Protocol

Systematic review of the diagnostic performance of non-invasive tests in diagnosing bladder outlet obstruction or detrusor underactivity in men with lower urinary tract symptoms

European Association of Urology Male LUTS Guidelines Panel

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Introduction

Description of the condition

Lower urinary tract symptoms (LUTS) are a highly prevalent and bothersome complaint in men and women of all ages. In 2008, it was estimated that 45% of the worldwide population were affected by at least one lower urinary tract symptom, and 2.3 billion people are projected to suffer from LUTS by 2018 (1). The presence of LUTS has been shown to have a significantly negative impact on general health-related quality-of-life, sexual function, and mental health, and they are associated with a significant economic burden for healthcare systems (2, 3).

The International Continence Society (ICS) categorises lower urinary tract symptoms (LUTS) into three groups depending upon the phase of the micturition cycle affected (4):

- Storage symptoms are those experienced during the storage phase and include frequency, nocturia, urgency and urge urinary incontinence
- Voiding symptoms are those arising during the voiding phase and include slow stream, splitting or spraying, intermittency, hesitancy, straining and terminal dribble
- Postmicturition symptoms are those experienced immediately following micturition and include a feeling of incomplete emptying and post-micturition dribble

Voiding LUTS in men are a common problem. A large multinational population-based study revealed an overall prevalence of LUTS of 62.5%, and voiding LUTS of 29.3%, in men aged 40 years and over (5), and it has been reported that 90% of men aged 50 to 80 suffer from voiding LUTS (6). Voiding symptoms are either the result of bladder outflow obstruction (BOO) or detrusor underactivity (DUA):

Bladder outflow obstruction is most commonly due to benign prostatic enlargement secondary to benign prostatic hyperplasia (BPH), although other common causes include bladder neck obstruction, urethral stricture, or functional BOO (7). The consequent resistance to outflow results in the typical voiding LUTS described above. The prevalence of histological BPH increases with age, from 20% for men in their 40's to 80-90% for men in their 80's (8), and it represents a significant public health burden with annual costs related to treatment reportedly at least $3.9 billion in the USA alone (9).

Detrusor underactivity is defined by the ICS as a detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span (4). Therefore, the clinical manifestations of DUA are the same as for BOO. Its aetiology is poorly understood but likely to be multifactorial, with age-related decline in detrusor contractility, reduction in contractility secondary to chronic overdistension as a result of BOO, and neuropathy thought to play a role (10). Prevalence of DUA varies depending on the definition used and population studied, but is reported to be up to 48% in men over 70 years old (11).

Determining whether a patient's symptoms are due to BOO or DUA is important in determining the optimal management. The success rate from surgical treatments such as transurethral resection of the prostate (TURP) are inferior in patients with DUA compared to those with BOO, and given the small but potentially serious complications from TURP
correct diagnosis is important for appropriate patient counseling and selection for surgery (12). It is not possible to reliably distinguish between BOO and DUA based on clinical symptoms, and the gold standard for diagnosis is through urodynamic assessment with cystometry. BOO involves the demonstration of a low maximum flow rate (Qmax) with a high detrusor pressure at this flow rate (PdetQmax), as opposed to DUA in which the patient has a low Qmax in association with a low PdetQmax. However, this is an invasive test with risks related to the procedure such as dysuria and urinary tract infection. Furthermore, it is a specialist test that requires dedicated equipment and specific expertise, and therefore incurs significant additional costs to the healthcare system. Consequently, a number of non-invasive tests have been described with the aim of providing an alternative to invasive cystometry for diagnosing BOO or DUA in men with LUTS.

Description of the intervention

A large variety of non-invasive tests for assessing men with LUTS have been described. These generally fall into 2 main categories - non-urodynamic tests and non-invasive urodynamic tests (13). All types of non-invasive test used for the diagnosis of BOO or DUA are eligible for inclusion in this systematic review, including the following:

Non-urodynamic tests:

1. Bladder or detrusor wall thickness as determined by transabdominal ultrasound scan

   The measurement of bladder wall thickness (BWT) or detrusor wall thickness (DWT) with transabdominal ultrasound has been used as a non-invasive test for BOO. It is based on the findings from animal models and morphological studies that BOO results in detrusor muscle hypertrophy (14, 15), leading to increased BWT and DWT. The measurement of BWT includes all layers of the bladder including the bladder adventitia (hyperechogenic), detrusor muscle (hypoechogenic) and bladder mucosa (hyperechogenic), whereas DWT measures the detrusor muscle layer (hypoechogenic) only. However, this measurement may be affected by other variables apart from BOO including age-related increases in bladder wall thickness, the presence of detrusor overactivity, the bladder volume at which the measurement is taken and the location of the measurement.

2. Bladder weight as determined by transabdominal ultrasound scan

   The measurement of ultrasound-estimated bladder weight (UEBW) is based on the same principle as that for BWT or DWT, with bladder weight acting as a measure of detrusor hypertrophy. It overcomes the effect that bladder filling-volume has on the measurement of BWT or DWT, and utilises a mathematical formula based on subtraction of the intravesical volume from the total bladder volume (including bladder wall and bladder contents), multiplied by the specific gravity (16). As for BWT or DWT measurements, the UEBW does not identify the cause of the detrusor muscle hypertrophy, which may be related to other factors independent of BOO such as ageing or the presence of detrusor overactivity.

3. Presumed prostate circle area ratio as determined by ultrasound scan
The presumed prostate circle area ratio (PCAR) is an ultrasound-derived measurement of prostatic configuration that is based on the theory that as the prostate grows it exerts pressure on the capsule surrounding the prostate. With further growth, the capsule reaches a point at which it no longer stretches and the prostate then begins to approximate the shape of a circle. Once this circular configuration is reached, the pressure applied to the urethra is maximal, and clinical effects become evident (17). The ratio tends towards 1 as the prostate becomes more circular. The PCAR is therefore a measure of how well the prostate approximates a circle, and as a result may be a predictor of BOO.

4. Intravesical prostatic protrusion as determined by transabdominal ultrasound scan

The intravesical prostatic protrusion (IPP) is another ultrasound-derived measure of prostatic configuration, based on the theory that the prostate protrudes into the bladder as it grows, and therefore leads to BOO as a result of a ball-valve effect (18). It is measured from the base of the bladder in the mid-sagittal plane. The IPP may however be affected by bladder volume at the time of measurement.

**Non-invasive urodynamic tests:**

1. Free flow rate study

The free flow rate is the commonest non-invasive test used to evaluate male patients with LUTS. The patient is asked to urinate into a container which measures the rate and volume of urine voided, and the post-void residual urine volume is then measured with ultrasound. This enables the calculation of the maximum flow rate (Qmax) in ml/s and the flow time, as well as allowing assessment of the pattern of flow. However, it is not possible to distinguish low flow rates due to BOO from low flow rates due to DUA based on the free flow test alone, and patients with high detrusor pressures may generate normal flow rates even in the presence of obstruction. Furthermore, flow rates show considerable variation at different times of the day which can make it difficult to draw accurate conclusions based on free flow rates alone (19).

2. Penile cuff test

The principle of the penile cuff test is to measure the isovolumetric bladder pressure (a measure of bladder contractility), which in combination with a free flow test would allow a low flow due to BOO or DUA to be differentiated. The test involves the placement of a pneumatic cuff around the penile shaft which is inflated on voiding, thereby interrupting flow. The pressure of the resultant fluid column in the urethra is estimated to be intravesical pressure, assuming a continuous column of fluid between the bladder and cuff. Three methods for the penile cuff technique have been described - the deflation, interruption, and continuous techniques. The deflation technique involves inflating the cuff, asking the patient to void against the closed cuff, and then deflating the cuff when the patient feels urine in the urethra (20). With the interruption technique, the cuff is inflated during voiding at a rate of 10cmH20 per second until flow is interrupted, and this cuff pressure is measured. The cuff is then rapidly deflated resulting in an initial surge in urine (Qsurg) followed by a steady state flow (Qss). This cycle can be repeated several times throughout voiding to obtain several discrete measurements. The penile compression ratio can then be calculated (Qsurg - Qss)/Qss, and maximum cuff interruption pressures can be
plotted on a nomogram in order to categorise men into obstructed, non-obstructed and equivocal groups (21, 22). The continuous method has recently been reported using an automatically-controlled penile cuff in order to measure voiding pressure continuously throughout voiding (23).

The penile compression and release (pinch) technique is based on the same principles as the cuff tests, but involve the patient squeezing the penis during voiding in order to interrupt flow. On release of pressure, the Qsurg and Qss can be measured and the penile compression ratio can be calculated and used to predict BOO (24).

3. Condom method (occlusion pressure-flow study)

The condom method is another way by which isovolumetric bladder pressure can be measured, and is based on the same principle as the penile cuff tests. The test involves voiding through a condom catheter attached to a valve, and at maximum flow the catheter is occluded and isovolumetric pressure measured via a side-port on the valve (25, 26).

Other tests as judged relevant by reviewers will also be eligible for inclusion.

*How the intervention might work*

The role of invasive urodynamics prior to surgical treatment of men with voiding LUTS is debatable due to the lack of clear evidence demonstrating improved outcomes. However, the International Consultation on Incontinence published a review of the evidence and recommended that this investigation should be performed prior to surgical treatment (27). The invasive nature of the test, with small rates of morbidity including urinary tract infection, and the need for specialist equipment and expertise, has limited its widespread use. The rate of urinary tract infection has been reported to be at least 3%, and the investigation is also associated with significant costs to healthcare systems (28, 29). Furthermore, it is an unpleasant investigation with high reported rates of anxiety and embarrassment (30). The development of non-invasive methods for measuring BOO would help to avoid the morbidity associated with the invasive urodynamic test and may make the procedure more acceptable to patients. If these non-invasive investigations are shown to be as accurate as traditional urodynamics in diagnosing the cause of a man's voiding LUTS, then their use may be more widely accepted.

*Why it is important to do this review*

Invasive urodynamic tests have been shown in some studies to be able to identify those men most likely to have a successful outcome following surgery for BOO (31), although this remains debatable. One of the reasons for the lack of widespread performance of urodynamic investigation in men with voiding LUTS prior to surgical treatment relates to the morbidity associated with this test, along with its associated need for specialist expertise and equipment and attendant costs. The development of non-invasive tests that can accurately diagnose BOO would avoid the morbidity associated with invasive urodynamics and as a result may be more acceptable to both patients and surgeons. With an increasing number of non-invasive methods for diagnosing BOO described in the literature, it is important to determine their relative diagnostic ability with reference to the gold standard invasive urodynamics, in order to identify their role in the assessment of men with voiding LUTS.
Aims and objectives

The aim is to perform a systematic review of the diagnostic performance of non-invasive tests in diagnosing bladder outlet obstruction or detrusor underactivity in men with lower urinary tract symptoms.

The objectives are:

1. To determine the diagnostic test accuracy (i.e. sensitivity, specificity, positive predictive value and negative predictive value) of non-invasive tests in diagnosing BOO or DUA in men with LUTS compared with pressure-flow studies
2. To determine the relative performance of the different non-invasive tests
3. To perform relevant subgroup and/or sensitivity analyses in the following subgroups:
   - Men with a high prevalence of BPE
   - Men with a high prevalence of DUA
   - Men with storage versus voiding LUTS
   - Severity of LUTS
   - Men with previous prostate surgery
   - Men treated with medical therapy for storage and/or voiding LUTS
   - Risk factors for BPE (PSA, Prostate volume, post-void residual)

These objectives will be met by a systematic and critical appraisal of the current evidence from trials assessing the diagnostic performance of non-invasive tests for the diagnosis of BOO or DUA.

Trial Eligibility Criteria

Types of studies

All studies that include at least 10 participants assessing the diagnostic accuracy of index tests compared to the reference standard, or studies comparing index tests together, will be eligible for inclusion.

Types of participants

All adult men (≥18 years) with LUTS as defined by the trial authors. Men with neurological disease or urethral stricture will be excluded. For mixed populations, studies in which excluded populations account for <10% will still be included.

Types of interventions

Index tests:
All types of non-invasive test used for the diagnosis of BOO or DUA are eligible for inclusion in this review, including the following:

- Penile cuff test
- Free flow rate study
- Bladder or detrusor wall thickness as determined by transabdominal ultrasound scan
- Bladder weight as determined by transabdominal ultrasound scan
- Condom method (occlusion pressure-flow study)
- Presumed circle area ratio as determined by transabdominal ultrasound scan
- Intravesical prostatic protrusion as determined by transabdominal ultrasound scan
- Others as judged relevant by reviewer

Reference standard:
Pressure-flow studies (conventional, video, or ambulatory urodynamics) will be used as the reference standard for the diagnosis of BOO or DUA.

Comparators:
Studies comparing the index test with the reference standard will be included. In addition, studies that compare an index test with another index test will also be included.

Types of outcomes measures

Primary outcomes:
- Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the diagnosis of BOO or DUA
- Diagnostic yield (i.e. defined as neither positive nor negative; e.g. equivocal; test failure; etc.)

Secondary outcomes:
- Validation of test
- Morbidity (as defined by trial authors)
- Patient satisfaction (as defined by trial authors)
- Cost effectiveness (as reported by trial authors). No formal economic analysis based on economic modelling will be made
Material and Methods

**Literature Search**

The Embase, Medline, Cochrane SRs, Cochrane Central (Cochrane HTA, DARE, HEED), Google Scholar, and WHO international Clinical Trials Registry Platform Search Portal databases will be searched for all relevant publications with no restriction on year of publication. Only English language articles will be included.

The literature search will be carried out based on the search strategy provided in Appendix 1.

**Data collection and analysis**

**Selection of studies**

Following de-duplication, two review authors (SM and AN) will independently screen the titles and abstracts of identified records for eligibility. The full-text of all potentially eligible records will be retrieved and screened independently by two review authors using a standardised form, linking together multiple records of the same study in the process. Any disagreements will be resolved by discussion or by consulting a third review author. The study selection process will be described using a PRISMA flow diagram (32).

**Data extraction and management**

Two review authors (SM and AN) will independently extract outcome data. Study characteristics will be extracted by one review author and a second review author will check data extractions for accuracy. Any disagreements will be resolved by discussion or by consulting a third review author. We will use a standardised data extraction form which will be piloted. In case of any incompletely reported data, study authors will be contacted.

Data to be extracted and included in the 'characteristics of included studies' table are: study design; locations where the data were collected; dates defining recruitment and follow-up; how intervention comparator groups were formed; for prospective studies, which parts of the study were prospective; whether there was an *a priori* protocol or analysis plan; participant demographic and clinical characteristics (essentially the same as pre-specified confounder variables shown in the 'risk of bias' section below); eligibility criteria for participants; the numbers of participants who were included in the study, assigned to each intervention comparator group, received intended treatment and analysed; losses and exclusions of participants, with reasons; description of interventions; study funding sources.

Risk of bias will be assessed using the QUADAS-2 tool (33). A list of the most important potential confounders for outcomes was developed *a priori* with clinical content experts (EAU Male LUTS guideline panel). For each study, we will ask whether each prognostic confounder was considered and whether, if necessary, the confounder was controlled for in analysis. The potential confounding factors to be assessed are:

- Whether indices for pressure flow study were determined automatically or manually
- Whether the quality of urodynamic study adhered to contemporaneous quality standards (i.e. International Continence Society standards for studies from 2002 onwards; for studies pre-2002, judgement will be made by the reviewer and panel member)

Assessment of heterogeneity and sensitivity analysis

Heterogeneity between studies will be assessed by visual inspection of plots of the data, the Chi² test for heterogeneity and I² statistics. We will consider substantial heterogeneity present if I² is greater than 50%. Possible reasons for heterogeneity will be explored, such as differences in the population studied, the treatment given, or the way in which the outcomes were assessed. If there are sufficient included studies, we will conduct a sensitivity analysis to assess the robustness of our review results by repeating the analysis only including studies with an overall medium to low risk of bias.

Assessment of reporting biases

The review authors will aim to minimise potential biases by conducting a comprehensive literature search for eligible studies.

Data synthesis

We will perform a narrative synthesis of all studies included in this systematic review. Meta-analysis will be performed if there is more than one randomised or quasi-randomised controlled trial reporting the same outcome. For studies with multiple publications, only the most up-to-date or complete data for each outcome will be utilized. Quantitative synthesis will not be undertaken for non-randomised studies. A fixed effects model will be used to calculate pooled estimates of treatment effect across similar studies and their 95% CIs. If clinical, methodological or statistical heterogeneity is indicated then a random effects model will be used. For time-to-event data, the log (hazard ratio) and its variance will be combined using the generic inverse variance method. Dichotomous outcomes will be combined using the Mantel-Haenszel risk ratio method. Continuous outcomes will be combined using the inverse variance mean difference method. If studies use different scales to assess the same continuous outcome, the standardized mean difference will be used instead of the mean difference.

Sensitivity analysis

Included studies are expected to be of mixed methodological quality, we plan to conduct sensitivity analysis by excluding studies with unclear and high risk of bias from the meta-analysis of each outcome.

Acknowledgements

Acknowledgements will be stated in agreement with the publications rules set by the peer reviewed journal that will accept this systematic review.
Contributions of authors

Contributions of authors will be stated in agreement with the publications rules set by the peer reviewed journal that will accept this systematic review.

Declaration of interest

Declaration of interest will be stated in agreement with the publications rules set by the peer reviewed journal that will accept this systematic review.

Administrative Aspects

Literature Search

The literature search will be carried out by Cathy Yuan using the search criteria specified in Appendix 1. Cathy Yuan will delete the duplicates to provide the final list of abstracts to be reviewed.

Study abstracts identified by the literature search will be reviewed by Sachin Malde and Arjun Nambiar following the procedures described in Appendix 2.

Data Collection, Management and Quality Control

Data on patient and disease characteristics, treatment and patient outcome will be extracted (collected) for each study by Sachin Malde and Arjun Nambiar.

Data will be stored in Excel files on Dropbox.

Basic quality control checks will be carried out on the database from each study in order to assess the quality of the data. A separate analysis will be done for each study and compared to the results in the original publication of the study.

Data Quality Control Committee

Data quality control will be assured by Arjun Nambiar and Thomas Lam.

Steering Committee

EAU Male LUTS Guidelines Panel.

Writing Committee

EAU Male LUTS Guidelines Panel in conjunction with reviewers involved in this systematic review.

Publication of the Results and Authorship

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Publication of results will be in a peer reviewed journal and authorship will be decided based on amount of contribution from each actively involved party.

**Timelines**

Literature search will be conducted in February 2015, Abstract and full text screening from February 2015 to April 2015, data extraction from April 2015 to June 2015 and summary analysis and drafting of systematic review article from June 2015 to August 2015.

**Finances**

This systematic review will be conducted through altruistic donation of time and knowledge from involved parties.

**References**


Appendix 1: Literature Search Strategy

The following databases will be searched using the provided search strategy:

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1974 to 2015 March 02>

Search Strategy:

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1 exp bladder neck stenosis/ or exp Urinary Bladder Neck Obstruction/ (10349)
2 exp bladder obstruction/ (2532)
3 (bladder adj2 (neck sclerosis or outflow obstruction or outlet obstruction or obstructed voiding)).tw,kw. (6834)
4 exp prostate hypertrophy/ or exp Prostatic Hyperplasia/ (48693)
5 (benign prostatic hyperplasia or BPH or benign prostatic obstruction or BPO or benign prostatic enlargement or BPE or BOO or prostate hypertrophy).tw,kw. (38856)
6 (((detrusor or bladder) adj2 (underactivit* or failure or acontractile or hypocontract*)) or DUA).tw,kw. (1283)
7 or/1-6 (69969)
8 (pressure adj2 flow).tw,kw. (21790)
9 exp urodynamics/ (29192)
10 exp cystometry/ or flow Cytometry/ (279584)
11 (urodynamic* or cystometrogram or cystometr* or cystometrography or cystomanometry).tw,kw. (31264)
12 exp bladder pressure/ (3205)
(detrusor pressure or bladder pressure).tw,kw. (4722)
or/8-13 (341697)
exp non invasive measurement/ (13860)
(non invasive adj2 (test or measurement)).tw. (5467)
(videourodynamicos or Video urodynamics).tw,kw. (773)
(uroflowmetry or Urine flowmetry or urine flow measurement or intraureteral flow measurement).tw. (4533)
((Penile cuff or UroCuff or free flow rate) adj3 (test or study)).tw. (32)
(Bladder wall thickness or detrusor wall thickness or Bladder weight).tw. (1273)
(Condom method or Presumed circle area ratio or Intravesical prostatic protrusion).tw. (258)
exp uroflowmetry/ (3529)
exp urine flow rate/ (4036)
or/15-23 (30218)
7 and 14 (8131)
7 and 24 (4818)
25 or 26 (10951)
exp Lower Urinary Tract Symptoms/ (38942)
(((lower urinary tract or bladder or urethra* or LUT) adj3 (symptom* or complain*)) or LUTS).tw. (21595)
28 or 29 (52494)
27 and 30 (3779)
(exp animals/ not humans/) or ((rats or mice or mouse or cats or dogs or in vitro or cell lines) not (human* or men or women)).ti. (8965382)
31 not 32 (3641)
(children/ not adult/) or ((children or pediatric* or paediatric*) not (aged or adult* or men or women)).ti. (2203351)
33 not 34 (3612)
36 women/ not (men/ or (men or male).mp.) (2025054)
37 not 36 (3489)
38 (case report/ or case reports/) not (case series or cases).ti,ab. (3122076)
39 not 38 (3443)
40 (note/ or editorial/ or Comment/ or news/ (2103719)
41 not 40 (3344)
42 remove duplicates from 41 (2447)

De-duplication of Identified Studies

Search results will be combined and duplicates removed by Cathy Yuan.
Appendix 2: Review of Studies Identified by the Literature Search and Searching Meeting Abstracts

The abstracts of studies that are identified by the literature search will be reviewed by a review team including:

Sachin Malde, Arjun Nambiar, Roland Umbach

The studies identified by the literature search will be divided among reviewers such that the abstract of each study is independently reviewed by two different reviewers.

Review of Studies Identified by the Literature Search

A separate Study Eligibility Form will be used as an aide in identifying eligible studies. It will be filled out by each reviewer for all studies that are identified as being potentially eligible or for which the eligibility is unclear based on their review of the abstract. This form will be e-mailed to Karin Plass/ Cathy Yuan to request the full publication of the study in order to allow a more detailed assessment by the reviewer.

The unclear and potentially eligible studies will be entered into an Excel database by the reviewer in order to keep track of the study’s status and final disposition. The Excel file will include information on whether or not the study is eligible and if not, the reason for exclusion. The columns will be: study ID, first author, and then the possible reasons for exclusion which will be listed in the same order of the questions on the Study Eligibility Form. The Excel sheets from the various reviewers will be combined after collection from all of the reviewers.

Final Assessment of Study Eligibility

Disagreements between reviewers on study eligibility should be worked out between the reviewers whenever possible. The list of studies proposed as being eligible and the studies for which agreement between the reviewers could not be reached will be reviewed by at least one of the members of the Steering Committee.