Definitions of Urinary Tract Infection Used in Interventional Studies Involving Neurourological Patients—A Systematic Review


Department of Neuro-Urology, Balgrist University Hospital, University of Zürich, Zürich, Switzerland; Department of Urology, Complejo Hospitalario Universitario de Canarias, Universidad de La Laguna, Tenerife, Spain; Department of Urology, Erasmus Medical Center, Rotterdam, The Netherlands; Department of Neuro-urolgy, Careggi University Hospital, Florence, Italy; Department of Neuro-urolgy, London Spinal Injuries Centre, Stanmore, UK; Department of Urology, Aix Marseille University, Marseille, France; Department of Urology, Assistance Publique-Hôpitaux de Paris, Pitié-Salpêtrière Academic Hospital, Sorbonne University, Paris, France; Neuro-Urology, Swiss Paraplegic Center, Nottwil, Switzerland

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Abstract

Context: Neurourological patients often encounter bacteriuria without any symptoms or may experience symptoms suspicious of urinary tract infections (UTIs). However, there is a lack of guidelines that unequivocally state the definition of UTIs in this specific patient group.

Objective: To present all used definitions of UTIs in neurourological patients.

Evidence acquisition: This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Studies were identified by electronic search of Medline, Embase, Cochrane controlled trials databases, and clinicaltrial.gov without a time limitation (last search September 2020) and by screening of reference lists and reviews. The occurrences of the various UTI definitions were counted and the frequencies calculated.

Evidence synthesis: After screening 7164 abstracts, we included 32 studies enrolling a total of 8488 patients with a neurourological disorder who took part in an interventional clinical study. UTI definitions were heterogeneous. The concordance to predefined definitions was low.

Conclusions: Interventional clinical studies rarely report specific definitions for UTIs, and both clinical and laboratory criteria used are heterogeneous. A generally accepted UTI definition for neurourological patients is urgently needed.

Patient summary: Patients suffering from neurological disorders often experience symptoms in their lower urinary tract that resemble urinary tract infections. Furthermore, they can have positive urine cultures without symptoms (the so-called asymptomatic bacteriuria). However, clinical studies rarely report specific definitions for urinary tract infections, and when it is done, they are heterogeneous. A generally accepted urinary tract infection definition for neurourological patients is urgently needed.

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1 These authors contributed equally to the manuscript.

* Corresponding author. Department of Urology, Complejo Hospitalario Universitario de Canarias, Universidad de La Laguna, Tenerife, Spain. Tel: +34667668867, Fax: +34922229891. E-mail address: padilla83@hotmail.com (B. Padilla-Fernández).
1. Introduction

Neurological patients are often affected by urinary tract infections (UTIs). In fact, one in five individuals with neurogenic lower urinary tract dysfunction (NLUTD) suffer from recurrent UTIs that are associated with significant morbidity and mortality and affect patients’ quality of life greatly [1]. Moreover, UTIs place a significant economic burden on the society [1]. There is a wide spectrum of clinical manifestations, ranging from asymptomatic bacteriuria (ASB) and afebrile UTIs to urosepsis and septic shock. In the long term, patients with suboptimal management of their NLUTD, including recurrent UTIs, can also develop chronic renal failure [2].

The underlying pathology of UTIs can vary between patients. In neurological patients, the presence of an indwelling catheter is still the greatest risk for developing catheter-associated UTIs (CAUTIs) [3,4]. Furthermore, detrusor pressure during the storage phase is also considered a key UTI risk factor [5]. However, morphological causes such as bladder stones [6] or elevated postvoid residual [5,7], along with immunological and inflammatory mechanisms, substantially contribute to the development of UTIs [8].

The clinical relevance of bacteriuria is still under debate. There is an on-going controversy in some medical forums about the adequacy of performing urine cultures in the absence of local and/or general symptoms [9]. The situation gets even more complicated when introducing new concepts as the nonsterility of the urine and the rich urinary microbiome that even differs between persons with lower urinary tract dysfunctions (not exclusively neurourological patients) and those without [10].

The European Association of Urology (EAU) guidelines on neurourolgy state that a UTI is defined as the onset of signs and/or symptoms accompanied by laboratory findings (bacteriuria, leucocyturia, and positive urine culture) [11], although no evidence-based cut-off values for the quantification of these findings could be found for the 2020 update [12]. This underlines the importance of precise cut-off values. Several authors have already raised awareness about the fact that UTI definitions vary between different disorders and different researchers [13]. To the best of our knowledge, the most efficient way to review the parameters and cut-off values used in interventional studies is performing a systematic literature search. We also aimed to see whether these differ between diverse neurological disorders.

2. Evidence acquisition

The present systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, 2020 version [14]. The protocol for the review is available on PROSPERO (http://www.crd.york.ac.uk/PROSPERO, CRD42019117817).

2.1. Data sources and searches

We systematically searched Medline, Embase, Cochrane controlled trials databases, and clinicaltrial.gov without a time limitation in 2018, retrieving 8857 references. Given that we wanted contemporary definitions of UTIs, we limited our search to papers published in the past 5 yr (2013-2018) to exclude any outdated papers and retrieved 5841 abstracts. In a second phase, an update literature search was performed including 1323 studies published between 2018 and 2020, resulting in 7164 abstracts that were retrieved and screened. Non-English texts were excluded. We additionally searched the reference list of all included studies and any relevant review articles. An example of the MEDLINE search strategy is provided in the Supplementary material.

2.2. Study selection

We aimed to include all interventional studies that reported on UTI definitions in neurourological patients to identify a limited number of studies with a minimum description of the diagnostic tools used for the suspicion and identification of UTIs. We considered randomised controlled trials (RCTs), comparative non-RCTs, and single-arm cohort studies with a sample of at least 50 neurourological patients. Interventional studies including non-neurourological patients were contemplated only if the neurourological population was \( \geq 90\% \) of the whole sample. Nonoriginal articles and studies not published as full text were excluded, as well as those papers not focusing on lower urinary tract function. Manuscripts reporting on children (patients under 18 yr of age) were also excluded from this systematic review. All identified abstracts were imported into bibliography management software (Endnote X9; Thomson Reuters, Philadelphia, PA, USA) and sorted according to the inclusion and exclusion folders by drag and drop. Titles and abstracts of all identified studies were reviewed independently by two authors (A.M.S. and B.P.F.), and disagreements were resolved by discussion together with a third reviewer (L’T H.). All interventional studies reporting on UTIs in neurourological patients with a predefined UTI definition were reviewed in full text.

2.3. Data extraction

The variables assessed included study design, countries, institutions where the data were collected, type of intervention, dates defining start and end of patient recruitment and follow-up, participant demographics, bladder management, and predefined UTI definition. The outcome data and study characteristics were extracted by one review author (A.M.S.) and checked by a second review author (B.P.F.). Disagreements were resolved by discussion and by consulting a third review author (L’T H.). In cases where median and ranges were reported, mean and standard deviation were estimated with a previously described method [15]. We considered the following as potential confounding factors: underlying neurourological disorder, gender, age, previous intervention/procedure/surgery for the lower urinary tract, types of bladder management (eg, indwelling catheter, intermittent catheters, suprapubic tapping, etc.), comorbidities (eg, diabetes, metabolic or immunological...
diseases, etc.), and any previous and/or current treatment (eg, steroids, immunodepressants, etc.).

2.4. Data synthesis

The occurrences of the various UTI definitions were counted and the frequencies were calculated.

3. Evidence synthesis

3.1. Search results

The PRISMA 2020 flow diagram (Fig. 1) shows the literature search and results. After screening 7164 abstracts, 258 studies were read in full text, and 32 were included in the qualitative synthesis, which summarised the interventional studies reporting a predefined UTI definition in neuromuscular patients. Of the 32 included studies, nine were RCTs [16–24], ten were comparative non-RCTs [25–34], and 13 were case series including at least 50 patients with a neurourological disease [35–47].

3.2. Study and patient characteristics

This systematic review retrieved 22 studies that investigated a pharmaceutical treatment, six investigated the use of a device, and four investigated a surgical procedure. Overall, the 32 included studies enrolled a total of 8488 patients: 2982 women (35%), 4513 men (53%), and 993 patients (12%) for whom the gender was not specified. Patients suffered from stroke (n = 3037), spinal cord injury (SCI; n = 3031), multiple sclerosis (MS; n = 1546), myelomeningocele (n = 186), other neurological disorders (n = 207), nonreported diseases (n = 284), non-neurological disorders (n = 34), or other known pathologies for which the exact number of patients in each category was not defined (n = 183). No differences were found between the definitions in men and women. Detailed characteristics of the included studies are described in Table 1.
## Table 1 – Characteristics of included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Type of study</th>
<th>Neurological disorder</th>
<th>Intervention</th>
<th>Placebo/control</th>
<th>Total neurological patients (female/male)</th>
<th>Mean age [yr] (SD)</th>
<th>Bladder management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourassa-Moreau [25]</td>
<td>2013</td>
<td>Comparative</td>
<td>Retrospective</td>
<td>SCI</td>
<td>Early surgery (&lt;24 h) OnabotulinumtoxinA (200 U) Late surgery (&gt;24 h) OnabotulinumtoxinA (300 U)</td>
<td>197 (32/165)</td>
<td>39.3 (15.8) NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kennelly [29]</td>
<td>2013</td>
<td>Comparative</td>
<td>Prospective</td>
<td>MS (n = 230), SCI (n = 157)</td>
<td>OnabotulinumtoxinA (200 U) OnabotulinumtoxinA (300 U)</td>
<td>387 (233/154)</td>
<td>46.4 (12.6) CIC (n = 101), spontaneous (n = 86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krebs [38]</td>
<td>2013</td>
<td>Single arm</td>
<td>Prospective</td>
<td>SCI</td>
<td>Catheterisation Corticosteroid treatment</td>
<td>NA</td>
<td>60 (0/60)</td>
<td>48.1 (13.7)</td>
<td>CIC (n = 60)</td>
</tr>
<tr>
<td>Rakusa [44]</td>
<td>2013</td>
<td>Single arm</td>
<td>Prospective</td>
<td>MS (n = 230), SCI (n = 157)</td>
<td>OnabotulinumtoxinA (200 U) OnabotulinumtoxinA (300 U)</td>
<td>249 (NR)</td>
<td>40 (11) CIC (n = 243)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darouiche [18]</td>
<td>2013</td>
<td>Single arm</td>
<td>Retrospective</td>
<td>SCI</td>
<td>Short (5 d) course of antibiotics</td>
<td>NA</td>
<td>55 (3/52)</td>
<td>59.9 (13.8)</td>
<td>CIC (n = 45)</td>
</tr>
<tr>
<td>Gallien [19]</td>
<td>2014</td>
<td>RCT</td>
<td>Prospective</td>
<td>MS</td>
<td>Cranberry (36 mg of proanthocyanidins daily)</td>
<td>Placebo</td>
<td>171 (125/46)</td>
<td>49 (10)</td>
<td>CIC (n = 58)</td>
</tr>
<tr>
<td>Chen [36]</td>
<td>2015</td>
<td>Single arm</td>
<td>Prospective</td>
<td>SCI</td>
<td>OnabotulinumtoxinA</td>
<td>59 (21/38)</td>
<td>42.1 (13.1) CIC (n = 59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chong [27]</td>
<td>2015</td>
<td>Comparative</td>
<td>Prospective</td>
<td>SCI</td>
<td>Single preprocedural dose of antibiotics</td>
<td>60 (1/59)</td>
<td>55.8 (12.9) Foley (n = 34), condom catheterisation (n = 14), urinary diversion (n = 5), CIC (n = 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kantor [20]</td>
<td>2015</td>
<td>RCT</td>
<td>Prospective</td>
<td>SCI</td>
<td>Dalfampridine extended release (5 or 10 mg twice daily)</td>
<td>Placebo</td>
<td>429 (300/129)</td>
<td>52.6 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Maier [32]</td>
<td>2015</td>
<td>Single arm</td>
<td>Prospective</td>
<td>Stroke</td>
<td>Beta-blockers No beta-blockers</td>
<td>625 (288/337)</td>
<td>73.4 (12.1) NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leitner [19]</td>
<td>2016</td>
<td>Single arm</td>
<td>Prospective</td>
<td>SCI</td>
<td>OnabotulinumtoxinA</td>
<td>154 (59/95)</td>
<td>52.5 (18) Spontaneous (n = 19), CIC (n = 76), indwelling catheter (n = 59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mukai [41]</td>
<td>2016</td>
<td>Single arm</td>
<td>Prospective</td>
<td>SCI</td>
<td>Catheterisation</td>
<td>259 (39/220)</td>
<td>49 (13.8) CIC (n = 259, 113 of whom at continuous catheterisation at night)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poirier [42]</td>
<td>2016</td>
<td>Single arm</td>
<td>Prospective</td>
<td>SCI</td>
<td>Weekly cycling antibiotics</td>
<td>50 (20/30)</td>
<td>51.3 (13.5) Self-catheterisation (n = 44), heterocatheterisation (n = 2), endoprosthesis (n = 2), reflex urination (n = 2), other (n = 2), missing data (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenzelius [33]</td>
<td>2016</td>
<td>Comparative</td>
<td>Prospective</td>
<td>Intracerebral/cranial bleeding (n = 49), stroke/cerebral vascular occlusion (n = 178), intracerebral tumour/metastasis (n = 6), cerebral infection/inflammation (n = 4), other neurological diseases (n = 51), non-neurological diseases (n = 34)</td>
<td>BIP-silicone catheter Silicone catheter</td>
<td>322 (156/166)</td>
<td>77.9 (12.9) Indwelling catheter (n = 232)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Year of publication</td>
<td>Study design</td>
<td>Type of study</td>
<td>Neurological disorder</td>
<td>Intervention</td>
<td>Placebo/control</td>
<td>Total neurological patients (female/male)</td>
<td>Mean age [yr] (SD)</td>
<td>Bladder management</td>
</tr>
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</tr>
<tr>
<td>Weglinski [45]</td>
<td>2016</td>
<td>Single arm</td>
<td>Prospective</td>
<td>SCI (n = 59), MS (n = 12), impaired conus medullaris (n = 4), cerebral lesion (n = 3), cauda equina syndrome (n = 2)</td>
<td>Antibiotic prophylaxis</td>
<td>NA</td>
<td>80 (36/44)</td>
<td>47.0 (13.1)</td>
<td>Self-catheterisation (n = 69), spontaneous voiding (n = 6), reflex voiding (n = 2), CIC (n = 3)</td>
</tr>
<tr>
<td>Bonfill [15]</td>
<td>2017</td>
<td>RCT</td>
<td>Prospective</td>
<td>SCI</td>
<td>BIP-silicone catheter</td>
<td>Silicone or silicone-latex catheter</td>
<td>489 (136/353)</td>
<td>56.3 (16.3)</td>
<td>Indwelling catheter (n = 489)</td>
</tr>
<tr>
<td>Christiansen [37]</td>
<td>2017</td>
<td>Single arm</td>
<td>Retrospective</td>
<td>MS/neurodegenerative disorders (n = 36), SCI (n = 28), myelomeningocele (n = 6)</td>
<td>OnabotulinumtoxinA</td>
<td>NA</td>
<td>70 (38/32)</td>
<td>48.5 (6.5)</td>
<td>CIC (n = 70)</td>
</tr>
<tr>
<td>Kennelly [30]</td>
<td>2017</td>
<td>Comparative</td>
<td>Prospective</td>
<td>MS (n = 231), SCI (n = 157)</td>
<td>OnabotulinumtoxinA</td>
<td>OnabotulinumtoxinA 300 U</td>
<td>388 (234/154)</td>
<td>46.4 (12.6)</td>
<td>CIC (n = 213), spontaneous (n = 175)</td>
</tr>
<tr>
<td>Loftus [40]</td>
<td>2017</td>
<td>Single arm</td>
<td>Retrospective</td>
<td>Spina bifida</td>
<td>Laparotomies for urological indications</td>
<td>NA</td>
<td>54 (17/37)</td>
<td>34.3 (11.5)</td>
<td>NR</td>
</tr>
<tr>
<td>Previnaire [43]</td>
<td>2017</td>
<td>Single arm</td>
<td>Retrospective</td>
<td>SCI</td>
<td>5-d course of antibiotics</td>
<td>NA</td>
<td>56 (13/43)</td>
<td>40.9 (16.8)</td>
<td>Self-intermittent catheterisation (n = 41), intermittent catheterisation (n = 10), reflex + intermittent catheterisation (n = 6)</td>
</tr>
<tr>
<td>Chen [26]</td>
<td>2018</td>
<td>Comparative</td>
<td>Retrospective</td>
<td>Stroke</td>
<td>Utilisation of portable bladder ultrasound scanning</td>
<td>No portable bladder ultrasound scanning</td>
<td>1928 (811/1117)</td>
<td>70.6 (13.6)</td>
<td>Urinary catheterisation (n = 198)</td>
</tr>
<tr>
<td>Maier [31]</td>
<td>2018</td>
<td>Comparative</td>
<td>Prospective</td>
<td>Stroke</td>
<td>Beta-blocker therapy</td>
<td>No beta-blocker therapy</td>
<td>306 (160/146)</td>
<td>73.5 (3.7)</td>
<td>Transurethral catheter (n = 149)</td>
</tr>
<tr>
<td>Sappal [22]</td>
<td>2018</td>
<td>RCT</td>
<td>Prospective</td>
<td>SCI</td>
<td>Concentrated proanthocyanidins</td>
<td>Placebo</td>
<td>144 (127/17)</td>
<td>51.6 (10.3)</td>
<td>Catheterisation as exclusion criteria</td>
</tr>
<tr>
<td>Tullman [24]</td>
<td>2018</td>
<td>RCT</td>
<td>Prospective</td>
<td>MS</td>
<td>OnabotulinumtoxinA</td>
<td>Placebo</td>
<td>144 (127/17)</td>
<td>41.6 (17)</td>
<td>CIC (n = 50)</td>
</tr>
<tr>
<td>Wikström [46]</td>
<td>2018</td>
<td>Single arm</td>
<td>Prospective</td>
<td>SCI (n = 70), cauda equina lesion (n = 7), menigitis (n = 1), cerebral palsy (n = 1)</td>
<td>Chlorhexidine</td>
<td>NA</td>
<td>50 (5/45)</td>
<td>44.1 (10.5)</td>
<td>Urinary catheterisation (n = 60), indwelling urethral catheter or cystotomy (n = 10)</td>
</tr>
<tr>
<td>Wu [47]</td>
<td>2018</td>
<td>Single arm</td>
<td>Retrospective</td>
<td>SCI (n = 117), SCI (n = 12), Guillain-Barré syndrome (n = 9), neurocystosomiasis (n = 7), bladder extrophy (n = 3), diabetes mellitus (n = 11), Parkinson's disease (n = 5), MS (n = 4), HTLV-1 seropositive (n = 9)</td>
<td>Augmentation enterocystoplasty</td>
<td>NA</td>
<td>79 (17/62)</td>
<td>39.4 (11.6)</td>
<td>Intraurethral self-retaining device (n = 86 adults)</td>
</tr>
<tr>
<td>Calisto [17]</td>
<td>2019</td>
<td>RCT</td>
<td>Prospective</td>
<td>MMC (n = 117), SCI (n = 12), Guillain-Barré syndrome (n = 9), neurocystosomiasis (n = 7), bladder extrophy (n = 3), diabetes mellitus (n = 11), Parkinson's disease (n = 5), MS (n = 4), HTLV-1 seropositive (n = 9)</td>
<td>Intraurethral self-retaining device</td>
<td>Clean intermittent catheterisation</td>
<td>177 (86 adults)</td>
<td>41 (17)</td>
<td>Intraurethral self-retaining device (n = 90), CIC (n = 87)</td>
</tr>
</tbody>
</table>
Fourteen studies exclusively included SCI patients, four studies included MS patients, three studies included a mixed population of SCI and MS patients, and three studies included only stroke patients. The remaining studies had patients with other neurourological disorders.

Bladder management was heterogeneous throughout the studies: 1921 patients were on intermittent catheterisation (IC) and 1006 had an indwelling urethral catheter; 941 voided spontaneously, 216 used a suprapubic catheter; 90 used an inraurethral self-retaining device, 36 emptied through reflex voiding, 14 collected the urine via condom catheters, five had undergone urinary diversion, and two had undergone endoprosthesis placement; six studies did not report patients’ bladder management.

Overall, the affiliated institutes of the 32 included studies were originated from all over the world. Thirteen were based in Europe [19,21,31–33,37–39,42–46], eight in North America [18,20,22,25,27,28,35,40], four in Asia [26,36,41,47], two in South America [17,34], and one in Australia [23]. Additionally, two studies included authors from several parts of the world [29,30], one was a multicentre European study [16], and the remaining study involved centres in Europe and North America [24]. Study details are described in Supplementary Table 1 [48].

3.3. Definition of UTIs

The 32 included studies reported 46 definitions: seven corresponding to ASB, 34 to UTIs, three to sepsis or bacteriemia, and two to CAUTIs.

The determination of a positive urine culture was needed in 36 (78.26%) of these definitions: a threshold value at 10² colony-forming units per millilitre (CFU/ml) was specified in three, 10³ CFU/ml in four, and 10⁴ CFU/ml in four, and 10⁵ CFU/ml in 18 definitions; other definitions required only a positive urine culture with bacteria typical for UTIs. Regarding microscopic investigations, 13 (28.26%) definitions demanded the number of white blood cells (WBCs) in urine, having either five or more or ten or more WBCs per high-power field (hpf) as a threshold. Additionally, four definitions utilised the presence of nitrite as a criterion too together with the number of CFUs. Four studies specified that urinary dipstick was used for the confirmation of infection instead of urinalysis [21,31,32,44]. Differences between routes of urine sampling could not be investigated because this information was not provided in most of the studies (Table 2).

We also evaluated the definitions using UTI-related symptoms in the studies. Some authors did not specify which symptoms should be considered as UTI related [26,31,32,37]. In contrast, other studies addressed only symptoms and required no additional laboratory tests [37,38]. Fever was included in 19 studies, UTI-related pain or tenderness (costovertebral, abdominal, and suprapubic) in 14, de novo incontinence or increased neurourological symptoms in 13, increased spasticity in ten, macroscopic changes in urine (cloudy urine, haematuria, mucus, detritus, etc.) in nine, frequency or dysuria in eight, autonomic dysreflexia in seven, malodorous urine in six, chills or...
Table 2 – Schematic representation of the urinary tract infection definitions used in the neurourological population

<table>
<thead>
<tr>
<th>Reference</th>
<th>Definition no.</th>
<th>Microscopic investigation</th>
<th>Urinalysis</th>
<th>Urine culture</th>
<th>Symptoms</th>
<th>Antibiotics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCI patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bourassa-Moreau</td>
<td>1: UTI</td>
<td>Bacteriuria</td>
<td>UTI related or systemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(2013) [35]</td>
<td></td>
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<tr>
<td>Krebs (2013)</td>
<td>1: UTI</td>
<td></td>
<td>UTI related</td>
<td></td>
<td></td>
<td>Recurrent UTI: &gt;2 UTIs/yr</td>
<td></td>
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<tr>
<td>[38]</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Darouiche (2014)</td>
<td>1: CAUTI</td>
<td>&gt;10 WBCs/hpf</td>
<td>≥10⁵ CFU/ml</td>
<td>&gt;1 UTI related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[18]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chen (2015)</td>
<td>1: UTI</td>
<td>&gt;10 WBCs/hpf</td>
<td>≥10⁵ CFU/ml or ≥2 bacterial species</td>
<td>Febrile episode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[36]</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chong (2015)</td>
<td>1: ASB</td>
<td>&gt;10⁵ CFU/ml or ≥2 bacterial species</td>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[27]</td>
<td>2: UTI</td>
<td>&gt;10⁵ CFU/ml or ≥2 bacterial species</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mukai (2016)</td>
<td>1: febrile UTI</td>
<td>≥10 WBCs/hpf</td>
<td>Febrile episode</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[41]</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pourier (2016)</td>
<td>1: UTI</td>
<td></td>
<td>≥10⁵ CFU/ml (&gt;1 bacterial species)</td>
<td>≥1 UTI-related or systemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[42]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Bondfil (2017)</td>
<td>1: CAUTI</td>
<td>≤2 bacterial species</td>
<td>≥1 UTI related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[16]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>2: Bacteriemia</td>
<td>≤2 bacterial species in urine + positive BC</td>
<td>≥1 UTI related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previnaire (2017)</td>
<td>1: ASB</td>
<td>&gt;10⁵ CFU/ml</td>
<td>UTI related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[43]</td>
<td>2: UTI</td>
<td>&gt;10⁵ CFU/ml</td>
<td>≥1 UTI related</td>
<td>UTI due to CIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sappal (2018)</td>
<td>1: UTI</td>
<td>&gt;10⁵ CFU/ml</td>
<td>≥1 UTI related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[22]</td>
<td>2: UTI</td>
<td>&gt;10⁵ CFU/ml</td>
<td>≥1 UTI related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wikström (2018)</td>
<td>1: ASB</td>
<td>&gt;10⁵ CFU/ml, &gt;1 bacterial species</td>
<td>UTI related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[46]</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Da Silva (2019)</td>
<td>1: UTI</td>
<td>Any bacterial growth</td>
<td>UTI related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[34]</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Pannek (2019)</td>
<td>1: UTI</td>
<td>Positive dipstick ab</td>
<td>UTI related</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>[21]</td>
<td></td>
<td></td>
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<tr>
<td>Toh (2019) [23]</td>
<td>1: UTI</td>
<td>10–100 WBCs/hpf or &gt;50 WBCs/HPU</td>
<td>≥10⁵ CFU/ml</td>
<td>≥1 UTI related or systemic</td>
<td>UTI related</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MS patients</strong></td>
<td></td>
<td></td>
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<tr>
<td>Rakusa (2013)</td>
<td>1: ASB</td>
<td>Positive dipstick b,c</td>
<td>≥10⁵ CFU/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[44]</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Galliers (2014)</td>
<td>1: UTI</td>
<td></td>
<td>&gt;10⁵ CFU/ml</td>
<td>UTI related</td>
<td>(Always preceded by culture)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[19]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kantor (2015)</td>
<td>1: UTI</td>
<td>≥5 WBCs/hpf</td>
<td>&gt;10⁵ and ≥10⁶ CFU/ml</td>
<td>UTI related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[20]</td>
<td></td>
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<td></td>
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<tr>
<td>Tullman (2018)</td>
<td>1: UTI</td>
<td>≥5 WBCs/hpf</td>
<td>10⁵ CFU/ml</td>
<td></td>
<td></td>
<td>Symptomatic and asymptomatic UTIs not distinguished</td>
<td></td>
</tr>
<tr>
<td>[24]</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>SCI and MS patients</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenneley (2013)</td>
<td>1: UTI</td>
<td>≥5 WBCs/hpf</td>
<td>&gt;10⁵ CFU/ml</td>
<td></td>
<td></td>
<td>Symptomatic and asymptomatic UTIs not distinguished</td>
<td></td>
</tr>
<tr>
<td>[29]</td>
<td>2: UTI</td>
<td>Positive</td>
<td>Required</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenneley (2017)</td>
<td>1: UTI</td>
<td>≥5 WBCs/hpf</td>
<td>&gt;10⁵ CFU/ml</td>
<td></td>
<td></td>
<td>Symptomatic and asymptomatic UTIs not distinguished</td>
<td></td>
</tr>
<tr>
<td>[30]</td>
<td>2: UTI</td>
<td>Positive</td>
<td>Required</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aharony (2020)</td>
<td>1: UTI</td>
<td></td>
<td>≥10⁵ CFU/ml</td>
<td>≥1 UTI related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[35]</td>
<td>2: ASB</td>
<td>≥10⁵ CFU/ml</td>
<td>≥1 UTI related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3: Sepsis</td>
<td>≥10⁶ CFU/ml</td>
<td>≥2 systemic</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Maier (2015)</td>
<td>1: UTI</td>
<td>Positive dipstick b,c</td>
<td>&gt;10⁵ CFU/ml</td>
<td>UTI related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[32]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Chen (2018)</td>
<td>1: UTI</td>
<td>Pyuria</td>
<td>UTI related</td>
<td>Required</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[26]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Maier (2018)</td>
<td>1: UTI</td>
<td>Positive dipstick c</td>
<td>&gt;10⁵ CFU/ml</td>
<td>UTI related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[31]</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

shivering in four, bladder signs in four, profuse sweating in two, and decreased bladder capacity in one. Supplementary Table 2 summarises the symptoms and signs included in each study for the definition of UTIs according to the baseline neurourological disorder.

3.4. Discussion

It is common to find references of the high prevalence of recurrent UTIs in patients with NLUTD [3]. However, when we specifically focus on the definitions used in interventional studies in this population, the descriptions are commonly “UTI was self-reported by patients” [49], “the diagnosis of a UTI [ . . . ] was accepted if the participant’s doctor had diagnosed, or confirmed the patient’s diagnosis of a UTI and had prescribed or authorised the use of antibiotics as a treatment” [50], or “[UTIs] were reported per the investigator’s clinical assessment” [51], with no more explanation about the diagnostic methods employed or the symptoms considered as suspicious. Other authors just published the percentage of UTIs (with or without symptoms, usually not differentiating them) diagnosed after an intervention [52] or reported the frequency of infections reviewing the medical records of the patients and checking the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes for UTIs [53].

Therefore, the Guidelines Panel decided that it was important to verify whether the definitions used in interventional studies focused on neurourological patients were following these recommendations and whether more precise cut-off values could be given. We also highlighted that these definitions could vary between the different underlying disorders since clinical manifestations can be limited in some cases. To the best of our knowledge, the worthiest way to achieve these aims is performing a systematic literature search and summarising the findings.

Madden-Fuentes et al [13] already reported that explicit definitions for UTIs are heterogeneous and infrequently applied in studies of spina bifida patients. In 2009, Massa et al [54] published a study about the value of signs and

<table>
<thead>
<tr>
<th>Reference</th>
<th>Definition no.</th>
<th>Microscopic investigation</th>
<th>Urinalysis</th>
<th>Urine culture</th>
<th>Symptoms</th>
<th>Antibiotics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2: UTI</td>
<td>Positive dipstick c</td>
<td>≥10⁵ CFU/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3: UTI</td>
<td>Positive with bacteria typical for UTI</td>
<td>≥10⁵ CFU/ml</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Other

Leitner (2016) [39]

1: UTI

≥10⁵ CFU/ml

UTI related

Stenzelius (2016) [33]

1: ASB

>10⁵ CFU/ml

All definitions refer to patients with indwelling catheters

2: Cystitis

>10⁵ CFU/ml

UTI related

Required

3: PN

>10⁵ CFU/ml

UTI related

Required

4: Sepsis

>10⁵ CFU/ml (urine) + positive BC

UTI related

Required

Weglinski (2016) [45]

1: UTI

Bacteriuria

≥1 UTI related or systemic

2: Persistent bacteriuria

≥10⁵ CFU/ml

UTI related

Required

Symptoms appear within 1 mo after BoNT-A injection

Christiansen (2017) [37]

1: UTI

Bacteriuria

≥10⁵ CFU/ml

UTI related

Required

Loftus (2017) [40]

1: UTI

Positive urine or BC

Febrile episode

Recurrence UTI: ≥3 UTIs/yr

Wu (2018) [47]

1: UTI

Positive urine or BC

Febrile episode

Recurrence UTI: ≥3 UTIs/yr

Calisto (2019) [17]

1: UTI

≥10⁵ CFU/ml

≥1 UTI related

Houman (2019) [28]

1: UTI

≥10⁵ CFU/ml

≥1 UTI related

UTI appears within 1 mo after BoNT-A injection

2: UTI

>10⁵ CFU/ml

ASB = asymptomatic bacteriuria; BC = blood culture; BoNT-A = botulinum neurotoxin-A; CAUTI = catheter-associated urinary tract infection; CFU = colony-forming units; CIC = clean intermittent catheterisation; hpf = high-power field; MS = multiple sclerosis; PN = pyelonephritis; SCI = spinal cord injury; UTI = urinary tract infection; WBC = white blood cell.

a Bacteriuria.
b Leucocyturia.
c Nitrites.
symptoms of UTIs for SCI patients on IC and the accuracy of these individuals at predicting their own UTIs. They assessed that "cloudy urine" had the highest accuracy, and "leucocytes in the urine" had the highest sensitivity. “Fever” and “autonomic dysreflexia” had the highest specificity, but these also had low sensitivity. They also found that individuals were able to predict their own UTIs with an accuracy of 66.2%, but the negative predictive value (82.8%) was higher than the positive predictive value (32.6%). Thus, reliance on a subjective diagnosis of UTIs can lead to antibiotic overuse and misuse, and can affect reported rates negatively.

Patient's experience of UTIs and the ability to report symptoms will depend on the aetiology of NLUTD, level of the lesion, method of bladder management, degree of sensation experienced by the patient, and the patient's neurological status. Additionally, symptoms frequently attributed to a UTI in people with a normally functioning bladder, such as incontinence or frequency, may have other aetiologies in neurourological patients [2,10].

3.4.1 UTI definitions in SCI patients

During the UTI Consensus Conference in January 1992, a consensus on the best practices for preventing and treating UTIs in individuals with SCI was developed, and several definitions were stated [55]:

1 Bacteriuria (quantitative urine-culture criteria):
   - Catheter specimens from individuals on clean intermit-
   tent catheterisation: \( \geq 10^2 \) bacteria per millilitre of urine
   - Clean-void specimens from catheter-free males using
     condom collection devices: \( \geq 10^4 \) bacteria per millilitre
     of urine
   - Specimens from indwelling catheters: any detectable
     concentration

2 UTIs: bacteriuria with tissue invasion and resultant tissue response with signs and/or symptoms

3 ASB: colonisation of the urinary tract without symptoms or signs

Later, in 2013, a working group of the American Spinal Injury Association, the International Spinal Cord Society, and the International Spinal Cord Injury Standards and Data Sets developed an international basic data set for the standardised collection and reporting of information related to a possible UTI in daily practice [56]. They included fever, urinary incontinence/failure of control or leaking around the catheter, spasticity, malaise, lethargy or sense of unease, cloudy urine, malodorous urine, pyuria/leucocyturia, back pain, bladder pain, dysuria, and autonomic dysreflexia as the signs and symptoms of interest when suspecting a UTI [56].

A third definition has been proposed: growth of \( \geq 10^5 \) CFU/ml of a known uropathogen on urine culture with at least ten urinary WBCs per hpf, as well as at least two of the following symptoms—fever, abdominal pain, new or worsened incontinence, pain with catheterisation, and malodorous or cloudy urine [13].

During the Joint SIU-JCUD International Consultation on the Urologic Management of the SCI Patient that took place in Buenos Aires in 2016, a symptomatic UTI was defined as urinary culture with \( \geq 10^2 \) CFU/ml and symptoms (lower urinary tract symptoms, urinary incontinence, increased spasticity, autonomic dysreflexia, pelvic discomfort, fever, and decreased energy level) [57,58]. They also specified that cloudy and foul-smelling urine may represent bacteriuria without UTIs and, by itself, may not warrant a urine culture [57].

These definitions have been considered insufficient by some authors. Ronco et al [59] performed a prospective, cohort-based study including 381 symptomatic UTI episodes in male SCI patients to determine whether both clinical and laboratory diagnostic criteria of UTIs should be used in this population undertaking IC. Their main findings included that leucocyturia seems to correlate with the severity of the infection and the associated inflammatory response, and that the number of clinical signs (including fever, cloudy and/or malodorous urine, onset of urinary incontinence or modification of bladder behaviour, fatigue or sense of unease, increased spasticity, and autonomic hyperreflexia) should be considered a major diagnostic factor. However, they recommended not to take into account fever as an isolated symptom since it could have many origins. Unfortunately, they were not able to find a significant cut-off value of either the WBC count or the CFUs that could be used in clinical practice.

The latter can be the explanation for the diverse criteria found when revisiting the definitions used in interventional studies including SCI patients. It is noteworthy that subjective urine quality may be the unique indicator of UTIs in patients with SCI [22], and that some symptoms may be absent in individuals with spinal cord lesions owing to alterations in sensation [56]; on the contrary, autonomic dysreflexia may develop or worsen due to a UTI [56].

Five studies in our review did not include a cut-off value of CFUs in the urine culture to define a UTI [21,25,36,38,41], disregarding the recommendations discussed above. Fever was considered as indicative of UTIs as a sole symptom in three studies [27,36,41], two with a “pathological” microscopic investigation and one with a positive urine culture, which can also disregard other febrile origins and overtreat patients. The other definitions are in concordance with the suggestions of the main scientific societies explained above.

3.4.2 UTI definitions in MS patients

UTIs and ASB are common in patients with MS, especially when they develop detrusor-sphincter dyssynergia, poor bladder contractility, and/or high postvoid residual urine; voiding modality also impacts bacterial growth in urine cultures [60–62]. The most common symptoms of UTIs in patients with MS are urgency, increased frequency, nocturia, urinary retention, and incontinence [63]. However, filling and voiding symptoms often coexist in MS patients at baseline and during relapses, jointly affecting up to 59% of men and 51% of women [60,64], so urinary dipstick, urinalysis, or urine culture is usually needed to confirm infection [65]. On the contrary, UTIs can exacerbate neurological
symptoms and/or precipitate an acute relapse [66], but they
not are not associated with an increased risk of permanent
worsening of disability [67].

Malodorous urine can be a predictor of UTIs in this
population [65]; however, it has not been included in the
definitions used in the studies involving exclusively MS
patients [19,20]. Increased spasticity was considered only
by Aharony et al [35] in a study comprising both SCI and MS
patients.

It is interesting to consider that MS patients frequently
need immunosuppressants and corticosteroid treatment,
which may turn ASB into UTIs; therefore, investigation
and treatment of ASB is a common practice [44,68]. It can
also be the reason for not considering symptoms to
define UTIs in the study by Tullman et al [24]. The French
Multiple Sclerosis Society recommends treating UTIs in
patients with MS according to the recommendations of
the general population and not to screen for ASB except
in special cases (pregnancy and invasive urological proce-
dures) [67].

3.4.3. UTI definitions in stroke patients
None of the three interventional studies included in this
systematic review specified which symptoms should be
considered relevant for UTI diagnosis in this group of
patients [26,31,32]. It is also the case in observational
studies [69], and even only laboratory findings are needed
in some protocols to diagnose UTIs [70].

3.4.4. Catheter-associated UTIs
CAUTIs are frequently defined as the appearance of fever in
a patient with a urinary catheter and positive urine culture.
In this review, only four studies defined UTIs as isolated
fever and positive urinalysis or urine culture [27,36,41,47].
However, these febrile UTIs did not refer to
CAUTIs: Chen and Kuo [36] recorded their development in
SCI patients after botulinum toxin injection; Chong et al [27]
studied them after elective, endoscopic urological surgical
procedures in SCI patients, Muki et al [41] focused specific-
ally on SCI patients with IC; and Wu and Kuo [47] focused
on urological patients who underwent augmentation
enterocystoplasty and had different bladder management
methods in the follow-up. These studies that addressed
CAUTIs combined laboratory findings with the appearance
of UTI-related and/or systemic symptoms [16,18].

In 2009, the Infectious Diseases Society of America
included patients with indwelling urethral catheterisation,
indwelling suprapubic catheterisation, or IC when explain-
ing the conditions for CAUTI diagnosis [71]. Following
the most recent recommendations of the Centers for Disease
Control and Prevention, a symptomatic CAUTI must meet
the following criteria [72]:

1 The patient had an indwelling urinary catheter that had
been in place for >2 consecutive days in an inpatient
location on the date of event (sign or symptom appear-
ance) and was either
  • Present for any portion of the calendar day on the date of
    event
  • Or removed the day before the date of event
2 The patient has at least one of the following signs or
  symptoms: fever (>38.0 °C), suprapubic tenderness (with
  no other recognised cause), costovertebral angle pain or
tenderness (with no other recognised cause), urinary
  urgency, urinary frequency, and dysuria (not if the cath-
  eter is in place).
3 The patient has a urine culture with no more than two
  species of organisms identified, at least one of which is a
  bacterium of ≥10^5 CFU/ml.

Some authors have drawn the attention to this issue and
questioned whether this definition captures a real infection
that can benefit from antimicrobial treatment [73]. If clini-
cians focus only on CAUTIs, several nonurinary aetiologies
for fever may be missed as a positive urine test result is
present in virtually all patients, and chronically catheterised
patients usually receive unnecessary antibiotics that
increase antimicrobial resistance [73,74].

Regarding the studies included in this systematic review,
in the article by Bonfill et al [16], they specify, as an inclu-
sion condition, that the indwelling catheter must be in place
for at least 7 d, and they comply with the symptoms and
laboratory criteria (fewer than two bacterial species are
found in the urine). In contrast, there is no information
about the period of time that the patients had to have the
indwelling catheter before the diagnosis of CAUTIs in the
study by Darouiche et al [18].

3.5. Implications for research

It is quite common that UTIs were diagnosed in interven-
tional studies without defining the clinical and laboratory
findings considered for their diagnosis. Furthermore, het-
erogeneous descriptions can be found even when matching
up the studies by neurourological disorders. Better adhesion
to established definitions would make it easier to compare
results between studies.

Given that both the CFU count to describe a positive
urine culture and the pathological urinary WBC count may
be different between bladder management methods, it
would be interesting to report the incidences of UTIs sepa-
ately if patients are on intermittent or indwelling cathe-
terisation, or if they void spontaneously or through an
external urine collection device.

3.6. Limitations and strengths of the study

We have used systematic review methods to identify exist-
ing UTI definitions reported in interventional studies
involving neurourological patients. This methodology
allowed us to identify a limited number of studies with a
minimum description of the diagnostic tools used for the
suspicion and identification of UTIs. Given the design of the
review, no result comparison is obtainable, and a meta-
analysis is not within the scope of this noninterventional
systematic review.

Please cite this article in press as: , et al. Definitions of Urinary Tract Infection Used in Interventional Studies Involving
4. Conclusions

Interventional clinical studies rarely report specific definitions for UTIs, and both clinical and laboratory criteria used are heterogeneous. We strongly recommend for future clinical research to clearly report the definition used for UTIs. Moreover, a generally accepted UTI definition for neurological patients is urgently needed.

**Author contributions:** Bárbara Padilla-Fernández had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Blok, Castro-Díaz, Del Popolo, Hamid, Groen, Karsenty, Kessler, Pannek.

**Acquisition of data:** *t Hoen, Padilla-Fernández, Sartori.

**Analysis and interpretation of data:** Padilla-Fernández, Sartori.

**Drafting of the manuscript:** Padilla-Fernández, Sartori.

**Critical revision of the manuscript for important intellectual content:** Blok, Castro-Díaz, Del Popolo, Musco, Hamid, Eccleston, Groen, Karsenty, Phé, Kessler, Pannek.

**Statistical analysis:** Sartori.

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**Supervision:** Pannek.

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**Appendix A. Supplementary data**

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**References**


