Universitat de Girona

END OF TERM PROJECT

COMPARISON BETWEEN BLADDER STIMULATION WITH MIDSTREAM CLEAN-CATCH URINE AND BLADDER CATHETERIZATION TO OBTAIN NON-CONTAMINANT URINE SPECIMENS IN FEBRILE CHILDREN UP TO 6 MONTHS OF AGE: A CROSS-SECTIONAL STUDY

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1. ABREVIATIONS

FWS	Fever without source
PER	Paediatric Emergency Room
SBI	Serious bacterial infection
OB	Occult bacteraemia
Hib	Haemophylus influenza type B
UTI	Urinary tract infection
EAU	European Association of Urology
AEPED	Asociación Española de Pediatria
ESRD	End-stage renal disease
VUR	Vesicoureteral reflux
WBC	White blood cells
HSV	Herpes simplex virus
LE	Leucocyte esterase
PPV	Positive predictive value
NPV	Negative predictive value
AAP	American Academy of Paediatrics
CFU	Colony-forming units
HUDJT	Hospital Universitari Doctor Josep Trueta
HVH	Hospital Vall d'Hebron
HSJD	Hospital Sant Joan de Déu

2. ABSTRACT

Background: UTI causes approximately 7% of the cases of fever without source in children up to 6 months of age. Performing a valid diagnosis procedure includes a dipstick urine test and a urine culture. To obtain urine culture a clean and non-contaminant urine specimen is needed. Nowadays, invasive methods as bladder catheterization and suprapubic bladder aspiration are considered the Gold Standard techniques in this age's range. A new non-invasive technique based in bladder stimulation with midstream clean-catch urine has been considered a valid technique to obtain non-contaminant urine samples in non-continent children.

Objectives: The goal of this study is to determine if bladder stimulation with midstream clean-catch urine technique is at least as effective as bladder catheterization for the urine specimen collection in non-continent children up to 6 months of age in order to replace the Gold Standard technique by the new technique. Secondary objectives are determination of the needed time, analysis of the cost, calculation of complication's frequency and evaluation of the proportion of failed procedures for each technique.

Methodology: A cross-sectional study, of non-inferiority is performed in PER of three tertiary hospitals (HDJT, HVH, HSJD). The study will be performed between 2017 and 2018.

Participants: All children up to 6 months of age with fever without source and a positive result in the dipstick urine test attended in Paediatric Emergency Rooms of three tertiary hospitals between April 2017 and July 2017.

Key words: (MeSH terms) fever without source, urinary tract infection, urine dipstick, urinalysis, urine culture, urinary bladder, bladder catheterization, urine collection.

3. INTRODUCTION

3.1. FEVER WITHOUT SOURCE

DEFINITION

Fever's definition is a rectal temperature of ≥ 38ºC. Fever is one of the most common chief complaint of children who are visiting emergency departments. Most febrile children have got identifiable causes of their fever but especially in young and non-continent children, fever can appear without any evidenced source.

We define fever without source as a rectal temperature of >38ºC without any known origin after conclusion of the history and physical examination (1).

Fever without a source in young children is caused in the most of the cases by infectious diseases. In children up to 6 months of age, other rare causes of this fever can be thirst or dehydration (1).

EPIDEMIOLOGY AND ETHIOLOGY

20% of febrile patients who visit Paediatric Emergency Rooms have fever without an apparent source of infection after history and physical examination. In most cases, the origin of this fever is a viral infection which doesn't need treatment, but there is a small proportion that may occult serious bacterial infection (SBI), including bacteraemia, UTI, occult pneumonia, bacterial meningitis, septic arthritis, osteomyelitis and enteritis (2–4).

Before the apparition of some immunization vaccine against Haemophilus influenza type b (HIb) and Streptococcus Pneumoniae, occult bacteraemia was find in the 3-10% of children younger than 3 months of age with fever without a source and 5% to 7% of children between 3 and 36 months of age (4). After the apparition of these vaccines, the prevalence of invasive Hib infection and the prevalence of invasive pneumococcal infection has declined reaching rates of <1% (5). Nowadays, occult bacteraemia due to these causes represents 2.2% of the cases of fever without source in children younger than 3 months of age (3) and 0.34% of the cases of FWS in children 3-36 months of age (4).

Due to the decrease of Streptococcus penumoniae and Hib infections, urinary tract infections are, nowadays, the most common source of serious bacterial infection in febrile children younger than three months, with a prevalence of UTI of 7.2% in this range of

age, arriving to a prevalence of 16% in white females younger than 12 months of age (6). Pathogens that are more frequent in these types of UTI are Escherichia Coli and Klebsiella. In children 3 to 36 months of age, UTI is the most common infection, followed by pneumonia caused by Streptococcus Pneumoniae. (7,8).

It is also studied that, in the last years, there is an increase in the E. Coli bacterial infections in patients older than 1 month of age that has produce an increase in the prevalence of occult UTI in children up to 10.8%. This fact has been associated with the increase in the resistances formed by this bacteria (9).

3.2. UTI AS A CAUSE OF FEVER WITHOUT SOURCE

DEFINITION OF UTI

Urinary tract infection (UTI) is a term that includes a heterogenic group of different conditions of different ethiologies with the same common denominator, which is the presence of germens in the urinary tract infection (which is sterile in normal conditions) associated with variable symptomatology (10).

SYMPTOMATOLOGY OF UTI

Clinical presentation of UTI varies among children due to the age of the patient, but also due to the location of the infection.

In young infants, clinical manifestations are often non-specific and is difficult to make early diagnosis of UTI. In some cases, young children only present fever without no other identifiable source. UTIs should be suspected in every febrile infant until proven otherwise, especially in children between 0-6 months of age. Inside these non-specific symptoms we can find: lethargy, fever, vomiting, malaise, failure to thrive, irritability or hyperexcitability, hypothermia, jaundice and odour urine (11,12).

In older children, the symptomatology is more specific and we can find clinical manifestations associated with lower urinary tract infection as alterations in the voiding history (frequency, urgency, stream, volume, suprapubic pain, dysuria, secondary enuresis and toileting practices), alterations in the fluid intake or alterations in the bowel habits (11–13).

In the physical exploration we can find: hypertension, palpable bladder, dribbling or straining, and loin or suprapubic tenderness (11).

3.3. EPIDEMIOLOGY OF UTI IN FEBRILE CHILDREN

There is one meta-analysis realised by Shaikh et al. (6) that analyses the prevalence of urinary tract infection in febrile children. This meta-analyses determined that prevalence of UTI varies widely by age, gender and circumcision status. In the meta-analysis, it is evidenced a prevalence of 7.5% and 8.7% respectively, among febrile girls and boys younger than 3 months of age, whereas corresponding numbers for febrile children aged 3 to 12 months of age are 8.3% and 1.7% respectively. Prevalence of UTI in febrile children between 12 to 24 months of age is evidenced as 2.1% in girls. The same study determinate a prevalence of UTI in febrile children 3 to 6 months of age of 5.7% in girls and 3.3% in boys (4,6).

Prevalence of UTI among febrile infants < 2 years of age is estimated of 7.0% (7.3% in girls and 8.0% in boys). According to the gender, boys have got highest prevalence rates during the first 3 months of life and declined thereafter. Girls have got highest prevalence rates during the first 12 months of life (6).

Prevalence of febrile UTI according to circumcision status is evidenced to be of 20.1% in uncircumcised children younger than 3 months of life, being the highest prevalence for any group. Comparing with the prevalence of febrile UTI in circumcised boys in this range of age, it is estimated that the prevalence is 10 time higher in uncircumcised boys (4,6,13).

The meta-analysis also estimated that UTI rates were significantly higher among white infants than among black infants (8.0% vs 4.7%) (4,6). Although that, there isn't a clear evidence of this fact.

Prevalence showed in Shaikh et al.'s study are done according to different studies around the world, all them are written in English language. So, we can consider that these data represent the world population.

In the EUA Guideline of children's UTI, they demonstrate that the prevalence of UTIs in the first year of life is 3.7% in boys and 2% in girls. In the two first months of life, the prevalence of UTI is 5% in girls and 20.3% in uncircumcised boys. Later, the

prevalence change and UTI is most frequent in girls than boys if they are > 2 years of age (12).

Some Spanish protocols which are published by AEPED, estimated that the global prevalence of UTI in paediatric population in Spain is about 5% and also calculated that the prevalence of UTI in children with fever without any other known focus is 5-8%. They demonstrate that in the first months of life, UTI is more typical in boys (with a boys:girls relationship of 4-5:1), and in children older 3 years old, UTI is most common in girls (with a girls:boys relationship of 10:1) (10,14,15).

3.4. UTI'S ETHIOLOGY

It's important to know which pathogen is producing the UTI in our patients because in this way we will be able to know the sensibility and possible resistances of it and we will be able to treat the infection properly. So, obtain a clear and non-contaminant urine sample to do a correct urine specimen is basic in the management of UTI.

Gram-negative bacteria are the most common. Between them, Escherichia Coli is the most common bacteria which caused urinary tract infection in children (>75% of UTIs), followed by Klebsiella (11). Other Gram-negative bacteria that caused some UTIs in children are: Klebsiella, Proteus, Enterobacter, Citrobacter, Pseudomonas (more common in children with renal malformations) and Serratia sp. Gram-positive bacteria are less common. Inside this group, the most important bacteria are: Streptococcus B, Enterococcus sp. and Staphylococcus spp. (more common in children with a catheter) (16).

One of the most important virus that can produce a UTI in children is adenovirus. Moreover, adenovirus can produce a haemorrhagic cystitis (16). Another virus that can produce an UTI in an infant is BK virus (polyoma virus) which is a causative organism associated with immunosuppression (11).

Fungus rarely causes UTI in children. Candida spp. is a fungus that can produce UTI in these children who are immunosuppressed, who have received recent antibiotic treatment or who have received a catheterisation (11).

In the following table, we resume the main pathogens in urinary tract infections of children:

BACTERIA	VIRUS	FUNGUS
Gram-negative bacteria: E. Coli Klebsiella Proteus Enterobacter Citrobacter Pseudomonas Serratia spp	Adenovirus BK virus or polyoma virus	Candida spp.
Gram-positive bacteria: Streptococcus B Enterococcus sp. Staphylococcus spp.		

Table 1. Pathogens which can cause urinary tract infections.

3.5. PATHOGENESIS OF UTI IN FEBRILE INFANTS

UTI'S PATHOGENESIS

Associated with UTI's pathogenesis, we know that most UTIs develop when uropathogens ascend from periureteral colonisations to the bladder (producing a cystitis). When pathogens are allocated in the bladder, they may ascend the urinary tract (producing a pyelonephritis) or invade the bloodstream (producing an urosepsis). Urine specimens are sterile but some conditions may produce the entry of some pathogens to the urinary tract and then, these pathogens can colonize this urinary tract and produce the infection. These different conditions may be: ureteral catheterisation and turbulent voiding patterns (11).

Other mechanisms that can produce UTIs are haematogenous invasion or direct invasion.

UTI'S SUSCEPTIBILITY

UTI susceptibility is determined by host and bacteria factors.

As a bacteria factors associated with an increase of the risk of UTI we find the type of fimbriae which the pathogen presents. Different types of fimbriae determine the severity of the infection.

As host factors we can find: age (more prevalent in boys younger 12 months of age and in girls older 12 months of age), gender (more prevalent in females than in males, except in first months of age), race/ethnicity (more prevalent in whites but some studies don't see significant differences), genetic factors, lack of circumcision, urinary obstruction, bladder and bowel dysfunction, vesicouretral reflux, sexual activity, bladder catheterisation, frequency of diaper's change, lack of breastfeeding and oxiurasis presence in girls (10,11,17,18).

3.6. UTI'S DIAGNOSIS PROCEDURE IN CHILDREN WITH FWS

3.6.1. *IMPORTANCE OF THE DIAGNOSIS OF UTI IN FEBRILE CHILDREN*

Urinary tract infection in children can produce short-term suffering and long-term adverse consequences if it isn't diagnosed and treated properly.

About short-term complications, we can find kidney abscess and acute lobar nephritis. The prevalence of kidney abscess is unknown but it is considered a very rare pathology and the prevalence of acute lobar nephritis is of 8.6% in febrile UTI (10).

Inside the long-term consequences we can find renal scarring, impaired renal growth, recurrent pyelonephritis, impaired glomerular filtration, hypertension, end-stage renal disease (ESRD) and pre-eclampsia (19,20). These are serious and chronic and can compromise the patient's life. The prevalence of permanent renal scarring after a first UTI is about 4.7% in girls and 4.3% in boys (10,21).

For this reason, in front of a febrile children without any evidenced source of his/her fever, we have to done an accurate and timely diagnosis to rule out or confirm the possibility of UTI as the cause of this fever. A timely diagnosis of UTI in young children may alleviate short-term suffering and prevent long-term complications (19).

Although clinical manifestations of the patients and dipstick test can aid us to diagnose an UTI, doing a properly diagnosis leads to having to collect a non-contaminant urine specimen of patients to analyse this specimen with a urine culture. With the results of this examination, doctors will be able to determine if the patient is suffering a UTI or if the UTI is discarded, the pathogen which is causing the infection in the patient and also possible resistances to the antibiotic treatment.

3.6.2. DIAGNOSIS PROCEDURE

In the Ishamine's study (1) it is concluded that in febrile children in whom any source has been found, the first step is to determine the age of the patient. Although this division, in each patient with a febrile syndrome without an evidenced source it will be necessary doing a biological diagnosis of UTI to discard or confirm UTI because this pathology is the main cause of FWS in children.

In febrile neonate (28 days or 4 weeks and younger) it is necessary a complete sepsis evaluation that have to include lumbar puncture and hospitalization for parenteral antimicrobial therapy pending the results of the assessment. In infants between 4 weeks and 12 weeks old, the main aim is rule out a possible UTI but a blood analysis is also needed. If results of blood analysis suggest a possible severe infection a lumbar puncture and a chest-ray prove will also be needed. In children between 3 to 36 months old, the main objective is also rule out UTI as the main cause of FWS, so and urinalysis and urine culture on valid urine specimens will be needed, especially with the presence of UTI's risk factors. Lumbar puncture and chest radiograph don't have to be caught if there isn't neurological or respiratory symptomatology. In this case, blood analysis should be only obtained with an evidence of possible OB (1,2,4,22).

In the UTI's biologic diagnose process, we can distinct two different steps. In the first step, we use a rapid urine test (dipstick or urinalysis) to determine the suspicious of urinary tract infection. In the second step it is used the urine culture as the most effectively examination to confirm the UTI diagnosis or to discard this possibility if there was a positive dipstick test and a negative urine culture. Urine culture also reveals the pathogen that is causing the infection and possible resistances of the pathogen for antibiotic treatment.

3.6.2.1. *Urine dipsticks tests and urinalysis*

Urine dipsticks tests and urinalysis can't substitute urine culture in the biological diagnosis of UTI but they are useful because urine culture results aren't available for at least 24 hours and in this way, it may predict the results of the urine culture to allow you treat the infection since the first encounter (13,23).

Urine dipsticks indicate the presence of leucocyte esterase (as a marker of pyuria) and urinary nitrite (which is produced for the metabolism of dietary nitrates due to the

presence of Gram-negative enteric bacteria in the urine). To see urinary nitrite in the urine, you need to have got the urine at least 4 hours in bladder because is the time needed to metabolize the dietary nitrites. Nitrite test is very specific but it isn't very sensitive in young children because they empty their bladder frequently. So, negative nitrite test doesn't allow us ruling out UTI but if it is positive, it is very helpful to diagnose UTI. Leucocyte esterase test has got high sensitivity but it has got low specificity. For this reason, a leucocyte esterase test has to be interpreted with caution due to the high levels of false-positive results (13,23). We will consider a positive dipstick urine test if leucocyte esterase and/or nitrite are positive.

It is accepted that urinalysis can be done on any specimen. In our media, urinalysis is realised on a urine specimen acquired with a sterile urine bag applied to the perineum. The specimen must be fresh (<1 hour after voiding in a room temperature or < 4 hours after voiding in the refrigeration). In the urinalysis we perform biochemical analyses of leucocyte esterase and nitrite with a microscopic examination, and also we analyse the presence of white blood cells (WBCs) and bacteria (23).

TEST	SENSTIVITY (RANGE)%	SPECIFICITY (RANGE)%
Leucocyte esterase test	83 (67-94)	78 (64-92)
Nitrite test	53 (15-82)	98 (90-100)
Leucocyte esterase and nitrite test positive	93 (90-100)	72 (58-91)
Microscopy, WBCs	73 (32-100)	81 (45-98)
Microscopy, bacteria	81 (12-99)	83 (11-100)
Leucocyte esterase test, nitrite test, and microscopy positive	99.8 (99-100)	70 (60-92)

Table 2. Sensitivity and Specificity of Components of Urinalysis, Alone and in Combination. Adapted from 2011 AAP Guideline (23).

DIPSTICK TEST AND URYNALISIS	SUSPECTED DIAGNOSIS
Nitrites and leukocyte esterase (+)	UTI very likely
Nitrites (+) and leukocyte esterase (-)	UTI likely
Nitrites (-) and leucocyte esterase (+)	It can be UTI or no.
Nitrites and leucocyte esterase (-)	It exclude UTI

Table 3. Suspected diagnosis according to the results of the urinalysis (24).

In Glissmeyer et al.'s study, the estimated sensitivity of urine dipstick, performed in urine specimens acquired by bladder catheterization, for the UTI diagnosis in children younger 3 months of age is 90.8% and its specificity is 93.8%. If urine dipstick is combined with urinalysis the sensitive is greater (94.7%), even though the specificity was worse (87.6%). PPV of dipstick for UTI is also greater than in the combination of dipstick and urinalysis (66.2% versus 51.2%). NVP is ≥98.6% (25). In the Schroeder's study, sensitivity estimated by the urinalysis in bladder catheterization specimens is approximately of 98% (26). In these study UTI is defined as a growth of ≥1 urine pathogen each with a quantity of >50.000 colony-forming per millilitre in the urinalysis. Dipstick is considered positive if either leucocyte esterase or nitrite was positive.

3.6.2.2. *Urine culture*

Urine specimens acquired by a urine culture have to be non-contaminant and for this reason, the technique used to collect this specimen have to associate low contamination rates. The American Academy of Paediatrics (AAP), concluded that most effectively techniques in non-continent children to recollect urine specimens for urine culture are bladder catheterization and suprapubic urine aspiration (considering suprapubic urine aspiration as the Gold Standard technique) with a sensitivity of 95%, ruling out sterile urine bag due to high contaminations rates that this technique has got. In continent children, the validate technique to recollect urine specimens is midstream clean-catch urine (23).

Urine specimens should be processed quickly if it is possible. If it isn't possible, the specimens should be refrigerated to prevent the growth of other organisms that can occur in urine at room temperature. After that, each urine specimen has to be inoculated on culture medium that will allow identification of urinary tract pathogens. After the time needed to allow bacteria growth, a laboratory's analyst will analyse the specimen (23).

Urine culture results are considered positive or negative on the basis of the number of CFUs that grow on the culture medium. As some of the UTI pathogens are also in distal urethra and periureteral area, low colony count may be present in a specimen obtained by voiding or bladder catheterization when bacteria are not present in bladder urine (13,23). Definition of positive urine culture's result differs according to the technique used to collect the urine sample.

In the following table, we determine the number of CFU/ml needed to determine a positive result in the urine culture for each of the urine collect techniques:

URINE SAMPLE COLLECTION TECHNIQUE	POSITIVE URINE CULTURE
Clean-catch urine	≥100.000 CFU/ml of a pathogen
Sterile bag urine	≥100.000 CFU/ml of a pathogen
Bladder catheterization	10.000-50.000 CFU/ml of a pathogen
Suprapubic urine aspiration	Any growth of Gram-negative pathogens. ≥100 CFU/ml of Gram-positive pathogens.
Bladder stimulation with midstream clean-catch urine	≥100.000 CFU/ml of a pathogen

Table 4. Positive urine culture according to the urine sample collection technique used (24,27).

3.7. TECHNIQUES TO COLLECT URINE SAMPLES IN UTI'S DIAGNOSIS IN FEBRILE AND NON-CONTINENT CHILDREN

Collection technique of urinary specimens to perform a urine culture will determine the CFU needed to establish the diagnosis of UTI. In the literature we can find different methods with different characteristics to obtain urine samples.

In continent children, midstream clean-catch urine is the Gold Standard technique to obtain the urine specimen but in non-continent children this technique is difficult and time-consuming. Due to this fact, in non-continent children, urine samples are collecting by some different techniques. Urine collection methods in non-continent children can be divided on invasive and non-invasive techniques. Invasive techniques are considered the Gold Standard and they include bladder catheterization and suprapubic urine aspiration (28). Until the last years, the only available non-invasive technique was sterile bag urine, which has got a high contamination rates. In 2012, a Spanish study introduced the concept of a new non-invasive technique defined as a bladder stimulation with midstream clean-catch urine that allows a collection of valid urine sample with low contamination rates (27).

In next sections we analyse different characteristics of each technique.

3.7.1. *STERILE URINE BAG*

Sterile urine bag is considered a non-invasive technique to obtain urine samples in non-continent patients. Nowadays, sterile urine bag is indicated in the urine collection sample to perform the dipstick urine test and the urinalysis in order to do a screening of UTI. Only negative dipstick urine test's results will be acceptable to rule out the diagnosis of UTI because the positive ones will most likely be false and we will have to confirm the result with valid urine collection techniques as bladder catheterization or suprapubic aspiration (29).

The technique process consists in a cleaning of the vulva or the penis and the perineum area and after, the application of an adhesive plastic bag in this area to collect the urine (20).

In some studies which analysed contamination rates of urine sterile bag, it was concluded that this method has got a highest rate of contamination (the contamination is estimated of 46% (30)) with a false positive rate of 88-99% (13,20,29). For this reason, some guidelines (especially AAP guidelines) discard sterile urine bag to collect the urine sample to determine the urine culture and the urinalysis. Even though, some Spanish Guidelines and most European Guidelines don't discard this method as a valid technique to obtain urinalysis, but it isn't suitable for the diagnosis of UTI and they conclude that

we need another urine specimen obtained by an invasive-technique or bladder stimulation with midstream clean-catch urine to confirm the diagnosis (11,23).

Although that, this technique has got some benefits as the non-invasively fact and also the capacity to discard UTI if the urinalysis performed with urine specimen acquired by it is negative (29).

3.7.2. *BLADDER CATHETERIZATION*

Bladder catheterisation is an invasive-technique indicated in infants unable to provide clean-catch urine specimen. It is considered the Gold Standard technique in our country due to the high rates of CCU contamination, while in North America or another European countries suprapubic urine aspiration is the Gold Standard (12,23). This method is also indicated in these patients who have got an acute urinary retention.

A midstream urine sample is collected using in and out catheterisation (it is used a foley paediatric catheter) after the cleaning of the genital and perineum area. Lignocaine 2% gel aids in insertion. All process is explained in the methodology section (11,20).

As some pathogens related with the appearance of urinary tract infection are also colonizing distal urethra and periureteral area, with this technique there are a potential risk of white cell and bacteria contamination (contamination rate is estimated in 12% (30)). This contamination can also be caused by the entry of the pathogens from the foreskin and the reflux of urine into the vagina. For this reason, it is considered a technique with false positive high rate, although the contamination can be reduced by discarding the initial stream (31).

For the diagnosis, we need to find between 10000-50000 CFU/ml of a clinically relevant organism to consider that the urine culture which is performed with a urine specimen that is acquired with this technique is positive.

As an invasive technique, it may cause some complications in the patients but bladder catheterization is considered less painful and less invasive than suprapubic urine aspiration (31). Some of these complications are urethral or bladder trauma, urine retention, catheter urinary tract infection, knot of the catheter in the bladder and vagina catheterisation.

3.7.3. SUPRAPUBIC BLADDER ASPIRATION

Suprapubic bladder aspiration is an invasive technique to collect urine sample directly from the bladder. It is considered the best technique to obtain urine specimen in newborns and non-continent children under 2 years of age because in this case, the urine pass through the urethra is avoided and contamination rates are lower (contamination rate is estimated in <1% (30)). It is considered the urine collection technique with the lowest contamination rates because skin flora contamination is rare (23). Although that, in children older than 1 year is difficult to do (11).

There are some specific indications for this urine collection method: infants unable to void on request, uncircumcised boys with redundant foreskin or phimosis, girls with labial adhesions and periureteral irritation. As a contraindications we can find empty bladder (due to recent voiding or dehydration), skin infection in the puncture site, abdominal alterations or hemorrhagic diastasis (11).

The process to collect urine specimen starts with a bladder palpation to determine that it is full of urine. This can be also made with ultrasonography. If full bladder is confirmed, a cleaning with antiseptic of suprapubic region will be done. After that, under ultrasound guidance or not (if it is doing with ultrasonography exit rates increase (20)), a needle is attached to 5 ml syringe and inserted into a full bladder, which is localized 1-2 cm above the pubic symphysis. A urine aspiration is performed when needle enters to the bladder (11,32,33).

As the contaminate rates of this technique are very low, any growth of an uropathogen in the urine specimen associated with pyuria or bacteriuria is considered as a UTI diagnosis (21).

Nowadays, suprapubic bladder aspiration is considered the best aseptic method to obtain urine specimens in febrile, non-continent children due to the fact of its lower contamination rates (11,23).

3.7.4. BLADDER STIMULATION AND MIDSTREAM CLEAN-CATCH URINE

In 2012, Herreros et al. described a new non-invasive technique to collect urine specimens in non-continent children. This technique is done in children who have been fed before with gentle tapping in the suprapubic area at a frequency of 100 taps or blows

per minute for 30s and a stimulation on the lumbar paravertebral zone in the lower back with a circular massage during 30s. The study concluded that this is a valid technique to obtain midstream clean-catch urine specimens in non-continent children younger than 3 months of age (27).

The pudendum efferent nerves are responsible for the guarding reflex to avoid micturition. This reflex is progressively controlled after 2 years of age but is not effective in newborns who void once an hour (20-24 times per day). So, voiding is spontaneous during the infancy. The main nerves in bladder function are pudendum nerve and pelvic splanchnic nerve. A sacral reflex is responsible of bladder emptying and it is present since 20 week of gestational age. In newborns, micturition is induced by proprioceptive stimulus of bladder straining and also by the pudendum reflex. Although that, until 2 years of age, pudendum nerve is unable to avoid micturition in the case on increased abdominal pressure or bladder stimulation. So, it is known that the activation of pudendum afferents can evoke reflex bladder contraction or relaxation (through the reflex contraction of the detrusor muscle which contracts to pass urine (27)), depending on the frequency of stimulation and the filling of the bladder (34).

So this technique has been considered a valid non-invasive technique to obtain urine specimens in a duration of less than 3 minutes in children younger than 3 months of age, depending on the weight of the patient (27,34). In one study that evaluates the new technique's efficacy, it has been demonstrated that this method has got a high sensitivity and a high specificity, with low false positive and false negative rates. Contamination rates are considered lower than the contamination rates using bladder catheterization (35). Although that, the achieved results of this study aren't representative due to the fact that it has got a small sample size.

Bladder stimulation with midstream clean-catch urine can be indicated in children younger than 6 months of age with a UTI's suspicious, to obtain a non-contaminant urine specimen to perform the urine culture needed to establish the diagnosis.

The contraindications of this technique are all these situations that disables the micturition of the patient (anatomical malformations) and continent children.

Its strength is that is a technique without evidenced complications during its procedure. The only complication that can be present is the falling of the baby which is very rare. Although that, it was described uneasy of the patient during the procedure (36).

4. JUSTIFICATION

Urinary tract infection represents 7.2% of cases of FWS in children under 3 months of age and 6.6% of febrile syndromes in children 3 to 6 months of age (13). Urine culture is a basic test to diagnose UTI in febrile children because it allows you to know the presence or absence of pathogens in the urinary tract, the identification of pathogen that is causing the infection in the patient and the detection of possible resistances in front of antibiotic treatments. Urine cultures are performed in a clear and non-contaminant urine specimens because the wrong collection or interpretation of specimens may contribute to underdiagnosis of UTI with the potential damage at renal scarring or overdiagnosis of UTI with unnecessary antibiotic treatment.

In continent children, clean-catch urine technique is a useful technique to collect non-contaminant urine specimens but in non-continent children this method is difficult, time-consuming and has got potential adverse effects (35). For this reason, in children who haven't got sphincter control, Gold Standard techniques are bladder catheterization or suprapubic urine aspiration. These two techniques are invasive and they have some complications as ureteral trauma in bladder catheterization, intestinal perforation in suprapubic urine aspiration and catheter infections in both techniques (31).

A new technique to obtain midstream clean-catch urine specimens in non-continent children is identified. This technique, which consists of feeding, bladder stimulation and lumbar massage, demonstrate the possibility to obtain the voiding of the child in less than 1 minute (25).

Given that clean-catch urine has been considered a valid technique in continent children, bladder stimulation with midstream clean-catch urine has also been considered valid to obtain urine specimens in non-continent children but its efficacy is only evaluated in children under 3 months of age. Moreover, its use isn't standardized as the Gold Standard technique in PER of Catalunya's hospitals. For this reason, we suggest studying the efficacy of this new technique in comparison to bladder catheterization (Gold Standard technique) in our region. We believe that bladder stimulation and midstream clean-catch urine is a technique at least as effective as bladder catheterization and for this reason, and if the results of this study are positive, we will consider that bladder catheterization could be replaced by bladder stimulation in the urine sample collection in patients of this age range.

There are already some studies that perform a comparison between this new technique and bladder catheterization, and although they concluded that two techniques are equally effective, these studies have got high limitations as their small sample size and also they only present results of a population under 3 months of age with a high suspicion of UTI, leaving without investigation non-continent children over 3 months of age who may also be benefited by this new technique and these patients who fulfil low-risk Rochester's Criteria for occult bacteraemia (33,34). Due to this fact, we propose increasing the age of our study sample to demonstrate that this technique may also be useful in children up to 6 months of age and include all children with FWS, independently of the fulfilling of Rochester's Criteria.

We consider that this study could be useful for the clinical practice to avoid invasive methods in urine specimen's collection in non-continent children, which can produce serious complications and painful in our patients, and which could be replaced by existing non-invasive methods as the bladder stimulation with midstream clean-catch urine.

To accomplish our objective, we propose the completion of a cross-sectional study with the performance of the new technique (bladder stimulation with midstream clean-catch urine) and the performance of the Gold Standard technique in our region (bladder catheterization) in patients up to 6 months of age with FWS and a positive dipstick urine test in order to measure the proportion of positive urine cultures in each technique. In this way, the aim of this study is evaluating if the new technique is at least as effective as bladder catheterization to rule out or confirm UTI in Catalunya's PER, and consequently bladder stimulation with midstream clean-catch urine can be considered as the new Gold Standard technique to collect valid urine specimens in children younger than 6 months of age. We will also analyse some other variables in order to make a better comparison between two techniques evaluated in the study. These variables are the proportion of complications, the time needed to obtain the sample, the cost, the proportion of failed procedures and the contamination's rate in each technique.

5. HYPOTHESIS AND OBJECTIVES

QUESTION

Is the bladder stimulation with midstream clean-catch urine at least as effectively as bladder catheterization to obtain non-contaminant urine specimens in non-continent children up to 6 months of age with FWS and urinary tract infection suspicion (represented by a positive dipstick urine test) to rule out or confirm the presence of UTI?

HYPOTHESIS

Bladder stimulation with midstream clean-catch urine is a non-invasive technique at least as effectively as an invasive technique like bladder catheterization to collect non-contaminant urine samples in non-continent children up to 6 months of age with fever of unknown origin and a positive dipstick urine test, to discard or confirm UTI as the cause of their fever.

The percentage of positive urine cultures in urine samples acquired by bladder stimulation with midstream clean-catch urine presents a difference of less than 10% respect the percentage of positive urine cultures in samples acquired by bladder catheterization in non-continent children up to 6 months of age with fever without a source and urinary tract infection suspicion.

OBJECTIVES

- PRIMARY
  - Compare the percentage of positive urine cultures in two different techniques that are used to obtain urine samples (bladder stimulation with midstream clean-catch urine and bladder catheterization) in a population of febrile children up to 6 months of age and a positive dipstick urine test to rule out or confirm the presence of UTI.
- SECONDARIES
  - Compare urine specimen's contamination rate in bladder stimulation with midstream clean-catch urine and urine specimen's contamination rate in bladder catheterization

- Determine the time needed between the start of the technique and the collection of the urine sample in bladder stimulation with midstream clean-catch urine and bladder catheterization.

- Evaluate the number and type of complications that appear in bladder catheterization versus number and type of complications in bladder stimulation with midstream clean-catch urine.

- Determine the cost of bladder stimulation with midstream clean-catch urine versus the cost of bladder catheterization.

- Determine the number and the percentage of failed procedures with each technique: bladder stimulation with midstream clean-catch urine and bladder catheterization.

6. METHODOLOGY

6.1. STUDY DESIGN

This is a cross-sectional study, of non-inferiority and multicentre, designed to evaluate the effectiveness of bladder stimulation with midstream clean-catch urine versus bladder catheterization used in the diagnosis of urinary tract infection in non-continent children up to 6 months of age to obtain a valid urine sample.

Two techniques to obtain valid urine specimens will be performed on each subject of our sample. First, a bladder stimulation and lumbar massage with midstream clean-catch urine will be performed after the feeding of the baby. 45 minutes later, a bladder catheterization will be performed as a reference technique (Gold Standard) to obtain other urine specimen for each patient.

We will compare the results from each technique to evaluate the efficacy of two techniques and also to determinate if the invasive technique (bladder catheterization) could be replaced by bladder stimulation with midstream clean-catch urine as the Gold Standard method in this age range.

6.2. SETTING AND POPULATION OF THE STUDY

Our study is intended for non-continent children under 6 months of age, who arrive at PER with FWS independently of its duration, in whom is performed a dipstick urine test with a urine specimen obtained by sterile urine bag and it has got a positive result.

To achieve a correct sample size, we decide that this will be a multicentre study. Population of the study will be collected in Paediatric Emergency Rooms of three different tertiary paediatrics reference hospitals of our Autonomous Community. Hospitals enrolled in this study will be:

- Hospital Universitari Doctor Josep Trueta.
- Hospital Vall d'Hebron.
- Hospital Sant Joan de Déu.

These hospitals will be chosen for the better feasibility due to their proximity.

6.3. INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA

- Children up to 6 months of age arrived on PER.
- Fever without and evidenced focus independently of its duration in whom paediatric considers necessary ruling out or confirm a UTI.
    - Fever is defined as a rectal temperature plus than 38ºC.
- Positive result in the dipstick urine test.
- Informed consent obtained by the parents.

EXCLUSION CRITERIA

- Informed consent no obtained by the parents.
- Inability to obtain urine sample.
- Hemodynamic instability or sepsis.
- External genitalia or bladder malformation that may be a contraindication for the technique, especially for bladder catheterization.
- Antibiotic treatment started for the suspicious of infection or previous antibiotic treatment for other process.

6.4. SAMPLE SELECTION

A consecutive random, non-probability sampling will be taken. We use this sampling method because we only include non-continent infants who arrive in PER with FWS and a possible urinary tract infection (defined as a positive dipstick urine test) in whom UTI has to be discarded by the performance of a urine culture in a valid and non-contaminant urine specimen. The sample will take part at three different hospitals which participate in the study for 1 year and 3 months. Children who fulfil the inclusion criteria will be approached in PER visit.

We will give an information sheet describing the study (see ANNEX 4) to all children's parents and if the parents are interested in participating in the study, we will

give them an informed consent (in ANNEX 5). If parents agree with the description of the study and the informed consent and they sign it, first we will perform a bladder stimulation and midstream clean-catch urine, and 45 minutes later, we will perform a bladder catheterization acquiring two valid and non-contaminant urine specimens to do urine cultures for each patient.

6.5. SAMPLE SIZE

To calculate the sample size we had to do some estimations. As we consider the presence of LE and/or nitrite as a positive result in the dipstick urine test, we have determined the sensitivity and specificity mean of this test calculating the mean between the sensitivity and the specificity of these situations with the values administrated by the AAP's guideline (23). So, we have estimated that the dipstick test sensitivity is 76% and dipstick test specificity is 83%. Using the UTI's prevalence in children younger than 6 months (approximately 7%) and these values, we estimate that the PPV is 25% with the following equation, where P is prevalence, SE is sensitivity and SP is specificity:

$$PPV = \frac{P \cdot SE}{P \cdot SE + (1 - P) \cdot 1 - SP}$$

So, we determinate that 25% of positive dipstick test results are really UTI.

The objective of our study is to determinate the efficacy of the urine culture performed in urine specimens acquired by two different techniques (bladder catheterization and bladder stimulation with midstream clean-catch urine). We consider that our control technique is the group of the patients in whom we perform a bladder catheterization to collect the urine for the urine culture due to the fact that this is the Gold Standard technique. The sensitivity of urine cultures with the urine specimen obtained by this method is 95%. For this reason, we estimate that the waited proportion of positive urine cultures in our control technique is 25%. In the other technique, as we want to do a non-inferiority study, we determinate that the maximum difference in the positive urine culture results obtained have to be of 10% and for this reason, we calculate that the proportion of positive urine culture in this method is 15%.

The calculator GRANMO is used to calculate the sample size. It was accepted an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test. As we have calculated, the

proportion of waited cases with the Gold Standard technique is 0.25 and with the new technique is 0.15. It was accepted an expected proportion of follow-up losses of 0.2.

It is needed a group of 310 patients. We need at least 310 patients with a urine specimen obtained by bladder catheterization and 310 patients with a urine specimen obtained by bladder stimulation with midstream clean-catch urine to detect that these two techniques are at least equally effective with an accepted risk of 5%.

6.6. ESTIMATED TIME OF RECRUITMENT

The PER of HUDJT attends 15000 patients/year. It is estimated that 20% of these patients are children up to 6 months of age. Of them, 20% present FWS as the main symptomatology due to, in this range of age, the prevalence of this manifestation is the highest. So, we determine that there are 600 patients/year who have got FWS in this range of age. In all of them a dipstick urine test is performed in a sterile bag urine specimen. As the prevalence of UTI in febrile children up to 6 months of life is 7%, we estimate that of these 600 patients, 42 patients have got UTI. Although that we have to take into account the false positive results of the dipstick test, which are estimate in 17%. For this reason, we conclude that in HUDJT there are 145 candidates/year for our study.

In HDUJT there are about 145 candidates/year and in other hospitals (HUSJD and HVH) the incidence of FWS and a positive dipstick urine test is about 435 patients/year. These data were provided by an email send to the Paediatric Emergency Room services of these hospitals. Our simple size to determinate the results in the effectiveness of the two techniques is of 310 patients. So, we estimate to need around 4 months to collect data and 1 year and 3 months to carry out the study.

Data of HUDJT are acquired presenting a request to the technical secretary's hospital, in which number of children presented in the PER up to 6 months of age is demanded.

6.7. PROCEDURE

In hospitals that participate in the study, first step to rule out a UTI as a possible diagnosis of a children up to 6 months of age with FWS, is to collect a urine bag specimen to perform a dipstick urine test. When the dipstick urine test is positive, a non-contaminant urine specimen is needed to perform the urine culture.

All urine sample extractions for the urine culture will be carried out in a specific room of PER of different hospitals which participate in the study. Bladder catheterization and bladder stimulation with midstream clean-catch urine will be performed by nurses who will be trained through an internet video and some practice sessions. Urine samples collected will be transported quickly to the specific microbiology laboratory of every hospital in order to evaluate them.

A laboratory's technician will be trained in order to analyse the samples of each patient without knowing the technique used and to try to send the results as fast as possible (maximum 24h after the sending of the samples). Laboratory's technician will inform about the presence of the colony forming unit number presents in the urine culture.

A paediatrician who participate in the study will realise a last analyse of the results of urine cultures of each patient to determine if the result is considered positive for a urinary tract infection, depending on the method performed.

6.7.1. MATERIAL AND STAFF NEEDED

BLADDER CATHETERIZATION

Collecting urine sample with bladder catheterization technique needs the following material:

- Small catheter for infants (5 Fr).
- Surgical lubricant.
- Sterile sample bottle.
- Gloves.
- Gauze or cotton, cloths and antiseptic solution of povidone-iodine or chlorhexidine.

Staff needed to realise this technique is two nurses. One nurse will catch the child so he/she won't move and the other nurse will realise the technique to obtain the urine sample (33).

BLADDER STIMULATION WITH MIDSTREAM CLEAN-CATCH URINE

To realise bladder stimulation with midstream clean-catch urine as the technique to obtain the urine sample, we need the following material:

- Water or formula milk to feed infants if they don't receive breast milk. If they receive breast milk, a breastfeed is needed.
- Sterile gauze.
- Warm water and soap to clean genital area.
- Sterile sample bottle.

We needed two nurses and the parents' aid to carry out this technique. One of the nurses will clean the genital areas. Then, parents of the child will take the child under the armpits. Other nurse will realise bladder simulation manoeuvres and lumbar massage. Then, the nurse who have cleaned the genital area of the child, will collect the midstream urine sample (34).

6.7.2. TECNIQUE'S PROCEDURE

BLADDER CATHETERIZATION

The different steps which you have to follow to realise this technique are (33):

1. After 45 minutes without urination: hold the child supine with thighs in abduction.
2. Apply an antiseptic solution around the meatus and sterile drapes on lower abdomen and legs.
3. Prepare urethral opening under sterile conditions.

   → Girls: it may be difficult to visualize the urethra.

   → Boys: with the non-dominant hand, soft traction of the penis to straighten the urethra and soft pressure to avoid reflex urination. If there is phimosis: align the preputial ring and the meatus. If it is not possible to visualize it, insert the catheter through the preputial ring in a slightly downward direction. If there is doubt about the catheter placement, abandon the process.

4. Place the wide end of the catheter into a sterile sample bottle.

5. Lubricate the tip of the catheter well and enter it to the urethra slowly. You have to advance the tube until it enters urine in the catheter.

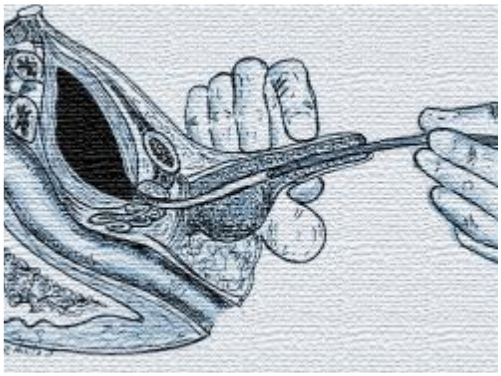
   → If there is resistance in the external sphincter, hold the catheter with minimal continuous pressure: the spasm usually subsides in a few minutes and then, the catheter easily passes into the bladder. If it isn't possible, suspect obstruction and discontinue the procedure.

   → Advance to the bladder. In girls, a few centimetres. In boys, a few centimetres more than the length of the penis.

6. Don't insert an extra length of the catheter to stabilize it because with this manoeuvre you can increase the risk of knotting.

7. Collect sample for urine culture. You mustn't catch the first millilitres of urine because they can contaminate the sample.

8. Carefully remove the catheter when the urine flow ceases.



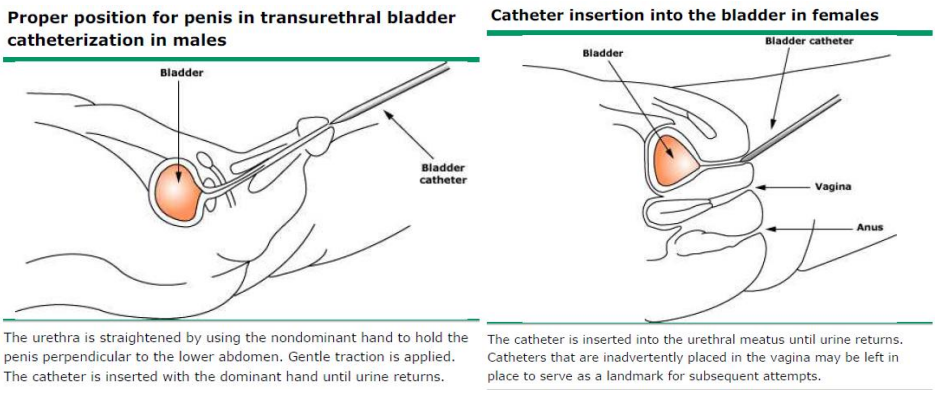


Figure 1. Bladder catheterization procedure (33).

BLADDER STIMULATION WITH MIDSTREAM CLEAN-CATCH URINE

The following steps are basics to realise this technique (34):

1. Feed the child 25 minutes before the technique accomplishment.
2. After these 25 minutes, clean the genital area with warm water and soap or an antiseptic (povidone-iodine solution). Then, dry the area with sterile gauze.
3. You can manage non-drug anaesthesia as non-nutritive sucking or 2% sucrose syrup.
4. One of the parents held the child under the armpits with legs dangling.
5. A nurse starts bladder stimulation manoeuvres by gently tapping the suprapubic area at a frequency of 100 taps per minute, for 30s.
6. Then, the same nurse make a circular massage in the lumbar paravertebral area in the lower back for 30s.
7. The nurse repeat both manoeuvres until micturition starts or for a maximum of 3 minutes.

    → If the micturition is not produced in 3 minutes, we will repeat all the procedure. If voiding isn't produced in 5 minutes we will abandon this technique.

8. The nurse who is in charge to collect the midstream clean-catch urine has to avoid the first and the last millilitres of urine and collect the midstream urine in a sterile sample bottle.

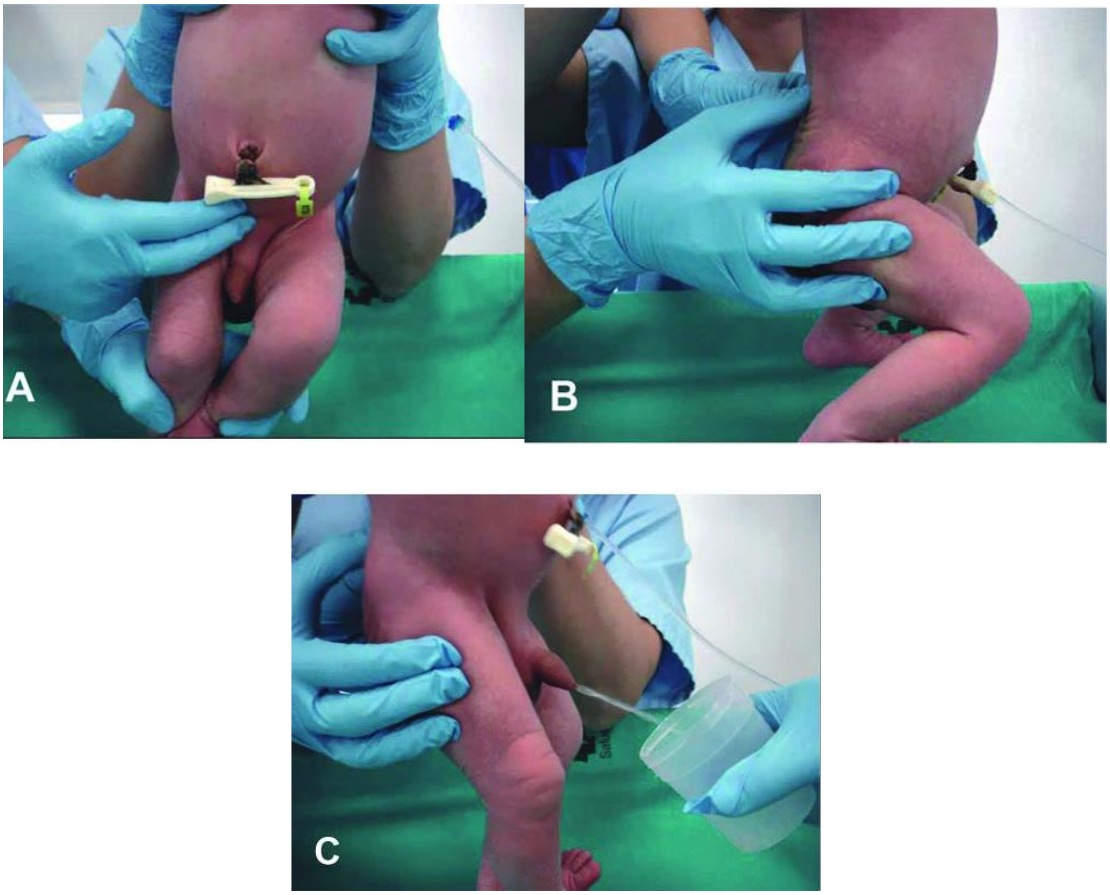


Figure 2. Bladder stimulation with midstream clean-catch urine procedure. (A) Tapping in the suprapubic area. (B) Stimulation of the lower back. (C) Midstream urine sample collection in a sterile container (27).

6.8. TERMINATION STANDARD

This study will stop before the end if there is a justification by the investigator of the Clinical Research Ethical Committee because of a violation of the law, alteration in the process to acquire the authorization, absence of accomplishment of the ethical principles in the RD 223/2004 or in order to protect rights and interests of subjects.

The Sanitary Authorities can suspend the study too.

6.9. WITHDRAWAL OF SUBJECTS FROM THE STUDY

The criteria to withdraw any subject of the study are:

- Informed consent is retired.
- Protocol is not accomplished.

- Bladder stimulation with midstream clean-catch urine technique doesn't allow voiding in 300s since the start of the technique.
    - In this case, as the bladder stimulation with midstream clean-catch urine has failed, bladder catheterization will be done to obtain the urine specimen and the patient will withdraw of the study.
- One patient has any unknown genital or ureteral malformation which prevents the placement of the ureteral catheter and bladder catheterization isn't possible.
    - In this case, we will try a bladder stimulation with midstream clean-catch urine or a suprapubic urine aspiration to obtain the urine specimen.

6.10. STUDY VARIABLES

In all the patients we will collect the following baseline characteristics.

INDEPENDENT VARIABLE

Our independent variable is defined as the technique used to obtain the urine sample. We have got two categories: urine specimens acquired by bladder stimulation with midstream clean-catch urine and, in the other hand, urine specimens acquired by bladder catheterization technique.

Each technique has been explained in the procedures section.

DEPENDENT VARIABLES

Primary dependent variable

Our dependent variable is urine culture's results which allows us to determine the efficacy of two different techniques (bladder stimulation with midstream clean-catch urine and bladder catheterization).

It will be categorized in two categories: one category will be positive results in urine cultures and other category will be negative results in urine cultures.

To determinate that a urine culture is positive, we will use two different definitions depending on the performed technique:

- BLADDER STIMULATION WITH MIDSTREAM CLEAN-CATCH URINE: a urine culture is positive when the analysis of the urine sample finds the presence of a pure growth > 100.000 colony forming units per ml. If we obtain < 10.000 CFU/ml in a sample, we will consider this urine culture as a negative result (27). If we obtain a result between 10.000-100.000 CFU/ml we will consider this result also as negative.

- BLADDER CATHETERIZATION: a urine culture is positive when the analysis of the urine sample find the presence of a pure growth > 10.000 colony forming units per ml. If we obtain < 1.000 CFU/ml in a sample, we will consider this urine culture as a negative result (27). If we obtain a result between 1.000-10.000 CFU/ml we will repeat the analysis.

Our outcome will aid us to estimate the sensitivity, the specificity, the PPV and the NPV of these two techniques in our region.

Secondary dependent variables

- Contamination's rate: urine culture is defined as a contaminate urine culture if it have mixed bacteria growth or growth of one or more non-pathogenic bacteria (Lactobacillus species, coagulase negative Staphylococci and Corynebacterium species), irrespective of the colony count and the used technique (35).

- Time needed to obtain the sample: it is defined as the time between the start of the technique and the urine sample collection. The time is measured with seconds.

  - *Bladder stimulation with midstream clean-catch urine:* sample collection time was defined as the time from the beginning of the stimulation procedure (the tapping) to the beginning of sample collection (2).

  - *Bladder catheterization:* measurement of the time (in seconds) between the introduction of the catheter and the output of urine.

  We will interpreted the results with different time intervals.

- Cost of each technique: the cost of the technique is defined as the spending money in the material and in the staff needed to perform each technique.

- *Bladder stimulation with midstream clean-catch urine:* water or formula milk to feed children, warm water, soap and sterile sample bottle. (34).

- *Bladder catheterization:* small catheter for infants, surgical lubricant, sterile sample bottle, gloves, gauze or cotton, cloths and antiseptic solution of povidone iodine or chlorhexidine. (33).

We will measure it in Euros because it is a European study.

- Number and type of complications: a collection urinary specimen's technique's complication is defined as any event caused by the use of the material or the manoeuvres of each technique that produce a damage to the patient, deteriorating his health.

  - *Bladder stimulation and midstream clean-catch urine:* the only complication that this technique can have is the falling of the child. In this case, we will measure the number of fallings happened in the patients of these group.

  - *Bladder catheterization:* the main complications are ureteral trauma and catheter infection. We will distinguish between these two categories of complications and their proportion.

- Number and percentage of failed procedures: a failed procedure is defined as a disability to obtain urine specimens after making one of the techniques. Failed procedures will be measured with absolute number and percentage in each technique. The definition is different in each technique:

  - *Bladder stimulation with midstream clean-catch urine:* failed procedure is defined as a disability to obtain the urine specimen in 300s since the start of the technique.

  - *Bladder catheterization:* failed procedure is defined as the disability to obtain the urine specimen after two attempts of catheterization.

COVARIATES

- Age: months and days at the time of the UTI suspicious.
- Genre: male or female.

6.11. DATA COLLECTION

Personal from the PER of hospitals involved in the study, who are previously informed and trained for the procedure evaluated in this cross-sectional study will work together for data collection using a specific sheet with the information needed for each patient who participate in the study (see ANNEX 7).

All the report cases sheet will be analysed by the statistical analyst in order to determinate that all the data is registered properly and that professionals of the study are acquiring the most accurate information for the results. The data will be classified according to the hospital, in order to be able to analyse the results of each hospital independently.

6.12. OTHER ACTIVITES FROM THE STUDY

Apart from the procedures involved in the study, this project will include the following tasks:

- **Meeting 1**: study coordinator (SC), paediatricians of different hospitals (Ped) and statistical specialist (SS)
  - The main aim in the first meeting is to determinate the protocol design in data collection phase and the task of each participant of the study.
- **Formation course**: SC, Ped and nurses involved in children care in the PER (Nur).
  - A formation course will be given to the nurses unrelated to child care in the PER and to the paediatricians. The aim of this course is to let know them the followed procedure in each technique to obtain a valid urine specimen in order to make sure that there are no differences between the procedures used in different centres of the study. This course will be done

with an explanation notebook, some video sessions and with some practices.

- **Meeting 2**: SC, Ped and SS.
  - The aim of this meeting is evaluating the results obtained until those moment and possible limitations of them.
- **Meeting 3**: SC, Ped and SS.
  - The main objective is evaluating the results obtained in the statistical analysis.

6.13. TASK AND RESEARCH TEAM

In the following section, tasks assigned to each group of professionals who participate in the study are described:

- **Study coordinator (SC):** Aina Sitjà
  - Coordination of the study.
  - Bibliography research.
  - Protocol design.
  - Study participation in data collection.
  - Interpretation of the results obtained and publication of the results.
- **Paediatricians (Ped):** 3 paediatricians per centre will participate in the study and will attend different meetings.
  - Final protocol design.
  - Recruitment of different patients.
  - Analyses of the urine cultures results that are contributed by the LT.
  - Data collection.
- **Laboratory's technicians (LT):** 1 LT per centre will be included in the study.

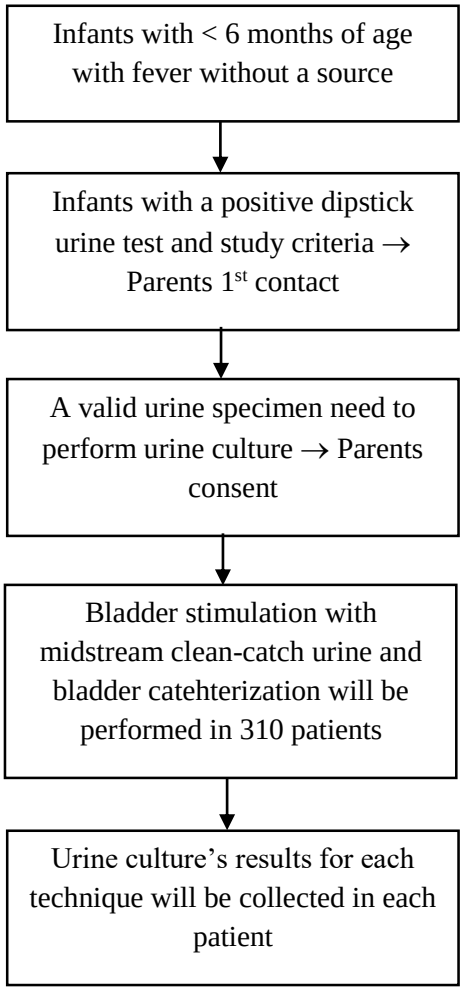
  - Performance of urine cultures in the laboratory.

- **Nurses (Nur):** between 4 and 6 nurses of the PER per centre will be trained to perform different techniques evaluated in the study and to collect properly data.
  - Children care.
  - Performance of different techniques to obtain a urine specimen of each patient.
  - Data collection.
- **Statistical specialist (SS):** 1 statistical specialist will be hire.
  - Monitoring and quality control of data collection.
  - Statistical analysis of results.

Each professional who will participate in the study will sign a researcher's commitment form (see ANNEX 6).

6.14. SUMMARY OF THE PROCESS

In the following diagram we can summarize all the procedure of this study.



7. STATISTICAL ANALYSIS

All statistical analysis will be performed using the IBM Statistical Package for Social Science (SPSS) 22.0 program. Microsoft Excel tool will be used to manage computed data.

UNIVARIATE ANALYSIS

In the univariate analysis, variables are defined as categorical or quantitative. Categorical variables of our study will be described using percentages and proportions, and they will be represented in bar charts. Quantitative variables will be described using mean ± standard deviation or median and interquartile range (25-75) depending on whether they were normally distributed or not, and they will be represented with histograms.

- INDEPENDENT VARIABLE: is defined as a dichotomous nominal variable. It will be described as the absolute number and the percentage of patients in whom bladder catheterization is performed and the absolute number and the percentage of patients in whom bladder stimulation with midstream clean-catch urine is performed.

- PRIMARY DEPENDENT VARIABLE: is used to evaluate our primary goal. It is defined as a dichotomous nominal variable. It will be described as the absolute number and the percentage of positive urine cultures in patients in whom urine specimens are acquired by bladder catheterization and the absolute number and the percentage of positive urine cultures in patients in whom urine specimens are acquired by bladder stimulation with midstream clean-catch urine.

  Contingency tables for our dependent variable are:

Bladder stimulation with midstream clean-catch urine		
URINE CULTURE RESULT	**ABSOLUTE NUMBER (N)**	**FREQUENCY % (IC)**
Positive urine cultures		
Negative urine cultures		

Bladder catheterization		
URINE CULTURE RESULT	**ABSOLUTE NUMBER (N)**	**FREQUENCY % (IC)**
Positive urine cultures		
Negative urine cultures		

- SECONDARY DEPENDENT VARIABLES: they are used to evaluate our secondary goals.
  - Contamination's rate: dichotomous nominal qualitative variable which is measured with absolute number and proportion of contaminated samples in two different evaluated techniques.
  - Time needed to perform the technique: continuous quantitative variable which is represented in seconds' intervals and that is described with time's mean and time's standard deviation or median and interquartile range.
  - Cost of each technique: measurement of a continuous quantitative variable in euros. It will be described with cost's mean and cost's standard deviation or median and interquartile range.
  - Complications: categorical variable that is described as the frequency of different complications associated with each technique.
  - Failed procedures: dichotomous nominal qualitative variable that is described as the absolute number and the percentage of failed procedures in each technique which are evaluated in this study.
- COVARIATES:
  - Age: quantitative variable that is measured with age's mean and age's standard deviation or median and interquartile range.
  - Genre: dichotomous nominal qualitative variable that is described with absolute number and percentage of females and absolute number and percentage of males.

BIVARIATE ANALYSIS

In the bivariate analysis, the independent and the primary dependent variables are nominal and qualitative. Therefore, the comparison between our independent variable (bladder catheterization or bladder stimulation with midstream clean-catch urine) and our primary dependent variable (negatives or positives urine cultures in each technique) will be carried out with Chi-Square test.

The bivariate analysis between the independent and the primary dependent variable will allow us to estimate the sensitivity, the specificity, the PPV and the NPV of each technique.

The bivariate analysis between independent variable and qualitative secondary dependent variables will be carried out with Chi-Square test.

The bivariate analysis between independent variable and quantitative secondary dependent variables will be carried out with T-student test.

MULTIVARIATE ANALYSIS

In the multivariate analysis, a logistic regression test will be used to estimate 95% confidence intervals. The relationship with the independent variable and dependent variables will be adjusted for confounding variables, which are defined in our study as a covariates.

8. ETHICAL CONSIDERATIONS

This study will be conducted according to the human rights and ethical principles established and defined on the World Medical Association in the Declaration of Helsinki of Ethical Principle for Medical Research Involving Human Subjects. The research protocol of our study must be presented, evaluated and approval by the Clinical Research Ethical Committee at HUDJT, and also it must be approval in others Clinical Research Ethical Committees of other centres involved in the study. It has also been approval by the CCAA. This process will be followed in the beginning and at the end of the study.

Personal and clinical information and other data collected for the study of all participants will be confidential and only used for research purpose according to "*Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal"*. Participants' parents will be informed by researchers and an information sheet will be given to them (see ANNEX 4). If they are according to the information received and with the procedure, they will have to sign voluntarily the informed consent (see ANNEX 5), according to "*Ley 41/2002 básica reguladora de la autonomía del paciente y de derechos y obligacions en material de información y documentación clínica"*.

According to Nüremberg Code (1947) each candidate participating in a study must have legal and real capacity to give his/her consent, and the patient must be in conditions which allow the free choice exercise, without external pressures, fraud, deception or coercion. The stressful situation that the parents will face must be taken into account. The informed consent have to be signed voluntarily and without any coercion, and parents of the child have to understand all the information given between the information sheet and the informed consent.

This study is made according to "*Ley 14/2007 de investigación biomédica relacionada con procedimientos invasivos, muestras biológicas y biobancos*" in which an invasive procedure is defined as an intervention performed with research objectives involving a physical or psychological risk for the affected subject.

The study will be stopped if there are collected data pointing a much better effectiveness of one of the techniques used over the other technique. Because of that, if during the coordination meetings any evidence like that is found, the possibility of

stopping the study will be discussed. The security of all the patients will be evaluated during all the study. Any compromise of patients' integrity will be reported and published.

9. LIMITATIONS

In the analysis of our study, we detected some limitations which may interfere in the research process. The most relevant limitations are explained below.

Due to the fact that this study hasn't got a randomized sample, one of possible limitations is that our sample could not be representative for our population and the results can be modified by this aspect.

Both techniques carried out in our study will be standardized in a formation course and nurses and physicians will be taught through the same information and the same videos. Although that, we have to consider that every procedure depends on each professional who performs the technique and that it may have got differences according to the professional in charge. Even thought, we consider that it has minim effects on the results of our study.

Due to the need of knowing the technique to may analyse the results of the urine culture in each patient and determinate if the results of the laboratory are considered positive or negative, the paediatric needs to know the performed method in each laboratory's result. Although this fact, urine cultures of each patient will be evaluated according indications of clinic guidelines and investigators are committed to not ignore any result and not modified collected data.

This study evaluates the accuracy of bladder stimulation with midstream clean-catch urine compared with the Gold Standard technique in our region, which is bladder catheterization. Despite this, suprapubic urine aspiration is considered the Gold Standard technique in other regions. For this reason, we suggest that a future protocol could study the accuracy of this new technique compared with the accuracy of suprapubic urine aspiration.

10. WORK PLAN

The research team of this study will be composed of: one study coordinator (SC), paediatricians of different centres involved in the study (Ped), nurses unrelated to child care in the PER of different centres involved in the study (Nur), one laboratory's technician of each centre involved in the study (LT) and one statistical specialist (SS).

This cross-sectional study will be performed in approximately 1 year and 3 months, and will be organized in the following stages:

- Preparation and coordination phase: 5 months.
- Field work and data collection: 4 months.
- Statistical analysis of data recollected and results evaluation: 3 months.
- Publication and dissemination: 3 months.

PHASE 1: PREPARATION AND COORDINATION PHASE

1. PROTOCOL DESIGN (**3 months**): during this first phase, hypothesis, objectives and protocol of the study will be designed. The SC will be in charge to initiate, manage and ensure the research of information and resources for the study.
2. COORDINATION OF DIFFERENT CENTRES INVOLVED IN THE STUDY (**1 month**): in this phase the research of different centres which may be involved in the study will be done. All the protocol will be discussed with the members of different centres to find the acceptance of all the procedures. At the end of this phase, the protocol will be present in the Clinical Research Ethics Committee of each centre which will evaluate and approve it.
3. MEETING 1: SC, Ped and SS will attend the first meeting in order to determinate the followed procedure in data collection phase and the task of each participant of the study.
4. FORMATION COURSE (**1 month**): a formation course will be given to the nurses unrelated to child care in the PER and to the paediatricians. The aim of this course is to let them know the followed procedure in each technique to obtain a valid urine specimen in order to make sure that there are no differences between

the procedures used in different centres of the study. This course will be done with an explanation notebook, some video sessions and with some practices.

PHASE 2: FIELD WORK AND DATA COLLECTION

5. STUDY AND DATA COLLECTION (**4 months**): patient recruitment and data collection of the urine culture's results of each patient. The duration of the study is estimated in 1 year and 3 months but its length can be modified if the sample needed isn't achieve with the estimated time. During this phase the following activities will be done:

    - Nur: application of techniques and obtaining of urine specimens. Data collection.

    - LT: analysis of the urine specimens and determination of the CFUs/ml of a pure growth pathogen. Data collection.

    - Ped: analysis of the laboratory results (number of CFUs/ml of a pure growth pathogen) and determination of positive or negative urine culture's results. Data collection.

6. MEETING 2 (**2 months after initiate data collection**) in this meeting, SC, Ped and SS will evaluate the results obtained until those moment and possible limitations of them.

PHASE 3: STATISTICAL ANALYSIS AND RESULTS EVALUATION

7. STATISTICAL ANALYSIS: it will be done by the SS. His/her tasks will be:

    - Monitoring and control of the quality of data during all the study.

    - Statistical analysis at the end of data collection (**2 months**): data from 310 patients will be analysed by the SS.

8. MEETING 3 (**after statistical analysis**): SC, Ped and SS will attend the last meeting in order to evaluate the results obtained in the statistical analysis. The aim will be the determination of significant differences of less than 10% between the positive urine cultures obtained with bladder catheterization and positive urine cultures obtained by bladder stimulation with midstream clean-catch urine in

order to conclude that bladder stimulation with midstream clean-catch urine may be considered as a Gold Standard technique to acquire valid and non-contaminant urine specimens in children up to 6 months of age.

PHASE 4: PUBLICATION AND DISSEMINATION

9. PUBLICATION OF THE RESULTS (**3 months**): SC will write and edit all the results obtained in the statistical analysis.

CHRONOGRAM:

STUDY PHASES	2016		2017												2018
	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J
PHASE 1: COORDINATION AND PREPARATION PHASE															
PROTOCOL DESIGN															
COORDINATION OF THE CENTRES															
MEETING 1															
FORMATION COURSE															
PHASE 2: FIELD WORK AND DATA COLLECTION															
DATA COLLECTION															
MEETING 2															
PHASE 3: STATISTICAL ANALYSIS AND RESULTS EVALUATION															
STATISTICAL ANALYSIS															
MEETING 3															
PHASE 4: PUBLICATION OF THE RESULTS															
RESULTS PUBLICATION															

11. BUDGET AND FESIABILITY

HUMAN RESOURCES

- The research team formed by paediatricians, nurses and laboratory technician is employed by the institution and it isn't required to work overtime, for this reason, these services aren't included in our budget.

- It is necessary a statistical specialist for the statistical analysis of the data collected by the research team. This statistical analyst will work part time and he/she will earns 35 €/h. It is estimated a time of 2 months to carry out this analysis, in which the statistical specialist will work 60h so we estimate a budget of 2.100 €.

- Monitoring and data quality control doing for the statistical specialist during 3 h/week between the three centres of the study (3 h/week) during the data collection time. We estimated 4 months of data collection so 16 weeks (48 h). The costs of the specialist work is 30 €/h so, we estimate a budget of 1.440 €.

MATERIAL AND SERVICES RESOURCES

- Ureteral catheters needed are estimated to be 320 (including some catheters more for possible defects). As the bladder catheterization is a technique used in the clinical practice of these hospitals we consider that their cost is supported by different hospitals.

- Collector urine systems are used in the clinical practice of the hospital, so different hospitals will support their cost.

- Material needed to realise a sterile cleaning of the genital area and a sterile procedure (soaps, chlorhexidine or povidone iodine, gloves, cotton or sauzes) are paid by the hospital budget.

- Extra milk needed to feed this children who are categorized in bladder stimulation and midstream clean-catch urine and who don't receive breastfeeding is already available in PER and it is funded by the hospital.

- Urine culture costs aren't taken account in this budget because it is considered as a needed practice whatever technique used.

- Other services which include the printing of information sheets, informed consents and collect data sheets have got an estimated cost of 50€.

- The price of formation course is estimated to be of 2.000€. It is paid 50 €/person for transport and meals. It is concluded that 30 persons will receive the formation course so it is needed 1.500€ to paid the personal. The equipment and space rental are at the expense of HUDJT. Professional services has got a cost of 500€.

- The costs of the meetings are of 50 €/person. In each meeting, it will participate three paediatricians (one of each centre), the study coordinator and the statistical specialist. For this reason, the estimated budget is 1000€.

PUBLICATION AND DISSEMINATION RESOURCES

- Publication costs are estimated in 2500€.

		COST
HUMAN RESOURCES	Statistical specialist	2.100 €
	Monitoring and data quality control	1.440 €
MATERIAL AND SERVICES RESOURCES	Formation course	2.000 €
	Meetings	750 €
	Other services	50 €
PUBLICATION RESOURCES	National and international journeys	2.500 €
		TOTAL: 8.840 €

12. CONFLICTS OF INTEREST

The authors of the study declare no conflicts of interest.

13. IMPACT

Invasive techniques are considered Gold Standard methods to obtain urine specimen of those children younger than 6 months of age and FWS to discard or confirm UTI as a possible cause of their fever. As invasive techniques, bladder catheterization and suprapubic bladder aspiration have got some complications in children in whom these procedures are performed. The presence of a new non-invasive technique which has been considered valid to obtain urine specimens from non-continent children make us to reconsider the possibility to change the Gold Standard technique (bladder catheterization in our media) for this procedure.

If we obtain positive results in our study, estimated to be a significant difference of less than 10% in the percentage of positive urine culture results in urine specimens acquired by bladder stimulation with midstream clean-catch urine and urine specimens acquired by bladder catheterization, we will be able to determinate that bladder catheterization can be substitute by bladder stimulation with midstream clean-catch urine as the Gold Standard technique to acquire non-contaminant urine specimens in febrile children up to 6 months of age in whom it is needed rule out a UTI as a possible cause of their fever.

This fact can bring many benefits for this children as a lower contamination rate (a decrease in the catheter infections prevalence and in the ureteral trauma prevalence) and also a decrease in the discomfort of the patient during this procedure.

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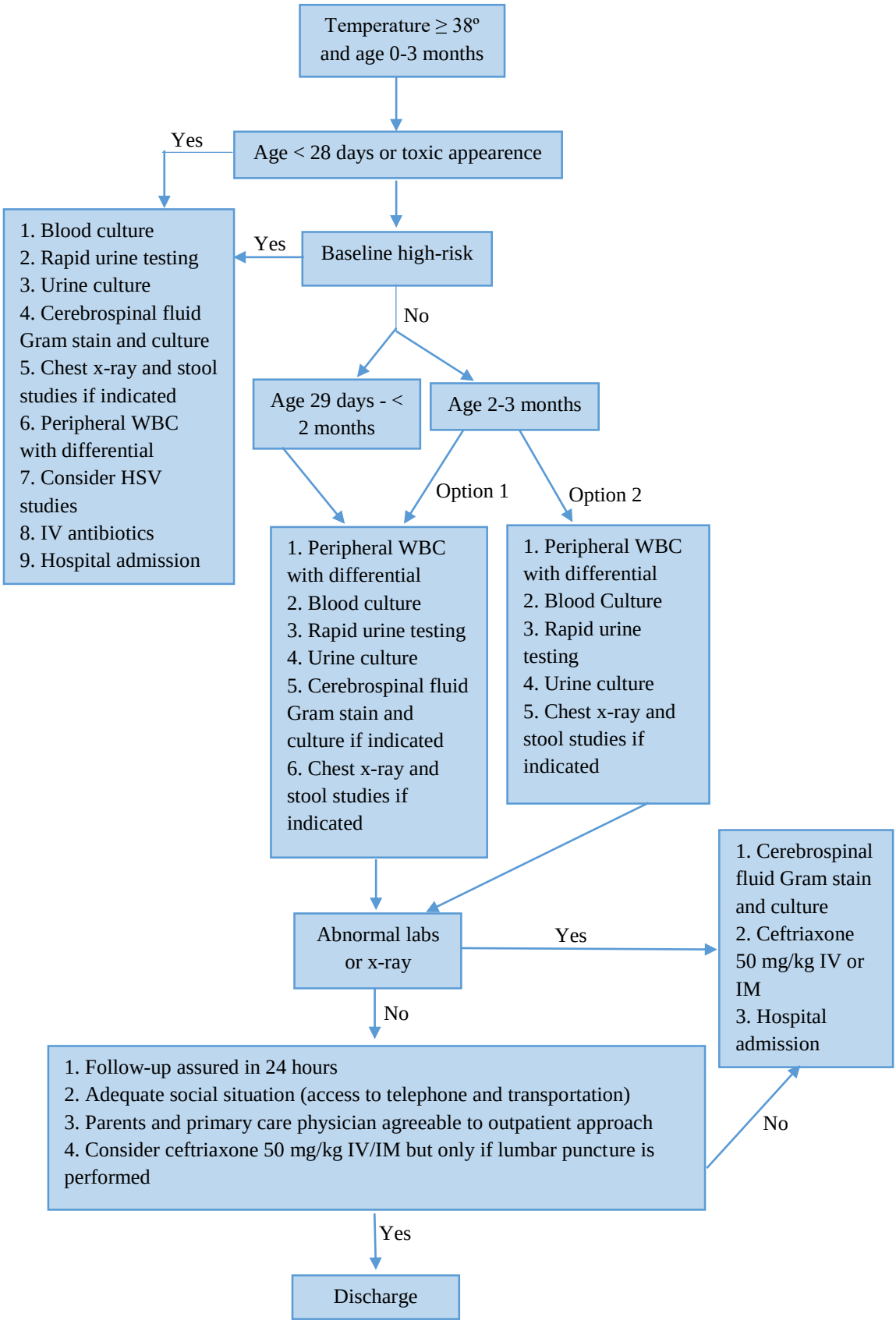
15. ANNEXS

ANNEX 1: UTI'S SYMPTOMATOLOGY ACCORDING TO THE AGE

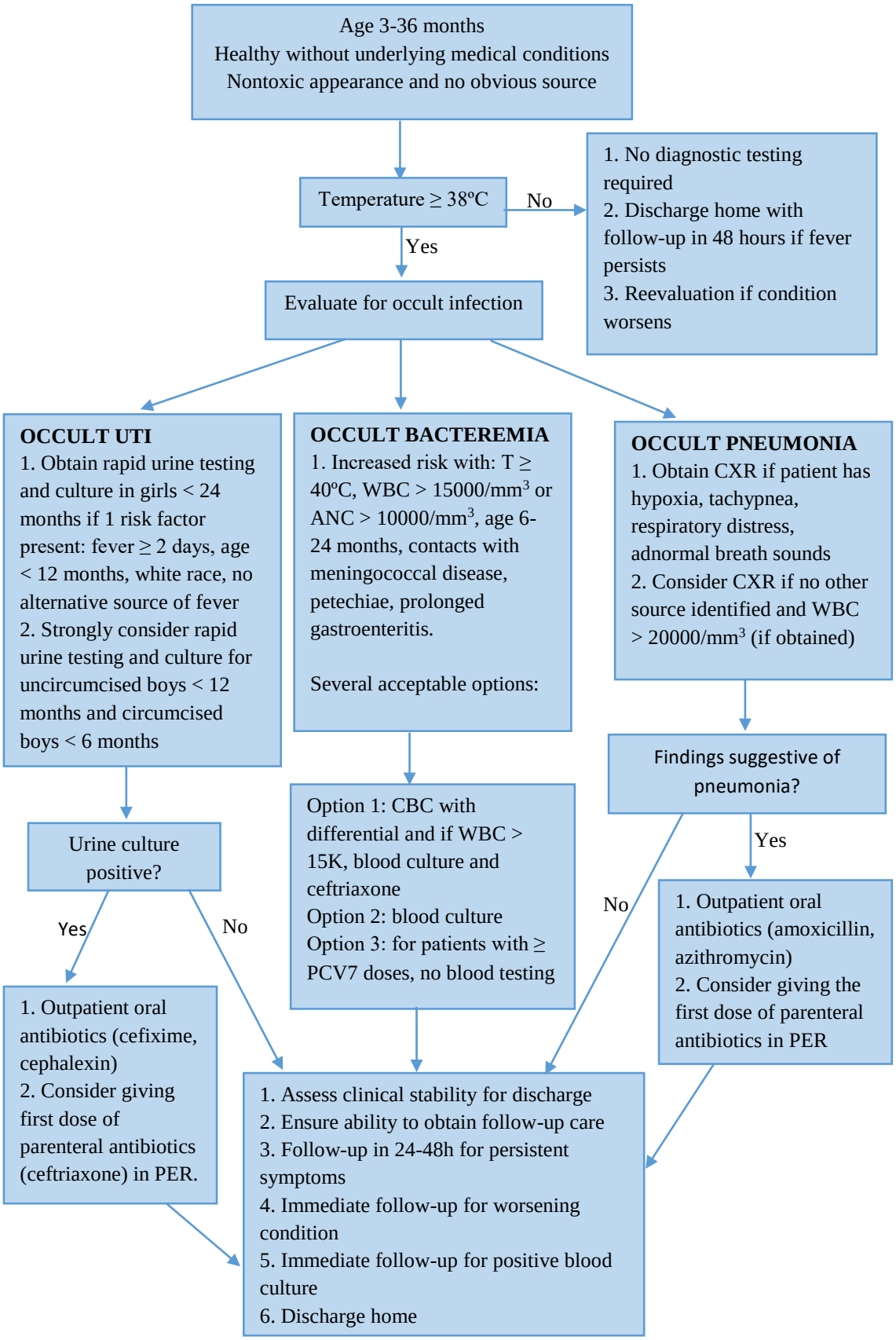
AGE GROUP		SYMPTOMS AND SIGNS MOST COMMON → LESS COMMON		
Children younger than 3 months		Fever Vomiting Lethargy Irritability	Poor feeding Failure to thrive	Abdominal pain Jaundice Haematuria Odour urine
Infants and children, 3 months or older	Preverbal	Fever	Abdominal pain Loin tenderness Vomiting Poor feeding	Lethargy Irritability Haematuria Odour urine Failure to thrive
	Verbal	Frequency Dysuria	Dysfunctional voiding Changes to continence Abdominal pain Loin tenderness	Fever Malaise Vomiting Haematuria Odour urine Cloudy urine

Table 5. Presenting symptoms and signs in infants and children with UTI. Adapted of 2007 NICE guideline: Urinary tract infection in children (21).

ANNEX 2: DIAGNOSIS PROCEDURE OF FWS IN CHILDREN YOUNGER 3 MONTHS OF AGE, ADAPTED FROM ISHIMINE'S STUDY (1)



ANNEX 3: DIAGNOSIS PROCEDURE OF FWS IN CHILDREN 3 TO 36 MONTHS OF AGE, ADAPTED FROM ISHIMINE'S STUDY (1)



ANNEX 4: INFORMATION SHEET

FULL INFORMATIU PELS TUTORS LEGALS DEL PACIENT

COMPARACIÓ ENTRE LA TÈCNICA D'ESTIMULACIÓ VESICAL AMB OTENCIÓ DE XORRO MIGF D'ORINA I LA TÈCNICA DEL SONDATGE VESICAL PER OBTENIR MOSTRES D'ORINA NO CONTAMINADES EN NENS DE FINS A 6 MESOS D'EDAT AMB FEBRE SENSE FOCUS

Estudi transversal multicèntric, en relació amb el maneig de dues proves diagnòstiques diferents per obtenir mostres d'orina, el cultiu de les quals permetrà descartar o confirmar una infecció del tracte urinari com a posible causa del síndrome febril en nens menors de 6 mesos. A cada una dels participants de l'estudi se'ls realitzaran les dues tècniques investigades en l'estudi per l'obtenció de mostres d'orina per a realitzar un cultiu d'orina.

Benvolgut,

Ens dirigim a vosté per convidar-lo a participar en un estudi de recerca que s'està portant a terme en el servei d'Urgències Pediàtriques de diferents hospitals de Catalunya, en relació amb el procés diagnòstic a seguir per descartar una infecció del tracte urinari en nens de fins a 6 mesos d'edat amb un síndrome febril sense focus evident d'infecció. Es pretén investigar si una tècnica no invasiva com és l'estimulació vesical amb obtenció de xorro mig d'orina, és igual d'eficaç que una tècnica invasiva com és el sondatge vesical, per obtenir mostres d'orina en infants de fins a 6 mesos d'edat.

Abans de prendre la decisió de participar o no en aquest estudi, és necessari que llegeixi i entengui el full informatiu següent en el qual s'especifiquen les principals característiques de l'estudi. Davant de qualsevol dubte que li pugui sorgir, pregunti al doctor que li convida a participar en aquest estudi.

Participació voluntària:

És important que prengui constància que participar en aquest estudi és voluntari i que pot no participar-hi sense que això interfereixi en l'activitat assistencial relacionada amb el pacient. Podrà canviar d'opinió o retirar el seu consentiment informat si ho desitja. En aquest full informatiu se li oferirà la informació necessària per a què pugui valorar la seva decisó adequadament.

Descripció de l'estudi:

Els professionals destinats a portar a terme aquest estudi són especialistes en pediatria, i concretament, especialistes en urgències pediàtriques.

L'estudi es realitzarà sobre una mostra de la població de nens menors de 6 mesos d'edat amb febre sense focus com a únic motiu de consulta i una tira d'orina positiva, realitzada en una mostra d'orina extreta mitjançant una bossa perineal, en els quals és necessari realitzar un cultiu d'orina a partir d'una mostra d'orina no contaminada. Per obtenir la mostra d'orina es disposa del sondatge vesical, tècnica invasiva considerada la més eficaç per aquest procediment. Actualment, ha sorgit una nova tècnica que permet obtenir mostres vàlides pel mateix procediment. Degut a aquest fet, aquest estudi proposa la substitució del sondatge vesical per una nova tècnica no invasiva com és l'estimulació vesical amb obtenció del xorro mig d'orina en la qual es minimitzen les complicacions que pot patir el pacient.

L'objectiu de l'estudi és comprovar si la tècnica del sondatge vesical pot ser substituïda per una tècnica menys invasiva com podria ser l'estimulació vesical amb obtenció del xorro mig d'orina, demostrant la mateixa eficàcia per les dues tècniques estudiades.

Procediment seguit:

En cada participant de l'estudi es realitzarà l'obtenció de dues mostres d'orina, la primera s'obtindrà a partir de la tècnica d'estimulació vesical amb obtenció de xorro mig d'orina i, al cap de 45 minuts, s'obtindrà l'altra mostra d'orina a partir de la tècnica del sondatge vesical.

Al cap de 24h, s'analitzaran els resultats obtinguts dels cultius de les dues mostres d'orina realitzats al laboratori de l'hospital per confirmar o descartar el diagnòstic d'infecció del tracte urinari.

Interrupció de l'estudi:

Qualsevol participant podrà abandonar l'estudi quan ho consideri oportú o necessari, ja sigui per motius personals o mèdics, per patir esdeveniments adversos greus o bé si no es compleixen els principis ètics del Reial Decret 223/2004.

Qualsevol desig d'interrupció de la seva participació en l'estudi haurà de ser comunicat al doctor/a que li ha ofert participar en aquest.

Beneficis:

Esperem poder determinar la substitució d'una tècnica invasiva per la obtenció de mostres d'orina no contaminades en el lactant menor de 6 mesos d'edat per una tècnica no invasiva com és l'estimulació vesical amb obtenció de xorro mig per tal de poder evitar les complicacions generades per la invasivitat de la citada tècnica (sondatge vesical).

Riscos:

En cas que alguna de les tècniques estudiades no es pugui realitzar correctament per les condicions prèvies del pacient o per problemes durant el seu procediment, es procedirà a realitzar una altra tècnica per a la obtenció de la mostra assegurant sempre el benestar del pacient.

Responsabilitat:

El doctor que convida a la participació de l'estudi es farà responsable de qualsevol inconvenient que pugui sorgir durant la seva realització així com també dels possibles danys ocasionats a les persones que hi participen d'acord amb la legislació vigent.

Confidencialitat:

Tota la informació recollida sobre els participants d'aquests estudi serà confidencial i en cap cas apareixerà la seva identitat en la publicació dels resultats d'acord amb la Llei Orgànica 15/1999 sobre Protecció de Dades Personals i el corresponent Reial Decret Nacional 1720/2007.

Compensació econòmica:

La participació en aquest estudi no serà beneficiària de cap compensació econòmica.

Consentiment informat:

En el cas de que vostè prengui la decisió de participar en aquest estudi, haurà de firmar el següent consentiment informat per tal d'evidenciar que coneix les diferents condicions esmentades en aquest full informatiu i que les accepta.

HOJA INFORMATIVA PARA LOS TUTORES LEGALES DEL PACIENTE

COMPARACIÓN ENTRE LA TÉCNICA DE ESTIMULACIÓN VESICAL CON OTENCIÓN DE CHORRO INTERMEDIO DE ORINA Y LA TÉCNICA DEL SONDAJE VESICAL PARA OBTENER MUESTRAS DE ORINA NO CONTAMINADAS EN NIÑOS DE HASTA 6 MESES DE EDAD CON FIEBRE SIN FOCO

Estudio transversal multicentrico, en relación con el manejo de dos pruebas diagnòsticas diferentes para obtener muestras de orina, el cultivo de las cuales permitirá descartar o confirmar una infección del tracto urinario como posible causa del síndrome febril en niños menores de 6 meses. A cada uno de los participantes del estudi se le realizaran las dos técnicas investigadas para la obtenció de muestras de orina para realizar un cultivo de orina.

Estimado,

Nos dirigimos a usted para invitarle a participar en un estudio de investigación que se está llevando a cabo en el servicio de Urgencias Pediátricas de diferentes hospitales de Cataluña, en relación con el proceso diagnóstico a seguir para descartar una infección del tracto urinario en niños de hasta 6 meses de edad con un síndrome febril sin foco evidente de infección. Se pretende investigar si una técnica no invasiva como es la estimulación vesical con obtención de chorro medio de orina, es igual de eficaz que una técnica invasiva como es el sondaje vesical, para obtener muestras de orina en niños de hasta 6 meses de edad.

Antes de tomar la decisión de participar o no en este estudio, es necesario que lea y entienda la hoja informativa siguiente en el que se especifican las principales características del estudio. Ante cualquier duda que le pueda surgir, pregunte al doctor que le invita a participar en este estudio.

Participación voluntaria:

Es importante que tome constancia de que participar en este estudio es voluntario y que puede no participar sin que ello interfiera en la actividad asistencial relacionada con el paciente. Podrá cambiar de opinión o retirar su consentimiento informado si lo desea. En esta hoja informativa se le ofrecerá la información necesaria para que pueda valorar su decisión adecuadamente.

Descripción del estudio:

Los profesionales destinados a llevar a cabo este estudio son especialistas en pediatría, y concretamente, especialistas en urgencias pediátricas.

El estudio se realizará sobre una muestra de la población de niños menores de 6 meses de edad con fiebre sin foco como único motivo de consulta y una tira de orina positiva, realizada en una muestra de orina extraída mediante una bolsa perineal, en los que es necesario realizar un cultivo de orina a partir de una muestra de orina no contaminada. Para obtener la muestra de orina estéril se dispone del sondaje vesical, técnica invasiva considerada la más eficaz para este procedimiento. Actualmente, ha surgido una nueva técnica que permite obtener muestras válidas para el mismo procedimiento. Debido a este hecho, este estudio propone la sustitución del sondaje vesical por una nueva técnica no invasiva como es la estimulación vesical con obtención del chorro medio de orina en la cual se minimizan las complicaciones que puede sufrir el paciente.

El objetivo del estudio es comprobar si la técnica del sondaje vesical puede ser sustituida por una técnica menos invasiva como podría ser la estimulación vesical con obtención del chorro medio de orina, demostrando la misma eficacia por las dos técnicas estudiadas.

Procedimiento seguido:

A cada participante del estudio se le realizará la obtención de dos muestras de orina, la primera se obtendrà a partir de la técnica d'estimulación vesical con obtención del chorro medio de orina i, 45 minutos después, se obtendrà otra muestra de orina a partir de la técnica del sondaje vesical.

Al cabo de 24h, los pediatras encargados del estudi analizaran los resultados obtenidos de les cultivos de las dos muestras de orina realizados en el laboratorio del hospital para confirmar o descartar el diagnóstico de infección del tracto urinario.

Interrupción del estudio:

Cualquier participante podrá abandonar el estudio cuando lo considere oportuno o necesario, ya sea por motivos personales o médicos, por sufrir acontecimientos adversos graves o bien si no se cumplen los principios éticos del Real Decreto 223/2004.

Cualquier deseo de interrupción de su participación en el estudio deberá ser comunicado al doctor/a que le ha ofrecido participar en éste.

Beneficios:

Esperamos poder determinar la sustitución de una técnica invasiva para la obtención de muestras de orina no contaminadas en el lactante menor de 6 meses de edad por una técnica no invasiva como es la estimulación vesical con obtención de chorro medio para poder evitar las complicaciones generadas por la técnica invasiva (sondaje vesical).

Riesgos:

En el caso de que alguna de las técnicas estudiadas no se pueda realizar correctamente por las condiciones previas del paciente o por problemas durante su procedimiento, se procederá a realizar otra técnica para la obtención de la muestra asegurando siempre el bienestar del paciente.

Responsabilidad:

El doctor que invita a la participación del estudio se hará responsable de cualquier inconveniente que pueda surgir durante su realización así como también de los posibles daños ocasionados a las personas que participan de acuerdo con la legislación vigente.

Confidencialidad:

Toda la información recogida sobre los participantes de este estudio será confidencial y en ningún caso aparecerá su identidad en la publicación de los resultados de acuerdo con la Ley Orgánica 15/1999 sobre Protección de Datos Personales y el correspondiente Real Decreto Nacional 1720/2007.

Compensación económica:

La participación en este estudio no será beneficiaria de compensación económica.

Consentimiento informado:

En el caso de que usted tome la decisión de participar en este estudio, deberá firmar el siguiente consentimiento informado para evidenciar que conoce las diferentes condiciones mencionadas en esta hoja informativa y que las acepta.

ANNEX 5: INFORMED CONSENT

CONSENTIMENT INFORMAT

COMPARACIÓ ENTRE LA TÈCNICA D'ESTIMULACIÓ VESICAL AMB OTENCIÓ DE XORRO MIG D'ORINA I LA TÈCNICA DEL SONDATGE VESICAL PER OBTENIR MOSTRES D'ORINA NO CONTAMINADES EN NENS DE FINS A 6 MESOS D'EDAT AMB FEBRE SENSE FOCUS

Jo (nom i cognoms) _____ en qualitat de _____ (relació amb el participant) de _____ (nom i cognoms del participant):

- He llegit el full informatiu de l'estudi que se m'ha entregat.
- He pogut resoldre dubtes sobre l'estudi en qüestió.
- He rebut informació adequada i correcte sobre l'estudi a realizar.
- He corroborat la informació donada amb l'investigador _____ (nom de l'investigador).
- He entès que la participació en aquest estudi és en tot moment voluntària.
- Entenc que puc retirar el meu consentiment de participació sempre que ho desitgi, sense necessitat d'explicacions i sense que tingui repercussions en l'assistència clínica del participant de l'estudi, informant sempre de la decisió a l'investigador que m'ha convidat a participar en dit estudi.

Dono la meva conformitat per tal que _____ (nom del participant) participi en l'estudi realitzat i dono el consentiment per tal que es pugui tenir accés i es puguin utilitzar les seves dades segons les condicions esmentades en el full d'informació realitzat pels tutors legals del pacient.

FIRMA DEL REPRESENTANT LEGAL FIRMA DE L'INVESTIGADOR

DATA: DATA:

CONSENTIMIENTO INFORMADO

COMPARACIÓN ENTRE LA TÉCNICA DE ESTIMULACIÓN VESICAL CON OTENCIÓN DE CHORRO INTERMEDIO DE ORINA Y LA TÉCNICA DEL SONDAJE VESICAL PARA OBTENER MUESTRAS DE ORINA NO CONTAMINADAS EN NIÑOS DE HASTA 6 MESES DE EDAD CON FIEBRE SIN FOCO

Yo (nombre y apellidos) _____ en calidad de _____ (relación con el participante) de _____ (nombre y apellidos del participante):

- He leído la hoja informativa del estudio que se me ha entregado.
- He podido resolver mis dudas sobre el estudio en cuestión.
- He recibido información adecuada y correcta sobre el estudio a realizar.
- He corroborado la información dada con el investigador _____ (nombre del investigador).
- He entendido que la participación en este estudio es en todo momento voluntaria.
- Entiendo que puedo retirar mi consentimiento de participación siempre que lo desee, sin necesidad de explicaciones y sin que tenga repercusiones en la asistencia clínica del participante, informando siempre de la decisión al investigador que me ha invitado a participar en dicho estudio.

Doy mi conformidad para que _____ (nombre del participante) participe en el estudio realizado y doy el consentimiento para que se pueda tener acceso y se puedan utilizar sus datos según las condiciones nombradas en la hoja de información realizada para los tutores legales del paciente.

FIRMA DEL REPRESENTANTE LEGAL FIRMA DEL INVESTIGADOR

FECHA: FECHA:

ANNEX 6: RESEARCHER'S COMMITMENT FORM

RESEARCHER'S COMMITMENT

Dr./Mr./Mrs.: _____

Service:

Centre:

Exposes:

I have read and evaluated the protocol of this prospective cross-sectional study titled: *comparison between bladder stimulation with midstream clean-catch urine and bladder catheterization to obtain non-contaminant urine specimens in febrile children up to 6 months of age.*

Referring to this study:

- This cross-sectional study respects ethical principles, according to good clinical practice recommendations which are exposed in the Declaration of Helsinki of Ethical Principle for Medical Research Involving Human Subjects and to the legal normative applicable.
- I agree to participate as a researcher of my centre in this cross-sectional study.
- I have all the material and human resources which are needed to carry out the cross-sectional study in my centre.
- I conclude that my participation in this study won't affect the performance of other studies carrying out in my centre or my usual duties.

DATES: ___/___/20___

ANNEX 7: CASE REPORT FORM

CASE REPORT FORM FOR THE STUDY: *comparison between bladder stimulation with midstream clean-catch urine and bladder catheterization to obtain non-contaminant urine specimens in febrile children up to 6 months of age.*

PARTICIPANT CODE: _____

- Patient's age (months): _____
- Gender: Female ☐ Male ☐
- Date and time of admission at PER: __/__/____ at __:__
- Signed consent: Yes ☐ No ☐

BLADDER STIMULATION WITH MIDSTREAM CLEAN-CATCH URINE

- Failed procedure: Yes ☐ No ☐
- Time needed to obtain urine sample (seconds): _____
- Material needed doing the procedure: _____ _____
- Complications related with the procedure:
  - Falling of the child: Yes ☐ No ☐
- Urine culture's result: Positive ☐ Negative ☐
- Contaminated sample: Yes ☐ No ☐

BLADDER CATHETERIZATION

- Failed procedure: Yes ☐ No ☐
- Time needed to obtain urine sample (seconds): _____

- Material needed doing the procedure: _____ _____

- Complications related with the procedure:
  - Ureteral trauma: Yes ☐ No ☐
  - Catheter infection: Yes ☐ No ☐
- Urine culture's result: Positive ☐ Negative ☐
- Contaminated sample: Yes ☐ No ☐