Epidemiology and Risk Factors of Pyelonephritis in Israeli Dairy Cattle

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ABSTRACT

Pyelonephritis epidemiology of dairy cows is not well understood, and the risk factors are ill defined. The primary objective of this study is to assess the risk of catheterization for urine sampling in dairy cattle. The secondary objectives are to describe the epidemiology and risk factors of pyelonephritis in Israeli dairy cattle. The research is a retrospective case control study conducted on Israeli dairy cows that calved during a seven years period in three commercial dairy herds treated by the ambulatory clinic of the Koret school of Veterinary Medicine. Seven-four cases of pyelonephritis (incidence=1.05%) were diagnosed during the study period. Forty percent of the cases were diagnosed during the first month of lactation; parity (Odds Ratio (OR) for 2nd and 3rd lactation or more cow = 2.381 and 2.891, respectively), twin calving, endometritis and ketosis (OR=2.927, 1.693 and 2.206, respectively) were associated with pyelonephritis in the study population. Urethral catheterization was not significantly associated with pyelonephritis. Forty-four urine samples were cultured. *Escherichia coli* was the most prevalent bacteria isolated from urine (30 cases; 65.9%). The second most prevalent bacteria were *Proteus Mirabilis* (6 cases; 13.6%). It was concluded that pyelonephritis of dairy cows is associated with calving diseases. The risk of contracting pyelonephritis increases with age. Urethral catheterization was not associated with increased pyelonephritis risk. The initial treatment of pyelonephritis in dairy cows should be effective against *E.coli*.

Key words: Dairy cow; Pyelonephritis; Urinary Tract disease; Calving; Bacteriology.

INTRODUCTION

Urinary tract infections (UTI) are uncommon in dairy cattle (1-4), and are not in the focus of veterinary research (5). As a result, pyelonephritis epidemiology is not well understood and the disease may be underdiagnosed and mistreated. Lack of knowledge may also lead to misperception of the risks in common procedures (2).

Pyelonephritis of dairy cows was first described at the beginning of the 20th century (6-8), and was considered as a condition refractory to treatment until the introduction of antimicrobial drugs (9). Since the introduction of antimicrobial drugs, the disease has been treated with various success rates, which may relate to the causative bacteria, onset – diagnosis interval and/or the treatment length (2, 9-12).

Corynebacterium renale is usually regarded as the main and most important causative organisms of bovine pyelonephritis (2, 8, 12-17), although other bacteria (*Escherichia coli*, *Proteus spp.*, *Pseudomonas aeruginosa* & *Streptococci*) have been described as urinary pathogenic in cows (5, 18, 19).

Prior study showed an association of pyelonephritis with age, and periparturient diseases (2). Urethral catheterization was also suspected as a risk factor for UTI (2). Pyelonephritis

has a high relapse rate (2, 5) and has been associated with higher culling rates (2, 18).

The main objective of this study was to define the risk of pyelonephritis associated with urine sampling via urethral catheterization; the secondary objectives were to describe the current epidemiology and define other risk factors for pyelonephritis in Israeli dairy farms.

MATERIALS & METHODS

Study design & Animals

The research is a retrospective case control study, which was conducted on lactating cows that calved between July 2006 and June 2013 in three commercial herds consisting of 250-450 Israeli Holstein dairy cows. Cows were housed in loose housing systems in large, completely covered open sheds and fed total mixed ration (TMR). In all herds, cows were milked three times daily in computer controlled milking parlors and the mean annual milk production was 12,000 kg per cow. All cows were identified by ear tags and freeze marking. The herds were within the practice area of the Ambulatory Clinic of the Koret School of Veterinary Medicine, which provided a complete herd-health service and all herds were visited at least twice a week during the trial period. Clinical, reproduction, production and management data were computer recorded by the herd manager and the attending veterinarians. Reproductive management was solely based on artificial insemination (AI) performed by highly trained technicians employed by the Artificial Insemination Service of the Israel Cattle Breeders Association (ICBA).

Clinical Examination

All the cows in the farms were examined routinely between five and 12 days after calving by trained veterinarians, who also diagnosed, treated and recorded all the periparturient disease conditions. At examination, all animals were body scored and comprehensively examined by intra-vaginal and trans-rectal palpation after thoroughly cleaning and disinfecting the perineal area. Cases of retained fetal membranes (RFM) were defined as the presence of placental tissues 24 hours or more after calving as observed by a trained farm employee or the attending veterinarian. In animals without a history or diagnosis of RFM, the diagnosis of Endometritis (EM) was based on the combined characteristics of vaginal discharge obtained by palpation per vagina and of cervical and uterine examination by palpation per rectum as previously described.

All cows with lower-than-expected milk production and poor appetite were examined for ketosis by placing a drop of urine obtained with a disposable plastic catheter on a reagent strip (Ketostix; Bayer, Holland) and comparing the color of the reaction after 5 seconds with a standardized color chart. Cows with urine acetoacetate (AcAc) concentration ≥15 mg/dl were recorded as ketotic.

The diagnosis of pyelonephritis was based on clinical manifestation of the disease as reported before. In brief, all cows went through a comprehensive clinical examination including rectal palpation and urine extraction via urethral catheterization. In some cases, urine was sampled using an aseptic catheterization technic as will be described. Treatment of the animals was initiated at diagnosis and altered, if necessary, according to bacteriological findings and antibiogram.

Bacteriology

The urine samples for bacteriology were taken after scrubbing the vulva and vestibule with soap and then with a single use cloth soaked with alcohol and chlorhexidine (Mediwipes; Dan-Mor, Ltd.). A new single use plastic insemination catheter was scrubbed with alcohol and chlorhexidine and then inserted into the urethra. The sample was taken from mid-stream, after the urine flow flushed the catheter. 10-20 ml urine sample was collected into a sterile 30 ml vial. The urine sample was refrigerated and sent for urine analysis and bacterial culture up to 48 hours after sampling. Upon arrival to the laboratory, bacterial culture was performed using standard methods, as has been described elsewhere (20). Briefly, a sterile plastic disposable bacteriological loop was used to spread 0.01 ml of each urine sample on a freshly prepared blood agar plate (Hy-labs; Rehovot, Israel), which contained 5% washed sheep red blood cells, and on MacConkey agar (Hy-labs; Rehovot, Israel). Plates were incubated aerobically at 37^0C and were examined for growth several times daily for the next few days. A negative culture was defined if no growth was detected within three days from inoculation. Positive cultures with pure bacterial growth on both agar plates were confirmed as *Escherichia coli* using an Enterotest kit (Hy-labs; Rehovot, Israel).

Statistical Analysis

Computerized data were retrieved from the herds and Israeli Cattle Breeders Association (ICBA) central computer and

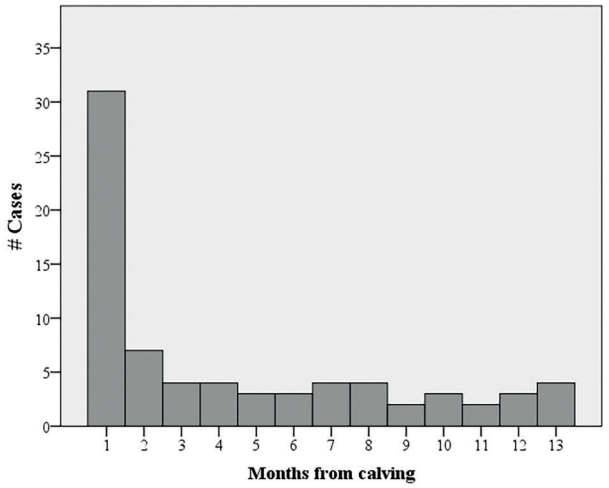

Figure 1: The occurrence of pyelonephritis at different stages of the lactation. A histogram describing the deviation of all 74 pyelonephritis cases as a function of time period from calving.

analyzed using Excel (version 2010, Microsoft, Redmond, WA) and SPSS (version 19, IBM Business analytics, NY USA). Descriptive statistics for the epidemiology of pyelonephritis was evaluated using data for all cows that calved during the study period. For the general population model, data of the total population was used. In order to assess the catheterization risk, a case control study was built where four cows were matched for each case of pyelonephritis. The control cows were matched by farm, parity and calving date (±14 days apart from the calving date of the case). For all cows in the case-control study, data regarding catheterization date for diagnosis of ketosis was obtained from the medical records of the cows. Only cows that went through urethral catheterization during the same lactation and before diagnosis of pyelonephritis were recorded as catheterized before pyelonephritis.

Lactation Incidence Risk (LIR) for all recorded calving diseases and culling data were evaluated for healthy control cows and for pyelonephritis cases.

Crude bivariate associations of pyelonephritis and potential risk factors were initially assessed by use of Pearson χ^2 asymptotic 2-sided tests of significance for the total population and for case-controls cows.

For multivariate analysis two models were built: a multivariate logistic regression using the binary logistic regression function for the general population, and conditional logistic regression using the Cox survival analysis function for the case control study. Factors with significance of P≤0.25 were included in primary multivariate models. The final models were built with exit criteria set at P>0.10. For analysis of the outcome, values of P<0.05 were considered significant, and values of 0.05<P≤0.1 were considered as tendency, and OR were calculated.

Table 1: Descriptive statistics. A table describing the lactation index risk of pyelonephritis and calving traits in the study population.

Factor		Healthy	Pyelonephritis	Total
Overall population		6978	74	7052
Farm:	a	1882	13	1895
		(27.0%)	(17.6%)	(26.9%)
	b	2021	26	2047
		(29.0%)	(35.1%)	(29.0%)
	c	3075	35	3110
		(44.0%)	(47.3%)	(44.1%)
Parity:	1	34.6%	14.9%	34.4%
	2	24.8%	24.3%	24.8%
	3 or more	40.6%	60.8 %	40.8%
Dry Period*:	Normal	49.5%	55.4%	49.6%
	Short (≤49)	38.6%	20.3%	38.4%
	Long (≥71)	11.9%	24.3%	12.0%
Summer calving**		54.5%	56.8%	54.6%
Induced calving		1.1%	2.7%	1.1%
Twins		6.1%	21.6%	6.3%
Dead at calving		6.1%	13.5%	6.2%
RP		9.9%	18.9%	10.0%
Endometritis		41.5%	71.6%	41.8%
Ketosis		15.3%	33.8%	15.5%
Left Displaced Abomasum		1%	2.7%	1%

*** – Normal dry period – 50-70 days.**
**** – Summer – May to October.**

RESULTS

Descriptive statistics

During the study period 7052 cows calved at the study farms. 74 cows (1.05%) were clinically diagnosed as suffering from pyelonephritis. Most of the cases were diagnosed at the beginning of the lactation (Figure 1), as 40% of all cases were diagnosed during the first 30 days, and 60% during the first 90 days of the lactation. The farm, parity and calving traits distribution are described in Table 1. No cases of relapse or culling as a result of pyelonephritis were recorded during the study period in the examined population.

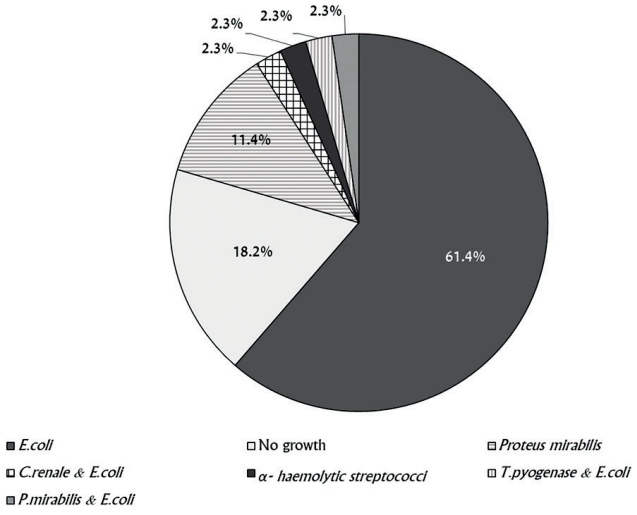

Figure 2 –Bacteria isolated from pyelonephritis urine samples. A pie chart describing the prevalence of different bacteria cultured from urine samples taken from cows diagnosed as suffering from pyelonephritis. (N=44).

Bacteriology

During the study period 44 urine samples were sent for bacterial analysis. The prevalence of the different bacteria cultured from the urine samples is described in Figure 2. *C. renale* was isolated only from one sample (prevalence of 2.3%; Fig. 2) in combination with *E. coli*. *E. coli* was the most prevalent bacterial isolate in urine samples from cows diagnosed with pyelonephritis (N=30; 27 cases as a sole bacterial species and three mixed infections; prevalence of 65.9% and 61.4% respectively; Fig. 2). The second most prevalent bacterial species was *Proteus mirabilis* cultured from six samples (13.6%; Figure 2) including one case of a mixed infection with *E. coli*. In eight cases no bacterial growth was demonstrated although bacteria, neutrophils and granular casts were demonstrated in cytology carried out in three cases.

Pyelonephritis risk factors

The final model describing the risk factors for pyelonephritis in the general population included Parity; Twin calving; Endometritis and Ketosis (Table 2). Older cows were found to be at risk for pyelonephritis in relation to 1st calf heifers (OR=2.381 and OR=2.891 for 2nd lactation and older cows respectively; Table 2). Endometritis, Ketosis and twin calving were also identified as risk factors for pyelonephritis (OR=2.927, 1.693 and 2.206 respectively; Table 2).

Catheterization before the diagnosis date of pyelonephritis was identified as a risk factor using the χ^2 test (OR=1.995, *P*=0.017). The final model included only the factors Number of calves, EM and Ketosis (Table 3). The effect of catheterization before the diagnosis of pyelonephritis was not significant in the multivariate conditional regression (*P*=0.133, data not shown) thus the factor was removed from the final model. In the case of matched control study population the identified risk factors for pyelonephritis were Twin calving, Endometritis and Ketosis, (OR= 2.568, 3.014 and 1.934, respectively; Table 3) as was found in the general population model.

Table 2: Risk factors for pyelonphritis. A multivariate logistic regression model describing the risk factors for pyelonephritis in the study population.

Factor	d.f.	P	O.R.	95% C.I. of the O.R.	
				Lower	Upper
Parity: 1st calf heifers	2	0.010			
2nd lactation	1	0.026	2.381	1.111	5.103
Adult cows[1]	1	0.002	2.891	1.460	5.728
Twin Calving[2]	1	0.009	2.206	1.220	3.987
Endometritis	1	<0.001	2.927	1.708	5.016
Ketosis	1	0.043	1.693	1.016	2.821
Constant	1	<0.001	.002		

1 – Adult cows – 3rd lactation or more.
2 – Twin calving – multi-claf calving.

Table 3: Risk factors for pyelonphritis. A conditional multivariate logistic regression describing the effect of the various factors on risk for pyelonephritis in the case and control population.

Factor	d.f.	P	O.R.	95% C.I. of the O.R.	
				Lower	Upper
Twining	1	0.030	2.568	1.094	6.028
Clinical Metritis	1	0.001	3.014	1.542	5.892
Ketosis	1	0.068	1.934	0.953	3.923

DISCUSSION

Bovine UTI epidemiology has been rarely described in veterinary literature. Most studies focused on the bacterial diversity of the causative organisms, and the risk factors for UTI were infrequently described (2).

Pyelonephritis in Israeli dairy cows is not a common disease. The Lactation Incidence Risk (LIR) found in this study was 1.05% (0.7%-1.3% in the study farms). The LIR in the study population was consistent with previous studies by Markusfeld *et al.* and Rosenbaum *et al.* (1, 2). A previous study

in Israel found LIR of 1.6% in the whole population including the farm in which an outbreak of pyelonephritis occurred (LIR of 6.2%) and LIR of 0.8% excluding this specific farm (2). Abattoir survey done in Pennsylvania demonstrated pyelonephritis prevalence of 0.87% in slaughtered dairy cows (1).

The risk of contracting pyelonephritis increases with age (OR of 2.381 and 2.891 for 2nd and 3rd or more lactations respectively). This finding is partially consistent with previous study demonstrating an elevated risk as cows become older (2). Markusfeld *et al.* found that cows in the 2nd lactation and cows in the 4th or higher lactation had the highest incidence rate. Interestingly, the cows at 3rd lactation were protected. In woman, the age group of 15 to 29 years of age has the highest incidence rate, followed by infants and older persons (21). The higher incidence in younger woman may be related to sexual activity, as will be discussed. In the presented study the higher incidence rate as the cow becomes older may be related to cumulative deformation of the genital tract from repeated damages in the calving process.

Calving diseases (twin calving, ketosis and EM) were demonstrated as a risk factor for pyelonephritis development. This finding is consistent with the time from calving to diagnosis of bovine pyelonephritis in the study population. Postpartum EM may serve as a source for bacteria that may infect the urinary tract. *E.coli* is considered as a main pathogen of the bovine uterus (22, 23), and as such may affect the urinary tract as well. Furthermore, EM was described as associated with dystocia that causes vaginal trauma (24, 25). Trauma to the genital tract, colonization of bacteria on wounds and distortion of the normal anatomy may contribute to the establishment of urinary tract infection. Genital trauma, as a result of frequent sexual intercourse, is also regarded as one of the most important contributors to UTI development (21, 26).

In contrast to this study, Markusfeld (2) found that cows without uterine diseases were at risk to develop pyelonephritis. This difference may be related to the different pathogens in the two studies. *Corynebacterium* species, mainly *C. renale*, are traditionally regarded as the important pyelonephritis pathogens. In the study by Markusfeld *et al.*, all cases were caused by *C. renale*. *C. renale* is, in general, a bacterium sensitive to tetracycline, the growth of which is inhibited by low concentrations of the drug (27). Since all uterine diseases in the study were treated by intrauterine antibiotic passeries containing tetracycline, it is possible that the treatment may have affected bacterial colonization and may have led to the relative protective effect of uterine disease found by Markusfeld *et al.* (2). In presented research, *C. renale* was present only in one urine sample (together with *E. coli*, as a mixed infection). In opposition to this former study done in Israel, *C. renale* was a rare finding in pyelonephritis urine samples in this study. *E.coli* is described as a major UTI pathogen both in human (21, 26, 28) and in other animals (29-32), and was described previously in bovine pyelonephritis (5, 18, 33, 34).

Another difference in the expression of the disease is the relapse rate and culling rate, as no culling due to pyelonephritis was recorded in the study population, while earlier studies (2, 33) showed high rates of culling of pyelonephritic cows. This finding may be related to rapid diagnosis and intervention, the difference in the causative bacteria discussed before, or the efficacy of the antibiotic treatment, as most of the cows were treated with marbofloxacin (Marbocyl™; Vetoquinol, France), a 3rd generation fluoroquinolone which is eliminated in its active form through the urine (35). The efficacy and long duration of activity against *E. coli* was demonstrated in cows and other species (36, 37).

Urethral catheterization is routinely used in Israel for diagnosis of ketosis. This practice was suspected before as a risk factor for UTI. In human medicine, urethral catheterization is regarded as the most common reason for nosocomial urinary infection (26). In the past, a metal reusable catheter was used, as opposed to the single use plastic cannula which has been applied in recent years. This fact, combined with the antimicrobial treatment of cows with uterine disease, may contribute to the relative low incidence of pyelonephritis in cows with uterine diseases (2). Pyelonephritis was not associated with urethral catheterization in the present study.

CONCLUSIONS

Pyelonephritis of the Israeli dairy cow is a disease associated with calving diseases (Twin calving, EM and Ketosis) and higher parity. The most prevalent bacteria isolated from urine of Israeli dairy cows with UTI in the study population were *E. coli*. Initial treatment of cows with pyelonephritis should be aimed at these bacteria, until bacterial isolation from the urine is obtained. In our study we found that urethral catheterization after thorough cleaning of the perineum with water and soap was not a risk factor for UTI in dairy cows.

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