

Comparative analysis of bacteriuria results on routine urinalysis and urine culture: a retrospective study

Análise comparativa dos resultados da bacteriúria em urinálise de rotina e cultura de urina: um estudo retrospectivo

Análisis comparativo de los resultados de bacteriuria en análisis de orina y urocultivo de rutina: un estudio retrospectivo

Received: 08/23/2021 | Reviewed: 09/01/2021 | Accept: 09/21/2021 | Published: 09/22/2021

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Abstract

Bacterial urinary tract infections (UTI) are among the most frequent infectious diseases of small animals. Although antimicrobial therapy is recommended for treating bacterial UTIs, the current consensus is that treatment may not be necessary for asymptomatic animals. The aim of this study was to evaluate the diagnostic ability of urinalysis to detect bacteriuria and to compare it with urine culture (gold standard method) to assess the risk of false-positive results. A retrospective study was conducted from January 2016 to July 2019 and urine samples of 119 dogs were analyzed. Diagnostic validation was performed for urinalysis, based on the morphological classification and intensity of bacteriuria. Agreement between the results was assessed using the kappa (κ) index. When the presence of cocci was used as a diagnostic criterion to suggest bacteriuria, it was observed that the agreement ($\kappa = -0.006$) was lower than that expected by chance. However, a poor agreement ($\kappa = 0.22$) was also found for bacilli during urinalysis ($\kappa = 0.23$). A significant degree of agreement was observed in cases with high intensity of bacteriuria. Therefore, urine culture must be performed for conclusive evidence of bacteriuria to avoid false-positive results during urinalysis.

Keywords: Bacteriuria; Canine; Cystitis; Urinary tract infection.

Resumo

As infecções bacterianas do trato urinário (ITU) estão entre as doenças infecciosas mais frequentes em pequenos animais. Embora a terapia antimicrobiana seja recomendada para o tratamento de ITUs bacterianas, o consenso atual é que o tratamento pode não ser necessário para animais assintomáticos. O objetivo deste estudo foi avaliar a capacidade diagnóstica da urinálise para detectar bacteriúria e compará-la com a cultura de urina (método padrão ouro) para avaliar o risco de resultados falso-positivos. Um estudo retrospectivo foi realizado de janeiro de 2016 a julho de 2019 e amostras de urina de 119 cães foram analisadas. A validação diagnóstica foi realizada para o exame de urina, com base na classificação morfológica e intensidade da bacteriúria. A concordância entre os resultados foi avaliada pelo índice kappa (k). Quando a presença de cocos foi utilizada como critério diagnóstico para sugestão de bacteriúria, observou-se que a concordância ($k = -0,006$) foi menor do que o esperado ao acaso. No entanto, uma concordância pobre ($k = 0,22$) também foi encontrada para bacilos durante o exame de urina ($k = 0,23$). Grau de concordância significativo foi observado nos casos com bacteriúria de alta intensidade. Portanto, a cultura de urina deve ser realizada para evidências conclusivas de bacteriúria para evitar resultados falso-positivos durante a urinálise.

Palavras-chave: Bacteriúria; Canino; Cistite; Infecção do trato urinário.

Resumen

Las infecciones bacterianas del tracto urinario (ITU) se encuentran entre las enfermedades infecciosas más frecuentes de los animales pequeños. Aunque se recomienda la terapia antimicrobiana para tratar las infecciones urinarias bacterianas, el consenso actual es que el tratamiento puede no ser necesario para los animales asintomáticos. El objetivo de este estudio fue evaluar la capacidad diagnóstica del análisis de orina para detectar bacteriuria y compararlo con el cultivo de orina (método estándar de oro) para evaluar el riesgo de resultados falsos positivos. Se realizó un estudio retrospectivo desde enero de 2016 hasta julio de 2019 y se analizaron muestras de orina de 119 perros. Se realizó una validación diagnóstica para el análisis de orina, según la clasificación morfológica y la intensidad de la bacteriuria. La concordancia entre los resultados se evaluó mediante el índice kappa (k). Cuando se utilizó la presencia de cocos como criterio diagnóstico para sugerir bacteriuria, se observó que la concordancia ($k = -0,006$) fue menor que la esperada por casualidad. Sin embargo, también se encontró una escasa concordancia ($k = 0,22$) para los bacilos durante el análisis de orina ($k = 0,23$). Se observó un grado significativo de concordancia en los casos con alta intensidad de bacteriuria. Por lo tanto, se debe realizar un cultivo de orina para evidencia concluyente de bacteriuria para evitar resultados falsos positivos durante el análisis de orina.

Palabras clave: Bacteriuria; Canino; Cistitis; Infección del tracto urinario.

1. Introduction

Urinary tract infection (UTI) of bacterial origin is a frequent occurrence in dogs and a significant reason for prescribing antimicrobials. The primary etiological agent of UTI is *Escherichia coli* (*E. coli*), which accounts for approximately 50% of the cases (Barsanti, 2012.; Johnson et al., 2003; Thompson et al., 2011; Weese et al., 2019). The gold standard for diagnosing UTIs is urine culture, which is indicated for animals with clinical signs of bacterial cystitis (Penna et al., 2010; Weese et al., 2019). A conclusive diagnosis of bacterial cystitis is essential to avoid unwarranted antimicrobial prescription in animals with non-bacterial conditions (Ishii et al., 2011; Weese et al., 2019). Furthermore, appropriate and targeted therapy is essential to avoid reinfections, treatment failure, prolonged treatment, and the development of bacterial multidrug resistance (Andrade et al., 2006; Carvalho et al., 2014; Pitout, 2012; Sørensen et al., 2019, Weese et al., 2019).

Urinalysis is a simple, rapid, and low-cost test that detects possible infections and provides substantial assessment of the urinary system. This includes physical, biochemical, and microscopic (sedimentoscopy) examination of urine (Bartges, 2004; Weese et al., 2019). (O'Neil et al., 2013) reported that leukocytes, red blood cells, nitrite, and bacteria are reliable indicators of bacterial UTIs. However, there may be a discordance between the results of cytology and urine culture as pseudobacteria may erroneously be identified as bacteria (Peterson et al., 2012, McGhie et al., 2014). Therefore, the assessment of urinary sediment in suspected UTI is an essential part of urinalysis; however, it must be analyzed in context with other diagnostic data (Bartges, 2004). In addition, although urinalysis may indicate UTI, few studies have demonstrated an association between urine culture and urinalysis results (Weese et al., 2019).

The present study aimed to compare the results of urinalysis and urine culture, to evaluate the concurrence between the microscopic visualization of bacteria in urine sediments and the occurrence of bacterial growth in urine culture.

2. Methodology

This retrospective study was conducted on the urine samples of 119 dogs (males and females) of various breeds and ages, who underwent urine culture and urinalysis from January 2016 to July 2019.

Urinalysis was performed with the urine sample at room temperature and included physical, semi-quantitative, quantitative, and sedimentoscopic evaluations. The physical examination of the sample included the evaluation of color, appearance, odor, specific density, and volume of the sample. The density was measured using a standard-calibrated refractometer (Megabrix). In addition, a semi-quantitative biochemical examination of urine was performed using a commercially available reagent strip (Combur10 Test®, Roche). This included the assessment of pH and the presence or absence of proteins, glucose, ketone bodies, occult blood, bilirubin, and urobilinogen in the urine.

For sedimentoscopic evaluation, 5 ml of the urine sample was centrifuged at 1500 rpm for 5 minutes. The pellet was resuspended in 1 ml of the supernatant. Next, 20 µL was placed on a dry and clean glass slide and covered with a coverslip (24 × 24 mm) for microscopic evaluation. The sediment was examined under a low-power field (10x objective) to identify cylinders and crystals. However, epithelial cells (kidney, pelvic, transitional, and urethral), leukocytes, red blood cells, bacteria, and other structures were identified under a higher magnification field (40x or 100x objective).

Qualitative methods were used to determine the etiological agents, wherein the bacteria present in the urine samples were isolated and identified. Samples were sent to the Laboratory of Routine Bacteriology and plated on blood agar supplemented with 5% equine blood (Difco™) and MacConkey agar media (Difco™) (Bartges, 2004), and incubated for 24-48 h at 37 °C. The isolates were characterized both microscopically (for gram staining) and biochemically (catalase and oxidase tests). The isolated samples were evaluated using routine biochemical identification kits (NF PROBAC™) and kits for the identification of *Streptococcus* species Staphy test (PROBAC™) (Procop et al., 2020).

To assess the diagnostic validity of urinalysis for bacterial UTI, sensitivity (S), specificity (E), positive (PPV) and negative (NPV) predictive values, and positive (PLR) and negative likelihood ratios (NLR) were determined with their respective 95% confidence intervals (CI). In addition, the pre-and post-test probability and the increase in diagnostic capacity (%) were also assessed. The Kappa (k) index was used to determine the concurrence between urinalysis and urine culture and the Fisher test was used to evaluate the statistical significance between sex-gender and age. Statistical analysis was performed by Software R 4.0.2.

3. Results and Discussion

The mean age of the patients included in the present study was 8.25 ± 4 years (age range, 1-17 years). A total of 61 males (51%) and 58 females (49%) were evaluated. The urine culture results revealed bacterial UTI in 77.5% females and 60.6% males. Of the 82 patients with positive urine cultures (69%), 32% (n = 26) females and 16% (n = 13) males were above 8 years of age, and 22% (n = 18) females and 27% (n = 22) males were below 8 years of age.. These findings are consistent with previous studies that report a greater prevalence of UTIs in females (Adamama-Moraitou et al., 2017; Sørensen et al., 2019) and in older age groups (Brložnik et al., 2016; Sørensen et al., 2019). However, no statistically significant differences between gender were seen ($p < 0.05$) in the present study. The higher prevalence in females can be explained by the anatomy and close proximity of the rectum to the genitourinary tract, favoring an increase in the growth of enteric bacteria (Bartges, 2004; Carvalho et al., 2014; Sørensen et al., 2019). In addition, comorbidities (diabetes, tumors) are more prevalent in patients with advancing age, which may predispose them to UTIs (Faria et al., 2018; Weese et al., 2019).

The frequency distributions showing the correlations between urine culture and urinalysis, are shown in Table 1. Of the total sample, 62% (n = 74), 9% (n = 11), 22% (n = 26), and 7% (n = 8) were classified as true positive (TP), true negative (TN), false positive (FP), and false negative (FN), respectively.

Table 1. Frequency distributions (percentage [%] and the number of animals [NA]) showing the correlation between urine culture and urinalysis of the 119 urine samples.

	Positive urine culture (NA)	Negative urine culture (NA)	Total (NA)
Positive urinalysis	62% (74)	22% (26)	84% (100)
Negative urinalysis	7% (8)	9% (11)	16% (19)
Total	69% (82)	31% (37)	100% (119)

Negative urine culture = absence of bacterial growth; Positive urine culture = presence of bacterial growth. Source: Authors.

Among patients with cocci in the urine samples, 21% (n = 22), 11% (n = 11), 64% (n = 66), and 4% (n = 4) were classified as TP, TN, FP, and FN. Among patients with bacilli in the urine samples, 51% (n = 42), 13% (n = 11), 7% (n = 6), and 28% (n = 23) were classified as TP, TN, FP, and FN. The results based on the morphological classification of bacteria are listed in Table 2.

Table 2. Frequency distributions (percentage [%] and the number of animals [NA]) of the morphological classification obtained from urine culture and urinalysis of the 119 urine samples.

Urinalysis	Urine culture				Total (NA)
	Absence of bacteria (NA)	Cocci (NA)	Bacilli (NA)	Mix population (NA)	
Absence of bacteria	58% (11)	21% (4)	21% (4)	0% (0)	100% (19)
Cocci	42% (22)	21% (11)	27% (14)	10% (5)	100% (52)
Bacilli	8% (1)	0% (0)	92% (11)	0% (0)	100% (12)
Mix population	8% (3)	6% (2)	75% (27)	11% (4)	100% (36)
Total (NA)	37	17	56	9	119

Source: Authors.

Statistical analyses for diagnostic confirmation were performed individually on the basis of the degree of comparison. The results of urinalysis were analyzed on the basis of morphological classification (Table 3) and the intensity of bacteriuria (Table 4).

Table 3. Comparison of diagnostic validation of urinalysis (for detection of bacteriuria) and urine culture, based on the morphological classification of the total sample.

Variable	Pre-test probability (%)	S (%)	E (%)	PPV (%)	NPV (%)	Likelihood ratio		UTI pre-test probability (%)	UTI post-test probability (%)	Post-test probability (%)	Increase in diagnostic capacity (%)	k
						(+)	(-)					
Urinalysis	68.91	90.24	29.73	74.0	57.89	1.28	0.33	2.23	2.85	74.02	5.11	0.23
Cocci	25.0	84.62	14.29	25.0	73.33	0.99	1.08	0.33	0.33	25.0	0	-0.006
Bacilli	79.27	64.62	64.71	87.5	32.35	1.83	0.55	3.76	6.89	87.32	8.05	0.22

E = specificity; k = Kappa index; NPV = Negative predictive value; PPV = Positive predictive value; S = Sensitivity; UTI = Urinary tract infection. Source: Authors.

Table 4. Comparison of diagnostic validation of the intensity of cocci and bacilli (for the detection of bacteriuria) and urine culture for the total sample.

Variable	Intensity (+)	Pre-test probability (%)	S (%)	E (%)	PPV (%)	NPV (%)	Likelihood ratio		UTI pre-test probability	UTI post-test probability	Post-test probability (%)	Increase in diagnostic capacity (%)	k
							(+)	(-)					
Cocci	1	23.21	46.15	46.51	20.69	74.07	0.86	1.16	0.3	0.26	20.44	-2.77	-0.05
	2	27.08	46.15	57.14	28.57	74.07	1.08	0.94	0.37	0.4	28.49	1.41	0.02
	3	21.28	30.0	54.05	15.0	74.07	0.65	1.29	0.27	0.17	14.79	-6.49	-0.11
	4	33.33	36.36	90.91	66.67	74.07	4.0	0.7	0.49	1.97	66.33	33	0.32
Bacilli	1	39.34	8.33	91.89	40.0	60.71	1.03	1.0	0.64	0.66	39.65	0.31	0.003
	2	50.72	37.14	100	100	60.71	0	0.63	1.03	-	-	-	0.36
	3	56.25	51.11	97.14	95.83	60.71	17.89	0.5	1.29	23.0	95.83	39.58	0.45
	4	43.55	18.52	97.14	83.33	60.71	6.48	0.84	0.77	5.0	83.33	39.78	0.18

E = specificity; k = Kappa index; NPV = Negative predictive value; PPV = Positive predictive value; S = Sensitivity; UTI = Urinary tract infection. Source: Authors.

In this study, a high sensitivity of urinalysis for detection of bacterial UTI was observed (90%-95%, CI = 81.7-95.7). The presence of cocci was also associated with high sensitivity (85%-95%, CI = 65.1-95.6), which suggests that patients with cocci in urine samples were more likely to be diagnosed with UTIs. Although these data were associated with PPV (25%-95%, CI = 21.6-28.7) and PLR (0.99%-95%, CI = 0.82-1.19) for cocci, it was observed that only a small percentage of positive animals were symptomatic. Therefore, a positive result was more likely to be an FP than a TP.

In contrast, despite the low sensitivity of bacilli (65%-95%, CI = 51.8-76), PPV (88%-95%, CI = 78.2-93.2) and RVP (1.83%-95%, CI = 0.94-3.57) values were higher than those for cocci. This is because the bacilli are easy to identify due to their unique shape (Kim et al., 2002; Oliver, 2005; Sørensen et al., 2016; Webb, 2016), thereby resulting in less FP results.

The ability of urinalysis (E = 30%-95%, CI = 15.9-47) and the presence of cocci (E = 14%-95%, CI = 7.3-24.1) and bacilli (E = 65%-95%, CI = 38.3-85.8) for the diagnoses of healthy patients is low. Although the specificity for bacilli was higher

than cocci, the probabilities of patients with a negative tests being healthy were greater in patients with cocci (NPV = 73%-95%, CI = 49-88.8; NRL= 1.08%-95%, CI = 0.38-3.09) than bacilli (NPV = 32%-95%, CI = 22.8-43.6; NRL = 0.55-95%, CI = 0.34-0.88). This can be explained by the fact that samples with negative results have small amounts of active sediments that decrease the possibility of mistaking pseudobacteria with cocci, thereby resulting in less FN results. In addition, high concentrations of bacilli are necessary for identification, and therefore, these may not be detected under a microscope but may show growth on urine cultures, thereby increasing the frequency of FN results.

Considering these results, the diagnostic accuracy during the evaluation of bacilli (65%-95%, CI = 53.3-74.9) was relatively higher as compared to cocci (32%-95%, CI = 23.1-42), confirming that the presence of bacilli is more likely in patients with UTIs.

Although of significant clinical importance, the manual analysis of urinary sediments can present several methodological constraints, such as misinterpretation of results and errors in the identification of cylinders, cells, crystals, and bacteria. The FP results may be due to several factors, including pre-analytical (inadequate collection, incorrect storage) and processing errors (centrifugation, decantation, resuspension, inadequate culture, incorrect handling) (Sørensen et al., 2016). These errors may lead to cellular degeneration and death (urinary debris), which may be misdiagnosed as bacteria, leading to underestimation or overestimation of results (Kim et al., 2002; McGhie et al., 2014; Swenson et al., 2004). According to a previous study, the presence of pseudobacteria (small lipid molecules, cytoplasmic debris, or amorphous crystals which resemble bacteria in size and shape) may be one of the reasons for inaccurate sedimentoscopy results ((Swenson et al., 2004).

Brownian motion, a phenomenon described by Albert Einstein, may also be a complicating factor in sediment analysis. This phenomenon can be explained as an irregular motion (“random dance”) of tiny particles in a solution, which may make it difficult to differentiate the bacterial movement (Silva & Lima, 2007). (Silva & Lima, 2007) reported that Brownian motion increases with increasing temperature and reduction in viscosity and density. In addition to increasing the Brownian motion, low urinary density makes it challenging to identify cells and bacteria during microscopy, thereby increasing the frequency of FN results (Tivapasi et al., 2009). Therefore, it is essential to consider the association between urinary density and bacteriuria before making diagnostic and treatment decisions.

The presence of a particular disease in a defined population is known as pre-test probability or prevalence. The probability is dependent on the results of the diagnostic tests (Hall et al., 2013)). The difference between the pre-and post-test probabilities, which is defined as diagnostic capacity, determines the accuracy of a diagnostic test (Knottnerus et al., 2002). According to the results of this study, an increase of 5% and 8% was observed during urinalysis and evaluation of bacilli, respectively, thereby demonstrating the low diagnostic accuracy of urinalysis. However, no increase was found during the assessment of cocci. Negative increase in the diagnostic capacity was observed during the evaluation of cocci due to increased erroneous results. However, increased bacteriuria increased the post-test probability, resulting in a significant increase in diagnostic capacity. Establishing a threshold (minimum detection limit) for the detection of bacteriuria, may improve the diagnostic accuracy of urinalysis. However, this may increase the frequency of FN results, thereby compromising the sensitivity of the test, which is a reliable indicator of bacterial UTI. Nevertheless, this may increase the specificity of the diagnostic test. Since antibiotics are commonly prescribed for bacterial UTIs, this would avoid unnecessary antimicrobial therapy and minimize the risk of bacterial resistance. Weese et al (2019), reported that antibiograms are most reliable for determining the appropriate antimicrobial therapy.

Using the kappa agreement scale (Landis & Koch, 1977), it was found that urinalysis showed poor agreement ($k = 0.23$, 95% CI = 0.050-0.41) as compared to urine culture. During the evaluation of cocci, a value of $k < 0$ ($k = -0.006$, 95% CI = 0.095-0.083) suggested that the agreement (32%) was lower than that expected by chance (32.5%), thereby raising the hypothesis that the agreement between cocci evaluation and urine culture was solely random (Silva RS Paes A, 2012). On considering the

severity of bacteriuria, it was observed that 4+ cocci had an insufficient degree of agreement ($k = 0.32$, 95% CI = 0.028-0.64). This was higher than the lower severities that had no or weak agreements. In this study, we observed that the presence of 4+ cocci substantially increased E (91%-95%, CI = 70.8-98.9) and NPV (74%-95%, CI = 64.2-82), and decreased the NLR (0.70%-95%, CI = 0.44-1.12), indicating a greater accuracy for diagnosing healthy patients. Compared to urinalysis, S (36%-95%, CI = 10.9-69.2) was decreased and PPV (67%-95%, CI = 30.1-90.3) was increased, indicating a decrease in FP results.

The evaluation of bacilli showed a poor agreement rate of 64.6% ($k = 0.22$, 95% CI = 0.018-0.410). In the present study, a specificity of over 90% was found during the evaluation of bacilli. Low sensitivity (associated with high PPV value) values indicated that most positive patients had UTI, except for 1+ that had a PPV of 40% (95% CI = 10.72-78.73). A possible reason is that a higher concentration of bacilli must be present for detection under a microscope. In this study, discrepancy in the results may have influenced the accuracy of the evaluation of 4+ bacilli. In our study sample, 4+ bacilli and cocci were observed in the urinary sediments; however, only *Enterococcus faecalis* was observed in the urine culture. Similar results can occur in organisms, cases with no growth on culture media, and/or contamination of culture media (Swenson et al., 2004, McGhie et al., 2014).

Screening tests do not conclusively diagnose or exclude a particular disease and are only suggestive of a particular disease (Swenson et al., 2004). A study comparing the urinary sediments of dogs with and without Gram staining, reported increased S (76% to 96%), E (77% to 100%), PPV (83% to 100%), and NPV (69% to 93%) with Gram staining (Way et al., 2013). Previous studies (McGhie et al., 2014; Swenson et al., 2004; Van Nostrand et al., 2000) have also reported significant improvements in the diagnostic accuracy of microscopic examination of urine sediments using Wright-Giemsa and Gram staining. In this study, we highlighted the importance of factors such as specific density of urine, morphological classification, and intensity of bacteriuria during diagnostic and treatment decisions.

This retrospective study had some limitations, including the lack of detailed patient history and absence of relevant clinical information (sample collection method). In patients with suspected UTI, cystocentesis is recommended for sample collection as there is a reduced risk of sample contamination and a lower concentration of active sediments (which may lead to incorrect bacterial classification) (Weese et al., 2019). For urine samples collected by less invasive methods, qualitative and quantitative analyses of the urine cultures are recommended to assess the pathogenic values and bacterial loads, respectively (Sørensen et al., 2019). Further large-scale studies are needed to standardize the sample collection methods and to evaluate the bacterial morphology and intensity of bacteriuria using different stains, in addition to quantitative analyses of urine cultures.

4. Conclusion

Based on the results of this study, it can be concluded that the concordance between bacteriuria during urinalysis and urine culture, particularly for cocci, is low. However, as the intensity of bacteriuria increases during urinalysis, the agreement and probability of a positive result in urine culture increases. Therefore, a conclusive diagnosis of UTIs must be established on the basis of the results of urine cultures.

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