *K. pneumoniae* and *S. epidermidis.* Overall, organisms were very similar between the two groups. A complete list of organisms isolated from this group of patients can be found below.

Table 12: Organisms isolated from patients with ABU

Organisms in urine culture	No. Patients
Escherichia coli	11
Klebsiella pneumoniae	4
Staphylococcus epidermidis	3
Enterococcus faecalis	2
Alpha hemolytic *Streptococcus*	1
Candida albicans/dubliniensis	1
Enterobacter clocae	1
Klebsiella oxytoca	1
MRSA	1
Pseudomonas aeruginosa	1
No culture taken	1
No growth	2
Mixed growth (probable contamination)	3

Twelve of the 26 patients in this group (46%) had no documented symptoms of a UTI anywhere in their charts. The remaining 14 patients displayed more unspecific symptoms of a UTI that were ruled by the clinical pharmacy specialists to be attributable to other causes. The most common of these was altered mental status, which could be explained by the following reasons: in this case mental illness, schizoaffective disorder, head injuries, heroin withdrawal, cocaine abuse, and alcohol withdrawal. According to the clinical pharmacy specialists, the fevers seen by the patients in this group were mostly post-operative or due to other medical problems and were likely not caused by urinary bacteria. Pain and tenderness in the flank and suprapubic regions were explained by ascites in the liver, benign prostatic hyperplasia, and injuries sustained from falls.

Table 13: Symptoms in patients with ABU explained by other reasons

Symptom	No. patients (%)
No symptoms documented	12 (46.2%)
Altered mental status	9 (34.6%)
Fever > 100˚F	4 (15.4%)
Suprapubic Pain/tenderness	3 (11.5%)
Flank pain	2 (7.7%)

Since no symptoms could be found, or the symptoms could be explained by other reasons, the medical records were searched for documented reasons why a UA was performed or why a urine culture was collected. Of the 26 patients, the records for 14 patients (56%) had no mention of why a UA was done and a urine culture was taken. For 3 patients, the UA/culture was done because the patient presented with a fever or altered mental status. For 3 patients, the UA/culture was done because of an abnormal color or smell of the urine, and for 2 patients, a UA/culture was done because there was blood in the patient's urine. Other reasons a UA/culture was taken was because of a patient's history of a UTI with chronic catheterization, urinary retention, low sodium levels, and because the Foley catheter was originally inserted in the wrong place.

Table 14: Reasons for screening in patients with ABU

Reasons for UA and Culture	No. Patients (%)
No reason noted	14 (53.8%)
AMS/Fever	3 (11.5%)
Abnormal urine color/smell	3 (11.5%)
Bloody urine	2 (7.7%)
Other	4 (15.4%)

Medical records were also searched to find a reason why these patients were diagnosed and treated for a UTI if there were undocumented or unspecific symptoms. Most patients received treatment for a UTI based on "a positive UA result" (53.8%). According to the clinical pharmacy specialists and Gandhi et al., a UA is considered positive if there are over 10 WBC/hpf counted, which would mean only 5 UA's were actually positive.[30] Five patients were treated for a UTI because they had a "positive urine culture" (19.2%), and no reason for treatment was documented for 7 patients (26.9%). What is particularly interesting is that in 3 charts, the

physician's notes specifically stated that the patient was asymptomatic, but would treat with antibiotics because of a foul smell in the urine, weakness, and positive culture.

Table 15: Reasons for treatment for patients with ABU

Reasons for Treatment	**No. Patients (%)**
Positive UA	14 (53.8%)
- 0 to 2 WBC	1
- 6 to 10 WBC	7
- *21 to 50 WBC*	*1*
- *50 to 100 WBC*	*1*
- "Occasional"	1
- *"Too numerous"*	*3*
Positive culture	5 (19.2%)
No reason documented	7 (26.9%)
** 3 patient's records noted specifically that the patient was asymptomatic, but treatment was initiated anyway	

From the charts, it was possible to determine if the patient was treated the same day as the culture and UA were taken. Interestingly, 21 of 26 patients (81%) of patients were given antibiotics at the same time as the urine culture was taken, and only for 5 patients did the physicians wait 2-4 days for culture results came back from the lab.

Table 16: Time between culture and treatment in patients with ABU

Time between culture and treatment	**No. Patients (%)**
Treatment initiated at time of culture	21 (80.8%)
Waited 2-4 days for results	5 (19.2%)

In total, the patients were treated for 99.5 antibiotic days and the length of stay for all patients was 187 days, which totals to 532.09 antibiotic-days/1000 patient days.

The following table calculates the defined daily doses (DDD) and DDD/1000 patient-days. The WHO DDD values were obtained from the WHO Collaborating Centre for Drugs Statistics Methodology.[33]

Table 17: Defined Daily Doses for patients with ABU

Drug	Code	WHO DDD	Total # Doses	Dose in g	Quantity dispensed (g) (Total # Doses x Dose in g)	DDD's (Quantity Dispensed/WHO DDD)	DDD/1000 patient days
Amoxicillin/ clavulanate (Augmentin) (875 mg)	J01CR02	3	5	0.875	4.375	1.46	7.80
Cefazolin (Ancef) (1000 mg)	J01DB04	3	65	1	65	21.67	115.86
Cefepime (1000 mg)	J01DE01	2	18	1	18	9.00	48.13
Ceftriaxone (Rocephin) (1000 mg)	J01DD04	2	12	1	12	6.00	32.09
Cefuroxime (250 mg)	J01DC02	3	4	0.25	1	0.33	1.78
Cephalexin (500 mg)	J01DB01	2	1	0.5	0.5	0.25	1.34
Ciprofloxacin (500 mg)	J01MA02	0.5	31	0.5	15.5	31.00	165.78
Meropenem (500 mg)	J01DH02	2	3	0.5	1.5	0.75	4.01
Nitrofurantoin (100 mg)	J01XE01	0.2	14	0.1	1.4	7.00	37.43
Piperacillin/ tazobactam (Zosyn) (2250 mg)	J01CR05	14	20	2.25	45	3.21	17.19
Piperacillin/ tazobactam (Zosyn) (4500 mg)	J01CR05	14	7	4.5	31.5	2.25	12.03
Trimethoprim/ sulfamethoxazole DS tablet (Bactrim) (160 mg)	J01EE01	4	31	0.16	4.96	1.24	6.63
Vancomycin (1000 mg)	J01XA01	2	12	1	12	6.00	32.09
					Total:	**90.16**	**482.15**

To estimate the pharmaceutical costs due to unnecessary antibiotic use, the cost of each treatment regimen was calculated by multiplying the price of the dose of antibiotic given by the total number of doses given for the entire regimen, including the prescriptions filled upon discharge from the hospital. The price of each antibiotic was provided by the hospital's purchasing records, and this information can be found in appendix C. The total cost of antibiotics given to the ABU group was $512.45 for a total of 353 doses. This calculation includes discharge antibiotics as well as inpatient antibiotics.

Table 18: Pharmaceutical costs of patients with ABU

Antibiotic administered (dosage)	**Total number of doses**	**Price per dose**	**Total Antibiotic Cost**
Amoxicillin/ clavulanate (Augmentin) (875 mg)	23	$0.95	$21.85
Cefazolin (Ancef) (1000 mg)*	65	$0.67	$43.55
Cefepime (1000 mg)	18	$4.22	$75.96
Ceftriaxone (Rocephin) (1000 mg)	13	$1.16	$15.08
Cefuroxime (250 mg)*	10	$0.28	$2.80
Cephalexin (500 mg)	1	n/a	n/a
Ciprofloxacin (500 mg)*	49	$0.14	$6.86
Meropenem (500 mg)	1	$5.52	$5.52
Nitrofurantoin (100 mg)	86	$1.98	$170.28
Piperacillin/ tazobactam (Zosyn) (2250 mg)	20	$3.45	$69.00
Piperacillin/ tazobactam (Zosyn) (4500 mg)	7	$6.93	$48.51
Trimethoprim/ sulfamethoxazole DS tablet (Bactrim) (160 mg)*	48	$0.15	$7.20
Vancomycin (1000 mg)*	12	$3.82	$45.84
		Total:	**$512.45**

It is important to note that the antibiotics marked with an asterisk may be inaccurate. The dosages received were slightly different from the doses priced by the pharmacy for one or two patients receiving these drugs. These prices were therefore estimated based on the prices available. Cephalexin was given once, but no information was available for the price of this drug at the time of submission.

4.2.3 Questionable Group

Of the 88 included patients, 11 patients (12.5% of included patients) were classified by the research team as "questionable" because documentation was not clear enough to indicate whether or not the patient had a UTI or ABU. There was either no documentation of symptoms or indications why the patient was diagnosed and treated with a UTI, or the patients had unspecific symptoms and it was unclear if other causes were responsible for these symptoms. These symptoms include altered mental status and fever. Some of these patients were dealing with strokes, falls with head injuries, medication changes, and alcohol withdrawal, but no conclusions could be drawn from medical records. The breakdown of patient symptoms and documentation is listed in the table below. Two patients presented with both altered mental status and fever over 100 degrees.

Similar organisms were isolated from the urine cultures of the patients in this group when compared to the other 2 groups. The most common organism was E. coli (54.5%), followed by *E. faecalis* and *K. pneumoniae*.

Table 19: Organisms isolated from patients with a questionable UTI diagnosis

Organisms in Urine	**No. Patients**
Escherichia coli	6
Enterococcus faecalis	3
Klebsiella pneumoniae	3
Enterobacter clocae	1
Streptococcus viridans	1

Table 20: Symptoms seen in patients with a questionable UTI diagnosis

Symptom	**No. Patients (%)**
Altered mental status	5 (45.5%)
Fever > 100˚F	3 (27.3%)
No documentation	5 (45.5%)

The charts were also reviewed to learn why the patient was cultured and treated. A distinct lack of documentation was observed, and no light could be shed on the appropriateness of the diagnosis and treatment. However, for those patients whose records had notes on the reasons why they were cultured and treated, like finding bacteria in a UA, drowsiness, or foul smelling urine and history of a UTI, are not criteria listed by the IDSA as reasons to screen or treat. For all patients, there were not specific notes of screening versus treatment, so all reasons found are compiled together in the table below.

Table 21: Reasons for screening and treatment for UTI in patients with questionable UTI diagnosis

Reasons for UA/Culture and Treatment	No. Patients (%)
No documentation	8 (72.7%)
Checked UA for hematuria, found bacteria	1 (9.1%)
Drowsiness	1 (9.1%)
Bad smell/History of UTI	1 (9.1%)

This group also shows a similar pattern of time passing between the time a culture was done and the time of antibiotic treatment initiation. 91% of patients received antibiotics the same day as their urine culture was done. Only 1 physician waited for the results to come back before beginning a treatment regimen. Those details are summarized in the table below:

Table 22: Time between culture and treatment in patients with questionable UTI diagnosis

Time between culture and treatment	No. Patients (%)
Treatment initiated at time of culture	10 (90.9%)
Waited 2-4 days for results	1 (9.1%)

In total, the patients were treated for 58.7 antibiotic days and the length of stay for all patients was 157 days, which totals to 373.67 antibiotic-days/1000 patient days.

The following table calculates the defined daily doses (DDD) and DDD/1000 patient-days. The WHO DDD values were obtained from the WHO Collaborating Centre for Drugs Statistics Methodology.[33]

Table 23: Defined Daily Doses for patients with questionable UTI diagnosis

Drug	Code	WHO DDD	Total # Doses	Dose in g	Quantity dispensed (g) (Total # Doses x Dose in g)	DDD's (Quantity Dispensed/WHO DDD)	DDD/1000 patient days
Amoxicillin/ clavulanate (Augmentin) (875 mg)	J01CR02	3	11	0.875	9.625	3.21	20.44
Cefazolin (Ancef) (1000 mg)*	J01DB04	3	14	1	14	4.67	29.72
Cefepime (1000 mg)	J01DE01	2	7	1	7	3.50	22.29
Ceftriaxone (Rocephin) (1000 mg)	J01DD04	2	4	1	4	2.00	12.74
Cefuroxime (250 mg)*	J01DC02	3	3	0.25	0.75	0.25	1.59
Ciprofloxacin (500 mg)*	J01MA02	0.5	11	0.5	5.5	11.00	70.06
Nitrofurantoin (50 mg)	J01XE01	0.2	30	0.1	3	15.00	95.54
Piperacillin/ tazobactam (Zosyn) (2250 mg)	J01CR05	14	9	2.25	20.25	1.45	9.21
Piperacillin/ tazobactam (Zosyn) (4500 mg)	J01CR05	14	9	4.5	40.5	2.89	18.43
Trimethoprim/ sulfamethoxazole DS tablet (Bactrim) (160 mg)*	J01EE01	4	30	1	30	7.50	47.77
Vancomycin (1000 mg)*	J01XA01	2	1	1	1	0.50	3.18
					Total:	**51.96**	**330.98**

To estimate the pharmaceutical costs due to unnecessary antibiotic use, the cost of each treatment regimen was calculated by multiplying the price of the dose of antibiotic given by the

total number of doses given for the entire regimen, including the prescriptions filled upon discharge from the hospital. The price of each antibiotic was provided by the hospital's purchasing records, and this information can be found in appendix C. The total cost of antibiotics given to the questionable group was $271.76 for a total of 234 dosages. This includes both inpatient and discharge antibiotics.

Table 24: Pharmaceutical costs of patients with questionable UTI diagnosis

Antibiotic administered (dosage)	**Total number of doses**	**Price per dose**	**Total Antibiotic Cost**
Amoxicillin/ clavulanate (Augmentin) (875 mg)	58	$0.95	$55.10
Cefazolin (Ancef) (1000 mg)	14	$0.67	$9.38
Cefepime (1000 mg)	7	$4.22	$29.54
Ceftriaxone (Rocephin) (1000 mg)	4	$1.16	$4.64
Cefuroxime (250 mg)	11	$0.28	$3.08
Ciprofloxacin (500 mg)*	27	$0.14	$3.78
Nitrofurantoin (100 mg)*	30	$1.98	$59.4
Piperacillin/ tazobactam (Zosyn) (2250 mg)	9	$3.45	$31.05
Piperacillin/ tazobactam (Zosyn) (4500 mg)	9	$6.93	$62.37
Trimethoprim/ sulfamethoxazole DS tablet (Bactrim) (160 mg)*	64	$0.15	$9.60
Vancomycin (1000 mg)	1	$3.82	$3.82
		Total:	**$271.76**

It is important to note that the antibiotics marked with an asterisk may be inaccurate. The dosages received were slightly different from the doses priced by the pharmacy for one or two patients receiving these drugs. These prices were therefore estimated based on the prices available.

5.0 DISCUSSION

5.1 SUMMARY OF RESULTS

The three groups showed similar demographics and a similar range of organisms isolated from the urine culture. More emphasis will be put into the analysis of the ABU and questionable groups. A large portion of the patients in this group appears to have acquired their bacteriuria in the hospital, some from catheter use. Since catheter-acquired ABU is the most common hospital acquired infection, this comes as no surprise.

The results indicate that at least 30% of patients in this cohort diagnosed with a UTI were asymptomatic and should not have received antibiotic treatment. However, if all of the patients who were classified as having a questionable UTI diagnosis were in reality asymptomatic, the percentage of patients who were treated in appropriately would be 42.5%. The antibiotics used on the patients with ABU cost the hospital $512.45 for 26 patients, but these costs could range upwards to $784.21 if the patients with a questionable diagnosis are included in the analysis. These unnecessary costs could have been saved by the facility if physicians and prescribers practiced stronger adherence to published IDSA screening and treatment guidelines. Antibiotic days per 1000 patient-days show that ABU group received a higher number of antibiotics proportionately than the questionable group. Data was not available to calculate patient days for patients with a clear UTI, which would have been the best comparison group. Because of the

unnecessary exposure to antibiotics these patients are at risk for colonization or proliferation of resistant bacteria, in the future they would be at higher risk of mortality due to resistant infections, longer lengths of hospitalization, and higher hospital bills. Both the ABU and questionable groups showed that there were several reasons physicians were culturing for treating these cases (foul smelling urine, weakness, low sodium, *etc*). Combined with the high rates of ABU, this suggests that physicians may need more education about the IDSA screening and treatment guidelines and may benefit from an intervention.

The 30-42.5% range of unnecessary ABU treatment fits nicely into the range other studies have shown. The table below summarizes recent publications that have found that patients with ABU were treated with antibiotics inappropriately.

Table 25: Summary of ABU overtreatment rates found in literature

Author	Year	Title of Paper	% of study patients with ABU	% patients with ABU treated
Bonnal et al.[34]	2008	Bacteriuria in a Geriatric Hospital: Impact of an Antibiotic Improvement Program	49%	20.1%
Cope et al.[19]	2009	Inappropriate Treatment of Catheter-Associated Asymptomatic Bacteriuria in a Tertiary Care Hospital	58.6%	32%
Chowdhury et al.[35]	2012	Preventing the inappropriate treatment of asymptomatic bacteriuria at a community teaching hospital	83%	47%
Dalen et al.[28]	2005	An evaluation of the management of asymptomatic catheter-associated bacteriuria and candiduria at The Ottawa Hospital	24.4%	52%
Gandhi et al.[30]	2009	Importance of Urinary Tract Infection to Antibiotic Use Among Hospitalized Patients	32.6%	100%
Khawcharoenporn et al.[36]	2011	Abnormal urinalysis finding triggered antibiotic prescription for asymptomatic bacteriuria in the ED	27%	20%
Lin et al.[31]	2012	Overtreatment of Enterococcal Bacteriuria	54%	32.8%
Linares et al.[18]	2011	Electronic Memorandum Decreases Unnecessary Antimicrobial Use for Asymptomatic Bacteruria and Culture-Negative Pyuria	73.6%	26%
Pavese et al.[37]	2009	Does an Educational Session With an Infectious Diseases Physician Reduce the Use of Inappropriate Antibiotic Therapy for Inpatients With Positive Urine Culture Results? A Controlled Before-and-After Study	54.8%	44.3%
Silver et al.[29]	2009	Positive urine cultures: a major cause of inappropriate antimicrobial use in hospitals	49%	64%
Zabarsky et al.[25]	2008	Sustained reduction in inappropriate treatment of asymptomatic bacteriuria in a long-term care facility through and educational intervention	69.3%	67.6%

Our study design was most similar to that of Gandhi et al., who looked at patients with a UTI diagnosis to determine if they were true UTIs or asymptomatic, who found almost identical rates of patients treated for a UTI who were asymptomatic.[30] This data adds to current literature that ABU overtreatment is factor in all healthcare facilities nationwide. Since some of the facilities in this table have undergone an intervention, this data may suggest that the UTH may also consider an intervention to increase knowledge of when to screen and treat to lower ABU treatment rates.

5.2 ANTIBIOTIC STEWARDSHIP

In response to the high rates of inappropriate use of antibiotics, the associated costs, and other harms, the concept of antimicrobial stewardship, endorsed by the Infectious Diseases Society of America (IDSA), was developed in an effort to ensure "appropriate selection, dosing, route, and duration of antimicrobial therapy" and improve patient outcomes in a healthcare setting by ensuring a proper diagnosis.[17] The purpose of an antimicrobial stewardship program (ASP) is to optimize patient outcomes and minimize adverse events through "quality-of-care improvements and disease-based management rather than antibiotic management and overall cost savings."[5] ASPs do this by following initiatives to help physicians choose the most appropriate drug, dosage, and duration of therapy in order to resolve a patient's infection with minimal side effects and pressures for the selection of resistant strains.[2] There are many different ASPs that healthcare facilities have begun to implement across the country with varying degrees of success. These methods include education, formulary restriction, prior approval programs, streamlining, antibiotic cycling, and computer assisted programs.

Studies have been conducted world-wide that have fully evaluated the effects of ASPs. These studies have shown that ASPs can reduce antibiotic usage, improve susceptibility patterns, decrease development of antimicrobial resistance, and reduce healthcare costs.[5] Reviews have also shown that ASPs can effectively reduce the incidence of *C. difficile* infections.[1]

The 2007 *IDSA/SHEA Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship* outlines 2 main strategies that should "provide the foundation for an antimicrobial stewardship program."[38] These two strategies are (1) prospective audit with intervention and (2) feedback and formulary restriction and preauthorization.[38] These two strategies have been shown to be effective in a variety of facilities and for different types of infections. IDSA/SHEA also lists 8 elements that "may be considered and prioritized as supplements to the core active antimicrobial stewardship strategies based on local practice patterns and resources."[38] These 8 elements are education, guidelines and clinical pathways, antimicrobial cycling, antimicrobial order forms, combination therapy, streamlining or de-escalation of therapy, dose optimization, and parenteral to oral conversion.[38] These 2 core strategies and 8 elements will each be discussed further.

5.2.1 Program Strategies and Elements

PROSPECTIVE AUDIT WITH INTERVENTION AND FEEDBACK

In this strategy, a member of the antibiotic stewardship team can review patient records to decide if physician's antibiotic choices, doses, and lengths of duration were the best choices he/she could have made based upon current guidelines. The team member then discusses with the physician about how to best improve their prescription choices and reduce inappropriate antibiotic use.[38] Although this method is labor intensive, it empowers physicians and is least

invasive into the patient treatment process. This is now the most popular technique found in hospitals that are developing ASPs in their facilities.[39]

FORMULARY RESTRICTION AND PREAUTHORIZATION

Formulary restriction refers to the removal of certain antibiotics completely from the pharmacy formulary so that no clinician can prescribe them to any patients. This is "the most direct method of influencing antibiotic utilization and containing drug costs."[2] Decisions of the specific drugs to maintain in the formulary should consider the local pathogen and resistance patterns. Drugs with similar targets and safety issues should be minimized, and costs, benefits, and toxicities should be considered when replacing an old drug with a newer but more expensive drug. Restricting the formulary can assist in containing costs and regulating prescribing practices, although it does not prevent overuse of broad-spectrum antibiotics.[2]

Preauthorization, or a prior approval program, is a system that requires the prescriber to contact the antibiotic stewardship to receive approval for the use of particular antibiotic.[38] These types of programs can be set up in a variety of ways: telephone approval systems where the prescriber calls a mobile phone of the stewardship team to get approval, antibiotic order forms with written justification for use, or automatic stop orders where the stewardship team can order the discontinuation of inappropriate antibiotics.[2] Preauthorization programs are "by far the most onerous interventions to physicians, but they are probably also the single most effective intervention to improve antibiotic use and decrease antibiotic costs."[2] A survey of physicians found that doctors are "less likely to prescribe restricted agents requiring preapproval."[24]

ELEMENTS

EDUCATION

Although education is the cornerstone to any effective public health intervention, when it is the only intervention, it is the least effective and has no long-term impact on changing the behaviors of physicians and clinicians.[1] Educational interventions come in many different forms, such as mailing or posting informational posters, newsletters, or emails, presenting information at staff conferences, lectures, or seminars, or dissemination of clinical guidelines.[2] Education alone, without an active intervention to accompany it, is "only marginally effective and has not demonstrated as sustained impact."[38]

GUIDELINES AND CLINICAL PATHWAYS

Interestingly, one of the suggested elements is the development of clinical practice guidelines or clinical pathways, similar to those produced by the IDSA for ABU screening and treatment. Guidelines as well as development of clinical pathways are helpful to help "streamline the decision making process for clinicians"[2] and help prescribers made good antibiotic choices for the best patient results. As seen in the results presented here, the high percentage of people with ABU being treated inappropriately suggests that these guidelines are not being strictly followed. Physicians generally agree with the principles of the guidelines but dissemination of guidelines alone is not effective,[2] and implementation of these guidelines seems to be where the breakdown occurs.[38] Local development of guidelines specific to the area, taking local resistance patterns into account, can increase interest and engage physicians in the process and implementation of guidelines and clinical pathways. Providing physicians with feedback and

education on antibiotic use and patient outcomes can also help integrate guidelines and pathways into routine clinical decision making.[38]

ANTIMICROBIAL CYCLING

Antimicrobial cycling is a method that rotates different classes of antibiotics for a patient's infection in an attempt to prevent the development of resistance to one antimicrobial class.[38] Although this strategy has received a lot of attention, different groups show conflicting results for this method. There is insufficient data for the IDSA to make a recommendation for the use of antimicrobial cycling to prevent or reduce resistance.[38]

ANTIMICROBIAL ORDER FORMS

Antimicrobial order forms have been shown to be effective in reducing antibiotic use and can "facilitate implementation of practice guidelines."[38] Physicians fill out this form when they would like to start a patient on a new treatment; physicians also fill out this form when they would like to change agents, doses, or routes of administration. The antibiotic stewardship team reviews the orders, then grants or denies the request. Forms can require physician specific justification for the requested antibiotic as the best choice.[38]

COMBINATION THERAPY

In combination therapy, multiple broad-spectrum antibiotics are administered simultaneously in the hopes of "reducing serious infections, improving clinical outcomes, and preventing resistance."[38] However, the IDSA feels that there is insufficient data to recommend this strategy as a component of an antibiotic stewardship program.[38]

STREAMLINING OR DE-ESCALATION OF THERAPY

Streamlining or de-escalation of therapy refers to changing an initial antibiotic regimen, usually a broad-spectrum agent, to one that is more targeted toward the causative organism's susceptibility and resistance profile after laboratory results are available.[2,38] The ISDA recommends this for use due to data that shows this method is effective in preventing the emergence of resistance,[2] reducing antimicrobial exposure, and saving the hospital substantial savings.[38]

DOSE OPTIMIZATION

The IDSA recommends a component of the antibiotic stewardship program that allows for optimization of dosages based on individual patient characteristics, causative organisms, site of infections, and pharmacokinetic and pharmacodynamics characteristics of the drug.[38] Dose optimization helps physicians get feedback to change their antibiotic choices based on these patient characteristics, which is a component of the feedback strategy previously discussed.

PARENTERAL TO ORAL CONVERSION

The IDSA recommends making a plan to switch patients from initial parenteral antibiotic treatment to oral treatments as soon as the patient's condition allows. Studies show that this method can reduce the patient's length of hospital stay and healthcare costs, because parenteral antibiotics are much more costly and difficult to deliver.[38] The healthcare facility may consider creating a set of clinical guidelines to facilitate this conversion at a systemic level as a part of their stewardship program.

5.2.2 Interventions at Other Facilities for ABU Overtreatment

The table below is a compilation of published studies of interventions to reduce treatment of ABU. There are very few published results of studies that have done interventions to specifically reduce the treatment of ABU in patients in healthcare facilities. All of the interventions described above have had success reducing the amount of antibiotics used for these patients. All of these interventions make use of informing physicians about treatment guidelines. However, all of these interventions only included educational components, which according to the IDSA is not very effective in changing long-term outcomes unless it is coupled with an active antibiotic stewardship intervention, and should only be included as an extra element, not standing alone. The conflicting success of these educational campaigns and the IDSA's recommendations produces many new questions worthy of discussion. Is an educational intervention for ABU treatment sufficient in healthcare settings? Are these results sustainable without a stronger antibiotic stewardship program the 2 core strategies in place? Preauthorization, formulary restriction, and audit with feedback mechanisms have all shown to reduce antibiotic resistance, costs, and adverse outcomes for patients with other types of infections. Will educational campaigns be enough to affect these downstream outcomes in the population? Future research will need to be done to compare results achieved by all of these strategies to determine which type of intervention is most effective to address the problem of overuse of antibiotics for ABU.

Table 26: Summary of Existing Interventions to reduce inappropriate treatment of ABU

First Author and Year	Intervention Components	Control group or Pre-intervention	Intervention group or Post-Intervention	Results
Bonnal (2008)[34]	Pocket cards with treatment guidelines; staff meetings, use of infectious diseases consultant and pharmacist to evaluate appropriateness of antibiotic treatment and provide feedback to physician	Total duration of treatment per patient with ABU: 7.8 +/- 3.2 days, total number of treatment days: 196, 20% of ABU cases treated	Total duration of treatment per patient with ABU: 6.5 +/- 1.9 days, total number of treatment days: 150, 18% of ABU cases treated	Total reduction of antibiotic for all bacteriuria patients: 21%, significant when just comparing change for patients with ABU (p=0.007)
Chowdhury (2012)[35]	Clinical vignettes highlighting ASB management and decision-making, pocket cards with IDSA guidelines, promotional letter sent to physicians to promote awareness of guidelines	47% of asymptomatic patients treated; total costs of inappropriately treatment: $1200	15% of asymptomatic patients treated; total costs of inappropriate treatment: $600	Reduction in percentage of asymptomatic patients treated (p =0.04); reduction in total costs of inappropriate treatment
Linares (2011)[18]	Electronic memorandum reminding physicians of evidence-based guidelines against treating ABU and culture-negative pyuria in the charts of patients receiving antibiotics	ABU patients received 6.3 +/- 4.2 mean antimicrobial-days	ABU patients received 2.2 +/- 3.06 mean antimicrobial days	Absolute mean reduction of 4.1 antimicrobial-days and relative reduction of 65% (p <0.001)
Loeb (2005)[40]	Small group sessions with nurses with case scenarios; treatment algorithms created and explained to physicians individually; pocket cards with algorithms; larger posters in nursing stations; symptom log for nurses	Rate of antimicrobial use for suspected UTIs 1.59 per 1000 resident days; proportion of total antibiotics prescribed for suspected UTIs: 39%	Rate of antimicrobial use for suspected UTIs 1.17 courses per 1000 resident days; proportion of total antibiotics prescribed for suspected UTIs: 28%	Rate of antimicrobial use for suspected UTIs decreased over time; proportion of total antibiotics prescribed for suspected UTIs significantly lower in intervention group
Pavese (2009)[37]	**Control:** physicians given treatment guidelines and data report of on inappropriate antibiotic use for UTIs; **Intervention:** Infectious diseases physician presented 1-hour seminar and discussion for other physicians with presentation of guidelines and data	Unnecessary antibiotic use for ABU: Pre-intervention: 55.2%, Post-intervention: 37.2%	Unnecessary antibiotic use for ABU: Pre-intervention: 73.5% Post-intervention: 16.7%; Lower rate of inappropriate empirical antibiotic therapy for ABU: Pre-intervention: 30.8% Post-intervention: 13.8%	Difference between groups in unnecessary use for ABU (p=0.01); Difference in rate of inappropriate use of antibiotics for ABU in intervention group pre- and post- intervention (p=0.03)
Zabarsky (2008)[25]	Interviews and education sessions with nurses and prescribers about harms of unnecessary antibiotic use, pocket cards with treatment guidelines; larger cards by computer stations; follow-up educational sessions for nurses	Overall rate of treatment of ABU: 1.7 per 1000 patient-days; total antimicrobial days of therapy: 167.7 per 1000 patient-days	Overall rate of treatment of ABU: 0.6 per 1000 patient-days; total antimicrobial days of therapy: 117.4 per 1000 patient-days	Reduction in overall rate of treatment for ABU (p=0.002); reduction in total antimicrobial patient days of therapy (P<0.001)

5.2.3 Future Recommendations

Based on the results, the facility could benefit from an antibiotic stewardship intervention. If the hospital is concerned about overuse of antibiotics for other types of infections throughout the facility and there are no mechanisms in place to curb excessive prescribing practices, the hospital should consider developing an antibiotic stewardship team. They should also consider establishing 1. an audit and feedback system or 2. a formulary restriction with preauthorization plan. These methods will produce important public health outcomes that will benefit the entire community. It should be noted that these strategies will be very costly and time consuming upfront, but will be cost-effective with time.. On the other hand, if the hospital is mostly concerned with the overtreatment of ABU, creating an educational campaign for physicians and nurses may be a good way to begin, especially if there is insufficient funding available to begin a stewardship program. The best way to determine the proper direction for the hospital to take is to engage the physicians, nurses, pharmacists, infection control units, administrations, and funders and create a dialogue of the facility's priorities. Effective programs that target physicians recognized that they will not change their prescribing practices "unless they are both aware and in agreement with the changes that are being proposed."[24]

5.2.4 Limitations

There are several limitations to this study. The main limitation is the retrospective studys design in which the research is dependent on the quality of documentation in the medical

records. Since the results of this investigation are hinged upon the presence or absence of UTI symptoms, missing information regarding a patient's symptoms was interpreted as an asymptomatic patient. This could have affected the accuracy of the data so it appeared that there were more patients with ABU that are being treated inappropriately. This could result in an inaccurate representation of the need for education or an intervention in this facility. If this is not the case and patients are all symptomatic for UTIs and being treated appropriately, implementing an intervention or taking efforts to reduce overtreatment of ABU will not be an efficient use of resources. Most clinical records accessed during this investigation were obtained from the database of handwritten chart notes that had been scanned into the electronic medical record system. The handwriting was often illegible or the scanning process made the documents "grainy" and difficult to read. Thus, human error could have been introduced during their interpretation.

Also, assumptions had to be made about patients whose symptoms were unspecific and that could have been explained by other clinical causes. The investigator attempted to minimize this by excluding any patients that were found to have any other type of bacterial infection and by having all unclear patients reviewed by the clinical pharmacy specialists with expertise in chart review, medical terminology, records, and symptoms and the proper treatment for UTIs.

Another limitation of this study is the inability to analyze the rates of adverse reactions due to antibiotics and susceptibility/resistance patterns of the organisms infecting the patients in the cohort. There is no approach to examine if patients experienced unnecessary exposure to antibiotics will experience a resistant infection later, experience longer hospital stays, increased mortality, or increased cost of care due to this infection, or a subsequent *C. difficile* infection.

The results of this study have several important public health implications. The findings show that publication of national treatment guidelines is insufficient for eliminating unnecessary antibiotic use for ABU in healthcare facilities. Educational interventions or establishing an antimicrobial stewardship programs within a hospital are better methods to reducing overtreatment and should be considered by this facility and all facilities across the nation. The most important component of either of these methods is that they take efforts to engage physicians and other prescribers. Physician support and involvement will directly impact the success of a program since they will be the recipient of any messages or programs; thus, components of the program need to directly address this specific group's concerns.

This study adds to the profile showing that ABU is unnecessarily treated all over the country and the world, in both large and medium scale facilities. More research needs to be done about how ABU is treated in smaller hospitals and rural communities, and how physicians interact with published treatment guidelines in their facilities. Separate issues may need to be addressed when investigating antibiotic overuse and initiating an intervention in these communities.

5.2.5 Final Notes

Although it is easy to say that physicians make mistakes that are costly to patients and the facility alike and that ASPs will save money, in reality there is grey area. Although overuse of antibiotics can cause antibiotic resistance, costs, and adverse effects, antibiotic use is good in many ways, and there are harmful effects that come from suboptimal treatment of a patient which need to be considered when implementing and evaluating an ASP.[5] It is important to remember that "in the midst of discussing all of the negatives associated with antimicrobial

use it should not be lost that these drugs save lives… [Antimicrobials] are not cigarettes or cocaine: they are highly valuable life-saving therapeutic agents that have been designed to benefit mankind by being used."[1]

6.0 CONCLUSION

Although antibiotics are good for hospital patients, they can produce unwanted consequences. When 50% of all antibiotic use is unnecessary, it is important to look into each facility to find ways to improve antibiotic prescription practices to assure the highest quality of patient care. The study facility, like many other facilities nationwide, can improve patient outcomes by adhering more strictly to published treatment guidelines produced by the IDSA to lower use of antibiotics for ABU in inappropriate patient populations. Although 30% treatment rate of ABU is similar to findings in other published studies, this facility has a responsibility to its patients to implement evidence-based methods to decrease these rates and lower subsequent risks of adverse drug reactions, *C. difficile* infections, and the emergence of antibiotic resistance. ASPs or educational interventions can improve ABU treatment rates and improve patient outcomes and should be considered in this facility.

APPENDIX A

CDC AND NHSN UTI DEFINITIONS

These definitions were published by the CDC and NHSN[41]

Criterion	Urinary Tract Infection (UTI)
	Asymptomatic Bacteremic Urinary Tract Infection (ABUTI)
	Patient with* or without an indwelling urinary catheter has no signs or symptoms (i.e., for any age patient, no fever (>38°C); urgency; frequency; dysuria; suprapubic tenderness; costovertebral angle pain or tenderness OR for a patient ≤1 year of age; no fever (>38°C core); hypothermia (<36°C core); apnea; bradycardia; dysuria; lethargy; or vomiting) *and* a positive urine culture of $\geq 10^5$ CFU/ml with no more than 2 species of uropathogen microorganisms** (see Comments section below). *and* a positive blood culture with at least 1 matching uropathogen microorganism to the urine culture, or at least 2 matching blood cultures drawn on separate occasions if the matching pathogen is a common skin commensal. *Patient had an indwelling urinary catheter in place for >2 calendar days, with day of device placement being Day 1, and catheter was in place when all elements of this criterion were first present together. **Uropathogen microorganisms are: Gram- negative bacilli, Staphylococcus spp., yeasts, beta-hemolytic Streptococcus spp., Enterococcus spp., G. vaginalis, Aerococcus urinae, and Corynebacterium (urease positive)+. +Report Corynebacterium (urease positive) as either Corynebacterium species unspecified (COS) or as C. urealyticum (CORUR) if so speciated. (See complete list of uropathogen microorganisms.)
	Other Urinary Tract Infection (OUTI) (kidney, ureter, bladder, urethra, or tissue surrounding the retroperineal or perinephric space) Other infections of the urinary tract must meet at least 1of the following criteria:

	1. Patient has microorganisms isolated from culture of fluid (other than urine) or tissue from affected site.
	2. Patient has an abscess or other evidence of infection seen on direct examination, during an invasive procedure, or during a histopathologic examination.
	3.Patient has at least 2 of the following signs or symptoms: fever (>38°C), localized pain*, or localized tenderness at the involved site* *and* at least 1 of the following: a. purulent drainage from affected site b. microorganisms cultured from blood that are compatible with suspected site of infection c. imaging test evidence of infection (e.g., abnormal ultrasound, CT scan, magnetic resonance imaging [MRI], or radiolabel scan [gallium, technetium]). * With no other recognized cause
	4.Patient <1 year of age has at least 1 of the following signs or symptoms: fever (>38°C core), hypothermia (<36°C core), apnea*, bradycardia*, lethargy*, or vomiting* *and* at least 1 of the following: a. purulent drainage from affected site b. microorganisms cultured from blood that are compatible with suspected site of infection c. imaging test evidence of infection, (e.g., abnormal ultrasound, CT scan, magnetic resonance imaging [MRI], or radiolabel scan [gallium, technetium]). * With no other recognized cause
Comment	•Report infections following circumcision in newborns as SST-CIRC.
	Symptomatic Urinary Tract Infection (SUTI) Must meet at least 1of the following criteria
1a	Patient had an indwelling urinary catheter in place for > 2 calendar days, with day of device placement being Day 1, and catheter was in place time when all elements of this criterion were first present together. *and* at least 1 of the following signs or symptoms: fever (>38°C); suprapubic tenderness*; costovertebral angle pain or tenderness* *and* a positive urine culture of $\geq 10^5$ colony-forming units (CFU)/ml with no more than 2 species of microorganisms. ----------OR---------- Patient had an indwelling urinary catheter in place for >2 calendar days and had it removed the day of or the day before all elements of this criterion were first present together and at least 1 of the following signs or symptoms: fever (>38°C); urgency*; frequency*; dysuria*; suprapubic tenderness*; costovertebral angle pain or tenderness* *and* a positive urine culture of $\geq 10^5$ colony-forming units (CFU)/ml with no more than 2 species of microorganisms. *With no other recognized cause
1b	Patient did not have an indwelling urinary catheter in place at the time of or the day before all elements of this criterion were first present together *and*

	has at least 1 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* a positive urine culture of $\geq 10^5$ CFU/ml with no more than 2 species of microorganisms. *With no other recognized cause
2a	Patient had an indwelling urinary catheter in place for >2 calendar days, with day of device placement being Day 1, and catheter was in place when all elements of this criterion were first present together and at least 1 of the following signs or symptoms: fever (>38°C); suprapubic tenderness*; costovertebral angle pain or tenderness* and at least 1 of the following findings: a. positive dipstick for leukocyte esterase and/or nitrite b. pyuria (urine specimen with ≥10 white blood cells [WBC]/mm^3 of unspun urine or >5 WBC/high power field of spun urine) c. microorganisms seen on Gram's stain of unspun urine and a positive urine culture of $\geq 10^3$and $<10^5$ CFU/ml with no more than 2 species of microorganisms. ----------OR---------- Patient with an indwelling urinary catheter in place for >2 calendar days and had it removed the day of or the day before all elements of this criterion were first present together *and* at least 1 of the following signs or symptoms: fever (>38°C); urgency*; frequency*; dysuria*; suprapubic tenderness*; costovertebral angle pain or tenderness* *and* at least 1 of the following findings: a. positive dipstick for leukocyte esterase and/or nitrite b. pyuria (urine specimen with ≥10 WBC/$mm^3$of unspun urine or >5 WBC/high power field of spun urine c. microorganisms seen on Gram's stain of unspun urine and a positive urine culture of $\geq 10^3$ and $<10^5$ CFU/ml with no more than 2 species of microorganisms. *With no other recognized cause
2b	Patient did not have an indwelling urinary catheter in place at the time of, or the day before all elements of this criterion were first present together *and* has at least 1 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: a. positive dipstick for leukocyte esterase and/or nitrite b. pyuria (urine specimen with ≥10 WBC/mm^3 of unspun urine or >5 WBC/high power field of spun urine c. microorganisms seen on Gram's stain of unspun urine and a positive urine culture of $\geq 10^3$ and $<10^5$ CFU/ml with no more than 2 species of microorganisms. *With no other recognized cause
3	Patient ≤1 year of age with**or without an indwelling urinary catheter has at least 1 of the following signs or symptoms: fever (>38°C core); hypothermia (<36°C core); apnea*; bradycardia*; dysuria*; lethargy*; vomiting*

	and a positive urine culture of $\geq 10^5$ CFU/ml 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. *With no other recognized cause **Patient had an indwelling urinary catheter in place for >2 calendar days, with day of device placement being Day 1, and catheter was in place when all elements of this criterion were first present together.
4	Patient ≤1 year of age with** or without an indwelling urinary catheter has at least 1 of the following signs or symptoms: fever (>38°C core); hypothermia (<36°C core); apnea*; bradycardia*; dysuria*; lethargy*; vomiting* *and* at least 1 of the following findings: a. positive dipstick for leukocyte esterase and/or nitrite b. pyuria (urine specimen with ≥ 10 WBC/mm^3 of unspun urine or >5 WBC/high power field of spun urine c. microorganisms seen on Gram's stain of unspun urine and a positive urine culture of between $\geq 10^3$and $<10^5$CFU/ml with no more than two species of microorganisms. * With no other recognized cause **Patient had an indwelling urinary catheter in place for >2 calendar days, with day of device placement being Day 1, and catheter was in place when all elements of this criterion were first present together.
Comments	• Elements of the criterion must occur within a timeframe that does not exceed a gap of 1 calendar day. • Laboratory cultures reported as "mixed flora" represent at least 2 species of organisms. Therefore an additional organism recovered from the same culture, would represent >2 species of microorganisms. Such a specimen cannot be used to meet the UTI criteria. • Urinary catheter tips should not be cultured and are not acceptable for the diagnosis of a urinary tract infection. • Urine cultures must be obtained using appropriate technique, such as clean catch collection or catheterization. Specimens from indwelling catheters should be aspirated through the disinfected sampling ports. • In infants, urine cultures should be obtained by bladder catheterization or suprapubic aspiration; positive urine cultures from bag specimens are unreliable and should be confirmed by specimens aseptically obtained by catheterization or suprapubic aspiration. • Urine specimens for culture should be processed as soon as possible, preferably within 1 to 2 hours. If urine specimens cannot be processed within 30 minutes of collection, they should be refrigerated, or inoculated into primary isolation medium before transport, or transported in an appropriate urine preservative. Refrigerated specimens should be cultured within 24 hours. • Urine specimen labels should indicate whether or not the patient is symptomatic. • Report secondary bloodstream infection = "Yes" for all cases of Asymptomatic Bacteremic Urinary Tract Infection (ABUTI). • Report only pathogens in both blood and urine specimens for ABUTI. •Report Corynebacterium (urease positive) as either Corynebacterium species unspecified (COS) or as C. urealyticum (CORUR) if speciated.

APPENDIX B

ABU/UTI RETROSPECTIVE STUDY – DATA EXTRACTION FORM

The data collection form used to record all data from medical records can be found below.

ABU/UTI RETROSPECTIVE STUDY – DATA EXTRACTION FORM

Name:_____

Account #:_____

MRN:_____

Identifier:_____

Age:_____ **Gender (circle):** Male / Female

ICD-9 Codes:

_____

Exclusions Identified:

□ ICU & urine culture on admission

□ Neutropenia

□ Taking antibiotics upon admittance

□ Concomitant infections requiring abx

□ Planned urological procedures

□ Pregnant

□ Duplicate urinary culture

Diagnostics performed:

☐ Urine culture ☐ Urinalysis (UA): WBC= ____

Organisms Present and colony count in culture:

_____

_____

Date collected:_____

TREATMENT

In Hospital

Antibiotics(s):_____

Dose & frequency:_____

#Days:_____

At Discharge

Antibiotics(s):_____

Dose & frequency:_____

#Days:_____

Symptoms present at time of culture or admit:

☐ Burning when urination ☐ Urinary frequency

☐ Urinary urgency ☐ Flank pain

☐ Suprapubic pain/ tenderness ☐ AMS

☐ Costovertebral angle tenderness

Signs present at time of culture or at admit:

Serum WBC:_____

Temperature: _____

COMORBIDITIES/HISTORY:

□ Diabetes mellitus □ HIV

□ UTI/pyelo (past 3 mo)

□ Benign prostatic hyperplasia

□ Spinal cord injury or paralysis

□ Ureteral reflux

□ Urinary tract obstruction

□ Catheter use and duration:

- □ Indwelling:_____
- □ In and Out: _____
- □ Condom: _____

□ Other Comorbidities:

_____

_____

Any notes made on reason for treatment:

_____

_____

DATA ANALYSIS

□ Appropriate / Inappropriate urine culture

□ Proper diagnosis of UTI (positive culture + at least 1 symptom)

□ Improper diagnosis of UTI

□ Patient treated inappropriately with abx:

Cost of antibiotics x duration of treatment: =

_____

APPENDIX C

COSTS OF ANTIBIOTICS FROM UTH PHARMACY

Inpatient Antibiotic Costs August 2012

Antibiotic (IV)	Cost $
Cefazolin 1 gram	0.67
Cefepime 1 gram	4.22
Cefepime 2 grams	6.79
Ceftriaxone 1 gram	1.16
Ceftriaxone 2 grams	2.63
Meropenem 500 mg	5.52
Meropenem 1 gram	11.39
Nafcillin 1 gram	10.39
Nafcillin 2 grams	20.59
Piperacillin/ tazobactam 4.5 grams	6.93
Piperacillin/ tazobactam 2.25 grams	3.45
Vancomycin 1 gram vial APP	3.82

Baxter mini-bag plus piggybacks:

NS 50 ml bag each $2.14

NS 100 ml bag each $2.14

Antibiotic (PO)	Cost $
Amoxicillin 250 mg capsule	0.09
Amoxicillin 500 mg capsule	0.14
Amoxicillin/ clavulanate 500 mg tablet	0.71
Amoxicillin/ clavulanate 875 mg tablet	0.95
Azithromycin 250 mg tablet	0.45

Cefuroxime axetil 250 mg tablet	0.28
Ciprofloxacin 500 mg tablet	0.14
Ciprofloxacin 750 mg tablet	0.29
Doxycycline hyclate 100 mg capsule	0.04
Nitrofurantoin BID 100 mg capsule	1.98
Trimethoprim/ sulfamethoxazole DS tablet	0.15
Vancomycin 125 mg capsule	18.50
Vancomycin 250 mg capsule	35.92

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