Evaluating the role of urinalysis for suspected cystitis in women undergoing pelvic radiotherapy

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Abstract

Purpose—To analyze the effectiveness of urinalysis parameters in predicting positive urine culture and to characterize urinary tract infections (UTIs) in gynecologic cancer patients receiving pelvic radiotherapy.

Materials and Methods—The records of 134 women receiving pelvic radiotherapy were retrospectively analyzed with a total of 241 urine specimens. Dipstick, urine microscopy, and urine culture data were recorded. Sensitivities, specificities, positive and negative predictive values (PPV and NPV), and diagnostic odds ratios (DOR) of dipstick and microscopy components for predicting positive urine culture were calculated. Organisms isolated from positive cultures and their antibiotic resistance data were recorded.

Results—A total of 84 (34.9%) urine cultures were positive for growth. The presence of either urine nitrites, leukocyte esterase (LE), or both had the highest sensitivity (91.7%) of all tested parameters for predicting a positive urine culture. The presence of both urine white blood cells (WBC) and urine nitrites had the highest specificity (95.5%), PPV (75.0%) and DOR (7.21 [2.92 – 17.83]) whereas the absence of urine WBCs had the highest NPV (87.0%). *Escherichia coli* was the most common grown in culture, isolated from 19 (22.6%) of specimens. When antibiotic sensitivity analysis was performed, 23.8% of pathogens were resistant to trimethoprim/sulfamethoxazole, 16.7% were resistant to ciprofloxacin, and 11.1% were resistant to nitrofurantoin.

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Conclusions—UA may be less accurate for predicting UTI in women undergoing pelvic RT compared to the general population, but is still useful. *Escherichia coli* was less common than expected and the rate of resistance to first-line antibiotics was relatively high, underscoring the importance of culture and sensitivity testing in order to confirm the efficacy of empiric antibiotic therapy.

Keywords

radiation; urinary tract infection; cystitis

Introduction

External beam radiation therapy (EBRT) is an important aspect of multidisciplinary treatment for many women with gynecologic cancer [1, 2]. This treatment modality has been associated with both acute and late urinary toxicity [3]. Radiation cystitis is a common acute adverse effect of pelvic EBRT [3, 4] and can negatively impact either short or long-term quality of life. Many women who receive EBRT will also receive brachytherapy, which can further increase the severity and frequency of cystitis [5, 6].

Despite the relative frequency of acute radiation cystitis, it remains a diagnosis of exclusion. Obtaining a urinalysis (UA) is an important step in ruling out other possible etiologies, including a urinary tract infection (UTI). In otherwise healthy women, urine nitrites and leukocyte esterase (LE) suggest the presence of nitrite producing bacteria and leukocytes, respectively, in the urinary tract. Urine nitrites have a reported sensitivity of 46–71% and specificity of 82–98% depending on the population and clinical setting [7–10]. LE can be used to identify nitrite-negative UTIs and other inflammatory processes [11] and, by comparison, LE tends to have a higher sensitivity (62–86%) and more variable specificity (70–93%) than nitrites [7, 9]. Urine microscopy is also utilized for the preliminary evaluation of cystitis, with the presence of leukocytes (>5/HPF) associated with an 84% sensitivity and 90% specificity for predicting a positive urine culture [12]. While urine culture is the gold standard for diagnosing a UTI, the components of the UA can be used to predict culture positivity and guide empiric therapy.

Radiation is known to cause inflammatory changes within the bladder, leading to symptoms in up to 42% of patients undergoing pelvic radiotherapy [13, 14], but the effect such changes have on the clinical interpretation of UA results is unclear. The primary aim of this study was to describe the diagnostic utility of the UA in a population of gynecologic cancer patients receiving radiation treatment. Furthermore, we sought to report the spectrum of organisms isolated by urine culture and antibiotic resistance of these organisms in this unique population.

Materials and Methods

The records of all women with a primary gynecologic malignancy (cervical, endometrial, vaginal, or vulvar) treated at XXX between January 2004 and January 2013 were reviewed. All patients who received EBRT and underwent UA of a bladder urine specimen (obtained via clean catch or urinary catheter) with confirmatory culture either during or within 6

months of radiotherapy completion were included in this analysis. Specimens obtained from nephrostomy or ileal conduit pouches were excluded. All UAs consisted reagent strip interpretation and microscopic evaluation. All UA and urine cultures were performed on the same specimen.

Patient and tumor characteristics, dipstick, urine microscopy, and urine culture data were recorded. These included urine nitrites, leukocyte esterase (LE), white blood cells (WBC), culture positivity or negativity, organism(s) grown, and antibiotic susceptibilities. Parameter combinations were also analyzed, including nitrites and/or LE (either or both positive), nitrites and LE (both positive), nitrites and WBC (both positive), and WBC and LE (both positive). Urine cultures were classified as positive or negative according to laboratory guidelines established by the American Society for Microbiology [15].

Each urine specimen was analyzed separately. Urine LE and WBC were analyzed using ordinal values (negative, trace, 1+, 2+ and 3+) and then dichotomized into positive or negative with trace, 1+, 2+ and 3+ LE values all considered positive. Specimens with urine WBC of 0–5 cells/HPF were categorized as negative, and all other values were categorized as positive. Cultures with intermediate susceptibility were classified as resistant.

The Pearson χ^2 test was used to compare the frequency of positive urine culture between groups. Sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) were calculated as compared to urine culture as the reference standard. Diagnostic odd ratios (DOR) and associated p-values were calculated using binary logistic regression. All statistical analyses were performed using IBM SPSS version 22.0.

Results

A total of 503 gynecologic cancer patients received radiation therapy in our department between January 2004 and January 2013. One hundred thirty-four women with a total of 241 urine specimens analyzed met the inclusion criteria. The median number of urine samples tested per patient was 1 (range 1 to 8 samples). Most (96%) cultures were performed on the same day of UA or within 1 day of UA and the median number days between repeated UA in patients receiving multiple UAs was 9 (range 0 to 102 days).

The median age of patients at the start of EBRT was 53.8 years (range 28–87 years). The most common primary malignancy was cervical cancer (70.1%), followed by endometrial cancer (13.4%), vaginal cancer (9%) and vulvar cancer (7.5%). Eighteen (12.7%) patients had stents or nephrostomy tubes. Concurrent chemotherapy was delivered to 105 (78.3%) patients and a brachytherapy boost was utilized in 93 (69.4%) cases.

Eighty four (34.9%) cultures were positive for growth. A comprehensive description of clinical setting in which each urine specimen was obtained is presented as Table 1. Forty seven of 164 (28.7%) clean catch specimens yielded positive culture results compared to 37 of 76 (48.1%) specimens obtained via urinary catheter ($p=0.008$); one specimen was obtained via suprapubic catheter and was negative. No other clinical parameter analyzed was associated with an increased rate of positive urine culture.

Urinalysis as a Predictor of Positive Urine Culture

A comprehensive description of the sensitivities and specificities of the individual components of the UA and urine microscopy are presented as Table 2. Urine nitrites had a specificity of 93.5%, PPV of 69.7% and NPV of 70.6%. LE had a sensitivity of 90.5% and NPV of 84.9%. Nitrites and LE both positive was associated with similar specificity (93.5%) and PPV (68.8%) compared to that of nitrites alone. Conversely, positivity for nitrites or LE (or both) yielded values similar to those of LE positivity alone, with a sensitivity of 91.7% and NPV of 86.3%. Positive WBC had a sensitivity of 90.9% and NPV of 87.0%. Nitrites and WBC (both positive) yielded values similar to those of positive nitrites alone, with a sensitivity of 25.3%, a specificity of 95.5%, PPV of 75.0%, and NPV of 70.6%. The presence of both LE and WBC positivity yielded values similar to WBC or LE alone, with a sensitivity of 83.1%, specificity of 47.7%, PPV of 46.3%, and NPV of 83.9%.

Given the increased rate of positive urine culture for samples obtained via catheter we repeated these calculations for subgroups stratified by the origin sample (Table 3). Most parameters were associated with a greater diagnostic utility for samples obtained via catheter compared to clean catch samples. Calculations were also repeated for subgroups stratified by the timing of UA with respect to EBRT (Table 3).

Urine Culture Results

A summary of organisms isolated by urine culture is presented in Table 4. Fifteen of 84 (17.9%) positive cultures grew 2 or more organisms. The most common organisms isolated were *Escherichia coli* in 19 (22.6%) samples, coagulase negative Staphylococcus species in 12 (14.3%) samples, Diphtheroids in 12 (14.3%) samples, and yeast in 11 (13.1%) samples.

Antibiotic resistance data are summarized in Figure 1. Antibiotic susceptibility testing was performed on a total of 42 organisms, with specific antibiotics included per physician orders and laboratory protocol. Of the 42 organisms tested for TMP/SMZ susceptibility, 10 (23.8%) were resistant. Two of 18 (11.1%) organisms tested for nitrofurantoin susceptibility were resistant. Both specimens resistant to nitrofurantoin were susceptible to either TMP/SMZ or ciprofloxacin. Six of 36 (16.7%) tested were resistant to ciprofloxacin, 4 of which were also resistant to TMP/SMZ.

Discussion

Women experiencing dysuria during pelvic radiation therapy present a management challenge. They are at increased risk of UTI [16, 17], but may also develop radiation induced cystitis or a combination of these problems. Despite the frequency of this clinical dilemma, the diagnostic utility of the UA has not been formally studied in women receiving pelvic RT for gynecologic malignancies. In this study, we found the diagnostic utility of the urine dipstick components, namely nitrite and leukocyte esterase, to be less predictive of the gold standard of positive urine culture than expected in the general population.

The diagnostic accuracy of the various components of the urine dipstick results is heavily dependent upon the patient population and clinical setting. In the meta-analysis by Deville *et al.*, the sensitivity, specificity, and DOR of urinary nitrites for predicting UTI were 50%,

82%, and 11, respectively, across 15 studies of the general population [7]. LE positivity was 62% sensitive and 70% specific across 33 studies of non-urological populations, with a DOR of 9 [7]. By comparison, the 27.7% sensitivity of nitrites and 29% specificity of LE were lower in our study population. The DOR of 5.52 for nitrites and 3.89 for LE were also notably lower suggesting that these two dipstick components have less ability to predict a positive urine culture in this patient population. In our study, we found that the addition of urine microscopy, namely evaluation for WBCs, improved the diagnostic utility of the UA. When nitrites were combined with WBCs (nitrites and WBCs both positive) the DOR was 7.21, the highest of any of the examined urinary parameter. When the presence of WBCs alone was considered in our study the PPV and NPV were 44.3% and 87%, respectively, similar to the values reported by Kupelian *et al.* in a study of more than 1,200 patients with lower urinary tract symptoms [18].

The only clinical parameter associated with an increased rate of positive urine culture was when samples were obtained via catheter. To further investigate how this may affect the interpretation of the UA we repeated the measures of test accuracy stratified by how the sample was obtained and found the DOR of the various UA components to be larger for samples obtained via catheterization than clean catch samples. The dipstick and microscopy parameters for samples taken during EBRT or within 3 weeks of its completion yielded similar PPV, NPV, and DOR to those of the cohort as a whole. While acute radiation cystitis tends to resolve shortly after therapy, radiation can induce a number of changes within the bladder urothelium which vary over time. We chose to include samples taken up to 6 months from completion of EBRT since this corresponds to when endothelial proliferation is typically observed [19]. Additional histologic changes within the bladder may occur for many years following radiotherapy and how these changes affect the susceptibility and diagnosis of UTI remains an important unanswered question.

The causative organisms and antibiotic resistance patterns in this population also appeared distinct from the general population. While *E. coli* was the most common causative organism in our study, it was isolated in only 22.6% of positive cultures, compared to 67% to 77% of cases in other ambulatory settings [8, 9, 20, 21]. Another notable finding is that nitrite-producing organisms only accounted for 31.8% of all culture isolates, which may explain why the sensitivity of urine nitrites in our patients was lower than in the general population. Atypical organisms, including diphtheroids and yeast, were more common than expected.

Forty-four cultured pathogens underwent antibiotic resistance testing. A significant portion of organisms tested for TMP/SMZ susceptibility demonstrated resistance; ciprofloxacin resistance was less prevalent, and nitrofurantoin resistance was least. By comparison, in a study of 347 women with symptoms of acute uncomplicated cystitis in the primary care setting 15% of positive cultures were resistant to TMP/SMX and only 2% were resistant to nitrofurantoin [20]. The perceived increase in antibiotic resistance noted in our study may be a result of the comparatively large proportion of atypical organisms and scarcity of *E. coli*. Overall, current recommendations for the first-line therapy of UTI [22] appear to remain valid for women receiving pelvic RT; however, clinicians should remain vigilant that

susceptibility testing may prompt a change in antibiotic therapy more often than in the general population.

Limitations of this study include its retrospective design, relatively small sample size from a single institution, and lack of antibiotic susceptibility from all positive cultures. Although there are inherent limitations of retrospective studies, we utilized strict inclusion criteria, and our diagnostic criteria and antibiotic resistance endpoints were objective. Antibiotic susceptibility data were not available for each positive culture because these tests were ordered according to laboratory protocol and physician orders. Lastly, this study only included women for whom a UA was performed, therefore conclusions regarding the frequency and pattern of UTI across all the entire population of women receiving pelvic EBRT cannot be made from this data.

In conclusion, the components of the urinalysis, both dipstick and microscopic evaluation, appear to be associated with slightly less diagnostic accuracy for predicting UTI for women receiving pelvic EBRT than in the general population. The spectrum of pathogens isolated from positive urine contained a lower than expected proportion of *E. coli*, a higher proportion of atypical organisms, and showed a slightly higher rate of resistance to first-line antibiotics. Future directions include investigating symptom resolution after antibiotic therapy and the development of clinical algorithms to better prepare clinicians to support women undergoing treatment of gynecologic cancers.

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⁴Trimethoprim/sulfamethoxazole

Figure 1.
Histogram of susceptibility testing results.

⁴Trimethoprim/sulfamethoxazole

Table 1

Clinical characteristics of urine specimens.

		N	No. Positive (%)	No. Negative (%)	<i>p</i> ¹
Primary tumor site	Cervix	166	57 (52.3)	109 (65.7)	0.261
	Uterus	27	6 (22.2)	21 (77.7)	
	Other	48	21 (43.8)	27 (56.3)	
Chemotherapy	Yes	181	60 (33.1)	121 (66.79)	0.334
	No	60	24 (40)	36 (60)	
Timing with respect to EBRT	During or within 3 weeks of completion	140	50 (35.7)	90 (64.3)	0.945
	3–12 weeks from completion	53	18 (34)	35 (66)	
	>12 weeks from completion	48	15 (31.3)	33 (68.8)	
Timing with respect to brachytherapy	Before first implant or no brachytherapy	152	53 (34.9)	99 (65.1)	0.667
	2 weeks from final implant	43	17 (39.5)	26 (60.5)	
	>2 weeks from final implant	46	14 (30.4)	32 (69.6)	
Sample source	Clean catch	164	47 (28.7)	117 (71.3)	0.008
	Urinary Catheter	76	37 (48.1)	47 (61.8)	
	Suprapubic Catheter	1	1 (100)	0 (0)	
Number of prior samples per patient	0	135	45 (33.3)	90 (66.7)	0.675
	1	51	17(33.3)	34 (66.7)	
	2+	55	22 (40)	33 (60)	
Prior positive culture?²	Yes	61	25 (41)	36 (59)	0.126
	No	45	12 (26.7)	33 (73.3)	
Stent	Yes	14	6 (42.9)	8 (57.1)	0.517
	No	227	78 (34.4)	149 (65.6)	
Nephrostomy	Yes	15	7 (46.7)	8 (53.3)	0.342
	No	226	77 (34.1)	149 (65.9)	

EBRT (external beam radiotherapy).

¹ Pearson χ^2 test.² Only includes patients with prior urine sample tested.

Table 2

Measures of urinalysis test accuracy across entire patient cohort.

Entire Sample Cohort (N = 241)						
	Sensitivity	Specificity	PPV	NPV	DOR [95% CI]	P
Nitrites	27.7%	93.5%	69.7%	70.6%	5.52 [2.48–12.3]	0.000005
LE	90.5%	29.0%	40.9%	84.9%	3.89 [1.73–8.71]	0.000479
Nitrites AND ¹ LE	26.5%	93.5%	68.8%	70.4%	5.23 [2.34–11.7]	0.000011
Nitrites OR ² LE	91.7%	28.6%	41.2%	86.3%	4.4 [1.88–10.29]	0.000244
WBC	90.9%	34.8%	44.3%	87.0%	5.34 [2.27–12.54]	0.000027
Nitrites AND WBC	25.3%	95.5%	75.0%	70.6%	7.21 [2.92–17.83]	0.000001
LE and WBC	83.1%	47.7%	46.3%	83.9%	4.5 [2.33–8.67]	0.000002
Blood	73.8%	33.5%	37.6%	70.3%	1.42 [0.80–2.57]	0.242
RBC	76.7%	27.6%	35.4%	69.9%	1.25 [0.61–2.58]	0.545
Protein	71.4%	35.5%	37.5%	69.6%	1.38 [0.77–2.45]	0.280
Ketones	16.7%	85.2%	37.8%	65.3%	1.15 [0.56–2.37]	0.711

PPV (positive predictive value), NPV (negative predictive value), DOR (diagnostic odds ratio), LE (leukocyte esterase), WBC (white blood cells), RBC (red blood cells).

¹ Both tests positive.

² One or both tests positive.

Table 3

Measures of urinalysis test accuracy stratified by specimen timing and how the specimen was obtained.

Samples taken during or within 3 weeks post EBRT (N = 140)						
	Sensitivity	Specificity	PPV	NPV	DOR ¹ [95% CI]	P
Nitrites	32.0%	93.1%	72.7%	70.4%	6.35 [2.29–17.62]	0.000086
LE	90.0%	28.4%	41.7%	83.3%	3.57 [1.27–10.04]	0.012
Nitrites AND ¹ LE	30.0%	93.2%	71.4%	70.1%	5.86 [2.10–16.34]	0.000213
Nitrites OR ² LE	92.0%	27.6%	42.2%	27.6%	4.38 [1.42–13.49]	0.006
WBC	91.3%	38.8%	46.2%	88.6%	6.54 [2.17–20.34]	0.000225
Nitrites AND WBC	28.0%	96.6%	82.4%	70.5%	11.15 [3.02–41.16]	0.000013
LE and WBC	83.7%	50.0%	48.2%	84.6%	5.13 [2.16–12.17]	0.000072
Blood	72.0%	35.2%	38.7%	68.9%	1.4 [0.66–2.98]	0.388
RBC	72.2%	28.4%	35.1%	65.5%	1.03 [0.42–2.54]	0.951
Protein	64.0%	34.1%	35.6%	62.5%	0.92 [0.45–1.9]	0.823
Ketones	14.0%	86.4%	36.8%	63.9%	1.03 [0.38–2.82]	0.953
Samples taken > 3 weeks post EBRT (N = 101)						
Nitrites	21.2%	94.0%	63.6%	70.8%	4.24 [1.14–15.75]	0.022
LE	91.2%	29.9%	39.7%	87.0%	4.4 [1.20–16.06]	0.017
Nitrites AND LE	21.2%	94.0%	63.6%	70.8%	4.24 [1.14–15.73]	0.022
Nitrites OR LE	91.2%	29.9%	39.7%	87.0%	4.4 [1.2–16.06]	0.017
WBC	90.3%	29.1%	41.8%	84.2%	3.83 [1.02–14.41]	0.037
Nitrites AND WBC	21.2%	94.0%	63.6%	70.8%	4.24 [1.14–15.75]	0.022
LE and WBC	82.4%	44.6%	43.8%	82.9%	3.72 [1.37–10.3]	0.008
Blood	76.5%	31.3%	36.1%	72.4%	1.48 [0.58–3.82]	0.412
RBC	83.3%	26.5%	35.7%	76.5%	1.81 [0.52–6.28]	0.349
Protein	82.4%	37.3%	40.0%	80.6%	2.79 [1.01–7.64]	0.043
Ketones	20.6%	83.6%	38.9%	67.5%	1.32 [0.46–3.78]	0.605
Clean catch samples (N = 164)						
Nitrites	19.1%	93.0%	52.9%	73.6%	3.14 [1.13–8.72]	0.023

Samples taken during or within 3 weeks post EBRT (N = 140)						
	Sensitivity	Specificity	PPV	NPV	DOR ¹ [95% CI]	P
LE	87.2%	29.6%	33.6%	85.0%	2.87 [1.11–7.39]	0.024
Nitrites AND LE	17.0%	93.0%	50.0%	73.3%	2.74 [0.96–7.81]	0.051
Nitrites OR LE	89.4%	28.9%	34.1%	86.8%	3.42 [1.24–9.41]	0.013
WBC	88.1%	35.0%	36.3%	87.5%	3.99 [1.44–11.05]	0.005
Nitrites AND WBC	17.0%	94.8%	57.1%	73.8%	1.76 [1.23–11.52]	0.014
LE and WBC	78.3%	49.6%	38.7%	84.8%	3.54 [1.6–7.81]	0.001
Blood	61.7%	36.5%	28.4%	70.0%	0.927 [0.46–1.87]	0.832
RBC	73.3%	29.9%	26.5%	76.5%	1.17 [0.46–2.97]	0.738
Protein	63.8%	36.5%	29.1%	71.2%	1.02 [0.5–2.05]	0.966
Ketones	14.9%	84.3%	28.0%	70.8%	0.94 [0.37–1.43]	0.903
Catheter (N=76) and suprapubic (N=1) samples						
Nitrites	38.9%	95.0%	87.5%	63.3%	12.09 [2.51–58.23]	0.000296
LE	94.6%	27.5%	54.7%	84.6%	6.64 [1.36–32.39]	0.01
Nitrites AND LE	38.9%	95.0%	87.5%	63.3%	12.09 [2.51–58.23]	0.000296
Nitrites OR LE	94.6%	27.5%	54.7%	84.6%	6.64 [1.36–32.39]	0.01
WBC	94.3%	34.3%	58.9%	85.7%	8.61 [1.76–42.16]	0.003
Nitrites AND WBC	36.1%	97.5%	92.9%	62.9%	22.04 [2.7–179.69]	0.000161
LE and WBC	89.2%	42.5%	58.9%	81.0%	6.1 [1.81–20.5]	0.002
Blood	89.2%	25.0%	52.4%	71.4%	2.75 [0.78–9.7]	0.107
RBC	80.0%	20.7%	51.1%	50.0%	1.04 [0.29–3.71]	0.948
Protein	81.1%	32.5%	52.6%	65.0%	2.06 [0.72–5.93]	0.175
Ketones	18.9%	87.5%	58.3%	53.8%	1.63 [0.47–5.68]	0.438

PPV (positive predictive value), NPV (negative predictive value), DOR (diagnostic odds ratio), LE (leukocyte esterase), WBC (white blood cells), RBC (red blood cells).

¹ Both tests positive.

² One or both tests positive.

Table 4

Description of pathogens isolated from positive urine cultures.

Nitrite producing organisms		N (%)^I
<i>Escherichia coli</i>		19 (22.6)
<i>Klebsiella pneumoniae</i>		7 (8.3)
<i>Proteus mirabilis</i>		3 (3.6)
<i>Serratia marcescens</i>		2 (2.4)
<i>Enterobacter cloacae</i>		2 (2.4)
<i>Klebsiella oxytoca</i>		1 (1.2)
Non-nitrite producing organisms		
Coagulase negative Staphylococcus spp		12 (14.3)
Diphtheroids		12 (14.3)
Yeast (including <i>Candida albicans</i>)		11 (13.1)
<i>Staphylococcus aureus</i>		9 (10.7)
<i>Streptococcus agalactiae</i>		6 (7.1)
Enterococcus spp		5 (6)
<i>Enterococcus faecalis</i>		5 (6)
<i>Streptococcus viridans</i> group		3 (3.6)
<i>Pseudomonas aeruginosa</i>		3 (3.6)
<i>Pseudomonas fluorescens-putida</i>		1 (1.2)
Lactobacillus spp		1 (1.2)
Group C Beta hemolytic Streptococci		1 (1.2)
Group G Beta hemolytic Streptococci		1 (1.2)
<i>Providencia stuartii</i>		1 (1.2)
<i>Alcaligenes spp</i>		1 (1.2)
<i>Morganella morganii</i>		1 (1.2)

^I Note that the sum of percentages is greater than 100 due to samples with multiple isolated pathogens.