Non-Invasive Urine Sampling in Infants: A Review Paper

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Abstract

Good quality urine samples play a crucial role in establishing an early and accurate diagnosis of urinary tract infection in infants. Invasive methods are more reliable but cause pain and discomfort in infants as well as anxiety in clinicians and parents. The current available non-invasive methods are less efficient and produce low quality urine samples being less apprehensive in infants and parents. To date, no studies have been conducted in South East Asia, including Malaysia, to identify the most feasible non-invasive urine sampling method. This literature review aimed to compare various non-invasive urine sample collection methods (bladder stimulation techniques, standard clean-catch urine, urine collection pads and urine bags) which could be more feasible for a district hospital setting in Malaysia. In total, 17 studies were included and reviewed. This review concluded that bladder stimulation techniques are potentially good and feasible alternatives to the current common practices in Malaysia (standard clean-catch urine and catherization) due to its high success rate, fast collection and low contamination rate. There is a higher likelihood to implement these techniques in a tertiary setting if further research on bladder stimulation techniques is found feasible in a less resourceful district hospital setting.

Subject Areas

Pediatrics

Keywords

Infants, Urinary Tract Infection, Urine Specimen Collection

1. Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections among infants, with a prevalence of 5% - 7% in children below age 24 months with a fever of unknown source [1] [2] [3] [4] [5]. Infants are at higher risk in the first few months of life due to their immune system, that is, not fully developed [6]. The prevalence and incidence of UTI are higher among boys during the first three months and higher among girls during the first year of life [5] [6]. In boys without circumcision, an increase in the frequency of UTI is noted, with a risk of developing UTI is 10 to 12 times higher during the first six months of life [6]. Circumcision has shown a protective effect by reducing the odds of UTI by 85% [7]. It is essential to identify febrile infants with UTI as they often present with non-specific symptoms, typically an unexplained high fever [1] [8]. An accurate diagnosis of UTI requires a good quality urine sample for urine culture and other screening tools. With an early accurate diagnosis, treatment can be initiated as soon as possible, meanwhile avoiding unnecessary therapies [3] [9] [10]. Early diagnosis is crucial to prevent progression to chronic complications such as pyelonephritis leading to renal scarring, renal failure, and hypertension [1] [5] [9] [11] [12].

Urine sample collection methods in infants are commonly classified as non-invasive and invasive. Examples of non-invasive methods are urine bag, clean-catch urine (CCU) and urine collection pads; and the invasive methods, namely catheterization and suprapubic aspiration (SPA). These methods are quoted in the Paediatrics Protocol for Malaysian Hospitals, Clinical Practice Guidelines of the Royal Children's Hospital (RCH) in Australia, National Institute for Health and Care Excellence (NICE), and American Academy of Paediatrics (AAP) [13] [14] [15] [16]. In all four guidelines, urine bag collection is the least recommended due to its high contamination rate. Paediatrics Protocol, RCH and NICE recommend CCU as the first-line method [13] [14] [15]. Only NICE considered urine collection pads in their guideline as to the second alternative for a non-invasive method before proceeding to make an attempt with invasive methods [15]. Invasive methods are more preferred for obtaining a clean and reliable sample [6]. However, these techniques cause pain, have higher the risk of complications, and may cause distress in parents [17]. Catheterization has a sensitivity of 95% and specificity of 99% as compared to SPA [13] [16], and the contamination rate as low as 10% [14]. SPA is known as the "gold standard" in both Paediatrics Protocol and the RCH guidelines [13] [14]. It yields the most reliable sample and lowest contamination rate of 1%, at the same time, it is the most technically challenging method [6] [14].

Mamta *et al.* (2019) stated that invasive methods have a high failure rate in newborns due to their anatomical characteristics and irregular voiding pattern [18]. In the AAP guideline, the urine sample collection method is determined clinically. If a febrile infant is in a very ill condition, highly suspected for UTI and requires immediate antimicrobial therapy, urine samples must be collected

via catheterization or SPA. Urine culture ordered before administration of antimicrobial therapy is crucial so that a definitive diagnosis of UTI can be established, and this is to prevent a missed diagnosis leading to long term sequelae if untreated, or an overdiagnosis causing overtreatment in infants. Urine samples collected via urine bag will not be able to confirm a diagnosis of UTI due to its high false-positive rate of 88%, which is not reliable [16]. A midstream CCU sample is more challenging to obtain from infants below the age of two as compared to older children who are toilet trained and can void voluntarily. Children are developmentally ready for toilet training between 18 months to 2.5 years old [19].

Fernandez-Herreros *et al.* (2013) proposed a new technique that incorporates bladder stimulation manoeuvres to facilitate the collection of CCU samples. Infants will receive a bladder stimulation via gentle tapping at the suprapubic area, followed by stimulation of the lumbar paravertebral zone with a light circular massage given at the lower back. The study showed a high success rate, fast sample collection, and no complications occurred with this new technique [20]. Many studies have been carried out on bladder stimulation techniques [1] [2] [4] [8] [9] [10] [11] [17] [18] [20] [21] [22]. Based on these available studies, bladder stimulation techniques manifested a good potential as a practical alternative to the two widely practiced methods in the current clinical setting in Malaysia, *i.e.* standard CCU that is time-consuming and catheterization that is relatively more invasive to infants. Nevertheless, insufficient data is available to evaluate its feasibility in a Malaysia clinical setting as no relevant studies were conducted yet in South East Asia, including Malaysia itself.

That is why this literature review has been conducted aiming to compare various non-invasive urine sample collection methods which could be more feasible for a district hospital setting in Malaysia. The non-invasive methods to be studied are standard CCU (without any additional stimulation), bladder stimulation techniques, urine collection pads, and urine bag.

2. Methods

The two databases, Google Scholar (n = 257) and PubMed (n = 206), were used in searching and identifying potential studies published from 2002 to 2020. The Medical Subject Headings (MeSH) terms "infants" AND "urinary tract infection" AND "urine specimen collection" were used to search relevant studies, generating 463 search results. Duplicates articles were removed by using Endnote citation manager software and narrowing the search results to 114 studies. Titles and abstracts of articles in the initial search results were screened according to inclusion and exclusion criteria, leaving 31 studies eligible. Following that, full-text articles of eligible studies were retrieved and further assessed. Finally, 17 studies (as shown in Figure 1 and Table 1) were included and data were extracted based on three major variables (success rate, sample collection time and contamination rate) for the analysis in this literature review.
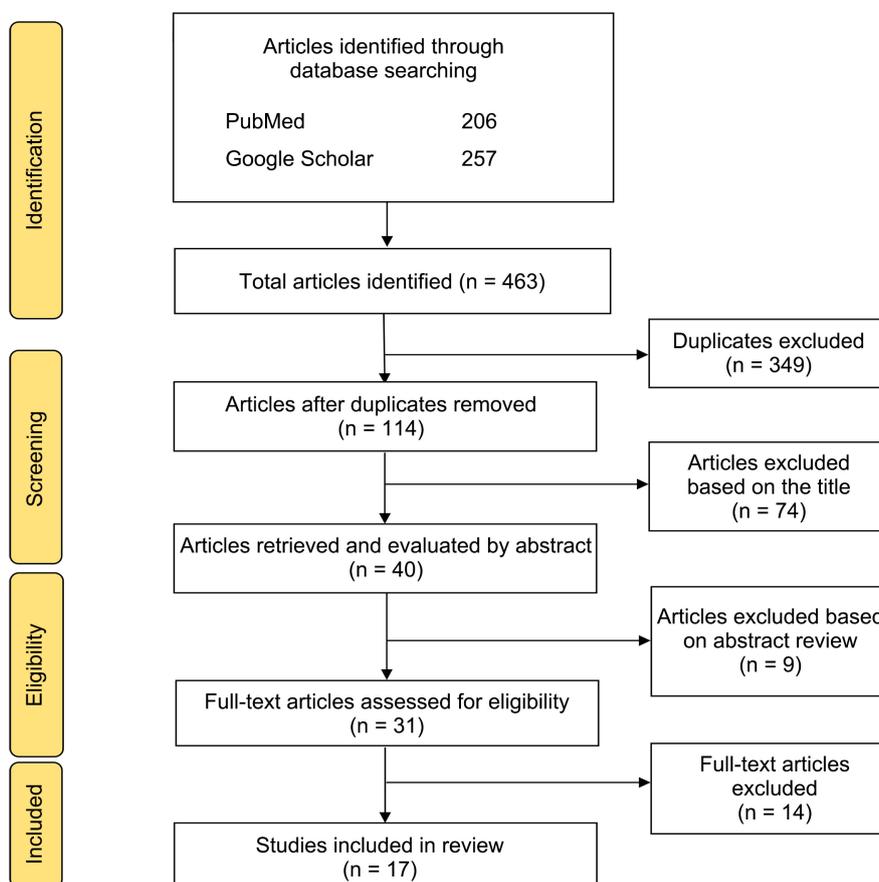
Figure 1. PRISMA chart used for the selection of articles.

Studies involved children aged below 24 months or 2 years, compared to any non-invasive urine sample collection methods and published in English were included in this literature review. There was no restriction for study design; any study reported one of the following outcomes was included: success rate of urine sample collection, time taken for urine sample collection, and contamination rate. Exclusion criteria were adult age group, non-English reports, only comparing invasive urine sample collection methods, and none of the above outcomes measured.

While extracting data, MPLC and NKJ[1] worked independently as the main reviewers. They extracted data in a standardized form (Table 1) which included the following information: study information like list of authors, country and year of publication, study design and sample size, main study findings and conclusion. This form was specifically developed for this review purpose in order to minimize human errors and biases. The third reviewer, either CGY or NKP[2], contributed when the main reviewers could not come to a general agreement. The whole review process was monitored and supervised by INCbS and YCY[3] to ensure the quality.

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Table 1. List of selected articles which are included in review with the main findings and conclusion.

Study; Country; Year of Publication [Reference no]	Type of study or study design	Sample size	Main findings	Conclusion
Chandy *et al.*; UK; 2020 [1]	Systematic review	NA	• Out of three randomised controlled trials (RCTs), two demonstrated an increased success in voiding within 5 min using stimulation techniques; third RCT using a mechanical vibration device demonstrated no difference in time to voiding from advice alone. • Non-randomised studies compared different temperatures for the gauze intervention and tapping alone versus urine bags. • Six uncontrolled studies tested the finger tapping and massage technique.	• Positive effect of stimulation techniques • Lack of replication in rigorous RCTs and heterogeneity of techniques and outcomes assessed prevent conclusive recommendations being made. • Further RCTs required comparing non-invasive stimulation methods and assessing time to successful collection, contamination rates, adverse effects, caregiver and clinical staff acceptability.
Labrosse *et al.*; Canada; 2016 [2]	Prospective cohort study	126	• CCU procedure was effective in 62 infants. • Infants 0 to 29 days; 30 to 59 days, and 60 to 89 days had more successful procedures, compared with infants >89 days. • 16% of contamination in the CCU group - not statistically different compared with the invasive method group.	• CCU procedure is a quick and effective non-invasive method in children aged <90 days. • Contamination proportions were similar to those reported in the literature for urethral catheterization.
Karacan *et al.*; Turkey; 2010 [3]	Observational study	1067	• Initial urine culture found 617 (57.8%) had negative culture results, 145 (13.6%) had positive culture results, and 305 (28.6%) had evidence of bacterial contamination. • CCU specimens showed a contamination rate of 14.3% and urethral catheterization specimens showed a similar contamination rate (14.3%). • Urethral catheterization was preferred in only a small number of cases (n = 7). • SPA was used in a small number of cases (n: 11) and the contamination rate for SPA was 9.1% (n: 1/11). • Significantly higher contamination rate for sterile urine bag (43.9%) than the other methods (p < 0.001).	• SPA showed the lowest contamination rate and sterile urine bag showed the highest contamination rate • Contaminated specimens, needed to be repeated and this procedure increased the cost of urine culture • Measures should be taken to reduce the contamination rate - an area where further investigation is required.
Kaufman *et al.*; Australia; 2017 [4]	Randomized controlled trial	344	• Quick-Wee method has significantly higher rate of voiding within five minutes compared with standard CCU (31% v 12%, P < 0.001). • Quick-Wee had a higher rate of successful urine sample collection and greater parental and clinician satisfaction. • No statistically significant difference in contamination between Quick-Wee and standard CCU (27% v 45%, P = 0.29). • Number needed to treat was 4.7 (95% confidence interval 3.4 to 7.7) to successfully collect one additional urine sample within five minutes using Quick-Wee compared with standard CCU.	• Quick-Wee is a simple cutaneous stimulation method that significantly increases the five-minute voiding and success rate of CCU collection.

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Tran *et al.*; France; 2016 [8]	Cross-sectional study	142	• CCU collected in 55.6% of infants with a median time of 52.0 s. • Success rate decreased with age from 88.9% (newborn) to 28.6% (>1 y) (p = 0.0001) and with weight, from 85.7% (<4 kg) to 28.6% (>10 kg) (p = 0.0004). • Success rate was 60.8% for infants without discomfort (p < 0.0001). • Heavy weight and discomfort associated with failure, with adjusted ORs of 1.47 [1.04 - 2.31] and 6.65 [2.85 - 15.54] respectively.	• Bladder stimulation seems to be efficient in obtaining midstream urine with a moderate success rate in our study sample. • A good alternative for infants before potty training. • Further randomized multicenter studies needed to validate this procedure.
Herreros *et al.*; Spain; 2018 [9]	Comparative diagnostic accuracy study	60	• A combined analysis of leukocyte esterase and, or, nitrites yielded a sensitivity of 86% and a specificity of 80% for the diagnosis of UTIs in CCU samples. • No statistical difference in samples obtained by catherization to the CCU samples for sensitivity of leukocyte esterase and, or, nitrites (p = 0.592).	• Urine dipstick tests using urine samples obtained by the CCU method was an accurate screening test for diagnosing UTIs in febrile infants of less than 90 days old. • A good alternative to bladder catherization when screening for UTIs.
Valleix-Leclerc et al; France; 2016 [10]	Prospective non-controlled study	48	• The procedure was successful in 27% of the cases overall but reached 46% for children aged less than 3 months. • Elevated weight was associated with failure of the procedure.	• Despite promising results in newborns, the cutaneous stimulation technique to provoke micturition appears to encounter limitations in older children. • The technique is still an attractive alternative to urethral catheterization or SPA for infants younger than 3 months.
Kumar & Nithin; India; 2019 [11]	Prospective bedside clinical study	120	• Success rate in obtaining a midstream urine sample within 5 min was 90%. • The mean time taken to collect urine was 64.24s, for males it was 62.55s and for females 65.93s.	• The technique has been demonstrated to be safe, quick and effective. • Discomfort and time consumption usually associated with bag collection methods as well as invasive techniques can be avoided.
Kapoor & Mekle; India; 2017 [17]	Parallel, single centre, non-blinded, randomized controlled trial	120	• New technique was successful in 88.3% neonates. • Median time for sample collection was 55 seconds and Inter Quartile Range (IQR) of 40 seconds. Mean time for sample collection was 61.76 + 43.62 sec. • In control group, success rate was seen in 86.67% patients. • Median time for urine collection by bag was 70 min and IQR of 25 min and mean time of 68.7 + 20.45 min. • Statistically significant difference (p < 0.001) of median time taken for urine collection among study and control group (55 seconds versus 70 minutes respectively)	• External bladder stimulation is an effective, fast, non-invasive and safe method of urine sample collection in neonates which avoids long waiting time required by bag collection

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Mamta *et al.*; Nepal; 2019 [18]	Experimental study	54	• Success rate of urine collection was ignificantly higher in the experimental group (88.88%) than in the control group (25.92%) p < 0.001. • Median time for sample collection was 1.07 minutes (64.2s) [IQR = 1.52 minutes (91.2s)] in experimental group and 1.52 minutes (91.2s) [IQR = 2.78 minutes (166.8s) for control group (p = 0.069) • Contamination was not found in urine samples collected by bladder & lumbar stimulation techniques in experimental group.	• Bladder and lumbar stimulation technique is safe, quick and effective way of collecting midstream clean catch urine in newborns.
Fernández *et al.*; Spain; 2013 [20]	Prospective feasibility and safety study	80	• Bladder and lumbar stimulation manoeuvres were successful in 86.3% of infants. • Median time to sample collection was 45s (IQR 30). • No complications other than controlled crying were observed.	• A new, quick and safe technique with a high success rate is described, • Discomfort and waste of time usually associated with bag collection methods can be avoided.
Hall-Million & Howard; US; 2017 [21]	Prospective study	344	• Intervention (Quick Wee) group showed a greater incidence of voiding within 5 min (31%) than the usual care group (12%). • Successful specimen collection occurred in 30% of infants in the intervention group compared with only 9% of infants in the usual care group (p < 0.001) • No statistically significant difference in specimen contamination between the two groups (p = 0.29). • Parental and health care professional satisfaction with the non-invasive specimen collection method was supported (p < 0.001).	• The results of this study support the usefulness of the Quick Wee method in efficient specimen collection and parent and health care professional satisfaction with the non-invasive process
Altuntas *et al.*; Turkey; 2015 [22]	Randomized controlled study	127	• Success rate of urine collection was significantly higher in the experimental group (78%) than in the control group (33%; p < 0.001). • Median time (interquartile range) for sample collection was 60 s (64.5 s) in the experimental group and 300 s (95 s) in the control group (p < 0.0001). • Contamination rates were similar in both groups (p = 0.770).	• Bladder stimulation and lumbar paravertebral massage is a safe, quick, and effective way of collecting midstream clean-catch urine in newborns.
Alam *et al.*; Brazil; 2005 [23]	Cross-sectional study	191	• Twelve children (6.3%) were considered to have true urinary tract infection, three were indeterminate and in 16 one or more samples were missing and all were excluded from analysis. • There were more missing samples using the CCU method (12%) than when using the bag (4%) or pad (4%). • Seventy-six of 160 (47.5%) children had evidence of bacterial contamination. • CCU specimens showed the least contamination (14.7%) and rates were similar between pads (29%) and bags (26.6%) (κ = 0.40). • Urine contamination rates were similar for sanitary pads and urine bags and significantly higher than for CCU (p < 0.01).	• CCU specimens showed least contamination than pads and bags which had the similar rate. • Pads were however a simple, non-invasive and comfortable alternative to bags.

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Rao *et al.*; UK; 2004 [24]	Randomized clinical trial	68	• 37 children in the single urine collection pad group and 31 in the replaced urine collection pad group. • In 12 children (15%), collection failed mainly because of faecal soiling of the pad. • UTI occurred in three children (4%). • Remaining 65 samples showed heavy mixed growth (>105 organisms/ml), occurred in 1/31 (3%) in the replaced urine collection pad group compared with 10/35 (29%) in the single urine collection pad group (p = 0.008) • No adverse effects from the use of the moisture sensitive audio alarm.	• Changing the urine collection pad every 30 minutes almost eliminates heavy mixed growth contamination of urine collection pad samples and substantially increases the proportion of UCP results that confidently exclude UTI. • This suggests a simple and clinically important improvement to the urine collection pad method which is reliable for diagnosing and excluding UTI in young children still in nappies • Urine collection pad has potential for use in outpatient clinics, in the primary healthcare setting, or at home.
Farrell *et al.*; UK; 2002 [25]	Pilot, method comparison study	20	• Despite concurrent samples there was a lack of agreement between bag and pad specimens on both main outcome measures. • Poor agreement between bag and pad specimens for the presence of WBC yielded a κ = 0.10 (95% CI: 0.19, 0.39) • Moderate agreement in bacterial growth where κ = 0.5 (95% CI: 0.12, 0.88) was calculated • Insignificant differences in proportions of the presence of WBC between bag and pad - 0.2 (95% CI: 0.00, 0.42, P = 0.062). • Cultures difference was calculated as 0.15 (95% CI: 0.05, 0.35, P = 0.125).	• Concurrent urine samples can be obtained without difficulty. • Despite poor to moderate agreement on outcome measures, the level of agreement is greater than reported in those other studies • Advantage of concurrent technique using non-current methods of urine collection • Larger scale studies to be undertaken using the concurrent collection technique to assess reliability of these findings.
Li *et al.*; Hong Kong; 2002 [28]	Cross sectional study	100	• Out of the 40 patients, 23 produced negative results in second urine collection and 17 produced positive results, where 5 out of 17 patients were confirmed with UTI. • False positive rate on first urine collection was 36.8%. • Patients with contaminated urine were found associated with waiting for more than one void to complete urine collection, and with uncircumcised boys as compared to those with negative results. • Proper counselling and repeating a second culture reduced the overall false-positive rate to 12.6%.	• Unacceptably high contamination rate of one bag urine culture (36.8%) which alternative methods • Contamination was associated with improper collection procedures and with uncircumcised boys. • Proper instructions and doing a second urine culture reduced the overall rate to 12.6%, but at the expense of delaying diagnosis and treatment.

3. Results

We included 17 studies in this review, and extracted data were grouped based on the outcomes (success rate, sample collection time and contamination rate) measured. A brief description of the techniques for each non-invasive urine sample collection method, compared in this review, is outlined below. Prior to each episode of collection of urine regardless of which non-invasive method, the genital area of infants is cleaned with soap and or water [4] [20] [23].

3.1. Standard CCU

A sterile urine container is prepared and ready to collect urine from the infant [23]. Without any additional stimulation or manoeuvres, the clinician, parent, or carer will wait until the infant to void spontaneously [4]. Urine container is not supposed to be in contact with the perineum [23].

3.2. Bladder Stimulation Techniques

This method collects a CCU sample with the same steps as a standard CCU but complemented with bladder stimulation techniques. Among the 17 studies included, two types of bladder stimulation techniques were described: Quick-Wee method and lumbar/bladder stimulation method. In the Quick-Wee method, a rub is given at the suprapubic area of an infant in a circular motion with gauze soaked in cold saline. A disposable plastic forceps is used to hold the gauze to maintain sterility of procedure [4]. The suprapubic rub is continued until a CCU sample is obtained or the duration of 5 minutes is reached [1] [4] [21].

The lumbar/bladder stimulation method proposed by Fernandez-Herreros *et al.* (2013) requires infants to be fed either breastfeeding or formula intake 25 minutes before urine collection commences. The genital area is cleaned, and non-pharmacological analgesia is given to infants prepared for urine collection. This stimulation technique needs at least two trained personnel, one holding the infant under the armpits with legs dangling, while another performs bladder stimulation followed by lumbar paravertebral zone stimulation. Bladder stimulation is done by gently tapping the suprapubic area at a rate of 100 taps per minute over 30 seconds. Then, a lumbar paravertebral zone stimulation is conducted by applying light circular massage at the lower back of the infant for 30 seconds. The two manoeuvres are repeated until a CCU sample is obtained [20].

3.3. Urine Collection Pads

The commonly used pads are Newcastle Sterile Urine Collection Packs (alternatively known as Euron Uricol Urine Collection Packs) [23] [24] [25] [26] [27]. Each pack consists of an instruction leaflet, two soft non-woven sample urine collection pads, a syringe and a specimen bottle. It is a urine sample collection system named after Newcastle University, which developed and supported by its clinical research [26] [27]. The urine collection pad is placed inside the infant's nappy. Urine is retrieved by aspiration using a syringe. To detect if the infant has voided, pad is checked every 10 or 30 minutes, or enuresis alarm is utilized. Pads soiled with stool will be discarded and replaced with a new pad to repeat urine collection [23] [24] [25]. In a study conducted by Alam *et al.* (2005), Newcastle pads were also compared with commercial sanitary pads [23].

3.4. Urine Bag

Urine bag is attached at perineum of an infant by a trained nurse using the standard perineal cleansing procedure [3] [23] [28]. The urine bag is left until

urine is collected or approximately for one hour without replacement unless indicated by leakage, stool contamination or detached from the skin [3]. After peeling off the urine bag gently, a collected urine sample will be poured into a sterile urine container and sent to the laboratory within 20 minutes to 1 hour [3] [23] [28].

3.5. Success Rate of Urine Sample Collection

A successful urine sample collection is defined as *urine collection within 5 minutes* [1] [2] [8] [10] [11] [17] [18] [20] [22]. Out of seven, six studies revealed a higher overall success rate (ranging from 49% to 88.9% with a statistically significant difference) of urine sample collection in lumbar/bladder stimulation method as compared to standard CCU methods [1] [2] [8] [11] [18] [20] [22]. Tran *et al.* (2016) modified the study adapted from Fernandez-Herreros *et al.* (2013), where the fluid is introduced after the failure of the first attempt and before the second attempt with the duration apart of 30 minutes (instead of prior to commencement of procedure). A sterile bag is placed onto the child in case of the infant passes urine before the second attempt. The success rate in the first attempt and second attempts was 42.3% and 23.3%, respectively [8].

Valleix-Leclerc *et al.* (2016) however reported an overall success rate is as low as 27% [10]. Kapoor & Mekle (2017) presented a success rate of 88.3% in the lumbar/bladder stimulation method, which is higher than its control group using a sterile adhesive bag (success rate 86.67%) [17]. Kaufman *et al.* (2017) and Hall-Million & Howard (2017) studied on the Quick-Wee method and found significantly higher success rates in contrast to standard CCU [1] [4] [21]. The success rate of urine sample collection has a very weak association with gender. Five studies with lumbar/bladder stimulation as an intervention found no statistically significant difference between boys and girls in terms of the success rate [1] [2] [3] [8] [10] [22]. Apart from the systematic review conducted by Chandy *et al.* (2020) that reported no significant association, three studies had shown that the younger age group results in a significantly higher success rate [1] [2] [8] [10].

In the study conducted by Labrosse *et al.* (2016), a higher proportion of success was seen in infants below 89 days old than those aged above 89 days [2]. Tran *et al.* (2016) presented a success rate of 88.9% in newborns and 28.6% in infants older than one year (p = 0.0001) [8]. A statistically significant decrease in success rate was noted with the weight of infants [8] [10]. The prospective non-controlled study conducted by Valleix-Leclerc *et al.* (2016) included 48 infants with a median weight of 8.7 kg. In this study, despite the low overall success rate of 27%, among children aged below three months with a median weight of 5.2 kg, the success rate of urine sample collection was 50%. Weight was a significant factor resulting in difficulties in positioning an infant [10].

There was no significant association of success rate with low oral intake and voiding within the hour before urine collection [2]. Discomfort during urine

collection with the lumbar/bladder stimulation method was reported at least once throughout the urine collection in 58.5% infants (95% CI = 50.4 - 66.6), with a significantly increased prevalence with age (p = 0.01) and weight (p = 0.012) [8].

3.6. Time Taken for Urine Sample Collection

Eight studies of lumbar/bladder stimulation that measured the time taken for urine sample collection showed significantly faster collection than the control groups (standard CCU, adhesive urine bag, or invasive methods). The mean time for urine sample collection ranged from 57 seconds to 2 minutes, and the median time ranged from 45 seconds to 60 seconds among the intervention group using the lumbar/bladder stimulation method [2] [8] [10] [11] [17] [18] [20] [22]. In the study by Altuntas *et al.* (2015), the median time for urine sample collection in the control group using standard CCU was 300 seconds (p < 0.001) [22].

Kapoor & Mekle (2017) presented a median time of 70 minutes for urine sample collection via adhesive urine bag, which is significantly longer (p < 0.001) than the lumbar/bladder stimulation where the median time was 55 seconds [17]. For urine collection pads, the minimum median time for urine sample collection was 45 minutes [24] [25]. Rao *et al.* (2004) compared single use of urine collection pads versus urine collection pads replaced every 30 minutes until a sample is obtained, revealed the median time of 80 minutes and 45 minutes, respectively, but no significant difference was found between these two groups (p = 0.056) [24]. Farrell *et al.* (2002) conducted a pilot, method comparison study to assess the reliability of urine collection pads in the microbiological examination. Urine samples were collected with urine bags followed by urine collection pads from all infants in the study population. A median time of 62.5 minutes was recorded for the entire urine collection process [25].

Studies on the Quick-Wee method did not record the time taken for urine sample collection; however, urine samples were collected within 5 minutes in 30% of the infants [4] [21]. As such, it can be said that among the four non-invasive methods, bladder stimulation technique was the fastest method, followed by standard CCU, and similar time is taken for urine collection pads and urine bags.

The association between gender and time taken for urine sample collection was evaluated in three studies. Fernandez-Herreros *et al.* (2013) reported a shorter mean and median time of urine sample collection in females than males using the lumbar/bladder stimulation method [20]. Kumar & Nithin (2019) reported the opposite result of a shorter mean time in males than females [11]. Nonetheless, both studies found no statistically significant difference between males and females in the time taken for urine sample collection [11] [20]. Mamta *et al.* (2019) compared the median time taken of urine sample collection between males and females in both methods, *i.e.* of lumbar/bladder stimulation

(intervention group) and standard CCU (control group). They reported the shortest median time in males of the intervention group, followed by females of the control group, males of the control group and females of the intervention group. In the intervention group, a significant difference was noted between males and females in the time taken for urine sample collection (p = 0.008) [18]. Kapoor & Mekle (2017) studied on the duration of the last feeding and found no correlation with the time taken for urine sample collection (p = 0.57) [17].

3.7. Contamination Rate

Six studies on bladder stimulation techniques measured the contamination rate as one of the outcomes [1] [2] [4] [18] [21] [22]. Mamta *et al.* (2019) and Altuntas *et al.* (2015) compared the lumbar/bladder stimulation with the control group using standard CCU method [18] [22]. An overall contamination rate in the whole population of 1.9% was reported by Mamta *et al.* (2019), which occurred in one of the infants in the control group who failed to give a urine sample [18]. Altuntas *et al.* (2015) reported a contamination rate of 24% and 29% in the intervention group and the control group, respectively (p = 0.77) [22]. A prospective cohort study by Labrosse *et al.*, (2016) which was also included in a systematic review by Chandy *et al.* (2020), revealed no statistically significant difference in the contamination rates between lumbar/bladder stimulation versus invasive methods of 16% and 6%, respectively [1] [2].

Another cross-sectional study included by Chandy *et al.* (2020) that compared lumbar/bladder stimulation and invasive methods too reported a low contamination rate in both groups, in addition, high sensitivity of 97% and specificity of 89% [1]. Studies of the Quick-Wee method showed low contamination rates in contrast to standard CCU and urine bag [1] [4] [21]. The contamination rate in the Quick-Wee method was 27% versus 46% in standard CCU but with no statistically significant difference (p = 0.29) [4] [21].

Chandy *et al.* (2020) however presented a statistically significantly lower contamination rate in the Quick-Wee method of 7.7% than 51% in urine bag from a non-randomized trial included in the systematic review [1]. Alam *et al.* (2005) conducted a study on standard CCU, urine collection pads, and urine bags, and found a significantly lower contamination rate in standard CCU (14.7%) than both urine collection pads (29%) and urine bags (26.6%). There was no statistically significant difference between urine collection pads and urine bags. This study also compared two types of urine collection pads: commercial sanitary pads and Newcastle pads. The contamination rate was found to be lower in Newcastle pads (26%) than commercial sanitary pads (36%), but there was no statistically significant difference [23]. Li *et al.* (2002) screened 100 infants who were followed up for previous UTI. Urine samples were collected via urine bag for urine culture, resulted in 95 of them with positive culture due to contamination and the remaining 5 with genuine bacteriuria. They reported a false-positive rate of 36.8%, a specificity of 63.2%, and positive predictive value of 12.5% [28].

Another study by Karacan *et al.* (2010) assessed urine bag and standard CCU with invasive methods and found the highest contamination rate of 43.9% in urine bag (p < 0.001), followed by standard CCU and catheterization (both 14.3%), and 9.1% in SPA [3]. Herreros *et al.* (2018) conducted a study evaluating the accuracy of the urine dipstick test in CCU samples as a UTI screening modality. There were 5% of CCU samples and 8% of samples obtained by catheterization contaminated, therefore excluded from the study [9].

In short, there was no statistically significant difference between bladder stimulation techniques and standard CCU in contamination rate, but a standard CCU provided a significantly lower contamination rate than urine collection pads and urine bags. There was also no significant correlation between gender and contamination rates of a urine sample [22] [23]. In the study by Altuntas *et al.* (2015), out of the entire study population (n = 127), the contamination rate in females was 34.3% and 20% in males (p = 0.86) [22]. Alam *et al.* (2005) found no statistically significant difference between males (12%) and females (19%) of infants using standard CCU method in the contamination rate (p = 0.3) [23].

3.8. Complications and Adverse Events

Apart from consolable crying, no other complications or adverse events were reported in almost all non-invasive urine sample collection methods [1] [10] [17] [18] [20] [22]. Local skin redness at sites of manoeuvres applied and discomfort in infants were noted in the lumbar/bladder stimulation method [1] [8] [10].

3.9. Satisfaction of Clinicians, Parents and Preference of Patient

Only three studies that adopted the Quick-Wee method evaluated the satisfaction of clinicians and parents. The Quick-Wee method is statistically significantly more favoured as compared to the control group using the standard CCU method [1] [4] [21]. Karacan *et al.* (2010) studied the preference of patients and found that a sterile urine bag was the most preferred method among children in all three age groups of newborns, 1 to 6 months, and 7 to 24 months old. Other methods compared in this study were standard CCU, catharization, and SPA [3].

4. Discussion

Based on this extensive review, bladder stimulation techniques are the ideal method due to its high success rate, fast collection and low contamination rate among the four non-invasive urine sample collection methods. Standard CCU is indeed a useful method of urine sample collection for UTI diagnosis. It has a contamination rate as low as catharization. However, it is less time-efficient where the duration of urine sample collection varying in each infant may be unpredictable. Urine collection pads and urine bags not only are time-consuming but high in contamination rate, further reduced its favourability, especially if indicated for urine culture [3] [11] [20] [21] [23] [28].

The lumbar/bladder stimulation method is found to have a significantly high success rate and fast collection of urine samples in infants. Unlike older children, newborns are yet to develop voluntary inhibition of spinal micturition reflex that control the contraction of detrusor muscles in the urinary bladder via the cerebral cortex. Fernandez-Hererros *et al.* (2013) proposed that this reflex can, however, be triggered in newborns [18] [20]. The success rate of urine sample collection was higher in younger age groups [4]. Spinal micturition reflex influenced by cortical feedback matures over time. By the age of three, voluntary control of periurethral striated muscle sphincter will usually be gained in the child [4] [10] [17].

Weight was another major limitation as presented by Valleix-Leclerc *et al.* (2016), contributing to difficulties in positioning the infant appropriately. The study may have reported no significant difference in terms of age, but considering the strong association between age and weight, this may justify a lack of power in the study instead [10]. Other limitations addressed in the studies were the absence of a control group, pre-requisite of two to three trained staffs which may be less feasible in heavier infants, fluid intake not standardized, an infant with low oral intake not excluded, and precautions to maintain sterility was not done [2] [4] [20].

The Quick-Wee method had a significantly higher success rate of collecting a urine sample within 5 minutes as well. It is easy to be carried out without any special equipment needed, hence can be adopted in clinical settings with low resources [4]. Nevertheless, Hall-Million & Howard (2017) doubted if a similar study designed as such could be delivered in a setting where urine sample collection is routinely done by nurses since no reports on reliability among the team in present studies are available [21]. The studies only included infants of 1 to 12 months of age but not neonates and non-toilet-trained children above 1-year-old. Therefore the findings may not be applicable across all paediatric age groups [4] [21]. Kaufman *et al.* (2017) addressed the issue of lacking a microbiological definition of contamination as one of the limitations in the study [4]. The difference in contamination rate that was not significant may be due to a small number of culture results available [21].

5. Conclusions

In summary, bladder stimulation techniques are the most favoured among all non-invasive urine sample collection methods. Limitations in the studies, as addressed above, require further research to ensure the reliability of urine sample collected so it could be turned into a common practice in the clinical setting. Further studies on lumbar/bladder stimulation as proposed by Fernandez-Herreros *et al.* (2013), the Quick-Wee method, as well as invasive methods, are also worth to be considered, measuring the same outcomes: a success rate of urine sample collection, time take for urine sample collection and contamination rates. From this literature review, the bladder stimulation technique is perceived as more

feasible for practice in a district hospital setting in Malaysia. There is a higher likelihood to implement this stimulation technique in a tertiary setting if research on new technique is found feasible in a less resourceful district hospital setting.

Currently, many studies have compared bladder stimulation techniques with other non-invasive or invasive methods, but not between the two bladder stimulation techniques. Invasive methods are suggested as a control group since catheterization is more widely practiced than standard CCU for its practicality and time-efficiency in busy hospital settings in Malaysia, despite the fact that standard CCU is the first choice recommended in the Paediatrics Protocol for Malaysia Hospitals [13].

Conflicts of Interest

All authors declared that they do not have any conflict of interest to disclose.

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List of Abbreviation (Sorted Alphabetically)

AAP   American Academy of Paediatrics
CCU   Clean-catch urine
MeSH   Medical Subject Headings
NICE   National Institute for Health and Care Excellence
RCH   Royal Children's Hospital
SPA   Suprapubic aspiration
UTI   Urinary tract infection