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# Criteria to evaluate neurological lower urinary tract dysfunction in children with Congenital Zika Syndrome: Revised version after the fourth year of use

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Network of care for patients with Congenital Zika Syndromeand urological sequelae

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DISCLAIMER

None of the authors have competing interests that could be perceived to bias this work. In the same way there was no influence of any of the financial support in the results presented.

ABSTRACT

Congenital Zika Syndrome (CZS) has been associated with microcephaly and other central nervous system abnormalities including areas that have been implicated in the control of the lower urinary tract [1]
Neurological lower urinary tract dysfunction (NLUTD) is a common condition among patients with CZS and microcephaly [2][1][3][4][5]. But the lack of knowledge that CZS causes NLUTD delays investigation and treatment.
This revised version includes changes based on the observations of four-years of experience using our first published protocol [6], the new sequels found in children with CZS, which are cryptorchidism [7] and the neurogenic bowel [5], and related publications [8][9]. This new version includes the vision of the authors, who are from five different institutions in Brazil. They have been working with patients with NLUTD and participate in the development of the new Urological care network for patients with CZS.
Our protocol aims to alert health professionals to the relationship between neurological lower urinary tract dysfunction and Congenital Zika Syndrome and to initiate an early investigation to minimize the risks associated with neurological lower urinary tract dysfunction and other genitourinary disorders that may be found in these children.
A thorough investigation of these children can reduce the impact of this important sequelae, which is the neurological lower urinary tract dysfunction, reducing comorbidities and consequent impairment of renal function and mitigating the disease burden for patients and families and the Health Systems.

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Initial assessment of urological screening:

## 1 Initial assessment of urological screening:

The initial assessment comprises a detailed clinical history, a comprehensive physical examination, lab tests, the urinary ultrasonography and the urodynamic study.

1. **Clinical history including**:

- prenatal and maternal history related to Zika (rash during pregnancy and/or low fever, myalgia, arthralgia, fatigue, conjunctival hyperemia), gestational period of exposure to Zika, perinatal complications
- prenatal and maternal history related to other urological conditions and congenital abnormalities.
- child ‘s history of urinary tract infection confirmed by urine culture.
- Investigation of the children’s bladder habits, including voiding patterns, urinary incontinence and retention, the number of diapers used per day, the wetness of diapers and the interval between changes (continence interval). It is important to investigate symptoms of urinary tract infection (UTI), including changes in the color and aspect of urine, fever, and dysuria.
- Investigation of bowel habits including water ingestion and type of diet, any special regimen for bowel emptying, the frequency of bowel emptying and the characteristic of stool - we recommend the use of the Bristol Stool Scale [7][8]

2. **Physical examination** (apart from the overall systemic evaluation):

- Measurement and recording of the child’s weight and length (or height)
- Evaluation of blood pressure
- Abdomen evaluation, with special attention to bladder and bowel and genitourinary evaluation, with special



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attention to cryptorchidism [9]
- Evaluation of Central nervous system: measurement of head circumference (to confirm if the grade of microcephaly influence on the severity of urological disturbance) and assessment of spine and upper and lower extremities irregularities.

**3. Lab tests**:

- urinalysis and culture for all patients during the initial assessment (we recommend urethral catheterization for culture)
- complete blood count (CBC), blood urea nitrogen (BUN) and serum creatinine

**4. Urinary ultrasonography based on kidney, ureter, and bladder evaluation** [10]

- **Kidney**: to investigate length, outline (smooth, irregular, or global thinning), cortico-medullar differentiation, calyceal/pelvic dilatation. The pelvic diameter measured transversely may be considered normal if ≤ 7 mm in neonates and≤ 10 mm in older children. Report any degree of renal dilatation found in patients with Congenital Zika Syndrome.
- **Ureters**: to investigate the presence of ureteral dilatation (longitudinal and transverse diameter).
- **Bladder**: pre-voiding evaluation (bladder wall, contents, and volume) and post-void residual (PVR) whenever possible (conditional to children age and cooperation).
- Measurement of rectal diameter

## 2 Urodynamic study (UDS):

UDS tests: For neurogenic bladder, urodynamic diagnosis is based on bladder and urethral sphincter behavior during filling and voiding phases. Early diagnosis improves prognostic [11].

**CMG**: performed after ruling out UTI, to determine bladder capacity, sensibility, contractility, compliance, emptying ability and degree of continence.Steps:

- Urethral catheterization is performed under topic anesthesia with lidocaine gel (1%), using ideally a double lumen pediatric catheter.
- Bladder pressure and bladder volume are measured just after urethral catheterization, but before emptying the bladder. This are physiological information that will be useful to compare with urodynamic measurements.
- The initial urinary residual volume is measured and evaluated by considering diaper wetness and the interval from last voiding or clean intermittent catheterization (CIC)
- Filling rate is calculated based on 5 to 10% of the expected bladder capacity for age (ml/min).
- Maximum bladder capacity is measured just before child voids, baseline bladder pressure stays above 40 cm $H_2O$, or the volume infused is 1,5 times the expected capacity for the age.
- Maximum bladder pressure is measured at the bladder capacity,
- Detrusor leak point pressure is the lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure.
- Opening detrusor pressure is measured when voids start.
- Post void residual (PVR) measured at the end of the exam, if the child voids during the exam.

Note: Whenever possible, pressure measurements are made considering the baseline, outside a bladder contraction. Bladder behavior is classified into one of four categories:

- **Normal bladder** (relaxed during filling, sustained bladder contraction upon reaching maximum capacity with relaxed sphincter, complete emptying without post-void residue);

- **Underactive bladder** (relaxed during filling and incapable of generating or sustaining contraction that allow complete bladder emptying);

- **Overactive bladder** (detrusor contractions during filling, elevated intravesical pressures, and early emptying before reaching maximum bladder capacity);



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- **Low bladder compliance** (loss of bladder capacity to remain relaxed during filling, progressive increase in intravesical pressure, elevated bladder pressures, and early emptying).

**EMG:** to measure sphincter activity during filling and voiding phase.

- EMG was performed using patch EMG electrodes
- Sphincter is normal (detrusor sphincter synergia) when sphincter activity remains present during the filling phase and reduces following a high bladder pressure during contraction, a leak or a voiding.
- Detrusor sphincter dyssynergia (DSD) occurs when the sphincter failed to relax, or increases activity during high bladder pressure contraction, leak or voiding.

Note: Pediatric urodynamics is challenging and requires trained professionals. The parents and the child need to be previously familiarized with urodynamic procedures and catheterization. The examination room needs to be adapted to promote a child friendly environment with toys and video/television showing children's films during the exam. Both parents are encouraged to stay in the room during the entire procedure to comfort and support the child.

## 3 Treatment:

- Chloridrate of oxibutynin/anticholinergic drugs: to control overactive bladder and low bladder compliance.
- Clean intermittent catheterization (CIC): whenever bladder emptying is ineffective, with recurrent urinary tract infections, renal and ureteral dilatation or presence of grade 4 and 5 Vesicoureteral reflux (VUR) [12]
- Antibiotics: for treatment of urinary tract infections confirmed clinically and through laboratory exams, according to the susceptibility test, as well as a prophylactic measure, according to the clinical and laboratory history of recurrent urinary tract infections.

Note: To increase treatment adherence, parents are trained to perform CIC. A specialized nurse is responsible for training and follow-up.

## 4 Voiding cystourethography (VCUG)

: to determine the presence or absence of bladder and urethral abnormalities, including vesicoureteral reflux (VUR).

Main Indication:

1. Ureteral or pelvic dilatation at renal US
2. High bladder pressure.

## 5 Renal scan (DMSA and DTPA):

DMSA: to evaluate renal morphology, particularly for detection of scarring and pyelonephritisMain Indications:

1. Abnormal renal US
2. Febrile UTI
3. Follow-up of pyelonephritis.

DTPA: to evaluate kidney excretionMain indications:

1. Abnormal US
2. High detrusor filling pressure
3. Urethral sphincter dyssynergia

## 6 Follow-up:



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1. Clinical re-evaluation every three to six months, depending on risk factors and treatment response.
2. Oriented parents to seek advice if any change in the color and/or smell of the patient's urine is observed or if the patients presents fever episodes without a known cause.
3. UDS and renal and bladder US repeated at an interval of six months to one year, depending on the risk factors presented.



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