



Urine cultures at the onset of febrile neutropenia rarely impact antibiotic management in asymptomatic adult cancer patients

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Abstract

Purpose There is a paucity of data regarding the utility of routine urine cultures in adults with febrile neutropenia (FN) without urinary symptoms receiving protocolised antibiotics. This is reflected by inconsistent recommendations in international and regional FN guidelines. We addressed this issue by retrospectively reviewing the impact of routine urine cultures on antibiotic management in haematology cancer inpatients at a tertiary hospital.

Methods All haematology inpatients over a 5-year period (2011–2015) were retrospectively reviewed for episodes of FN (neutrophil count $< 0.5 \times 10^9/L$ and fever $> 37.5^\circ C$). For each episode, demographic data, urinary tract symptoms and signs (absence of which was termed ‘asymptomatic’), urinalysis and urine culture results, antibiotic therapy and duration, and patient outcomes were collected. A urine culture was considered positive if $> 10^5$ colony forming units (CFU)/L were detected. Empiric antibiotic therapy for FN consisted of intravenous piperacillin/tazobactam in stable patients, with the addition of vancomycin and a single dose of gentamicin if systemically compromised.

Results Four hundred and thirty-three episodes of FN were identified in 317 patients. Urine cultures were performed in 362 (84%) episodes. Cultures were positive in 9 of 48 (19%) symptomatic episodes versus 8 of 314 (2.5%) asymptomatic episodes (RR = 7.4, $p < 0.0001$). A change in antibiotic management due to a positive urine culture occurred in only 5 episodes (1.4%): 3 of 48 (6.3%) symptomatic and 2 of 314 (0.6%) asymptomatic episodes respectively (RR = 9.8, $p = 0.01$).

Conclusion Routine urine cultures in FN patients without urinary symptoms who are already receiving protocolised broad spectrum antibiotics rarely impact subsequent antibiotic management.

Keywords Febrile neutropenia · Urine culture · Haematological malignancy · Antibiotics · Cancer

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Introduction

Patients receiving myelosuppressive therapy for haematological conditions are at significant risk of febrile neutropenia (FN). International guidelines are in consensus that peripheral blood cultures, a full blood count, serum electrolytes, renal, and liver function tests should be routinely performed in the initial assessment [1, 2]. While urine cultures are also commonly ordered in this context, there is less agreement regarding their utility as a routine investigation. The Infectious Disease Society of America (IDSA) states a urine culture is only indicated ‘if signs or symptoms of urinary tract infection exist, a urinary catheter is in place, or the findings of urinalysis are abnormal’ [1]. The European Society for Medical Oncology (ESMO) previously recommended a culture irrespective of symptoms until their most recent update in 2016 [2]. Despite this, several other regional guidelines are more conservative, advising urine cultures in all patients [3–8].

This inconsistency likely reflects the paucity of robust large-scale data supporting the utility of routine diagnostic urine cultures in adults receiving protocol-specified antibiotics. This topic remains pertinent as laboratory and labour costs are not inexpensive and specimen collection may delay the administration of antibiotics.

We aimed to address this issue by performing a retrospective study evaluating the impact of routine urine cultures on antibiotic management and outcomes in adult haematological cancer patients with FN.

Methods

Patients and study design

Patients were retrospectively identified from an Australian tertiary hospital database between January 2011 and December 2015. Eligible patients were ≥ 16 years, undergoing recent myelosuppressive chemotherapy for an underlying haematological condition and diagnosed with FN, defined as temperature ≥ 38.3 °C and a neutrophil count of $< 0.5 \times 10^9/L$ or and predicted decline to $< 0.5 \times 10^9/L$ over the next 48 h. In selected patients deemed to be at high risk of poor tolerance of FN, typically elderly patients with co-morbidities, a temperature threshold of > 37.5 °C was used at consultant discretion. Recurrent episodes of FN in the same patient were included in the analysis separately.

Local protocolised investigations for newly diagnosed FN included a urine culture, blood culture, chest X-ray, full blood count, serum electrolytes, and liver function tests. Institutional practice was to collect the urine specimen before the initiation of antibiotics whenever possible, although this may not have always occurred if the patient was too unwell or dehydrated to provide a timely sample. Prophylactic oral antibiotics were not

used in these patients. Empiric antibiotic therapy for FN consisted of intravenous (IV) piperacillin/tazobactam in stable patients, with the addition of vancomycin and a single dose of gentamicin if systemically compromised. The study was approved by the institutional review board (LNR/15/AUSTIN/431).

Data collection

All information was obtained from hospital patient records. For each episode, demographic data, underlying haematological diagnosis, clinical symptoms and signs (dysuria, frequency, haematuria, acute incontinence, suprapubic pain or tenderness, flank pain or tenderness), presence of a catheter, laboratory urinalysis results (leucocytes and nitrites), urine culture results (chemistry, microscopy, culture, and sensitivities), blood culture results, antibiotic therapy and duration, and patient outcomes (death, length of stay) were collected. ‘Symptomatic’ patients were defined as those with one or more clinical symptoms or signs.

A urine culture was considered positive if $> 10^5$ colony forming units (CFU)/L were detected [9]. Cultures with three or more organisms were reported as ‘mixed growth’ and considered contaminants [9]. Any subsequent change in antibiotic management and further diagnostic investigations in response to a positive culture were recorded. Each positive culture and impact on antibiotic therapy was reviewed by an independent infectious disease physician.

Data analysis

Descriptive statistics were used to summarise baseline demographics, urinalysis and urine culture results, and changes in management. Numerical data were compared by the unpaired *t* test or the Mann-Whitney *U* test. For categorical data, the N-1 chi-squared or Fischer’s exact test were used as appropriate. A *p* value < 0.05 was considered significant. Relative risk was calculated when applicable, with 95% confidence intervals and *p* values based on a chi-square statistic. A subgroup analysis was performed on patients that met the IDSA and ESMO definition of FN (oral temperature ≥ 38.3 °C). Relative risks (RR) were compared based on the established statistical methods of Altman and Bland (2003) [10]. The Kruskal-Wallis test was used to evaluate differences in median values of three or more independent groups.

Results

Four hundred and thirty-three episodes of FN were identified in 317 patients. Table 1 describes age, gender and disease demographics, and characteristics of the FN episodes. Using the Multinational Association for Supportive Care in Cancer

Table 1 Baseline characteristics of 433 episodes of FN in 317 patients

	N (%)
Patients	
Median age in years (range)	59 (17–90)
Male gender	183 (58)
Haematological condition	
Leukaemia	129 (41)
AML	86
ALL	19
CLL	15
Lymphoma	118 (37)
Myeloma	65 (21)
Other	5 (1.6)
Previous kidney stones, or genitourinary structural abnormality	8 (2.5)
Catheterised	4 (1.3)
Episodes	
Median days between onset of FN and last chemotherapy (range)	10 (0–70)
FN characteristics	
Fever > 37.5 °C	433 (100)
Fever ≥ 38.3 °C	278 (64)
Neutrophil count < 0.5 × 10 ⁹ /L	361 (83)
Fever ≥ 38.3 °C AND neutrophil count < 0.5 × 10 ⁹ /L	236 (55)
Median neutrophil nadir during admission × 10 ⁹ /L (range)	0 (0–1.5)
Localising urinary tract signs or symptoms	54 (12)
Urine cultures performed	
Symptomatic	48
Asymptomatic	314

(MASCC) [11] scoring system recommended in the IDSA and ESMO guidelines, 415 (96%) episodes were classified as high risk for serious complications such as death or ICU admission.

Urine cultures were performed in 362 (84%) episodes; the reasons the remaining episodes did not have urine cultures were not able to be ascertained from the chart review. There was no significant difference in the baseline characteristics in those patients who were cultured and those who were not, apart from temperature, with cultured patients having a higher mean temperature at baseline (38.6 °C and 38.4 °C respectively, $p = 0.03$). Fifty-four patients had urinary symptoms or signs, most commonly dysuria and frequency, six of whom did not have a urine culture.

Table 2 details urine culture results and changes to antibiotic management, according to the presence or absence of symptoms. The rate of contamination (21%) was identical in both symptomatic and asymptomatic episodes. Cultures were more commonly positive in symptomatic episodes with a relative risk of 7.4 ($p < 0.0001$, 95% CI 3.0–18) versus asymptomatic episodes. Only one patient (who was asymptomatic) had a concomitant pathogen on blood culture (*Citrobacter braakii*). Four patients were catheterised at the time of specimen collection, all of whom were asymptomatic and had

negative urine cultures. Eight patients had previous renal calculi or a genitourinary structural abnormality, of whom one was symptomatic with a positive culture.

Five of 362 patients (1.4%) had a change in antibiotic management due to a positive urine culture. A change was more common in symptomatic patients, occurring in 3 of 48 (6.3%) episodes, compared with 2 of 314 (0.6%) asymptomatic episodes (RR = 9.8, $p = 0.01$, 95% CI 1.7–57). A direct switch of antibiotics occurred in three episodes (one symptomatic and two asymptomatic), and the addition of an antibiotic happened in two further symptomatic episodes. These changes reflected the sensitivity results of the cultured organism. The duration of IV antibiotics was not statistically different between those with a positive, negative, or no urine culture (7 vs. 6 vs. 5 days respectively, $\chi^2 = 0.47$, $p = 0.79$). Two patients, both symptomatic, underwent further work-up investigations following a positive culture.

Culture outcomes were stratified by oral temperature (Online Resource 1, Table S1). Of the 278 patients with a temperature ≥ 38.3 °C, urine cultures were performed in 239 (86%). In this sub-group, 6 of 31 (19%) symptomatic patients had a positive culture, compared with 6 of 208 (2.9%) asymptomatic patients (RR = 6.7, $p = 0.0005$, 95% CI 2.3–19).

Table 2 Urine cultures results, impact on antibiotic management, and further investigations

	Symptomatic, <i>n</i> = 48	Asymptomatic, <i>n</i> = 314	RR (95% confidence interval, <i>p</i> value)
Contaminated ^a	10 (21%)	67 (21%)	0.98 (0.5–1.8, 0.94)
No growth	29 (60%)	239 (76%)	0.8 (0.6–1.0, 0.056)
Positive (organism)	9 (19%) <i>E. coli</i> = 7 <i>E. coli</i> and <i>Klebsiella pneumoniae</i> <i>Candida albicans</i>	8 (2.5%) <i>E. coli</i> (ESBL) = 2 Enterococcus faecalis = 2 <i>Enterobacter aerogenes</i> Pseudomonas aeruginosa Citrobacter braakii Klebsiella pneumoniae and Citrobacter koseri	7.4 (3.0–18, <0.0001)
Change in antibiotics due to culture result	3 (6.3%)	2 (0.6%)	9.8 (1.7–57, 0.01)
Urinary tract investigations following positive culture	2 ^b	0	

ESBL extended spectrum beta-lactamases

^a Contaminated, three or more organisms

^b Renal tract ultrasound (*n* = 1) and CT scan kidneys, ureters and bladder, and rigid cystoscopy (*n* = 1)

Cultures led to a change in management in three symptomatic episodes (9.7%) and one (0.5%) asymptomatic episode (RR = 20, *p* = 0.008, 95% CI 2.2–187). The relative risks of a positive culture and change in antibiotic management in symptomatic versus asymptomatic patients in this subgroup were not significantly different compared to patients with a temperature < 38.3 °C (*p* = 0.75, *p* = 0.24 respectively).

Dipstick urinalysis was performed by the laboratory microbiologists in 361 of 362 (99.7%) episodes. Urinalysis was performed on the same urine sample used for culture. Nitrites were detected in 6 of 17 patients with positive cultures, compared with 3 of 344 with negative cultures (*p* < 0.0001). The positive and negative predictive values of detectable nitrites were 67% and 97% respectively. Leucocytes were detected in 5 of 17 patients with positive cultures, compared with 14 of 344 with negative cultures (*p* < 0.0001). The positive and negative predictive values of detectable leukocytes were 26% and 96% respectively. Leukocytes and nitrites were both positive in only one episode, which had a positive urine culture (sensitivity = 6%, positive predictive value = 100%, negative predictive value = 96%).

No deaths attributable to urosepsis occurred. There was no statistical difference in the median length of stay post FN between those with a positive, negative or no urine culture (10 vs. 8 vs. 7 days respectively, $\chi^2 = 0.43$ *p* = 0.8).

Discussion

This study was designed to address the clinical relevance of routine urine cultures in adult cancer patients with FN receiving protocolised broad-spectrum antibiotics. The results

demonstrated that cultures in asymptomatic patients rarely impacted antibiotic therapy, the critical element in FN management, and rarely lead to further work-up for a urinary source of fever. The low positive culture rate in asymptomatic episodes is unsurprising as clinically documented infections occur in only 20–30% of episodes; in the absence of microbiological findings, translocation of bowel organisms has been identified as a likely cause of fever [12].

In contrast, urine cultures altered antibiotic selection much more frequently in symptomatic patients (6.3% vs. 0.6%), which suggests they are more justifiable in this group. Notably, there was no increased mortality or length of stay post FN in the cohort of patients who did not have a urine culture.

To our knowledge, this is the largest analysis of the utility of routine urine cultures in FN patients. Our observations are broadly consistent with the only comparable study of which we are aware, a smaller review of 133 episodes of FN restricted to patients with acute leukaemia, in which urine cultures did not alter antibiotic management within 1 week in any of the 12 asymptomatic patients with bacteriuria [13].

Our study is subject to the caveats of a retrospective review although we made every effort to ensure our collection of the data was thorough and complete. In this study, a urine culture was considered positive if > 10⁵ CFU/L were grown. However, it is recognised that colony counts of < 10⁵/L in the presence of genitourinary symptoms may be significant, especially for *Escherichia coli* [14]. In this cohort, only one symptomatic patient grew < 10⁵ CFU/L on culture (*Enterobacter aerogenes*); this was classified as a negative culture. Reclassification of this as a positive culture did not change the outcome of the statistical analysis.

We also intentionally included patients with low-grade fever (< 38.3 °C), in order to reflect real-life practice in which many institutions take a cautious approach to the fever threshold for antibiotic initiation [15]. In our sub-analysis, we found no significant difference in the relative risk of positive cultures and changes in management in these patients compared with those with a temperature ≥ 38.3 °C.

Another potential criticism of our results is the likelihood that some patients were too unwell to provide an immediate sample prior to the prompt commencement of parenteral antibiotics. This reflects real-life practice and follows the recommendation that specimen collection should not delay antibiotic initiation [1, 2]. The time of urine sampling with respect to the commencement of antibiotics was documented in the electronic notes, but we are not confident that these times are sufficiently accurate to evaluate further. In discussion with senior nursing staff, in patients unable to provide an immediate urine sample, the sample was generally taken within an hour of antibiotic commencement. The likelihood of this impacting on the rate of urine culture positivity is unclear and to our knowledge has not been addressed in the literature. However, due to the delay in achieving peak serum levels and subsequent active tubular secretion, therapeutic antibiotic levels in the bladder are unlikely to be attained immediately [16], and hence we contend that culture positivity is unlikely to be affected.

Previous studies assessing the value of dipstick urinalysis in FN have found that pyuria is an unreliable indicator of infection in neutropenic patients, but did not assess the diagnostic performance of urinary nitrites [17]. In our cohort, the presence of nitrites had a high negative predictive value and was significantly associated with positive cultures, suggesting it may be reasonable to proceed to a urine culture when nitrites are detected. In contrast, the comparatively low positive predictive value of leucocytes (26%) indicates they are a less accurate marker.

In conclusion, our study provides evidence to broadly support the IDSA and ESMO recommendations that urine cultures should only be performed in adult patients with FN if symptoms are present, a catheter is in place or urinalysis is abnormal. Routine urine cultures in asymptomatic patients rarely impact antibiotic selection and we have ceased this practice at our institution.

Compliance with ethical standards

The study was approved by the institutional review board (LNR/15/AUSTIN/431).

Conflict of interest SG, PD, DJ, ZL, OE, and AP declare no conflict of interest. EH: Research funding: BMS, Merck Serono, Celgene, and Merck Sharpe Dohme. Advisory board: BMS, Janssen, Celgene.

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