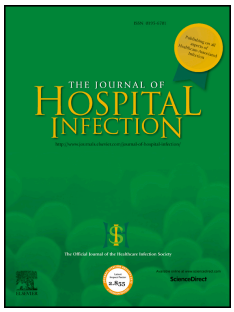
Accepted Manuscript



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PII: S0195-6701(17)30538-8

DOI: 10.1016/j.jhin.2017.09.029

Reference: YJHIN 5243

To appear in: *Journal of Hospital Infection*

Received Date: 14 August 2017

Accepted Date: 27 September 2017

Please cite this article as: Shallcross L, Gaskell K, Fox-Lewis A, Bergstrom M, Noursadeghi M, Mismatch between suspected Pyelonephritis and microbiological diagnosis: a cohort study from a UK teaching hospital, *Journal of Hospital Infection* (2017), doi: 10.1016/j.jhin.2017.09.029.

Mismatch between suspected Pyelonephritis and microbiological diagnosis: a cohort study from a UK teaching hospital

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Running title: Clinical versus microbiological diagnosis of pyelonephritis

Keywords: urinary tract infection; antimicrobial resistance; antibiotic stewardship; diagnostics

Summary

Urinary tract infection (UTI) syndromes are a common reason for empirical antibiotic prescribing in the Emergency Department (ED). We investigated the role of microbiological culture and urinalysis in the diagnosis of pyelonephritis by extracting data on 105 patients with a clinical diagnosis of pyelonephritis at a London teaching hospital.

96/102 patients were treated empirically with intravenous antibiotics but only 55/100 patients who were sampled had microbiological evidence of infection in urine and/or blood. Almost half (10/21) of patients with a negative urine dipstick test had a positive urine culture. Diagnostic uncertainty in this context undoubtedly drives inappropriate antibiotic use.

Introduction

Urinary tract infections are a common reason for hospital admission affecting an estimated 150 million people per year worldwide.[1] More than half of women will experience at least one UTI in their lifetime with an estimated societal cost of $3.5 billion per year in the United States alone.[2–4]

UTIs are differentiated into lower (cystitis) and upper UTIs (pyelonephritis) based on the patients clinical presentation. Cystitis is usually managed in the community but patients with pyelonephritis may require hospital admission for treatment with intravenous antibiotics.[5]

Distinguishing UTI from other diseases with a similar clinical presentation can be difficult, particularly in settings such as the Emergency Department (ED) where diagnostic information may be limited and there is a need to make rapid treatment decisions.[6] Physicians often rely upon imperfect laboratory or bedside tests such as urinalysis to support clinical decisions around the need for empirical antibiotics, despite the fact that these tests lack the sensitivity and specificity to distinguish bacterial UTI in an individual patient. Microbial culture can identify the cause of infection and may be important to guide the choice of antibiotic therapy, particularly in the context of antimicrobial resistance. However the results of culture-based tests take at least 48 hours, by which time many patients have either recovered or been discharged from hospital.

We investigated the contribution that urinalysis and microbial culture make to the diagnosis of pyelonephritis to assess for evidence of a mismatch between clinical and microbiological diagnosis.

Materials and methods

We undertook a cohort study in adult patients with a clinical diagnosis of pyelonephritis. Patients were eligible for the study if they had been admitted to University College London Hospital (UCLH) via the ED between 29/12/2014 and 5/2/2016.

UCLH is a teaching hospital in central London, England, which provides care to approximately 1 million outpatients and 170,000 inpatients per year. Medical staff extracted demographic, clinical and microbiological data from the hospital records for cases of pyelonephritis, defined by: evidence of infection (at least one of: core temperature >37.5^{o}C, rigors, elevated peripheral blood white cell count or C reactive protein); evidence of a urinary source (at least one of dysuria or increased urinary frequency, bacteriuria, urinary leukocytes

or urinary nitrites); and renal involvement (renal angle tenderness or radiological evidence of renal or perinephric inflammatory changes). To confirm the diagnosis of pyelonephritis, the responsible medical Consultant for each case reviewed all the available clinical data. Admission details, examination, urinalysis, microbiological results and antibiotic choice were extracted from electronic and paper hospital records. All data were recorded directly into an Excel spreadsheet and analysed using Stata 14. We estimated the proportion of patients with a microbiological diagnosis of UTI and/or abnormal urinalysis and assessed patterns of antibiotic prescribing and antimicrobial resistance. A positive microbiological culture was defined as identification of a pathogen in blood and/or urine, taking a colony count of > 10^5 cfu/mL as the laboratory cut-off for bacteriuria. Micrococci, coagulase negative staphylococci and candida were classified as contaminants.

To investigate the role of urinalysis in the diagnosis of pyelonephritis, we evaluated the performance of this test compared to urine culture by calculating sensitivity, specificity and positive and negative predictive values.

The data presented in this study were collected as part of routine care and audit at the Trust. Ethical approval for this study was therefore not required.

Results

Data were available for 105 patients with a clinical diagnosis of pyelonephritis. The median age was 29.3 years (IQR 22.7-51.1) and 84.9% (84/99) of patients were female. The majority of patients (80/105) were clinically well at admission with a low national early warning score (NEWS),[7] and the median duration of hospital admission was 3 days (IQR 2-4 days).

Information on antibiotic treatment was available for patients 102/105 patients, 99 of whom were treated empirically with intravenous antibiotics on admission to hospital. 87/105 (82.9%) patients were treated empirically with one intravenous antibiotic, 11 (10.5%) were prescribed two antibiotics and 1 (1.0%) patient was treated empirically with 3 antibiotics. Three patients were treated with oral ciprofloxacin and for the remaining three patients antibiotic treatment was either not given or not recorded. Cefuroxime was most commonly prescribed as the first-line antibiotic, Table I. 99/105 (94.2%) patients were treated with oral step-down antibiotics, with ciprofloxacin as the commonest choice (76/105) patients. 85/88 (96.6%) patients for whom a urine culture was submitted were treated with intravenous antibiotics.

Urine dipstick tests were performed in 104 patients and were negative in 24 (23.1%). A pathogen was identified from 49/88 (55.7%) urine culture samples and from 17/91 (18.7%) blood cultures. 11 patients had both a positive urine and blood culture. Blood and/or urine specimens were submitted for culture in 100/105 patients and overall 55/105 (52.4%) patients had microbiological evidence of infection. None of the individual components of the urine dipstick test reliably predicted bacteriuria. 79% of patients with bacteriuria had a positive urinalysis, defined as at least one abnormal component of the test. By contrast urinalysis was negative in only 11/37 patients who did not have clinically relevant bacteriuria, **Error! Reference source not found.**.

E.coli was identified from urine and/or blood in 49/105 patients (46.7%) and three patients (2.9%) had *E.coli* with extended spectrum beta-lactamases (ESBLs). A single case was identified for each of *Klebsiella* (blood and urine), *Proteus* (urine) and *Pseudomonas* (urine).

Discussion

The majority of patients in this study were treated empirically with intravenous antibiotics, yet almost half of them had no microbiological evidence of infection. Microbiological investigations were undertaken for the majority of these patients, highlighting the discrepancy between clinical and microbiological diagnosis in patients with suspected pyelonephritis.

Patients with a clinical diagnosis of pyelonephritis would be expected to have a positive urine culture, although up to 20% of women with pyelonephritis have urine cultures with $<10^5$ cfu/mL, leading to false negative culture results.[11] Previous studies have also suggested that 15-20% of women who are admitted to hospital with pyelonephritis have bacteraemia, highlighting the need for blood culture sampling in these patients.[11,12] Possible explanations for the low rate of microbiological diagnosis in our cohort could relate to the diagnostic threshold that was used to identify suspected cases, tending to over-diagnose pyelonephritis. However the clinical diagnosis for each case was verified by the responsible medical Consultant which makes this explanation less plausible. It is possible that specimens were collected after the patient had already started antibiotic treatment, which could potentially reduce the likelihood of obtaining a culture result.[10] Meanwhile factors affecting the processing or transportation of urine specimens would tend to overestimate rather than underestimate the prevalence of bacteriuria.[11] Perhaps the most likely explanation for the low rate of microbiological diagnosis relates to the cut-off values which are used to define bacteriuria, which in common with most laboratories are defined as the presence of $>10^5$ cfu per mL of urine.[12] These cut-off values were defined for women with

acute pyelonephritis and may underestimate the prevalence of bacteriuria in other patient populations.[12] For this reason some guidelines recommend the use of lower cut-off values in the diagnosis of UTI. [5,13]

Urinalysis is generally regarded as a test with low sensitivity and high specificity making it well suited to rule out significant bacteriuria.[8] In our study the positive predictive value of the urinalysis tests for leukocyte esterase and nitrites were comparable to those reported in the literature.[8] However, we found the negative predictive value of these tests to be around 50%, significantly lower than the reported 80-90%.[8] Urinalysis has been shown to be of value to rule out UTI in settings with a low rate of culture-positive UTI,[9] but the role of urinalysis in settings where patients have a high probability of infection has previously been questioned.[10] Alternatively the low NPV could reflect difficulties with how urinalysis results are read or recorded in the context of a busy ED.

The major limitation of our study is that it was conducted at a single site. We did not collect information on symptoms, but all the study participants had a clinical diagnosis of pyelonephritis so we anticipate that the prevalence of asymptomatic bacteriuria would be low in this cohort. In addition, information was not extracted on whether the patient was catheterised when the urine specimen was collected, although usually this information would be communicated to the microbiology laboratory and used to inform selection of appropriate cut off values for bacteriuria.[(12)]

Taken together, the extent to which our findings represent false negative microbiological tests or over-diagnosis of UTI is difficult to disentangle. Either way, our study highlights a greater discrepancy between clinical and microbiological diagnosis of pyelonephritis than has been reported in previous studies.(18)] This diagnostic uncertainty undoubtedly contributes to inappropriate antibiotic use and antimicrobial resistance. There is a clear need to develop and implement novel diagnostic strategies in the ED to reliably differentiate patients who require antibiotic treatment for UTI syndromes.

Funding

This research did not receive any specific grant funding from funding agencies in public, commercial or not-for-profit sectors.

Conflict of interest: none

MN and LS designed the study. KG, MB and AFL undertook the data extraction. LS analysed the dataset and wrote the first draft of the manuscript. All authors contributed to drafts of the paper. LS is the guarantor and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table I. Empirical antibiotic treatment and relationship to microbial culture

Intravenous drug treatment[1]	**Number of patients**	**Number of patients with at least one positive microbial culture (%)[2]**
Cefuroxime	87	44 (52.4)
Co-amoxiclav	5	5 (100)
Gentamicin	6	5 (83.3)
Flucloxacillin	1	1 (100)
Ciprofloxacin	2	2 (100)
Daptomycin	1	1 (100)
Teicoplanin	1	1 (100)
Piperacillin-Tazobactam	2	2 (100)
Carbapenem	7	5 (71.4)

[1] A single antibiotic was prescribed empirically for 87 patients, 11 patients were prescribed two antibiotics and one patient was treated empirically with three antibiotics. For six patients antibiotic treatment was either not prescribed or not recorded.

[2] Excluding contaminants

Table II. Test performance of urinalysis to predict bacteriuria[1]

Component of urinary Test	Number of patients with positive test (%)	Sensitivity[2] (%)	Specificity[3] (%)	Positive predictive value [3] - PPV (%)	Negative predictive value[4] - NPV (%)
Blood	63 (60.6)	30/48 (62.5)	18/37 (48.7)	30/49 (61.2)	18/36 (50.0)
Leukocytes	67 (64.4)	33/48 (68.8)	16/37 (43.2)	33/54 (61.1)	16/31 (51.6)
Protein	46 (44.2)	23/48 (47.9)	22/37 (59.5)	23/38 (60.5)	22/47 (46.8)
Nitrites	35 (33.7)	22/48 (45.8)	26/37 (70.3)	22/33 (66.7)	26/52 (50.0)
Glucose	2 (1.9)	2/48 (4.2)	37/37 (100)	2/2 (100.0)	37/83 (44.6)
Ketones	22 (21.2)	12/48 (25.0)	31/37 (83.8)	12/18 (66.7)	31/67 (46.3)
Negative test[4]	24 (23.1)	11/37 (29.7)	38/48 (79.2)	11/21 (52.4)	38/64 (59.4)
Total	104 (100)				

[1] Analysis of test performance restricted to 85 patients who had both urinalysis and urine culture performed (contaminants excluded)
[2] Sensitivity is the proportion of true positives that are correctly identified by the test; specificity is the proportion to true negatives that are correctly identified by the test
[3] PPV: Proportion of urinalysis test positives confirmed as positive by urine culture; NPV Proportion of urinalysis test negatives confirmed negative by urine culture
[4] To exclude bacteriuria i.e. a negative urinalysis was reported in 11/37 patients without bacteriuria; urinalysis was positive in 38/48 patients with bacteriuria.