


Benign prostatic hyperplasia

Author: Brazilian Society of Urology, Brazilian Medical Association

Participants: Ricardo L. V. Nunes¹, Alberto A. Antunes¹, Antonio Silvinato¹,  Wanderley M. Bernardo²

Final version: May 7, 2018

1. Brazilian Society of Urology, Rio de Janeiro, RJ, Brasil.
2. Brazilian Medical Association, São Paulo, SP, Brasil.

<http://dx.doi.org/10.1590/1806-9282.64.10.876>

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors. The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

SUMMARY

The minimally invasive procedures (mips) for the treatment of symptoms of benign prostatic hyperplasia (bph) are presented as attractive techniques due to their ease of accomplishment and the possibility of outpatient treatment. This guideline aims to present recommendations that may assist in decision making in patients with benign prostatic hyperplasia and indication of the different minimally invasive therapies. For this, a systematic review of the literature was performed, with the descriptors according to the pico: patient with benign prostatic hyperplasia, minimally invasive therapy, clinical outcome and adverse events. With no time restriction, in medline, cochrane central and lilacs databases via vhl, 1,007 papers were retrieved, of which 16 were selected to respond to clinical doubt. Details of the methodology and results of this guideline are set out in annex I

INTRODUCTION

The minimally invasive procedures (MIPs) for the treatment of symptoms of Benign Prostatic Hyperplasia (BPH) are presented as attractive techniques due to their ease of accomplishment and the possibility of outpatient treatment. The development of newer minimally invasive procedures seeks new approaches that rival the standard methodology, ideally providing an effective therapy and with fewer adverse effects. From a patient's point of view, a successful MIP would provide: good tolerability, rapid and long-lasting relief of symptoms, short recovery time with rapid return to daily activities, minimal adverse events and accessibility. As many men discontinue drug therapy, but of these, proportionately, few seek surgery, there is a great medical need for

an effective treatment that is less invasive than traditional surgery, reducing the risk of imminent bladder dysfunction.

RESULTS

What is the efficiency and safety of different minimally invasive therapies in the treatment of low urinary tract symptoms in benign prostatic hyperplasia?

1. Transurethral Thermotherapy with microwaves (Tumt)

In Tumt method, the emission of microwave radiation through an intraurethral antenna provides heat to the interior of the prostate, which leads to

tissue destruction, apoptosis and denervation of α -receptors, thereby reducing resulting infravesical obstruction¹ **(A)**.

A systematic review (RS) with meta-analysis including 15 randomized controlled trials (RCTs) evaluated Tunt in 1,585 patients with symptomatic BPH with a follow-up of 3-60 months. Comparing Tunt with "sham" thermotherapy, Tunt reduced the severity score of clinical symptoms measured by the International Prostate Symptom Score (IPSS) weighted mean difference [WMD] -5.15, IC 95% -6.04 to -4.26] in the analysis of four studies with 482 patients and increased maximal urinary flow (Qmax) [WMD 2.01 mL/s, IC 95% 0.85-3.16 mL/s] in the analysis of six trials with 643 patients. Tunt also showed a significant improvement of IPSS (WMD -4.20, IC 95% -3.15 to -5.25) and Qmax (WMD 2.30 mL/s, IC 95% 1.47 to 3.13) in comparison with alpha-blockers (in a study of 103 patients). This RS also found that transurethral resection of the prostate (TURP) was better for Qmax (119% vs. 70%) and that these patients (1/100 person/year) were less likely to require retreatment in patients treated with Tunt (8/100 persons/year). In contrast to TURP, Tunt was associated with reduced risks of retrograde ejaculation, stenosis treatment, hematuria, blood transfusions, and transurethral resection syndrome, but increased the risks of dysuria, urinary retention, and retreatment of BPH symptoms. No studies have evaluated the effects of symptom duration, patient characteristics, prostate specific antigen levels or prostate volume in response to treatment 2 **(A)**.

Tunt is an outpatient procedure and an alternative for elderly patients with comorbidities who are at elevated anesthesia and/or surgical risk or are unfit for invasive treatment¹² **(A)**.

2. Transurethral prostatic ablation with needle (Tuna)

In Tuna method, a low level of radiofrequency energy is supplied to the prostate through transurethral needles inserted up to the prostatic parenchyma.

A RS with meta-analysis of 35 low quality studies, of which only nine (26%) were comparative, showed that Tuna significantly improved the IPSS and Qmax in relation to the baseline. However, compared to RTU, these improvements were significantly lower at 12 months (mean difference [DM] from 4.7 to IPSS and 5.9 mL/s for Qmax). Tuna was associated with a higher rate of retreatment (analysis of 17 non-comparative studies), with a mean follow-up not reported

(odds ratio [OR] 7.44, IC 95% 2.47-22.43) and lower rate of complications (OR 0.14, IC 95% 0.05-0.14)³ **(B)**.

In comparison to TURP, Tuna is associated with a lower prevalence of adverse events, including mild hematuria, urinary tract infections, urethral stenosis, urinary incontinence, erectile dysfunction, and ejaculatory disorders.

Tuna is not suitable for prostates > 75 mL or isolated obstruction of the bladder neck. In addition, Tuna can not effectively treat the median lobe⁵ **(D)**.

3. Prostatic Stent

Prostatic stents were designed primarily as an alternative to delayed bladder catheterization in patients without clinical conditions for the surgical procedure; however, were also evaluated as a primary treatment option in patients without significant comorbidities. The use of stents requires well-functioning detrusor muscles⁶ **(A)**. Permanent stents are biocompatible, allowing epithelialization. Temporary stents are non-epithelializable and may be biostable or biodegradable⁷ **(D)**.

There are no studies comparing stenting with other treatments or sham, only one RCT compared two versions of a temporary stent in patients with benign prostatic obstruction (OPB)⁸ **(B)**.

A RS with 20 series of cases evaluated the placement of the biocompatible and re-epithelializing permanent urethral stent in 990 patients with BPH. Fourteen studies included only patients at high surgical risk. These studies reported significant improvements in symptoms and Qmax. Data combined with catheter-dependent patients showed that 84% of patients (148/176) regained urination capacity after treatment. In 606 patients evaluated, a total of 104 stents (16%) failed in one year and migration was the most common cause of failure (38 stents or 37%). The majority of patients had perineal pain or urinary irritation symptoms after stenting. Therefore, 1 in 6 patients had the stent removed within a year due to complications and the inadequate follow-up prevented conclusions on stent durability beyond one year⁹ **(C)**.

Another RS included data from 14 case series and evaluated the efficiency of self-expanding, non-epithelializing metal prostatic stenting in 839 high-risk patients with BPH. Most studies were of poor quality and poor follow-up. Five studies reported reduction in IPSS from 11 to 19 points after stent insertion. All seven studies evaluating Qmax showed an increase in their rate (3-11 mL/s), and the four studies that

described post-urination residual volumes showed a reduction of Qmax¹⁰ (C).

Temporary stents may provide short-term relief of lower urinary tract symptoms secondary to OPB in patients temporarily unsuitable for surgery or after minimally invasive treatment.

4. Prostatic Urethral Lift (PUL)

Prostatic Urethral Lift (PUL) is a minimally invasive treatment performed by cystoscopy under local anesthetic associated with sedation, or general. The PUL consists of a non-absorbable suture wire with metal bundles at each end that act as anchors. It is implanted by transfixing the lateral lobes of the prostate, where one end is externally located in the capsule and the other inside the adenoma. It acts by compressing the lateral lobes and enlarging the lumen of the obstructed urethra. The procedure aims to create a continuous light from the bladder neck to verumontano.

In a RCT, 206 patients with at least 50 years of age with an Auasi Index (American Association Symptom Index), 13 or greater, Qmax \leq 12 mL/d and prostate gland from 30 to 80 cc, were randomized 2:1 for prostatic urethral lift (N=140) or simulated procedure (N=66). The primary endpoint evaluated was the comparison of the Auasi reduction at three months. Patients in the PUL group were followed for up to one year and evaluated for symptoms of lower urinary tract, maximum urinary flow, quality of life and sexual function. At the three-month follow-up, the PUL group had a 50% reduction in relation to the initial Auasi score (22.1 to 11.0 points - $p < 0.001$), which remained stable up to 12 months¹¹ (A).

The Auasi change was 88% higher for the PUL group than for the sham control. Also, Qmax increased significantly from 8.1 to 12.4 mL/s compared to baseline at three months, and this result was still maintained at 12 months ($p < 0.001$). The difference for Qmax between the two groups was favorable to PUL and showed statistical significance ($p = 0.005$). There was no difference between the two groups in relation to residual post-urination volume ($p = 0.30$)¹¹ (A).

A three-year analysis of this study showed a mean improvement from the baseline significant for the total IPSS (41.1%), quality of life (48.8%), Qmax (53.1%) and IPSS. Symptomatic improvement was regardless of the prostate size. There were no "again" events of ejaculatory or erectile dysfunction, and all evalua-

tions of sexual function showed stability or average improvement after PUL. Fifteen of the 140 patients in the PUL group (10%) required reoperation due to treatment failure up to three years¹² (A).

Another RCT compared PUL with TURP randomizing 80 patients with lower urinary tract symptoms secondary to BPH (45 PUL, 35 TURP). At 12 months, IPSS improvement was -11.4 for PUL and -15.4 for TURP ($p = 0.05$). There was no retrograde ejaculation among patients with PUL, while 40% of patients in the TURP group lost the ability to ejaculate ($p < 0.0001$). Surgical recovery was measured using a validated instrument and confirmed that recovery quality was higher with PUL ($p < 0.01$). The increase in Qmax was higher in the TURP group ($+13.7 \pm 10.4$ mL/s) compared to PUL (4.0 ± 4.8 mL/s) after 12 months of the procedure¹³ (B).

A meta-analysis of prospective and retrospective studies showed an overall improvement after PUL, including IPSS (-7.2 to -8.7 points), Qmax (3.8 to 4.0 mL/s) and quality of life (QoL -2.2 to -2.4 points). Sexual function was preserved with a small improvement estimated at 12 months (standardized mean gain of 0.3-0.4)¹⁴ (B).

The most common complications reported in the postoperative period included hematuria (16-63%), dysuria (25-58%), pelvic pain (5-17.9%), urgency (7.1-10%), transient incontinence 3.6-16%) and ITU (2.9-11%). Most of the symptoms were from mild to moderate severity and were resolved within two to four weeks after the procedure^{11,12} (A) ^{13,14} (B).

The obstruction caused by median lobe enlargement could not be effectively treated by PUL, and efficiency in large prostates has not yet been demonstrated. Long-term studies are needed to evaluate the duration of effect compared to other techniques 5 (D)¹⁴ (B).

5. Intraprostatic Injection of Botulinum Toxin type A (BoNT-A)

The main mechanism of action of BoNT-A is inhibition of the release of neurotransmitters from cholinergic neurons by cleavage of synaptosome-associated protein 25 (Snap-25). BoNT-A also appears to act at several other levels, modulating the neurotransmissions of sympathetic, parasympathetic and sensory nerve terminals in the prostate, leading to reduced growth and promotion of prostatic apoptosis¹⁵ (D).

A recent systematic review with meta-analysis showed no difference in the efficacy of BoNT-A com-

pared to placebo, concluding that there is no evidence of clinical benefit. Three studies were included, with a total sample of 522 patients (260 in the BoNT-A group and 262 in control group). The duration of the studies ranged from 8 to 24 weeks. The standardized mean difference grouped at the change in the IPSS for the BTX-A group versus the placebo group was -1.02 (IC 95% C - 1.97, - 0.07). The other outcomes (Qmax, prostate volume and post-urination residual volume) were not statistically different between the two groups. The placebo effect in the single-group analysis ranged from 0% to 27.9% for IPSS and from -1.1 to 28.7% for Qmax (lower to higher, respectively)¹⁶ (A).

RECOMMENDATION

In patients with BPH:

Tumt is an outpatient procedure and an alternative for elderly patients with comorbidities who are at elevated anesthesiological risk or are unfit for invasive treatment. (A)

Tumt is comparable to TURP in improving symptoms; is associated with decreased morbidity, but with less improvement in urinary flow.

TURP has lower retreatment rates compared to Tumt. (A)

Tuna is not suitable for prostates > 75 mL or isolated obstruction of the bladder neck and cannot effectively treat median lobe. (D)

Tuna is a minimally invasive alternative, with reduced morbidity compared to TURP, but with less efficiency. (B)

Retreatment rates are lower with TURP compared to Tuna. (A)

Temporary stents may provide short-term relief of lower urinary tract symptoms secondary to OPB in patients temporarily unsuitable for surgery or after minimally invasive treatment. (C) Regarding adverse events, the high rate of stent migration is noted. (C)

Prostatic urethral lift improves IPSS, Qmax and quality of life. (A)

There is a low incidence of sexual side effects with use of prostatic Urethral Lift. (A)

A median lobe enlargement obstruction cannot be effectively treated with prostatic urethral lift, and efficiency in large prostates has not yet been demonstrated. (B)

There is currently no evidence to support the use of BoNT-A in patients with lower urinary tract symptoms due to BPH. (A)

ANNEX I

Clinical question

What is the efficiency and safety of different minimally invasive therapies in the treatment of low urinary tract symptoms in benign prostatic hyperplasia?

Eligibility criteria

The main reasons for exclusion were: did not respond to PICO and study design.

Narrative reviews, case reports, case series, and preliminary results were initially excluded.

Search for articles

Database

The basis of scientific information consulted was Medline (via PubMed) and references of the selected studies.

Identification of descriptors

P	Patients with lower urinary tract symptoms due to benign prostatic hyperplasia
I	Minimally invasive therapy
C	Other therapy
O	Clinical outcomes, adverse events

Search strategy

Medline/PubMed - (Lower Urinary Tract Symptoms OR benign prostatic obstruction OR benign prostatic hyperplasia OR benign prostatic hypertrophy OR BPH OR Prostatic Hyperplasia) AND (minimally invasive treatment OR minimally invasive therapy OR minimally invasive therapy* OR MIST OR Microwaves OR Transurethral Needle Ablation OR Catheter Ablation OR embolization therapeutic OR Stent* OR Stents* prostatic stent* OR prostatic urethral lift OR intraprostatic injection OR Bacterial Toxins OR Botulinum Toxins, Type A)

Central (Cochrane) - (Lower Urinary Tract Symptoms OR benign prostatic hyperplasia) AND (minimally invasive treatment OR minimally invasive therapy OR Microwaves OR Transurethral Needle Ablation OR prostatic stent OR prostatic urethral lift OR intraprostatic injection OR Bacterial Toxins OR Botulinum Toxins, Type A)

Lilacs via BVS - (Lower Urinary Tract Symptoms OR benign prostatic hyperplasia) AND (minimally invasive treatment OR minimally invasive therapy)

Critical Evaluation

Relevance - clinical importance

This guideline was prepared through a clinically relevant question to gather information in medicine to standardize the conduct and assist in decision making during minimally invasive therapy in the treatment of low urinary tract symptoms by benign prostatic hyperplasia.

Reliability - Internal validity

Obtaining the evidence to be used followed the following steps: elaboration of the clinical question, structuring the question, searching for the evidence, critical evaluation and selection of the evidence, exposure of the results and recommendations.

The bases of scientific information referred to were Medline via PubMed, Central (Cochrane) and Lilacs via BVS. Manual search from references of narrative reviews, as well as selected works, was performed.

The selection of the studies, the evaluation of the titles and abstracts obtained with the search strategy in the information bases referred to was conducted independently and blinded, obeying the inclusion and exclusion criteria, separating the works with potential relevance. When the title and abstract were not illuminating, the article was searched in its entirety. Only works which complete texts were available were considered for critical evaluation. There was no restriction on the year of publication.

Languages: Portuguese, English, Spanish.

Application of results - External validity

The level of scientific evidence was classified by type of study according to Oxford¹⁷ (Table 1).

TABLE 1: GRADE OF RECOMMENDATION AND STRENGTH OF EVIDENCE

A: Experimental or observational studies of better consistency.
B: Experimental or observational studies of lower consistency.
C: Uncontrolled case reports/studies.
D: Opinion lacking critical evaluation, based on consensus, physiological studies or animal models.

The selected evidence was defined as a randomized controlled clinical trial (RCT), which was submitted to an appropriate critical evaluation checklist (Table 2). The critical evaluation of ECR allows classification according to the Jadad score 18, considering the Jadad < three (3) trials as inconsistent (grade B), and those with a score ≥ three (3), consistent (grade A).

When the selected evidence was defined as a comparative study (observational cohorts or non-randomized clinical trial), it was subjected to an appropriate critical evaluation checklist (Table 3), allowing the classification of the study according to the New Castle Ottawa score Scale 19, considering cohort studies consistent with score ≥ 6 and inconsistent <6.

TABLE 2 - DIRECTIONS FOR CRITICAL EVALUATION OF RANDOMIZED CONTROLLED CLINICAL TRIALS

Study Data Reference, Study Design, Jadad, Strength of evidence	Sample calculation Estimated differences, power, level of significance, total of patients
Selection of patients Inclusion and exclusion criteria	Patients Recruited, randomized, prognostic differences
Randomization Description and allocation blindfolded	Patient follow-up Time, losses, migration
Treatment Protocol Intervention, control and blind method	Analysis Intent of treatment, intervention and control analyzed
Items considered Primary, secondary, instrument of measure of the outcome of interest	Result Benefit or damage on absolute data, benefit or damage on average

Method of extraction and analysis of results

For results with available evidence, the population, intervention, outcomes, presence or absence of benefit and/or damage and controversies will be defined in a specific way, whenever possible.

The results will be preferentially exposed in absolute data, absolute risk, number needed to treat (NNT) or number to produce damage (NNH), and possibly in mean and standard deviation (Table 4).

TABLE 3 - DIRECTIONS FOR CRITICAL EVALUATION OF COHORT STUDIES

Representativeness of subjected and selection of non-subjected (max 2 points)	Exposure Definition (max 1 point)	Demonstration that the outcome of interest was not present at the start of the study (max 1 point)	Comparability on the basis of design or analysis (max 2 points)	Outcome evaluation (max 1 point)	Appropriate follow-up time (max 2 points)	Score and level of evidence
---	-----------------------------------	--	---	----------------------------------	---	-----------------------------

TABLE 4 - SPREADSHEET USED TO DESCRIBE AND PRESENT THE RESULTS OF EACH STUDY MEAN

Evidence included
Study Design
Selected population
Follow-up time
Outcomes considered
Expression of results: percentage, risk, odds, hazard ratio, mean

Results

Recovered work (05/2018)

TABLE 5 - NUMBER OF WORKS RETRIEVED WITH THE SEARCH STRATEGIES USED FOR EACH SCIENTIFIC INFORMATION BASE

INFORMATION BASE	WORK NUMBER
Primary	
PubMed-Medline	1,007
Central (Cochrane)	242
Lilacs via BVS	3

Application of evidence - Recommendation

The recommendations will be prepared by the authors of the review, with the initial characteristic of synthesis of the evidence, being submitted to the validation by all the authors participating in the preparation of the guideline.

The available evidence will follow some principles of exposure - will be by outcome and will have as components: number of patients, type of comparison, magnitude and precision (standard deviation and IC 95%).

It will have its estimated strength (Oxford¹⁷/Grade²⁰) in 1b and 1c (grades A) or strong and in 2a, 2b and 2c (grades B) or moderate or weak or very weak.

Conflict of Interests

There is no conflict of interest related to this review to be declared by any of the authors.

Final Declaration

The Guidelines Project, an initiative of the Brazilian Medical Association in conjunction with the Specialty Societies, aims to reconcile medical information in order to standardize behaviors that aid the physician's reasoning and decision making. The information contained in this project should be submitted to the evaluation and criticism of the physician responsible for the conduct to be followed in view of the reality and clinical condition of each patient.

REFERENCES

1. Floratos DL, Kiemeny LA, Rossi C, Kortmann BB, Debruyne FM, de La Rosette JJ. Long-term follow-up of randomized transurethral microwave thermotherapy versus transurethral prostatic resection study. *J Urol* 2001;165:1533-8.
2. Hoffman RM, Monga M, Elliott SP, Macdonald R, Langsjoen J, Tacklind J, et al. Microwave thermotherapy for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2012 12;CD004135. PMID: 22972068
3. Bouza C, López T, Magro A, Navalpotro L, Amate JM. Systematic review and metaanalysis of Transurethral Needle Ablation in symptomatic Benign Prostatic Hyperplasia. *BMC Urol* 2006 21;6:14. PMID: 16790044
4. Boyle P, Robertson C, Vaughan ED, Fitzpatrick JM. A metaanalysis of trials of transurethral needle ablation for treating symptomatic benign prostatic hyperplasia. *BJU Int* 2004;94:83-8. PMID: 15217437
5. Gravas S, Bach T, Drake M, Gacci M, Gratzke C, Herrmann TR et al. EAU GUIDELINES ON NONNEUROGENIC MALE LUTS INCLUDING BENIGN PROSTATIC OBSTRUCTION. European Association of Urology 2017. (disponível em: <https://uroweb.org/wp-content/uploads/Male-LUTS-2017-pocket.pdf>)
6. Guazzoni G, Montorsi F, Coulange C, Milroy E, Pansadoro V, Rubben H, et al. A modified prostatic UroLume Wallstent for healthy patients with symptomatic benign prostatic hyperplasia: a European Multicenter Study. *Urology* 1994;44:364-70.
7. Vanderbrink BA, Rastinehad AR, Badlani GH. Prostatic stents for the treatment of benign prostatic hyperplasia. *Curr Opin Urol* 2007;17:1-6. PMID: 17143103
8. Kijviki K, van Dijk M, Pes PL, Lertsithichai P, Wijkstra H, de la Rosette J. Clinical utility of "blind placement" prostatic stent in patients with benign prostatic obstruction: a prospective study. *Urology* 2006;68:1025-30. PMID: 17113894
9. Armitage JN, Cathcart PJ, Rashidian A, De Nigris E, Emberton M, van der Meulen JH. Epithelializing stent for benign prostatic hyperplasia: a systematic review of the literature. *J Urol* 2007;177:1619-24. PMID: 17437773
10. Armitage JN, Rashidian A, Cathcart PJ, Emberton M, van der Meulen JH. The thermo-expandable metallic stent for managing benign prostatic hyperplasia: a systematic review. *BJU Int* 2006;98:806-10. PMID: 16879446
11. Roehrborn CG, Gange SN, Shore ND, Giddens JL, Bolton DM, Cowan BE, et al. The prostatic urethral lift for the treatment of lower urinary tract symptoms associated with prostate enlargement due to benign prostatic hyperplasia: the L.I.F.T. Study. *J Urol* 2013;190:2161-7. PMID: 23764081
12. Roehrborn CG, Rukstalis DB, Barkin J, Gange SN, Shore ND, Giddens JL, et al. Three-year results of the prostatic urethral L.I.F.T. study. *Can J Urol* 2015; 22:7772-82. PMID: 26068624
13. Sønksen J, Barber NJ, Speakman MJ, Berges R, Wetterauer U, Greene D, et al. Prospective, randomized, multinational study of prostatic urethral lift versus transurethral resection of the prostate: 12-month results from the BPH6 study. *Eur Urol* 2015;68:643-52. PMID: 25937539
14. Perera M, Roberts MJ, Doi SA, Bolton D. Prostatic urethral lift improves urinary symptoms and flow while preserving sexual function for men with benign prostatic hyperplasia: a systematic review and meta-analysis. *Eur Urol* 2015;67:704-13. PMID: 25466940
15. Magistro G, Stief CG, Gratzke C. New intraprostatic injectables and prostatic urethral lift for male LUTS. *Nat Rev Urol* 2015;12:461-71. PMID: 26195444
16. Shim SR, Cho YJ, Shin IS, Kim JH. Efficacy and safety of botulinum toxin injection for benign prostatic hyperplasia: a systematic review and meta-analysis. *Int Urol Nephrol* 2016;48:19-30. PMID: 26560471
17. Levels of Evidence and Grades of Recommendations - Oxford Centre for Evidence Based Medicine. Disponível em <http://www.cebm.net/blog/2009/06/11/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
18. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17:1-12
19. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American college of chest physicians task force. *Chest* 2006;129(1):174-81. PMID: 16424429
20. Wells G, Shea B, O'Connell D, Robertson J, Peterson J, Welch V, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. Disponível em: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

