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Faculty of health sciences

Urinary tract infections in children treated at the University Hospital of North Norway – a 10-year material

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Rapport: MED-3950 masteroppgaven kull 2013
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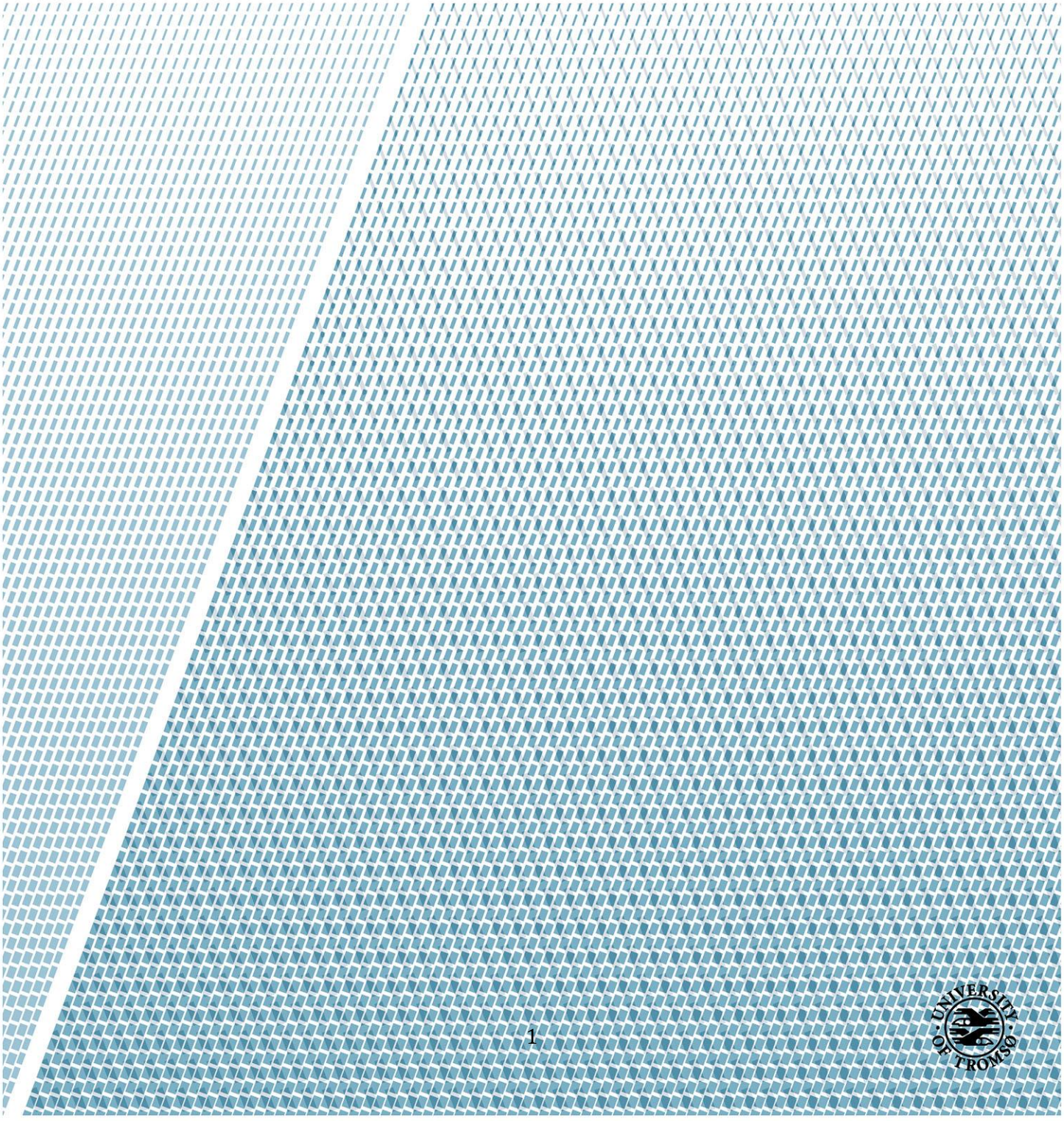
Profesjonsstudiet i Medisin, Tromsø 2018
UiT Norges Arktiske Universitet



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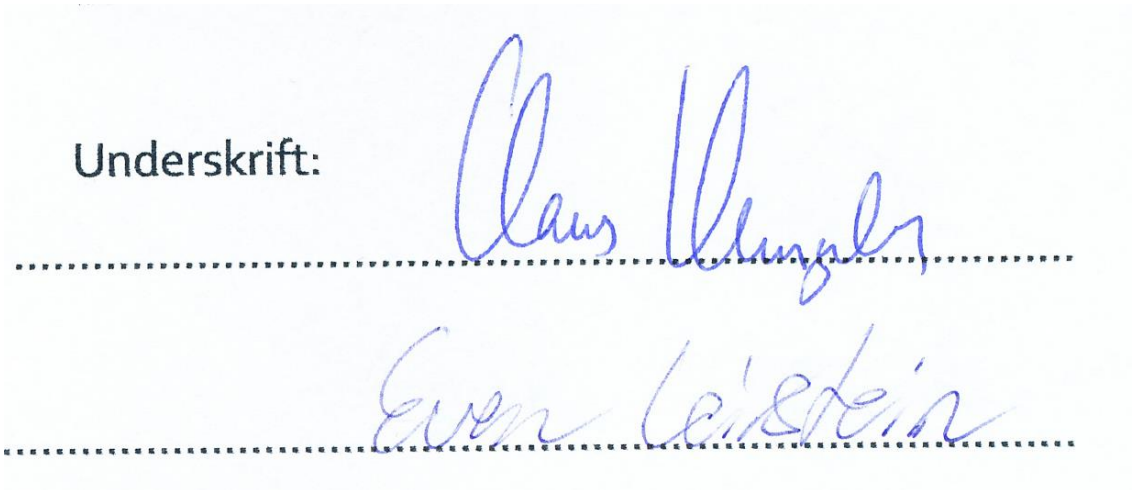
Preface:

The paper was written due to interest in the presentation of urinary tract infections in children. I had little knowledge of the subject before I started the study, but I was always interested in paediatrics and keen to learn more such a common disease. The objective of the study was to register the presentation of urinary tract infections, their risk factors, the blood and urinary samples and see what treatment they received. The thesis question was shaped in collaboration with Claus Klingenberg, whom I knew beforehand as a lecturer, and was continuously worked upon.

The data collection, plotting and analyzation was performed by me with guidance from Claus.

A big thanks goes to the my counsellor Claus Klingenberg for guidance, teaching, supporting and discussing my paper, providing the necessary changes.

Date: 04.06.2018 Place: Tromsø



Summary

Background and objective: Urinary tract infections (UTI) are common in children and can be hard to diagnose early. They range from benign to life threatening conditions, sometimes requiring prompt treatment. The objective of this paper is to register the basic information and the signs, symptoms and risk factors of children with UTIs, what diagnostics were performed, their results and what treatment and follow-up they were given.

Material and methods: A retrospective study was conducted using data available from the University Hospital of North Norway (UNN) departments of Tromsø, Harstad and Narvik. The data was collected in the summer of 2017, going through medical records from 01.01.2007-31.12.2016. The relevant data related to the paper was anonymized and subsequently categorized in an SPSS file. The study was approved as a quality study by the representative of the Institutional review Board (Personvernombudet) at UNN, Per Bruvold.

Results: Of 396 patients in the hospital's records, 133 had a confirmed febrile urinary tract infection. Mean age was 3.3 years, 68.4% of the patients were female. The single most common presenting symptom was fever 45/133 (33.8%), especially in children <2 years of age where it was 35/82 (42.7%). The prevalence of any structural genitourinary abnormality was 57/133 (42.9%). Of 125 urine samples cultured, 97/125 (72.9%) were positive. E.coli was the most common pathogen 74/97 (76.3%). Blood culture was sampled in 109/133 (82.0%), the prevalence of bacteremia was 11/109 (10.1%).

Conclusion: This study has shown that the gender and age distribution was in accordance to available literature. Dipstick analyses were performed in 97.7% and the urine cultured in 94.0% of the cases. The signs, symptoms and risk factors differed significantly ($P<0.05$) based on the factors of age, gender, pathogens and CRP-values. Risk factors were associated with higher age, male gender, non-*E.coli* and higher CRP-values. There were 72.9% cases of significant bacteruria and 10.2% cases of significant bacteremia. *E.coli* was the most prevalent pathogen found, representing 76.3 % of urine isolates and 63.6% of the blood cultures. Ultrasound was performed in 110 patients and MCUG in only 18. Abnormal genitourinal findings had a prevalence of 57/133 (42.9%), and VUR was found in 15/133 (11.3%). Antibiotics were given to 131/133 (98.5%) of the patients, of which empirical treatment followed Norwegian guideline standards in 114/126 (90.5%) of the cases. Ampicillin-Gentamicin IV was the most commonly used antibiotic in both the empirical (85.7%) and during the admission (47.7%).

Introduction

The idea to this thesis came from Claus Klingenberg, my supervisor. I had little prior knowledge about febrile urinary tract infections in children and subsequently thought it a brilliant idea to boost my knowledge.

Claus Klingenberg is a professor at the institute of clinical medicine and a physician at the paediatric ward at UNN Tromsø. He is the lead author of the current acute paediatric guidelines about urinary tract infections in Norway (1) and has held lectures about it for years, including for my class. He therefore had a wish of mapping out the typical patient and see what the current practices at the hospital were.

Before I started working on this thesis I had limited knowledge about urinary tract infections other than dipsticks and painful, frequent voiding. I have learned a lot more about the typical patient, how he or she presents and what background they often have.

Theoretical background

ICD-10 defines urinary tract infection (UTI) as "a bacterial infectious process affecting any part of the urinary tract, most commonly the bladder and the urethra. Symptoms include urinary urgency and frequency, burning sensation during urination, lower abdominal discomfort, and cloudy urine" (2). It is further divided into lower (cystitis) and upper (pyelonephritis) UTI. Cystitis is less common than pyelonephritis in children below 2 years of age (3), whereas in adults cystitis is much more common than pyelonephritis (4).

UTI is a common disease in children. At the age of 8 years, 7-8% of all girls and 2% of all boys have experienced at least one episode of UTI (5). Around 7.0% of children below 2 years of age presenting with fever are reported to have a UTI. In the US it is reported that girls, infants <1 years of age, white children and uncircumcised children are at greatest risk of having UTI (6).

Renal scarring and risk factors

Renal scarring is one of the feared consequences of upper UTI. A meta-analysis including 1280 children and adolescents from 0-18 years of age with a first episode of UTI found renal scarring in 15.5%, of which 50.3 % had vesicoureteric reflux (VUR) (7).

General risk factors associated with increased risk for developing scarring are recurrent febrile UTIs, delay in treatment, bladder and bowel dysfunction, obstructive malformations and VUR (8). Urostasis is a good culture medium for uropathogens (8), hence obstructive urological diseases increase the risk of UTIs. Two predisposing risk factors for UTIs are VUR and bowel and bladder disorder.

VUR is a retrograde passage of urine from the bladder into the upper urinary tract and occurs in nearly 1% of all neonates (9). In its primary form, it results from incomplete closure of the ureterovesical junction during contraction of the bladder. It is diagnosed through micturating cystourethrogram (MCUG)(10). VUR is graded from I-V, depending on the severity of the reflux, with dilation of the upper tract in grade III-V (Figure 1). VUR is also associated with renal scarring, and the risk increases with each grade of VUR (7).

Bladder and bowel dysfunction is a disorder of variable pathophysiology, but in general it is characterized by dysfunction of the pelvic muscles, bladder and/or the sphincter (8). The prevalence of bladder and bowel dysfunction is estimated to be 15% in children, but symptoms of it are reported in up to 40% of toilet trained children with their first UTI and 80% in children with recurrent (3 or more) UTIs (8). Strong predictors for development of renal scarring were VUR, (especially higher grades IV-V), abnormal renal bladder ultrasonography, inflammatory markers including CRP > 40 mg/L or a polymorphonuclear cell count >60%, temperature ≥39 °C or a causative uropathogen other than *Escherichia coli* (*E. coli*).

The long-term consequences of renal scarring caused by UTIs are not clearly understood. A Finnish study from 2011 reported that among 366 patients with chronic kidney disease (CKD) there was only one-1 case in which recurrent UTIs seemed to be the cause of CKD (11). In a Swedish study from 1995 where they followed 111 high-risk girls from their first UTI in childhood until median 15 years later, 7 out of 54 with renal scarring developed decreased glomerular filtration rate, all of whom had VUR. No one developed end-stage renal disease (ESRD) (12). The limited evidence of long-term sequelae in those with renal scarring associated with UTI, has led some to doubt the effectiveness of aggressive treatment of it (13). Moreover, diagnosis of renal scarring is by scintigraphy, and it is challenging to differentiate between congenital dysplasia and scarring. This means that some cases coined as scarring may have been congenital and non-preventable.

Signs and symptoms

The primary and sometimes only symptom of UTI in children younger than 2 years of age is fever (14). In a study conducted from 1976 through 1981, 63 out of 100 children aged 5 days to 8 months with clinical signs and features of UTI, were brought to medical attention because of fever (15). For neonates, some of the recorded numbers for fever as the main symptom have been 32/80 (40%) (16) and 11/64 (17%) (17). In other instances, vomiting (16/43), jaundice (16/43) and failure to thrive (13/43) were more prominent features than fever (9/43), with poor feeding and loose stools/diarrhoea being more seldom (17, 18). In a meta-analysis of studies including children with UTI (19) a history of previous UTI (Likelihood ratio (LR) 2.3-2.9) and fever > 40ºC (LR 3.2-33) were the two most helpful signs in identifying UTI in children below 2 years of age. Older children present also with fever, symptoms of the lower urinary tract and abdominal pain. Flank pain, chills and fever is suggestive of pyelonephritis (14). Abdominal pain (LR 6.3), back pain (LR 3.6), frequency and/or dysuria (LR 2.2-2.8) and new-onset urinary incontinence (LR 4.6) were the most useful signs in predicting UTIs in verbal children (19). In the case of acute cystitis, children typically present with absence of fever and symptoms from the lower urinary tract, which includes dysuria, frequency, urge, new-onset urinary incontinence, suprapubic/abdominal pain and/or haematuria (20).

Diagnostics

According to the Norwegian guidelines, which came into effect in 1998 and were revised in 2013 (1), the diagnosis of UTI requires **clinical symptoms**, **pyuria** and **significant bacteriuria**. The clinical examination focus on possible foci of infection. In a child with fever and no obvious focus (e.g from the respiratory tract) UTI should always be suspected. The guidelines recommend that highly febrile children, or those with poor appearance, should receive the same examination as if you suspect possible sepsis. That includes checking for cleared airways, respiration rate, oxygen saturation, pulse, capillary filling time, blood pressure, mental state (awareness and reaction), diuresis, and looking for a focus by checking clinical signs by organ.

According to the National Institute for Health and Care Excellence (NICE) the history taking and clinical examination should focus on the following risk factors for UTI; poor urine flow, history suggesting previous UTI or confirmed previous UTI, recurrent fever of uncertain

origin, antenatally-diagnosed renal abnormality, family history of VUR or renal disease, constipation, dysfunctional voiding, enlarged bladder, abdominal mass, evidence of spinal lesion, poor growth and high blood pressure (21). The clinical examination should focus on the urogenital area in regards to lesions, phimosis and/or urethral meatal stenosis in boys and labial adhesion in girls (1).

Urine sampling and analyses

The Norwegian guidelines recommend midstream urine in children capable of doing so. A clean catch sample taken during spontaneous voiding when a small child is undressed is a good alternative. Urine bag collection is often used in the youngest children, but has limitations due to possible contamination leading to high risk of false positive results (22). Preferably, two bag collections should be performed and if both include the same single species of uropathologic bacteria these can often be trusted. Urine samples obtained by catheterization and suprapubic aspiration (SPA) are less commonly contaminated and thus of higher quality, but more invasive, especially SPA.

The urine is often analysed with dipstick, microscopy and culture. The advantages of dipstick is that they are convenient and inexpensive, and little dependent on operator skills. The leukocyte esterase (LE) and nitrite tests are performed, the tests having a sensitivity of 84% and 50% and a specificity of 78% and 98%, respectively (23). Urine microscopy is dependent on operator skill (24). At UNN, they use a centrifuged sample (25), where one searches for leukocytes, cylinders and bacteria (1). For culture, the sample should be sent for analysis soon or be cooled down. Bacteriuria is defined as >10.000 CFU/ml, but lower numbers do not rule out UTI as the urine in children remains in the bladder for a shorter time and thus carries less bacteria. More than one species found in urine culture is likely to be a contamination. Finally, any culture result needs to be interpreted in conjunction with the clinical picture and the dipstick and/or microscopy results.

Microbiology

The most common pathogen causing UTI in children is *E. coli*, which accounted for 79% of urinary isolates in an American study (26). The same study found great differences in males and females, with *E. coli* accounting for 50% and 83% of UTI cases, respectively. The next most common pathogens among males were *Enterococcus* spp. (17%), *Proteus mirabilis*

(11%) and *Klebsiella* spp. (10%). In a Norwegian study from 2001 (27), *E. coli* accounted for 56.7% of inpatient and 68.3% of outpatient UTI cases. The differences between the American and the Norwegian outpatient numbers could possibly be explained by the lack of culture performed in uncomplicated UTIs in women (28). Coagulase negative staphylococci and enterococci were significantly more likely to occur in urine samples from inpatients (12.5% and 7.9%) than in those obtained from outpatients (7.5% and 4.7%).

Antibiotic resistance rates for *E. coli* in urine cultures (Table 1) in Norway is 34.1% for ampicillin and 23% for trimethoprim, whilst the resistance rates for other antibiotics were generally lower. For *Klebsiella spp*. in urine cultures (Table 2), the overall antibiotic resistance is generally lower than for those seen in *E. coli*. For *Enterococcus spp.* in urine cultures (Table 3), it showed a 5.4% resistance towards ampicillin and 15.8% towards gentamicin (29). *Proteus mirabilis* in Norway is susceptible to most antibiotics, except for innate resistance towards nitrofurantoin and a 25% resistance rates to trimethoprim (30, 31).

Imaging

The Norwegian guidelines, based on the NICE guidelines, for imaging of children with their first episode of febrile UTI have age dependent criteria. For children below 3 years of age, a renal and bladder ultrasonography (RBUS) should be performed within 3 days if < 3 months of age and/or other risk factors are present. These risk factors are; age < 6 months of age, urosepsis, inadequate response to treatment within 48 hours, hydronephrosis on prenatal ultrasound, recurrent upper UTIs, pathogen other than *E. coli*, older boys, elevated s-creatinine and elevated blood pressure. Otherwise, a RBUS should be performed within 4-6 weeks.

The indications for MCUG in children below 3 years of age are based on ultrasound and clinical findings/evidence. If the ultrasound is normal, MCUG should be performed in girls with risk factors, the same as the ones listed above, or in infants with a primary UTI before 3 months of age. If the ultrasound is pathological/indicating a VUR, an MCUG should be performed. Pathologies include dilation of the renal pelvis, calyces and/or ureters, in addition to a big bladder or small kidneys. MCUG could be used in the case of recurrent UTIs.

In children older than 3 years of age, RBUS should be performed after the first episode of upper/febrile UTI and if three or more lower UTIs, the graver the earlier.

Treatment

The Norwegian guidelines for antibiotics usage (1) differentiate between acute pyelonephritis and cystitis. The recommended treatment plans are 7-10 and 3-5 days, respectively. Initial intravenous (IV) treatment is recommended if the patient; is <2 months of age (liberally until 6 months), in very ill patients, if nauseated/vomiting and/or has any known renal-urinary anomaly. Empirical first choice IV treatment for acute pyelonephritis is ampicillin 50 mg/kg x 3-4 and gentamicin 7 mg/kg x 1, which covers Gram-negatives and enterococci. Alternatively, one can use ceftriaxon 50–75 mg/kg x 1, which covers Gram-negatives very well, but not enterococci.

Treatment should not be initiated before adequate urine samples have been obtained. Treatment is to be adjusted depending on culture and susceptibility tests. If the patient becomes clinically stabile, the medicine can be given orally. Empirical first choice peroral (PO) treatment is pivmecillinam (15 mg/kg x 3). Amoxicillin-clavulanic acid mixture (15–20 mg/kg x 3) is an option, but currently still needs to be imported from abroad if needed. Cephalexin in mixture or as tablets (12.5-25 mg/kg x 4) is another option, though it is not optimally suited for Gram-negative coverage. For cystitis PO trimethoprim (3 mg/kg x 2), nitrofurantoin (1.5 mg/kg x 2) or pivmecillinam (7.5 mg/kg x 3) are recommended.

Objectives of this thesis

The objective of this master thesis was to study clinical symptoms, diagnostics tests used, therapy and outcome of children with febrile UTI (pyelonephritis) admitted to the hospital. The following topics were investigated in a thorough retrospective study:

1. Gender and age
2. Signs, symptoms and risk factor frequencies
3. What imaging was performed?
    - Which were used and what did the results show?
4. Urine results?
    - Dipsticks, how many were performed and what did they show?
    - What was the pathogen
5. Blood results?
    - What did the most relevant lab values show?
    - Blood culture, which pathogens were seen?

6. Antibiotic treatment
    - What did they receive?
    - How did they receive it?

Material and methods

The project was planned and shaped in October 2016. In meetings with Claus Klingenberg (Department of Paediatrics at UNN) we decided on a thesis statement and for him to act as main supervisor of the project. The project was approved and the contract of supervision signed.

Terminology

In this thesis the terms “febrile urinary tract infection” and pyelonephritis were seen as equivalent. We defined them as having a temperature above 38 °C and having a urinary dipstick ≥ 2+ leucocytes or another certain diagnosis of UTI based on clinical symptoms, pyuria and bacteriology.

Study design and search criteria

We conducted a retrospective cohort study by reviewing medical records. The study population were children admitted to UNN’s three hospitals, Tromsø, Harstad and Narvik with a confirmed diagnosis of pyelonephritis. Children with diagnoses of cystitis or pyelonephritis without confirmed culture, significant dipstick or radiological evidence were excluded from the study.

We identified the possible cases of UTI by searching the patient administrative system for all children (0-15 years) diagnosed with UTI according to the International Classification of Diseases, 10th revision (ICD-10) and admitted to the Paediatric Department UNN during the study period 01.01.2007 - 31.12.2016. The diagnosis-codes included were N10, N39.0, N11.0, N11.8, N11.9 and N12.

The data was collected over a 2-month period in June and August of 2017 from a computer connected to UNN's patient record system, DIPS. The children's medical records were reviewed.

The included patients were 0-15 years of age, admitted to the hospital and discharged with a confirmed diagnosis of pyelonephritis. The children excluded were either non-febrile, had uncertain urine findings or were treated as an outpatient.

The categorization of the data was made on the basis of gender, age, signs and symptoms, diagnostic modalities, microbes and findings, including predisposing conditions, and antibiotic treatment.

Statistics

The statistics program SPSS v. 25 was used. Data are presented using descriptive analyses with frequency tables, means, median and range. Comparisons of two groups were done by using t-tests (continuous data) and chi-square tests (categorical data). Age was dichotomized into children younger or older than 2 years, reflecting their verbal ability (32). Urine culture findings were dichotomized into *E. coli* and non-*E. coli*. CRP values were dichotomized into below or higher than 100 mg/l. Temperature was dichotomized into below 40ºC, and 40ºC and above as some literature suggests (33).

When collecting the antibiotic resistance data, intermediary resistant microbes were classified as sensitive as many intermediate resistant microbes are sensitive to antibiotics in UTIs. "Known VUR" includes every case of VUR. From previously diagnosed, diagnosed while admitted or after discharge, they were all categorized as the same.
The cases selected for the risk stratification were the following: Age < 6 months or if <3 years old and urosepsis, recurrent upper UTIs, pathogen other than *E.coli*, boys 2 years and older, or elevated s-creatinine.

The reference creatinine values were gathered from UNN's "Laboratoriehåndbok" for each age group.

Variables

For a complete list of variables, see Table 4.

Literature

The literature was mainly gathered through articles used in meta-analyses, but also from searching NCBI with MESH searches through a period of October 2016 to June 2018.
The searches included:

- Urinary tract infection + Children
- Urinary tract infection + Children + sepsis.
- Pyelonephritis + children
  Pyelonephritis + children + sepsis

References were managed using Endnote x8

Ethics

The study was approved as a quality study by the representative of the Institutional review Board (Personvernombudet) at UNN, Per Bruvold. They concluded that the handling of persondata would be regulated by § 7-12 in "Personopplysningsforskriften" and authorized by "Helsepersonelloven" § 26. A more detailed description of the complete certificate of approval will be attached as an appendix.

Results

A total of 396 children were registered with the ICD-10 diagnoses that were searched for. Most of them were not included as they were treated as outpatients. Others were excluded because of uncertain UTI-diagnoses. Some patient data were missing due to transfer to other hospitals or lack of documentation.
I therefore ended up including 133 children < 15 years of age that were admitted and treated for a febrile UTI during the study period (Table 5)

Urine dipsticks results

Table 6 shows that 130/133 (97.7%) were performed of which 113/133 (85.0%) were positive. For another view of the diagnostics, look to figure 3 for a flow-chart.

Urine sampling method

Table 7 shows that 50/125 (40.0%) of the samples was collected by mid-stream or clean catch, 48/125 (38.4%) were collected through bags, 17/125 (13.6%) were collected through single-use catheters. In 12/125 (9.6%) of the cases the method was not specified. For a

Urine culture results

125/133 patients (94.0%) urinary samples were cultured in total. A total of 112/125 (89.6%) samples were taken before administration of antibiotics, 10/125 (8.0%) after and in 3/125 (2.4%) cases the timeline was not clearly documented. In 97/125 (72.9%) of the cultures were positive, 16/125 (12,8%) were probably contaminated and 12/125 (9.6%) showed no growth. Table 8 and Figure 2 show an overview of the culture results. Around 90% were Gram negative.

Blood culture results

Table 9 shows that 109/133 (83.5%) blood samples were taken for culturing, of which 11/109 (10.1%) showed significant growth, and two were likely to be contaminated. One of the positive samples was one were *Staphylococcus Epidermidis* was found on the blood sample, while *Klebsiella* was found in the urine sample. If excluded, the bacteremia rates are 10/109 (9.2%). The most common pathogen was *E.coli* 7/11 (63.6%) followed by *Klebsiella* 2/11 (18.2%).

Table 10 shows the different bacteraemia rates among gender and age groups. Male gender and low age was more commonly associated with bacteraemia .

Signs, symptoms and risk factors

Table 11 shows an overview of the patients' signs, symptoms and risk factors. The most common general symptom was poor condition 112/133 (84.2%) and feeding or difficulties 89/133 (66.9%). The most common risk factors were renal abnormalities 48/133 (36.1%) and a previous UTI 40/133 (30.1%)

Age differences

The median age of the children was 1 year and the mean 3.25 years. The differences between the children <2 years of age and those ≥2 years of age can be seen in Table 12. Fever as the presenting symptom was more common among the younger children, whilst in older children micturition-associated symptoms and signs were more common. The older children carried more risk-factors than the younger children, such as previous UTIs and bladder and bowel disorders.

Gender differences

The differences between the genders can be seen in Table 13. Several significant differences in symptoms were seen between the genders. However when adjusting for age differences however, no significant differences in symptoms were found between the genders. The only differing risk factors in general was bladder catheterization between the genders. However, for children under the age of two, foul-smelling urine was significantly more common in girls, whilst bladder and bowel dysfunction was more common in boys. For children of 2 years of age or above, bladder and bowel dysfunction, bladder catheterization and VUR were more common in boys.

E. coli vs non-*E. coli*

The differences between *E.coli* and non-*E.*coli can be seen in table 14. Divided into groups of *E.coli* and non-*E.coli*, no significant differences were found in symptoms. VUR, other kidney abnormalities, bladder catheterization, bladder and bowels dysfunction and male gender was more commonly seen in cases with non-*E.coli*.

Divided by gender, amongst males previous UTI and VUR was more common in cases with non-*E-coli*. For females, bladder catheterization was more commonly seen in cases with a non-*E.coli* pathogen.

C-reactive protein (CRP)

Table 15 shows the differences between two dichotomized groups of CRP, showing significantly more nausea and or vomiting in the group with CRP ≥100 mg/L, no other general differences were found.
Among children <2 years of age, nausea and/or vomit was significantly more common among those with CRP ≥ 100 mg/L. For children ≥ 2 years of age, CRP ≥100 mg/L was more common in those with no prior UTI and no known bladder or bowel disorder.

Radiological investigations

As table 5 shows, 51/117 (43.6%) ultrasounds were pathological. VUR was found in 15/133 (11.3%) patients. In the group with pathological ultrasound, 13/51 (25.5%) suffered from VUR. An overview of all radiological examinations is presented in Table 16. Sixty-three children were considered at-risk by guidelines definition, as explained earlier in the paper. Of these, 47/63 (74.6%) had an ultrasound taken while admitted, 6/63 (9.5%) did not have any ultrasound performed. Twenty-five children <3 years were not at risk. 21/25 (84%) had an ultrasound performed while admitted and 1/25 (4%) after discharge.

Twenty-five of 45 (55.6%) children ≥3 years of age had an ultrasound while admitted and 7/45 (15.6%) after discharge. In 8/45 (17.8%) children it was done previously. In 5/45 (11.1%) cases it was never performed.

MCUG is only indicated in children <3 years of age when defined as at-risk. Fifty-eight children were considered “at risk” and of these 42/58 (72.4%), an MCUG was never performed. MCUG is also recommended if there is an abnormal ultrasound in children >3 years of age. Of these 23 children, 15/23 (65.2%) never had an MCUG performed.
In total, 110 ultrasounds and 18 MCUGs were performed.

Table 17 shows that 33/133 (24.8%) children had several known recurrences of UTIs, 20/33 (60.1%) had one known recurrence of UTIs and 80/133 (60.2%) had no known recurrences. Amongst the children with known renal or urological abnormalities 22/57

(38.6%) had several known recurrences of UTIs compared to 11/74 (14.9%) in the group with no known abnormalities ($P<0.05$)

Of the children with known renal or urological abnormalities, 29/57 (50.9%) received prophylactic treatment through antibiotics or Hiprex, compared to 4/76 (5.3%) for those with no known abnormalities. In total 33/133 (24.8%) patients received prophylactic treatment.

Antibiotic choice and duration

Table 18 demonstrates the antibiotic agents used in the different treatment stages.
The route of administration changed from 98/126 (77.8%) for initial antibiotic treatment to 80/130 (61,5%) after blood and urine results were available. For 115/131 (87.8%) patients there was documentation about the treatment period at home. The mean home treatment period was 7.5 days. Mean total length of treatment was 10.5 days

Antibiotic resistance data

Table 19 shows the resistance pattern for E. coli isolates in comparison with NORM-data from 2015.

Temperature

The temperature taken at admission was dichotomized into below 40°C and 40°C and above, see table 20. T-test comparisons between the groups showed significant decrease in haemoglobin and sodium in temperatures ≥40°C. There was a slight increase in CRP and leucocytes when the temperature were ≥40°C, but not statistically significant

CRP

The maximal CRP recorded for each child was dichotomized into groups below 100 mg/L and from 100 mg/L and above, see Table 21. T-test comparisons between the groups showed an increase in leucocytes and maximal potassium, and a decrease in hemoglobin and minimal sodium with CRP-values ≥ 100mg/L. There also an association with rising creatinine levels and age with CRP-values ≥100mg/L, but the differences were not significant.

Discussion

The age differences and the gender distribution was as expected. Most children were young and the majority female. The females were on average older than the males, in line with the available literature [5].

Urinary dip stick was performed in 97.7% of the cases, which indicates that most doctors are aware of the unspecific signs and symptoms of UTIs in children. Some where performed in an out-patient clinic before admission and several were repeated while admitted.
Culturing was performed in 94% patients. In most cases (89.6%) the urinary sample was collected before antibiotics were administered, further indicating that Norwegian doctors are aware of the insidious nature of pyelonephritis and the importance of guided antibiotic treatment to lower the antibiotic resistance drive.

Almost ¾ of the cultures showed significant growth. E.coli was the most commonly found pathogen with 74/97 (76.3%), followed by *Klebsiella* and Enterococcus spp. Unfortunately our data set was not big enough to fully represent the total pathogen frequency, but the rate between *E. coli* and *non-E.coli* can be discussed. For males, *E. coli* represented 18/31 (58.1%) of the culture results, whilst for females they constituted 56/66 (84.8%). This is similar to another study (26) where the numbers where 50% for males and 80% for females.

The bacteraemia rates found in our study (10%) were higher than those found in a recent Israeli study at 5.6% (34). Moreover, for boys these rates in Israel were 10.9%, whilst ours were 18.9%. Although these children were both younger, and they were circumcised, skewing the results. We included one sample of *Staphylococcus epidermidis* in our results, were *Klebsiella*, which makes it a dubious result. Excluded, that leaves us with 9.2%. One study in adults found a bacteraemia prevalence of 15% in patients 16 years of age and older(35). A study in infants found a bacteraemia prevalence of 20% (15), similar to our findings of 13.6% in children <2 years of age. Overall the rates seem to differ greatly, but our numbers seem to fall somewhere in between.

The most frequent signs and symptoms seen were reduced general condition 112/133 (84.2%) and difficulty in feeding or drinking (66.9%). This is expected for a child sick enough to be

admitted to a hospital. The single most frequent reason for contacting health services was fever, as seen in another study (15). The pre-verbal children have few signs and symptoms to express their discomfort, and fever is the most objective one measureable at home. The older children typically had several symptoms, as parents can then rely on a broader clinical picture before contacting health services. The signs and symptoms differed on the basis of age, gender, pathogens and CRP-values.

Nausea and/or vomit, frequent and/or painful voiding was more commonly seen in female children than male, however it was not significant when adjusting for age. This suggests that these symptoms are age related, as they are seen more often in older children in general. Irritability was more common in male children, but adjusted for age it was not significant. These differences can be explained by the age difference between the genders, the males were younger than the females. None of the gender specific signs and symptoms showed significance when adjusting for age differences. This indicates that most of the reported symptoms were also largely age-related, rather than gender specific, however risk factors are more prevalent in male children than female.

VUR was more commonly seen in patients with non-*E.coli* pathogens, a well-known mechanism for developing UTIs and non-*E.coli*. The link between non-*E.coli* pathogens and an underlying renal or urological abnormality has been shown before (36), although we couldn't find any specific reasons as to why. Although we know children who have recently finished antibiotic treatment are at risk, and that urostasis provides an excellent medium for bacterial growth and that these abnormalities provide risk of both.

The increased nausea and/or vomit rates seen in high CRP values in the younger age group could be explained by the general poor condition of the child (37). There were increased rates of high CRP values in children ≥ 2 years of age with no prior UTI or bladder and bowel disorder. One explanation for that parents and children in cases of recurring UTIs might be more aware of the symptoms, contacting the health services earlier, diagnosing the disease before it has evolved further. The increase in leucocytes with rising CRP-values could be explained by CRP's role as an opsonizing agent in the immune response, where leucocytes play a vital part. The association to increased potassium and decreased levels of haemoglobin and sodium might be due to the fluid resuscitation given during the acute phase of the hospital

admission or potentially associated with slight renal affection of sorts due to the infection. It is however known that acute bacterial infection can cause anaemia in children(38).

In around 40% of the children included the RBUS showed some kind of pathology, which was similar to some previous studies. However, when extracting these data, temporary ultrasound changes deemed "pyelonephritis like changes" were included. The degree of permanent scarring before or after the pyelonephritis is hard to quantify as there in many cases were neither prior, nor later ultrasounds to compare with. These results are similar to the results found in an Australian study(17) where they found a 56% prevalence of any radiological abnormality. These children were however younger than our children, and the rate of VUR much higher, 42% vs 11.3%. This could be explained by the more aggressive investigative measures taken, as well as the age difference.
In children with known VUR, 13/15 yielded pathological ultrasounds. VUR is hard to diagnose with ultrasound alone, but this seems to indicate that ultrasound is a relatively sensitive tool for diagnosing VUR, having a sensitivity of 86.7%. MCUG, the gold-standard tool for diagnosing VUR, was only performed in 18 patients, meaning there is a chance that several children never got diagnosed with a low grade VUR. The prevalence of VUR was in one study estimated 17.2% in the normal population and 31.1% in children with VUR(39). The latter number does correlate well with the prevalence of VUR in our study amongst those who had an MCUG performed, 31.1% vs 33.3%.

Ultrasound is indicated in every child with a first time febrile UTI. Amongst the children <3 years of age, the guidelines were followed in 47/63 children at-risk, and in 22/25 children not at risk. In total, 9/88 (10.2%) children under 3 years of age never received an ultrasound scan. Amongst the children 3 years of age the results were slightly different, as it recommends that there be taken one after a febrile UTI. In 40/45 (88.9%) of the cases the guidelines were followed. These numbers can be improved upon, although many children only stayed at the hospital for a few days and therefore had to take the ultrasound as a policlinic patient later. Ultrasound is however a quick and easy examination and could yield treatment altering information. MCUG was only performed in 18 children. In children under two years of age, the guidelines were only followed in 16/58 (27.6%) of the children. Amongst children above two years of age, the guidelines were only followed in 8/23 (34.8%).

Recurrences were more common in children with renal or urological abnormalities, further stressing the importance of diagnosing these children. Out of the 22 children these abnormalities and several UTI recurrences, 13 received prophylactic treatment compared to 1 in 11 without these risk factors. Identifying these children could be important and yield therapeutic intervention. Increasing the amount of MCUGs performed in children deemed at-risk could potentially result in more targeted prophylactic treatment.
The results show that more than 90% of initial antibiotic treatments was in line with Norwegian empirical regime standards (1). Almost half of the patients were still receiving ampicillin and gentamicin in IV-form after some test results were available. In some cases the culture was negative or showed likely contamination, yielding no viable resistance patterns to guide the treatment. In other cases the antibiotic treatment was continued due to clinical progression where the child was seen as too sick to receive oral antibiotics.
The prescription of amoxicillin-clavulanic acid as part of home treatment was widespread. This shows that hospital culture in many cases determine treatment.

The antibiotics resistance pattern of the E. coli cultures overlapped well with the data collected from NORM. As previously stated, the intermediary resistant were classified as sensitive, which was done for the NORM-table as well to get more representative numbers. Only slight differences were found, probably related to the relatively small data. The NORM data also only represents one year of data collection, whilst ours represents 10 different years where the resistance rates vary.

Limitations of the study

This thesis has many limitations that are inherent with retrospective studies. The author opted to include a large number of variables. Some of these variable/data were missing or difficult to retrieve and some were probably missed or mislabelled due to inexperience.
Inadequate response to treatment within 48 hours, hydronephrosis on prenatal ultrasound and elevated blood pressure were not included in the risk group stratification analyses as the data was not extracted and hence not present in the data set.
When searching for symptoms, the wording was slightly different for each patient and many times the words came from the general practitioners, from which many children were directed to the hospital.

Risk factors were hard to detect, especially since many doctors never asked and the patients' never informed them. Some were even gathered from reviewing journals of their siblings due to matching surnames, creating a substantial amount of detective work.
When missing, signs, symptoms and risk factors were treated as not present during the statistical analyses.
Some blood values were hard to make representative as some were ordered at different timings, but most were extracted from the same blood set.
In regards to the home treatment, we cannot tell for sure how long they were actually taken, just the dosage prescribed. Therefore the length of antibiotic treatment was set at hospital treatment start for all patients.
Urinary results varied for each patient was not always documented and sometimes had to be extracted from texts or referrals from the outpatient clinics. Another weakness with the study comes from the lab-reports, as the sampling method was often labelled "mid-stream urine", although that is the standard
Not every risk factor for ultrasound and MCUG indication could be applied to the risk-stratification as some data necessary were never collected. This possibly left some at-risk children out of the pool, not representing the entire truth. However, pyelonephritis-likely changes were also categorized as pathological as labelled by the radiologists.
Leucocytes was grouped rather than divided into different cell lines, not giving a fully representative picture.

Conclusion

This study has shown that the gender and age distribution was in accordance to available literature. It has also shown that doctors at UNN and the outpatient clinics in Tromsø, Narvik and Harstad are highly aware of urinary tract infections as a differential diagnosis, performing dipstick analyses in 97.7% and culturing the urine in 94.0% of the cases, in which the sample was clearly collected before the administration of antibiotics in 89.6%.
The signs, symptoms and risk factors differed significantly ($P<0.05$) based on the factors of age, gender, pathogens and CRP-values. The differences in signs and symptoms were mostly age related, probably related to the child's ability to report their discomfort. Risk factors were associated with higher age, male gender, non-*E.coli* and higher CRP-values. Although in CRP-values, a lower incidence of risk factors were seen in children with higher CRP-values.

This was probably related to patient information, and urgent hospital visits when signs and symptoms of UTI presented themselves.

There were 72.9% cases of significant bacteruria and 10.2% cases of significant bacteremia. *E.coli* was the most prevalent pathogen found, both in urine and blood culture. It represented 76.3 % of urine isolates and 63.6% of the blood cultures with significant growth. The second most prevalent bacteria was *Klebsiella*, constituting 8.2% of urine and 18.2% of blood cultures.

Ultrasound was performed in 110 patients and MCUG in only 18. Abnormal genitourinal findings had a prevalence of 57/133 (42.9%), and VUR was found in 15/133 (11.3%). This was a lower prevalence of VUR than expected from literature, but it was diagnosed in 6/18 (33.3%) MCUGs performed. This indicates that the prevalence might be higher than that found in this study.

Antibiotics were given to 131/133 (98.5%) of the patients, of which empirical treatment followed Norwegian guideline standards in 114/126 (90.5%) of the cases. Ampicillin-Gentamicin IV was the most commonly used antibiotic in both the empirical (85.7%) and during the admission (47.7%). Amoxicillin-clavulanic acid was the most used antibiotic during the home treatment phase (45.7%), even being used in 3/33 cases were it was resistant. Antibiotic resistance patterns gathered from E.coli isolates correlated well with those found in NORM-VET 2015.

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Figure 1: Grading of vesicoureteric reflux (40)

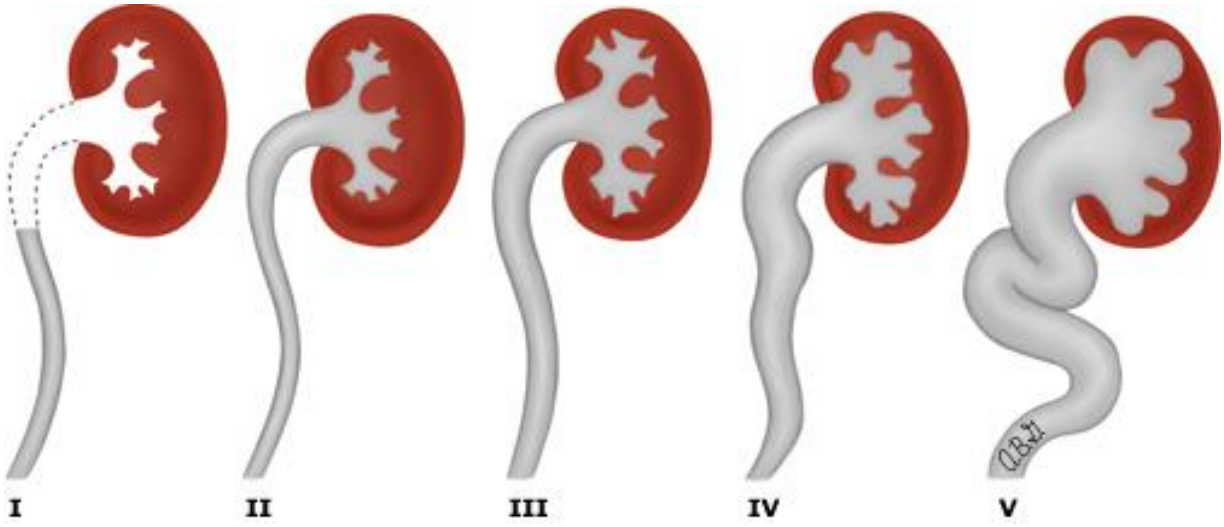

Figure 2: Pathogen distribution pie chart

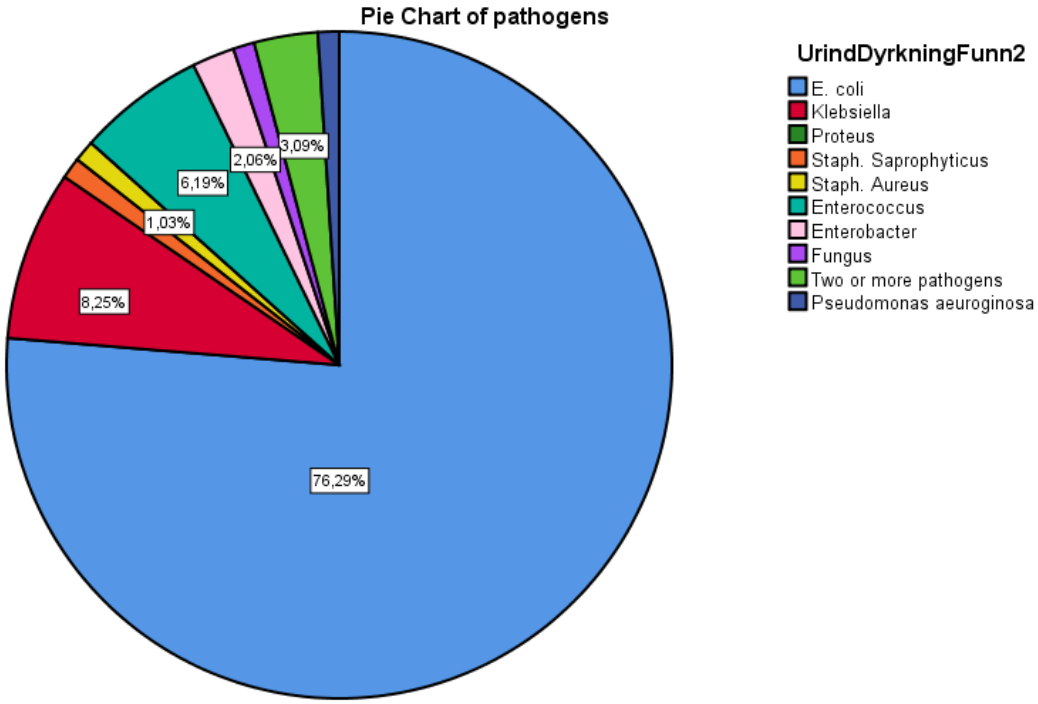

Table 1: *Escherichia coli* in urine (29)

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	65.9	-	34.1
Mecillinam	≤ 8	> 8	94.9	-	5.1
Amoxicillin-clavulanic acid*	≤ 32	> 32	93.9	-	6.1
Cefuroxime	≤ 8	> 8	95.6	-	4.4
Cefotaxime	≤ 1	> 2	96.7	0.1	3.2
Ceftazidime	≤ 1	> 4	96.5	1.0	2.5
Meropenem	≤ 2	> 8	99.9	0.1	0.0
Gentamicin	≤ 2	> 4	96.2	0.4	3.4
Ciprofloxacin	≤ 0.5	> 1	92.4	0.3	7.3
Nitrofurantoin	≤ 64	> 64	99.0	-	1.0
Trimethoprim	≤ 2	> 4	76.9	0.1	23.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	78.4	1.1	20.5
ESBL	Negative	Positive	96.9	-	3.1

Table 2: *Klebsiella* spp. in urine (29)

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Mecillinam	≤ 8	> 8	89.0	-	11.0
Amoxicillin-clavulanic acid*	≤ 32	> 32	93.6	-	6.4
Piperacillin-tazobactam	≤ 8	> 16	89.7	6.3	4.0
Cefuroxime	≤ 8	> 8	91.6	-	8.4
Cefotaxime	≤ 1	> 2	96.3	0.4	3.3
Ceftazidime	≤ 1	> 4	94.1	2.3	3.6
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	97.2	0.5	2.3
Ciprofloxacin	≤ 0.5	> 1	94.3	2.2	3.5
Trimethoprim	≤ 2	> 4	79.9	1.7	18.4
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	84.8	1.7	13.5
ESBL	Negative	Positive	96.7	-	3.3

Table 3: *Enterococcus* spp. in urine (29)

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	94.4	0.2	5.4
Gentamicin*	≤ 128	> 128	-	84.2	15.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Trimethoprim*	≤ 0.032	> 1	0.0	79.0	21.0
Trimethoprim-sulfamethoxazole*/**	≤ 0.032	> 1	0.0	85.0	15.0
Vancomycin (any genotype)	≤ 4	> 4	100.0	-	0.0
Vancomycin (Van A or VanB)	Negative	Positive	100.0	-	0.0

Table 4: A complete list of all variables

Age	The age of the child at the admission
Gender	Male or female
Temperature	
- Temperature maximum before or after 24 hours of admission	Recorded in Celsius, either from an out-of-hospital setting or while admitted
- Temperature at admission	Recorded temperature at admission in Celsius
Signs and symptoms:	Here we recorded the following signs and symptoms from either the patients at admission or reports from the outpatient clinic: Answered yes or no
- Reported pain in the back or the abdomen of the child	
- Nausea and/or vomit	
- Diarrhoea or loose stools	
- Irritability	
- Poor general condition	
- Painful and/or frequent urination	
- Poor condition	
- Jaundice	
- Foul-smelling urine	
- Tenderness in the abdomen or back	As observed by the clinician
Risk factors	**Here we recorded the following risk factors from either the patients at admission, reports from the outpatient clinic or hospital data: Answered yes or no**
- Previous UTI	Any previous UTI, both cystitis and pyelonephritis was included
- Bladder and bowel dysfunction	Includes diaper-needing patients, from CP and other neurological disorders, chronic obstipation and other gastrointestinal disorders, and those with any functional urinary problems.
- Family history of UTI	
- Bladder catheterization	Any recent or current use of bladder catheterization

- VUR	Any grade was included. The timing of the diagnosis was not documented
- Any other renal abnormality	Lists all known renal abnormality known previously or diagnosed by a radiologist
Urine dipsticks	
- **Leucocytes**	Negative, traces or + to 4+
- **Erythrocytes**	Negative, traces or + to 4+
- **Nitrite**	Negative, traces or positive
Urine culturing	
- Timing	Before or after the administration of antibiotics
- Sampling method	Recorded the method used for collecting the sample, categorized into: Bag, catheter, suprapubic catheter, clean catch/mid stream and no information
- Results	The culture result was categorized into significant growth, likely contaminated and no growth. Each pathogen was recorded.
Ultrasound	
- Timing	While admitted, after admission or not performed during this episode
- Results	The results were gathered from the radiologist's description, and labelled as such. Catergorized into pathological or normal
MCUG	
- Timing	While admitted, after admission or not performed during this episode
- Results	The results were gathered from the radiologist's description, and labelled as such. Catergorized into pathological or normal
Blood values	Each patient's most extreme blood values were gathered, taken from one single blood sample when possible
- CRP (C-reactive Protein)	Highest recorded value during admission
- Leucocytes	Highest recorded value during admission
- Haemoglobin	Lowest recorded value during admission

- Thrombocytes	Lowest recorded value during admission
- Creatinine	Highest recorded value during admission
- Sodium (Na^+)	Lowest recorded value during admission
- Potassium (K^+)	Highest recorded value during admission
Blood culturing	
Results	The culture result was categorized into significant growth, likely contaminated and no growth. Each pathogen was recorded.
Antibiotic resistance patterns	The resistance pattern for each pathogen was recorded, intermediary resistance was plotted as susceptible.
Antibiotics	
- Type of antibiotics	Each antibiotic used was recorded for three phases: Empirical treatment, after culture or blood results and home treatment
- Route of administration	Categorized into intravenous (IV), per oris (PO) or not specified.
- Treatment days	Both hospital treatment days and home treatment was recorded
Admission length	Recorded in days
Recurrency of UTI	Did not distinguish between cystitis and pyelonephritis
Prophylaxis	Hiprex or antibiotics, either using before or given after admission

Table 5: Descriptive overview of the patients

Variable	**N**	**%**	**Mean (SD)**	**Median (IQR)**
Patients	133	100%		
Age (in years)			3.3 (4.5)	1 (0.25-4.5)
- Females	91	68.4%	3.8 (4.5)	1.8 (0.6-5.5)
- Males	42	31.6%	2.1 (4.2)	0.3 (0.2-0.9)
Temperature at admission			38,7 (1.1)	
Positive urine culture	97	72.9%		
Admitted (days)			3.0 (2.1)	3.0
Pathological ultrasound	51	43.6%		
Known VUR	15	11.3%		

SD: Standard deviation, IQR: Interquartile range

Table 6: Descriptive table of urine dipsticks results

Leucocytes	**Frequency**	**Percent**
0	7	5.4%
+	9	6.9%
2+	23	17.7%
3+	46	35.4%
4+	44	33.8%
Traces	1	0.8%
Total	130	100%
Nitrite	**Frequency**	**Percent**
Negative	65	50%
Positive	58	44.6%
Missing data	6	4.6%
Traces	1	0.8%
Total	130	100%
Erythocytes	**Frequency**	**Percent**
Neg	14	10.8%
Traces	11	8.5%
1+	16	12.3%
2+	31	23.8%
3+	31	23.8%
4+	17	13.1%
Missing data	8	6.2%
Total	130	100%

Table 7: Urine sampling methods

Urine sampling	**N**	**%**
Urinary sampling before or after antibiotics:	125	100%
- Before	112	89.6%
- After	10	8.0%
- Not known	3	2.4%
Culture method:	125	100%
- Bag	48	38.4%
- Catheter	17	13.6%
- Clean catch	50	40.0%
- No info	12	9.6%

Table 8: Pathogen overview from urine cultures

	N	%
Samples - Significant growth - Likely contamination - Negative - Not performed	133 97 16 12 8	100% 72.9% 12.0% 9.0%% 6.0%
Pathogen	**N**	**%**
E.coli	74	76.3%
Klebsiella	8	8.2%
Enterococcus	6	6.2%
Two or more pathogens	3	3.1%
Enterobacter	2	2.1%
Staph. aureus	1	1.0%
Staph. saprophyticus	1	1.0%
Pseudomonas aeruginosa	1	1.0%
Fungus	1	1.0%
Total	**97**	**100%**

Table 9: Blood culture results

Variables	n	%
Samples	133	100%
- Negative	96	72.2%
- Significant growth	11	8.3%
- Likely contamination	2	1.5%
- Not performed	24	18.0%
Pathogen detected in blood culture:	11	100%
- *E. coli*	7	63.6%
- *Klebsiella*	2	18.2%
- *Enterococcus*	1	9.1%
- *Staph. epidermidis*	1	9.1%

Table 10:

Chi-square analysis of the differences in bacteremia rates in gender and age.

Variable		**Bacteremia N=11**	**No bacteremia N=98**	**p-value**
Gender	Male Female	7 (18.9%) 4 (5.6%)	30 (81.1%) 68 (94.4%)	0.028
Age	<2 years of age ≥2 years of age	9 (13.6%) 2 (4.7%)	57 (86.4%) 41 (95.3%)	0.128

Table 11: Signs, symptoms and risk factors of the 133 patients:

Signs and symptoms	**n**	**%**
Reduced general condition	112	84.2%
Feeding or drinking difficulties	89	66.9%
Nausea and/or vomiting	65	48.9%
Irritability	54	40.6%
Tenderness in the abdomen or back	48	36.1%
Pain in the abdomen or back	47	35.3%
Foul smelling urine	29	21.8%
Frequent and/or painful micturation	27	20.3%
Diarrhoea and/or loose stools	18	13.5%
Jaundice	1	0.8%
Risk factors	**n**	**%**
Other renal abnormalities	48	36.1%
Previous UTI	40	30.1%
Bladder and bowel dysfunction	27	20.3%
VUR	15	11.3%
Positive family history	14	10.5%
Bladder catheterization	5	3.8%

Table 12: Analysis by age groups

Variable	**Age < 2 years** **N=82**	**Age ≥ 2 years** **N=51**	**P-value**
Reported pain	12 (14.6%)	35 (68%)	< 0.001
Nausea / Vomit	30 (36.5%)	35 (68%)	< 0.001
Diarrhoea / loose stools	14 (17.1%)	4 (7.8%)	0.13
Frequent / painful micturation	2 (2%)	25 (49.0%)	< 0.001
Irritability	48 (58.5%)	6 (11.8%)	< 0.001
Jaundice	1 (1.2%)	0	0.43
Poor condition	67 (81.7%)	45 (88.2%)	0.315
Poor feeding	56 (68.3%)	33 (66.7%)	0.669
Foul-smelling urine	19 (23.2%)	10 (19.6%)	0.628
Tender abdomen/back	14 (17.1%)	34 (65.4%)	0.000
Previous UTI	7 (8.5%)	33 (64.7%)	0.000
Other renal abnormality	26 (31.7%)	22 (43.1%)	0.182
Positive family history	9 (11.0%)	5 (9.8%)	0.830
Bladder catheter	3 (3.8%)	2 (3.9%)	0.938
Bladder and bowel dysfunction	9 (11.0%)	18 (35.3%)	0.001
VUR	7 (8.5%)	8 (15.7%)	0.205

Table 13: Analysis by gender:

Variable	**Female N=91**	**Male N=44**	**P-value**
Reported pain	36 (39.6%)	11 (25%)	0.134
Nausea /Vomit	50 (54.9%)	15 (35.7%)	0.039
Diarrhoea /loose stools	13 (14.3%)	5 (11.4%)	0.709
Frequent /painful micturation	23 (25.3%)	4 (9.5%)	0.036
Irritability	31 (34.1%)	23 (52.3%)	0.024
Jaundice	1 (1.1%)	0	0.495
Poor condition	78 (85.7%)	34 (77.3%)	0.484
Poor feeding	65 (71.4%)	24 (54.5%)	0.104
Foul-smelling urine	25 (27.5%)	4 (9.5%)	0.628
Tender abdomen/back	37 (40.7%)	11 (25%)	0.106
Previous UTI	31 (34.1%)	9 (20.5%)	0.140
Other renal abnormality	30 (33.0%)	18 (40.9%)	0.270
Positive family history	7 (7.7%)	7	0.117
Bladder catheter	1 (1.1%)	4 (9.5%)	0.018
Bladder and bowel dysfunction	15 (16.5%)	12 (27.3%)	0.107
VUR	7 (7.7%)	8 (18.2%)	0.054

Table 14: Analysis by pathogens:

Variable		**E-coli N=74**	**Non-E-coli N=23**	**P-value**
Reported pain	Yes	27 (36.5%)	8 (34.8%)	0.882
Nausea / Vomit	Yes	38 (51.4%)	12 (52.2%)	0.945
Diarrhoea / loose stools	Yes	10 (13.5%)	4 (17.4%)	0.644
Frequent /painful micturation	Yes	17 (23.0%)	3 (13.0%)	0.304
Irritability	Yes	29 (39.2%)	11 (47.8%)	0.462
Jaundice	Yes	1 (1.4%)	0	0.575
Poor condition	Yes	64 (86.5%)	18 (78.3%)	0.341
Poor feeding	Yes	51 (68.9%)	13 (56.5%)	0.273
Foul-smelling urine	Yes	21 (28.4%)	2 (8.7%)	0.053
Tender abdomen and/or back	Yes	31 (41.9%)	6 (26.1%)	0.173
VUR	Yes	5 (6.8%)	7 (30.4%)	0.003
Other kidney abnormality	Yes	23 (31.1%)	14 (60.9%)	0.010
Previous UTI	Yes	23 (31.1%)	10 (43.5%)	0.273
Positive family history	Yes	11 (14.9%)	1 (4.3%)	0.181
Bladder catheterization	Yes	1 (1.4%)	3 (13.0%)	0.014
Bladder and bowels abnormalities	Yes	12 (16.2%)	9 (39.1%)	0.020
Age	Above 2 years	30 (41%)	8 (34.8%)	0.621
Gender	Male	18 (24.3%)	14 (60.9%)	0.004
CRP	≥100	39 (52.7%)	14 (60.9%)	0.531

Table 15: Analysis by CRP-values

Variable	**CRP < 100 mg/L N= 55**	**CRP ≥ 100 mg/L N=77**	**P-value**
Reported pain	15 (27.3%)	32 (41.6%)	0.091
Nausea / Vomit	18 (32.7%)	47 (61.0%)	0.001
Diarrhoea / loose stools	7 (12.7%)	11 (14.3%)	0.797
Frequent /painful micturation	7 (12.7%)	20 (26.0%)	0.063
Irritability	22 (40.0%)	32 (41.6%)	0.858
Jaundice	1 (1.8%)	0	0.235
Poor condition	44 (80.0%)	67 (87.0%)	0.277
Poor feeding	32 (58.2%)	57 (74.0%)	0.056
Foul-smelling urine	10 (18.2%)	19 (24.7%)	0.374
Tender abdomen/back	15 (27.3%)	32 (41.6%)	0.091
VUR	4 (7.3%)	11 (14.3%)	0.211
Other kidney abnormality	18 (32.7%)	29 (37.7%)	0.559
Previous UTI	14 (25.5%)	21 (27.3%)	0.384
Positive family history	5 (9.1%)	9 (11.7%)	0.633
Bladder catheterization	1 (1.8%)	4 (5.2%)	0.316
Bladder and bowels abnormalities	12 (21.8%)	15 (19.5%)	0.743

Table 16: Imaging modalities used

Radiological examination:	**N**	**%**
Ultrasound <3 years months at risk:	63	100%
• While admitted:	47	74,6%
• After discharge:	9	14,3%
• Done previously	1	1,6%
• Not performed:	6	9,5%
Ultrasound <3 years months not at risk:	25	100%
• While admitted:	21	84%
• After discharge:	1	4%
• Done previously	0	
• Not performed:	3	12%
Ultrasound >3 years:	45	100%
• While admitted:	25	55,6%
• After discharge:	7	15,6%
• Done previously:	8	17,8%
• Not performed	5	11,1%
MCUG <3 years at-risk:	58	100%
• While admitted:	3	5,2%
• After discharge:	12	20,7%
• Done previously:	1	1,7%
• Not performed	42	72,4%
MCUG>3 years with abnormal ultrasound:	23	100%
• While admitted:	0	0,0%
• After discharge:	2	8,7%
• Done previously:	6	26,1%
• Not performed	15	65,2%

Table 17: Association between renal abnormalities, recurring UTIs and prophylaxis

Variable		**Normal findings N=76**	**Renal or urological abnormality N=57**	**P value**
Known recurrences	None One Several	59 (77.6%) 6 (7.9%) 11 (14.5%)	21 (36.8%) 14 (24.6%) 22 (38.6%)	0.000
Prophylaxis	No Yes	72 (94.7%) 4 (5.3%)	28 (49.1%) 29 (50.9%)	0.000
		Normal findings and several known recurrences of UTI N=11	**Renal or urological abnormality and several known recurrences of UTI N=22**	
Prophylaxis	No Yes	10 (90.9% 1 (9.1%)	9 (40.9%) 13 (59.1%)	0.006
Variable		**Normal findings**	**VUR**	
MCUG performed	No Yes	106 (92.2%) 12 (66.7%)	9 (7.8%) 6 (33.3%)	0.001

Table 18: Antibiotic use

Variable	**N**	**%**
Antibiotics	131	98.5 %
Antibiotics before test results	126	94.7%
Recommended antibiotics:		
Ampi-Genta	114	85.7%
Cefotaxime/ceftria	81	64.3%
Pivmecillinam PO	10	7.5%
Amoxi-clav PO	4	3.0%
Cephalexine PO	17	12.8%
Other?	2	1.5%
Other antibiotics used:		
Cerfuroxim	1	0.8%
Ciprofloxacin	2	1.5%
Other combination	5	3.8%
Trimetoprim-Sulpha (TMS)	4	3.0%
Route of empirical administration:	126	100%
IV:	98	77.8%
P.O.:	28	22.2%
Variable	**N**	**%**
Antibiotics after test results:	130	100%
Ampi-Genta IV	62	47.7%
Cefotaxime / ceftriaxone IV	10	7.7%
Pivmecillinam PO		
Amoxi-clav PO	4	3.1%
TMS	30	23.1%
Cephalexine PO	7	5.4%
Meropenem	2	1.5%
Nitrofurantoin	1	0.8%
Trimetoprim	2	1.5%
Ciprofloxacin	3	2.3%
Ampi	3	2.3%
Other combination	1	0.8%
	5	3.8%

Variable	**N**	**%**
Route of administration:	130	100%
- IV:	80	61.5%
- PO:	50	38.5%
Antibiotics at discharge:	126	100%
Pivmecillinam PO	16	12.6%
Amoxi-clav PO	58	45.7%
TMS PO	28	22.0%
Cephalexine PO	11	8.7%
Amoxicillin	6	4.7%
Nitrofurantoin	2	1.6%
Trimetoprim	3	2.4%
Ciprofloxacin	2	1.6%
Treatment length	**Mean**	**Median**
Antbiotic home treatment (days)	7.5	7
Total antibiotic treatment (days)	10.5	10.5

Table 19: Resistance pattern for E. coli – This study versus NORM 2015.

Antibiotic	Number tested in our study	Resistant isolates (%) This study	Resistance rate in NORM (year)
Amoxiclav	68	5.9%	6.1%
Ampicillin	73	28.4%	34.1%
Cefotaxime	70	1.4%	3.2%
Cefuroxime	70	2.9%	4.4%
Ciprofloxacin	72	2.8%	7.3%
Gentamicin	69	1.4%	3.4%
Mecillinam	72	4.2%	5.1%
Meropenem	69	0%	0%
Nitrofurantoin	74	0%	1%
Trimethoprim	72	22.2%	23.0%
Trimethoprim-sulfamethoxazole	73	19.2%	20.5%

Table 20: Temperature below or above 40 ºC

Variable	Temp.	N	Mean	SD	P-value
CRP	<40º C	110	127.5	93.3	0.117
	≥40º C	20	163.0	88.1	
Leucocytes	<40º C	109	17.7	6.3	0.088
	≥40º C	20	20.4	7.0	
Hemoblobin	<40º C	108	11.5	2.0	0.035
	≥40º C	20	10.9	1.0	
Thrombocytes	<40º C	105	341.0	149.8	0.940
	≥40º C	19	343.7	114.0	
Creatinine	<40º C	102	36.7	36.8	0.241
	≥40º C	19	26.7	10.4	
Sodium	<40º C	102	137.4	3.1	0.010
	≥40º C	19	135.4	2.9	
Potassium	<40º C	89	4.4	0.8	0.403
	≥40º C	17	4.2	0.4	
Age	<40º C	111	3.3	4.7	0.646
	≥40º C	20	2.9	3.1	

Abbreviations: SD: Standard deviation

Table 21: Variables compared to CRP below or above 100 mg/L

Variable	CRP mg/L	N	Mean	SD	P-value
Leucocytes	<100	55	15.4	6.1	0.000
	≥100	76	20.0	6.2	
Hemoblobin	<100	54	12.0	2.2	0.004
	≥100	76	11.1	1.4	
Thrombocytes	<100	50	368.1	148.1	0.085
	≥100	76	322.9	139.4	
Creatinine	<100	48	28.8	12.7	0.053
	≥100	75	38.9	41.9	
Sodium	<100	47	137.4	2.7	0.000
	≥100	75	135.4	3.0	
Potassium	<100	40	4.6	0.6	0.021
	≥100	67	4.3	0.8	
Age	<100	55	2.4	4.0	0.063
	≥100	77	3.8	4.7	

Abbreviations: SD: Standard deviation

Reference: Drew JH, Acton CM. Radiological findings in newborn infants with urinary infection. Archives of disease in childhood. 1976;51(8):628-30.	**Design:Cohort study**	
	Documentation level	II
	Grade:	C

Objective	Material og method	Results	Discussion
To report the total spectrum of presenting symptoms and the incidence of renal tract abnormalities during the newborn period. **Conclusion** Because of this high incidence of abnormalities, which when diagnosed might alter management, it is suggested that radiological investigations be performed in newborn infants with proven urinary infection. **Country** **Australia** **Year of data collection** 1971 - 1974	From the opening of the Mercy Maternity hospital until December 1974, particular attention was given to the diagnosis of urinary infection in newborn infants. Suprapubic bladder puncture (Pryles et al., 1959) was performed in all infants presenting with jaundice of unknown aetiology, failure to gain weight, excessive weight loss, diarrhoea, vomiting, or a clinical picture of sepsis. A diagnosis of infection was accepted if there was any bacterial growth from the urine obtained by this method, and all such infants received a course of parenterally administered antibiotics. After 7 days of treatment they were subjected to intravenous pyelography and micturating cystourethrography. At the time of performing the cystourethrogram, urine was collected via the catheter and cultured; in only 2 infants was there still a significant growth of organisms.	Selective suprapubic urine aspiration was performed in 905 infants; 64 were found to have urinary infection, representing 0.5% of all live-births over the 47 months of the study 54 (84%) were males and 10 (16%) were females. 14 (22%) were born before 37 weeks of gestation and 50 (78%) were term infants. Mean day of age at presentation was day 10 for term infants and 18 for preterms. Mean length of stay of infants in the hospital was 10.6 days; 33 % remain 10 or more days. Thirty (56%) of the 54 male infants and 5 of the 10 female infants were found to have a radiological abnormality (Table II). In 27 infants vesicoureteric reflux was the only abnormality present. The vesicoureteric reflux was bilateral in 14 and unilateral in 13 infants. 6 infants were found with hydronephrosis; 3 with obstruction and 3 with megasystems associated with gross reflux. In the 3 infants in whom hydronephrosis was associated with megasystems and reflux, the diagnosis was initially suspected on the pyelogram and subsequently proven on the cystourethrogram. The megasystems were each unilateral.	The groups were recruited from the same ewborn infants, although no background factors were adjusted for. The group is partly representative for the, although they were selected due to presenting reminiscent UTI-symptoms, narrowing the study population. The study was a prospective cohort study with sufficient follow-uptime to document the UTIs they were studying No drop-outs were discussed, except the children who died The exposition and outcome was measured using objective criteria with standardized procedures. The people who reviewed the results were not blinded, nor were any confounders identified. The study was a big prospective study including a lot of highly detailed radilogogical A weakness of the study is the fact that no limitations were discussed, and that no statistical analyses were performed.

Referanse: Edlin RS, Shapiro DJ, Hersh AL, Copp HL. Antibiotic resistance patterns of outpatient pediatric urinary tract infections. The Journal of urology. 2013;190(1):222-7.	**Design: Case series**	
	Documentation level:	III
	Grade:	B

Objective	Material and method	Results	Discussion
To characterize the current national patterns of antibiotic resistance of outpatient pediatric urinary tract infection. **Conclusion** ***E. coli remains the most common pediatric uropathogen. Although widely used, trimethoprim-sulfamethoxazole is a poor empirical choice for pediatric urinary tract infections in many areas due to high resistance rates. First-generation cephalosporins and nitrofurantoin are appropriate narrow-spectrum alternatives given their low resistance rates. Local antibiograms should be used to assist with empirical urinary tract infection treatment.*** **Country** **USA** **Year of data collection** 2009	Outpatient urinary isolates from patients younger than 18 years in 2009 were examined using The Surveillance Network®, a database with antibiotic susceptibility results and patient demographic data from 195 United States hospitals. The prevalence and antibiotic resistance patterns for the 6 most common uropathogens, ie Escherichia coli, Proteus mirabilis, Klebsiella, Enterobacter, Pseudomonas aeruginosa and Enterococcus was determined. Differences in uropathogen prevalence between males and females using chi-square analysis were compared	E. coli was the most common uropathogen overall but the prevalence of E. coli was higher among females (83%) than males (50%, p <0.001). Other common species among males were Enterococcus (17%), P. mirabilis (11%) and Klebsiella (10%). However, these uropathogens each accounted for 5% or less of female isolates (p <0.001). Resistance among E. coli was highest for trimethoprim-sulfamethoxazole (24%) but lower for nitrofurantoin (less than 1%) and cephalothin (15%). E. coli resistance rates increased for trimethoprim-sulfamethoxazole (from 23% to 31% in males and from 20% to 23% in females) and ciprofloxacin (from 1% to 10% and from 0.6% to 4%, respectively).	The data came from a selected patient group, but was relevant for the disease. It is however more relevant to its geographical area due to the nature of antibiotic resistance drive. The inclusion criteria were clearly defined, but no follow-up was made. All the data was collected through labs, so the yield was high. The study goes well into detail about its limitations, and how it compares to other studies. Even though it is a retrospective study, it follows clearly objective criteria and has a lot of data.

Referanse: Maherzi M, Guignard JP, Torrado A. Urinary tract infection in high-risk newborn infants. Pediatrics. 1978;62(4):521-3.			**Design: Cohort study** Documentation level: II Grade: C
Objective	**Material og methods**	**Results**	**Discussion**
To define the characteristics of UTI in high-risk neonates and to decide if systematic screening for bacteriunia is justified in this population. **Conclusion** ***That symptomatic high-risk newborn infants should be screened for bacteniuria, and that radiological investigations be performed in those with proven infection. Pediatrics 62:521-52.3, 1978, urinary tract infection, high-risk neonates, urologic abnormalities, hacteriuria, vesicoureteral reflux.*** **Country** **Siwtzerland** **Year of data collection** 1974-1978	1935 newborn infants were admitted to the neonatal intensive care unit of Lausanne, Switzerland, during four consecutive years. Cestational age was assessed according to the method of Dubowitz and associates. Neonates were classified as follows, according to gestational age: premature, less than 259 days; term, 259 to 293 days; postterm, more than 293 days. Urine cultures were performed when symptoms were suggestive of UTI or at the end of the stay in the unit in asymptomatic patients. Urine was always obtained under sterile conditions, using standard methods. Any colony growth from urine obtained by suprapubic aspiration was considered to be mdicative of significant bacteriunia. Intravenous pyelography (IVP) and micturating cystourethrography (MCU) were carried out whenever possible on all patients with symptomatic UTI. Cystourethrography was performed after the urine had been sterilized by appropriate treatment.	The prevalence of neonatal urinary tract infection (UTI) was studied in 1,762 high-risk neonates. There were 1,006 boys and 756 girls. Age on admission to the unit was up to 28 days. A urine culture was performed in 1,762 of them Symptomatic bacteriuria was found in 1.9% and asymptomatic bacteriuria in 0.5% of these neonates. Male preponderance was 5: 1 . Clinical manifestations were extremely vanable-vomiting, weight loss, and diarrhea being the prominent symptoms. Bacteremia was associated with UTI in six infants. The organisms identified in the urine obtained by suprapubic aspiration were Escherichia co/i, Klebsiella, and Proteus. A mixed infection was found in four patients. Roentgenographic examination of the urinary tract showed abnormalities in 44% of the symptomatic patients.	The groups were recruited from the same high-risk newborn infants, although no background factors were adjusted for. The group is partly representative for the initial risk group, although they were then selected for UTI-symptoms, further narrowing the study population. The study was a prospective cohort study with sufficient follow-uptime to document the UTIs they were studying No drop-outs were discussed, except the children who died. The exposition and outcome was measured using objective criteria with standardized procedures. The people who reviewed the results were not blinded, nor were any confounders identified. The strength of study is the sheer number of patients studied prospectively. The limits of the study is the limited discussion and the limited statistical analyses it provides.

Reference: Martinell J, Lidin-Janson G, Jagenburg R, Sivertsson R, Claesson I, Jodal U. Girls prone to urinary infections followed into adulthood. Indices of renal disease. Pediatric nephrology (Berlin, Germany). 1996;10(2):139-42.	**Design: Cohort control**	
	Documentation level	II
	Grade:	C

Objective	Material and method	Results	Discussion
To study the link between pyelonephritis and kidney disease **Conclusion** **That renal function was well preserved in most cases of renal scarring in girls with recurring UTIs.** **Country** **Sweden** **Year** 1995	111 women recruited from their first UTI episode in childhood. They were selected because of a clinical risk of complications that at the age of 15-18 years led to referral to an adult unit for continued follow-up. The main indications for referral were renal scarring in 54 and predisposition to UTI in 57; 36 of those with renal scarring had a predisposition to UTI. Controls were recruited from females who had participated in a school screening program for bacteriuria performed between 1971 and 1974. Each child was examined for blood pressure, creatinine and. albumin. β_2-Microglobuli in urine and serum Renal scarring was defined as parenchymal reduction with clubbing of the adjacent calyx Voiding cystourethrography was performed using a standard technique and reflux graded on a five-grade scale	The diastolic blood pressure was higher in females with severely scarred kidneys than controls (P<0.05). The glomemlar filtration rate was lower in women with severe renal scarring than controls (P < 0.005), while there was no difference between those with moderate scarring and controls. In females with severe scarring, 4 of 19 had a glomerular filtration rate below the lower reference limit (< 80 ml/min per 1.73 m2), but the filtration was only moderately decreased to between 70 and 78 ml/min per 1.73m 2 The glomerular filtration rate correlated with the total renal area (P<0.001). The total renal area was significantly smaller in women with severe as well as moderate scarring, compared with those without scarring (P<0.01) Creatinine concentrations in serum were higher for women with severe scarring than controls (P<0.05) β_2-Microglobulin in serum was higher in women with severe scarring than controls (P < 0.05); the corresponding value for women with moderate scarring was P = 0.05. The excretion of β_2-microglobulin in urine was higher in women with severe renal scarfing than controls (P < 0.05) the corresponding value for moderate scarring compared with controls was P = 0.05	No background factors were accounted for The girls recruited in this study came from the same population, and were selected due to+++ The controls are from the same age demographic as the study population and should carry the same exposure. The study was prospective, following the girls regularly by the same two clinicians, examined over a 3 year period There is no mentioning of drop outs from the study, only the ones included There was no mentioning of confounders in the study or any other forms of limations. The follow-up-time was 15 years, which is not enough time to fully see the effects of renal damage, as it usually targets the elderly. These patietnts were young on average. The study was not blinded.

Reference: Ginsburg CM, McCracken GH, Jr. Urinary tract infections in young infants. Pediatrics. 1982;69(4):409-12.	Design: Case series	
	Documentation level	II
	Grade:	C

Objective	Material og method	Results	Discussion
To show the clinical presentation of urinary tract infections in infants	From March 1976 through February 1981, 100 infants with acute urinary tract infections were admitted to the hospital from the acute care clinic of Children's Medical Center or from the emergency room of Parkland Memorial Hospital, Dallas.	Male infants accounted for the majority of urinary infections in the first three months of life, but female infants predominated thereafter. Only 5% of male infants in this study were circumcised There was no correlation between fever, the initial WBC count, or presence of roentgenographic abnormalities and a positive blood culture. A lumbar puncture was performed in 88 patients and all CSF cultures were sterile. Sepsis was documented in 20 of 91 infants from whom blood cultures were obtained. Approximately 85% of these positive blood cultures were in infants less than 2 months of age and only one of 18 infants aged more than 3 months had sepsis. Absence of significant pyuria did not rule out urinary tract infection. Less than 10 and 5 WBCs/HPF were found in 27% and 21% of urine samples, respectively. Bacteria were present on stained smears of most of these specimens and this proved the most reliable initial mdicator of infection. Roentgenographic abnormalities were present in 18% of patients, 78% of whom were girls. The incidence of radiographic abnormalities in the girls in this study was relatively large (45%) and significantly greater than that (7%) in boys. All infants responded promptly to antimicrobial therapy.	The sole inclusion criteria was admission for UTI during infancy at the There was no mentioning of confounders in the study, but it does mention its limits as a retrospective study. The diagnose were validated through urine culture, although 4 patients in this study did not have any significant growth and were not mentioned. The follow-up-time was sufficient to highlight the end points, which were to show the acute presentation of a disease
Conclusion ***The data do emphasize the importance of obtaining urine and blood cultures on all young, febrile infants with suspected UTI.***			
Country **USA**			
Year of data collection 1976-1981			