Restricted Reporting for Positive Urine Cultures Randomized Controlled Trial Protocol

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Peter Daley, Carla Penney, Sarah Boyd, Emeka Chinaka

Introduction

Asymptomatic bacteriuria (AB) is a condition in which bacteria from the bowel are detected in significant numbers by culture of a specimen of collected urine, but the patient does not have urinary-specific symptoms or signs.[1] In contrast, urinary tract infection (UTI) is the presence of bacteria in urine specimens with defined symptoms or signs.[2, 3] The use of inappropriate antibiotic treatment for AB is a systemic stewardship problem, causing harm due to antibiotic adverse effects, selection of bacteria toward drug resistance, and wasted cost.[4]

Recognizing the inappropriate treatment of AB to be a concern among long term care (LTC) residents, Peter Daley, Carla Penney and colleagues performed an observational study in St. John's.[5] 101 consecutive positive urine cultures submitted from six LTC facilities were included, and nurses were interviewed regarding reasons for collection, antibiotic treatment given, and patient response to treatment after seven days. In most cases, basic investigations such as vital signs and urinalysis were not performed. The rate of positive cultures was the same as the expected AB rate. Most considered reasons for urine collection did not correlate with positive culture. Physicians did not treat according to culture results, and treatment did not correlate with improvement in activities of daily living score. The conclusion was that urine culture may not be a useful investigation in LTC, and that changes were required in the selection of patients for testing and antibiotic treatment decisions.

Because urine represents half of all specimens received in Eastern Health microbiology laboratories, with 30 percent of specimens requiring bacterial identification and antibiotic susceptibility testing, significant cost savings may be realized by improvements in policy, so further research is being proposed.

Literature Review

UTI's are among the commonest indications for antimicrobial therapy, among inpatients, outpatients and LTC patients. Prevalence of AB varies from 1-5% among healthy premenopausal women, to 25-50% among women in LTC, to 100% among patients with chronic indwelling catheters.[6] Treatment of AB with antimicrobial therapy does not reduce incidence of symptomatic UTI, complications or death, and is associated with adverse events.[7] Among women with AB randomized to treatment, resistance to antibiotics among isolated bacteria increased.[8] Even among pregnant women, the treatment of AB may not provide significant benefit.[9, 10]

Various interventions have been proposed to reduce inappropriate antibiotic treatment for AB. Physicians have difficulty avoiding treatment when presented with positive culture results. A cluster randomized trial of an algorithm for diagnosis and treatment of UTI failed to reduce urine culture collection rate.[11] 169 residents and staff physicians demonstrated poor knowledge of published AB treatment guidelines, suggesting education may be of benefit.[12] Prospective audit and feedback to physicians reduced treatment duration, but not treatment initiation decisions in one study,[13] and reduced culture orders and treatment during and after an intervention period in another study.[14] An educational intervention reduced inappropriate treatment during the intervention period.[15] Audit and educational interventions require considerable effort and may not lead to sustainable change.

A novel approach to inappropriate therapy changes the way urine culture results are provided to physicians. In a pilot study, non-catheterized inpatients with positive urine cultures were reported by the microbiology laboratory with a general statement suggesting the physician call the lab if specific culture information was considered clinically necessary.[16] This provided

a barrier to access to positive culture results. In the intervention group (415 specimens, 17.8% culture positive, 2% had clinical evidence of UTI), restricted reporting reduced inappropriate therapy from 48% to 12%, with no incidence of UTI or sepsis. Among 37 positive cultures reported in the restricted way, only 5 calls were received to the laboratory requesting complete culture report. The study used retrospective and catheterized control groups.

The use of restricted reporting could provide a cheap and sustainable intervention to reduce inappropriate treatment for AB. Because the study was not randomized, the estimate of true effect may be biased. An ideal design would include randomization of positive cultures between restricted and standard reporting.

Research Objectives

Research Question: Among inpatients with positive urine cultures reported by Health Sciences microbiology laboratory, would restricted reporting, as compared to standard reporting, lead to a reduction in the rate of inappropriate antibiotic therapy without an increase in UTI or pyelonephritis (kidney infection)?

Primary efficacy outcome: proportion of inappropriate antibiotic therapy prescribed by physicians based on published diagnostic criteria for AB and UTI [2, 4, 17] in an intention to treat population. Inappropriate therapy is defined as any treatment for AB, or no treatment for UTI, or treatment for UTI to which the isolated bacteria is resistant.

Primary safety outcome: proportion of untreated UTI and untreated bacteremia.

Secondary efficacy outcomes: proportion of calls from physicians requesting complete report, drug cost savings based on reduction in treatment.

Methodology

The proposed study is a randomized trial of two methods of laboratory reporting in which physicians are the main research participants. At the time of positive urine culture results, the patient will be randomized by computer generated random number placed into serially numbered sealed, opaque envelopes in two equal groups. One group will receive restricted reporting, with a report that states "This POSITIVE urine culture may represent asymptomatic bacteriuria or urinary tract infection. If urinary tract infection is suspected clinically, please call the microbiology laboratory at 777-6936 between 0900 to 2300, or the microbiology technologist on-call at 570-9133 at night, for identification and susceptibility results." The other group will receive conventional reporting of identification and susceptibility. Physicians will then have the option of calling the laboratory to receive the results or not. Complete results will be released by telephone and Meditech to physicians who call to request them. Physicians will be informed about the study prior to initiation, and debriefed about the study after the results have been collected.

Inclusion criteria will include consecutive positive urine cultures collected from adults in acute care that are greater than or equal to 18 years of age. Inpatients must be admitted to Health Sciences Center or St. Clare's Mercy hospitals only, in order to facilitate access to inpatient records. Exclusion criteria will include pregnancy, antibiotic treatment at the time of collection, collection from an indwelling urinary catheter, patients in the Intensive Care Unit and patients with blood neutrophils <1.0 within 7 days, which will help protect immunocompromised individuals. Furthermore, Dr. Peter Daley will review patient charts at 24 and 72 hours and 7 days after collection to ensure patients experience minimal adverse events.

After randomization and reporting, a physician investigator will assess inpatients for the true diagnosis of AB or UTI. Health records will be accessed including demographics, treatment

decisions and outcomes (untreated UTI or pyelonephritis). Frequency of physician calls requesting complete reporting will be recorded.

The microbiology laboratory at Health Sciences Center receives 130 urine specimens per day, with 30 percent reported as significant growth (40 specimens per day). Twenty-five percent are submitted from inpatients. Method of collection will be determined prior to randomization. Study data collection and analysis will take place at the microbiology laboratory only.

The research hypothesis is that restricted reporting will reduce the rate of inappropriate treatment prescribed by physicians. Among inpatients, the expected rate of inappropriate treatment in the control group will be 45 percent, and 15 percent in the intervention group. Accepting a risk of type 1 error of five percent, and a risk of type 2 error of twenty percent, the study will recruit 84 patients. In order to account for missing data, recruitment will be increased to 100 patients. This will require approximately ten days of recruitment. The statistical test to be used is a comparison of proportions between two groups (T test, two sided analysis). Because true diagnosis may be biased by lack of access to clinical information, an intention to treat analysis including all patients randomized will be performed.

Physicians must remain unaware of the research project so that their treatment decisions are unbiased. However, a general notice will be sent to all physicians regarding the study design, and a debrief will be provided in which study results are presented and the option to withdraw data will be provided. This will cause physicians to feel less deceived while still not informing them of the study and thus will not change their behavior.

Physicians of discharged inpatients will be contacted at 7 days to assess for adverse events. Because recruitment will be brief, it is unlikely that physicians will have a second patient in the study.

Ethics permission will be sought from the local ethics board. Consent of patients or physicians will not be requested. In compliance with TCPS requirements, participants will experience no more than minimal risk. Dr. Daley who will assess inpatient charts at 24 and 72 hours and 7 days to surveil adverse events. If an adverse event occurs, the patient will be removed from the study immediately and given standard treatment. Physician consent will not be requested, as awareness of the study would bias treatment decisions.

The benefit of this study to patients includes a reduction in adverse events caused by inappropriate treatment. The risk to patients includes possible untreated UTI. The benefit to physicians includes education toward appropriate treatment of AB. The risk to physicians includes additional effort to access laboratory results for UTI.

Data collection will use a paper case report form, and entry into a password protected online database. Analysis will be performed using SPSS 20.0 (IBM). The only expense of the project will be the graduate student to collect the data, perform the analysis and write the manuscript. The manuscript will be published in a peer-reviewed journal and presented at a national conference.

Implications

The implications of significant results will be powerful. A reduction in inappropriate antibiotic treatment may reduce complications of treatment such as diarrhea due to *Clostridium difficile*, selection of bacteria towards drug resistance, and cost of treatment. A demonstration that untreated UTI or pyelonephritis is rare may educate physicians and nurses to be more

selective in urine collection. This could reduce workload and cost in the microbiology laboratory. The results will generalize to adult inpatients in Canada and around the world. If the results agree with the previous study, evidence may justify restriction of access to urine culture based on pretest probability of UTI.

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