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Prevention of recurrent urinary tract infections: bridging the gap between clinical practice and guidelines in Latin America

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Abstract: The branches of the immune system work in concert to defend against pathogens and prevent tissue damage due to excessive inflammation. Uropathogens in general, and uropathogenic *Escherichia coli* (UPEC) in particular, have evolved a diverse range of virulence mechanisms to avoid detection and destruction by the mucosal immune system of the urinary tract. Research towards a vaccine active against UPEC continues but has yet to be successful. Orally administered immunomodulatory bacterial lysates both stimulate and modulate the immune response in the urinary tract *via* the integrated mucosal immune system. The 2018 European Association of Urology (EAU) guidelines on treating acute uncomplicated cystitis recommend aiming for rapid resolution of symptoms, reduction of morbidity, and prophylaxis against reinfection. Recommended short-term antibiotic therapy has the advantage of good compliance, low cost, few adverse events, and low impact on bacterial flora. Antibiotic treatment of asymptomatic bacteriuria is only indicated during pregnancy and before invasive interventions. For recurrent infection, prophylaxis using behavioral modification and counseling should be employed first, then nonantibiotic prophylaxis, and, finally, low-dose continuous or postcoital antibiotic prophylaxis. The 2018 EAU guidelines give a strong recommendation for the oral bacterial lysate immunomodulator OM-89. All other nonantibiotic prophylactic strategies require more data, except for topical estrogen for postmenopausal women. For last-resort antibiotic prophylaxis, nitrofurantoin or fosfomycin trometamol are recommended. Guidelines for Latin America are currently being drafted, taking into account the unique ethnicity, availability of medicines, prevalence of antibiotic resistance, and healthcare practices found throughout the region.

Keywords: immunology, prophylaxis, treatment guidelines, urinary tract infections

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Introduction

The following narrative review is based on presentations from the 2° Foro en Infecciones Urinarias Recurrentes (FIUR2) symposium, a Latin American forum to discuss current trends and challenges in treating recurrent urinary tract infections.

A clear understanding of the immune response in the urinary tract is an important aid for physicians to reduce recurrent infections in the context of multi-resistant and pan-resistant bacteria. A simplistic view of the immune system solely as a defense against infection belies not only the complexity of its role in infection control, but also the importance of its role in functions such as tissue repair, elimination of neoplastic cells, and homeostatic communication with the microbiome. Immunity can be subdivided into three branches: constitutive, innate, and adaptive immunity. Constitutive immunity comprises ever-present protective mechanisms which require no activation. In contrast, both the innate and adaptive branches of immunity require a stimulus to mount a response. Broadly, innate immunity can be viewed as rapid, nonspecific, and lacking a memory function, while

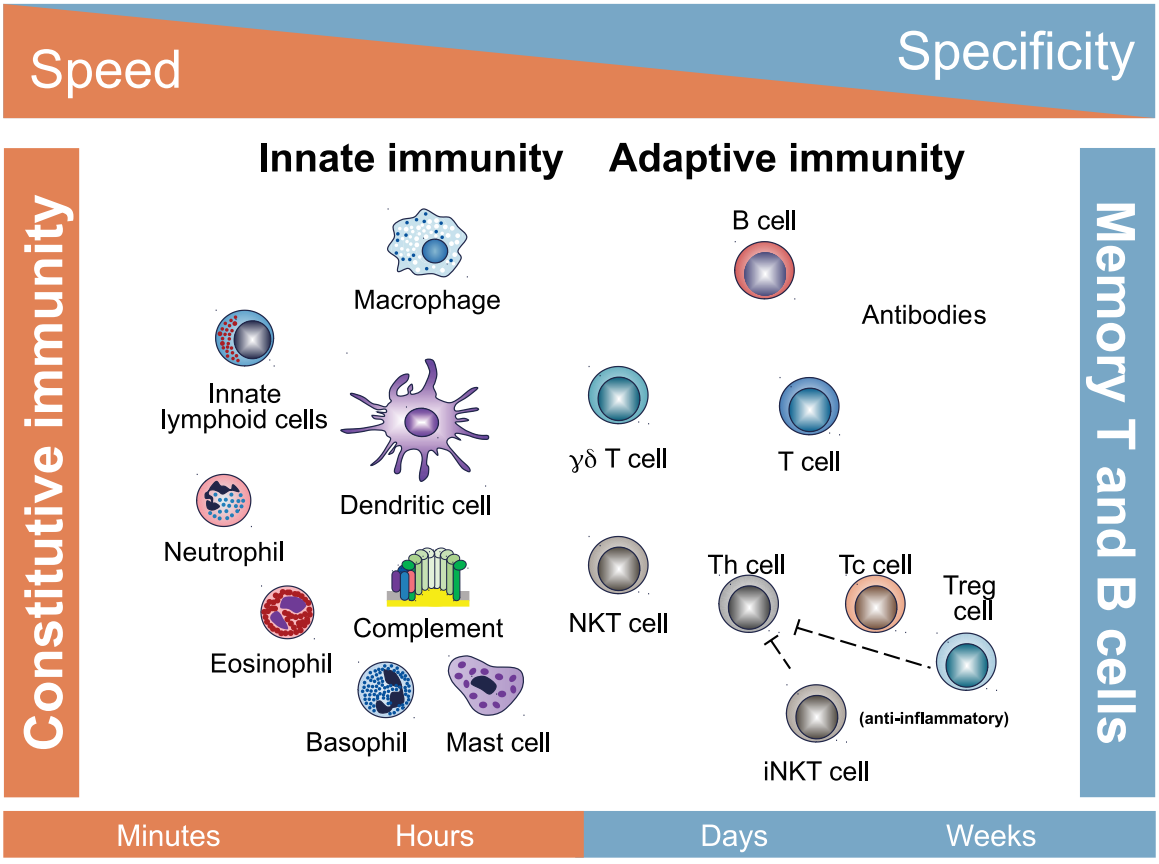

Figure 1. Components of the immune system function along a gradient of speed and specificity.[1]
iNKT cell, invariant natural killer T-cell; NKT cell, natural killer T-cell.

adaptive immunity provides a slower, specific, adjustable response which leaves a memory.

The immune system can be thought of as an orchestra, with separate elements acting in concert much like instruments. Depending on the nature, location, and previous contact with an infectious agent or stimulus the immune response may be that of a concerto, with a prevailing form of immunity predominating, or like a symphony, without any form taking a lead role. The major components of constitutive immunity include barriers (e.g. epithelial cells), enzymes and antimicrobial peptides (AMPs), and mucociliary transport. The major players in innate immunity are: type 1, type 2, and type 3 lymphoid cells; macrophages, basophils, neutrophils, and eosinophils; the nonspecific antigen receptors expressed by cells involved in innate immunity; and complement proteins. The key effectors of the adaptive response are T-helper cells (Th cells), cytotoxic T-cells (Tc cells), regulatory T-cells (Treg cells), and B lymphocytes, which produce various immunoglobulins (Igs) including IgM, IgG, IgA, and IgE. The various cells of the immune systems exist along a sliding scale from rapid nonspecific response in the innate immune system to slower highly specific response in the adaptive immune system (Figure 1).

Like an orchestra, the components of each branch of immunity overlap and support one another. The AMPs of the constitutive immune system are wide-spectrum 'antibiotics' active against bacteria, viruses, fungi, protozoa, and neoplastic cells. These AMPs typically form channels or pores, disrupting cell membranes and causing the cell to lyse. In addition, they have several intracellular cytotoxic effects. AMPs affect the stimulus-dependent branches of immunity by promoting chemotaxis towards pathogens, regulating the inflammatory response, aiding tissue repair, and modulating the adaptive response.[1]

Toll-like receptors (TLRs), and patterns recognition receptors (PRRs) in general, are a key nonspecific bridge between the different branches of the immune response. Multiple forms of TLRs/

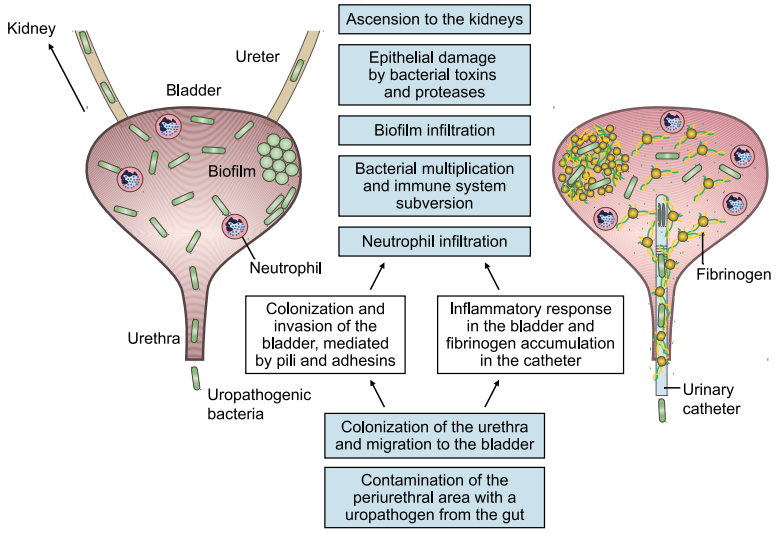

Figure 2. Colonization of the bladder by uropathogenic bacteria with and without catheterization.[3]
Adapted by permission from Springer Nature: Nature, Nature Reviews Microbiology, Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. 2015.

PRRs have been identified, expressed both in and on various cell types including epithelial cells of the mucus membranes, macrophages, and dendritic cells. Binding of TLRs to pathogen-associated molecular patterns (PAMPs) induces rapid responses such as cytokine release, recruitment and attraction of phagocytic cells, and increased phagocytic efficiency. PAMP activation of TLRs/PRRs on dendritic cells induces maturation of these cells into an antigen-presenting cell type. Subsequent interaction with Th cells, most often in lymph nodes, begins the adaptive immune cascade, in which numerous pathways are activated, including production of pathogen-specific antibodies by B lymphocytes and activation of memory T-cells. The adaptive immune cascade both produces and is supported by cytokines.

Immunology of the urinary tract

The kidneys, ureters, bladder, and urethra form the urinary tract. The proximity of the urethra to the intestine makes colonization by uropathogenic *Escherichia coli* (*E. coli*) (UPEC) a frequent occurrence, particularly in catheterized patients. Ascending movement through the urethra can lead to bladder infections, and further ascent through the ureter may lead to inflammation and protease release resulting in kidney damage and hematogenic dissemination of the infection.[2]

UPEC is the dominant organism in urinary tract infections (UTIs), particularly in uncomplicated UTI. Other common uropathogens include *Klebsiella pneumoniae*, *Proteus mirabilis*, *Staphylococcus saprophyticus*, and *Enterococci faecalis* and *faecium*. All these uropathogens express virulence factors which aid adhesion (e.g. pili, adhesins), nutrient release (toxins), immune evasion (capsules etc.), and iron acquisition (aerobactin etc.).[2] UPEC strains express a variable suite of virulence factors allowing adherence (fimbriae), invasion and defense again immune cells (endotoxins), movement and migration up the urinary tract (flagella), nutritional intake (iron receptors), and immune system evasion (capsule). UPEC counteract urinary tract defenses and are able to avoid neutrophils by forming biofilms. (Figure 2).[2] Biofilms aid proliferation and colonization of the urethra and bladder by sacrificing the outer cells to protect the inner core. Intracellularly, UPEC can escape TLR4-mediated expulsion, manipulate lysosomes to impair their degenerative capacity, and remain within the autophagosome membrane to avoid phagocytosis when expelled.[3] The breadth of virulence factors found in UPEC strains distinguishes them from some commensal strains found in the intestine.[4] A key determinant of UPEC virulence is the *Ubil* gene, which is essential for the expression of type 1 pili, biofilm formation, and pathogenesis.[5]

Defense against uropathogens

Though previously considered sterile, the bladder's microbiome is increasingly thought to have

a protective role alongside that of the urethra.[6,7] In addition, acidic pH and urine transport act as barriers to pathogenic bacterial colonization of the urinary tract. The urothelium forms the major constitutive barrier to infection consisting of mucus glycosaminoglycans, which retard pathogen adherence, several layers of infection-resistant multinucleated umbrella cells, and glycoprotein plates called uroplakins. Apoptotic infected epithelial cells are released into the bladder lumen through exfoliation, reducing the bacterial load, and are replaced by inner basement stromal cells which produce new urothelium. Within the interstitium, soluble factors, such as the AMP cathelicidin (LL-37), form an important component of the response to pathogens like UPEC by targeting virulence factors. Immune cells are also present in both the epithelium and interstitium. In the upper urinary tract, dendritic cells, macrophages, neutrophils, and lymphocytes interact to defend against microorganisms. In the lower tract, mast cells, macrophages, neutrophils, and, in particular, natural killer (NK) cells act to combat colonization.[3]

In addition to their barrier function, epithelial cells express TLRs which trigger responses to pathogens. Activation of urothelium-expressed TLR4/5 leads to the release of proinflammatory cytokines, AMPs, and chemokines, which attract neutrophils from the bloodstream into the bladder lumen where they act as phagocytes. Both macrophages and NK cells release cytokines to promote this process, while mast-cell derived factors (e.g. histamine) cause vasodilation to aid cell migration.[3]

As in all immune responses, the stimulus-dependent portions of the immune system in the urinary tract should balance between potency of response and excessive inflammation. An imbalance may result in bacteria persisting, causing subsequent infection, or inflammatory damage to the urothelium. For example, TLR/PRR activation induces cell-specific inflammatory responses aimed at defense but is also associated with kidney disease.[8] In order to maintain balance, neutrophils are expelled in the urine to reduce inflammation. Regulatory invariant NK T-cells (NKT cells) and Treg cells exert anti-inflammatory effects on Th cells (Figure 1). In the latter stage of infection, mast cells take on an inhibitory role, keeping dendritic cells in an immature T-cell inhibitory state and reducing inflammation though interleukin (IL)-10 production. In addition, neutrophils are capable of producing anti-inflammatory metaprotease enzymes.[8]

Prevention of UTIs: a focus on immunomodulation

Vaccines remain the gold standard for preventive infectious-disease control. While E. coli-vaccine research continues, the expression of multiple suites of virulence factors by UPEC strains remains a stumbling block. Despite these challenges data from animal models showing that antibody titers correlate with bacterial load and infection duration suggest that vaccine-based prophylaxis can be effective.[4] Immunomodulation using bacteria-derived preparations offers an alternative route for prophylaxis. Several bacterial lysate therapies are available for UTI prevention. Of these, OM-89 is the best studied and consists of 18 strains of UPEC.[9]

OM-89 mode of action

OM-89 has a dual mechanism, acting as an immunostimulator increasing both the innate and adaptive response, and also as an immunoregulator acting on dendritic cells and promoting Treg cells. This dual immunomodulatory mechanism begins with nonspecific activation of dendritic cells in the gut-associated lymphoid tissue. This drives innate immunity by substantially increasing the production of phagocytosis-related cytokine interferon (IFN)-γ and through a small increase in the proinflammatory cytokine IL-6.[10] Interaction of these activated dendritic cells with T and B lymphocytes, aided by increased expression of CD80/CD86 co-stimulatory molecules, occurs in the Peyer's patches of the intestinal mucosa. This in turn leads to increases in Th cell, Tc cell, memory T-cell, and B lymphocyte production, followed by IgG and secretory IgA release. The integrated mucosal immune system allows cell migration and the mounting of an immune response in the urothelium and other mucosal tissue.[11] The immunomodulatory effect of OM-89 has been demonstrated in a mouse model of lipopolysaccharide-induced cystitis, reducing edema and stopping hemorrhage and infiltration by leukocytes.[10,11]

Guidelines for UTIs

Acute uncomplicated cystitis and pyelonephritis of a complicated or uncomplicated nature form the two major subdivisions in guidelines dealing with UTIs. The heterogeneous group of nosocomially

acquired UTIs and complicated UTIs (excluding pyelonephritis), each require separate guideline classification. These complicated infections are often related to comorbid disease or urological conditions. In addition, guidelines define treatment strategies for potentially life-threatening urosepsis and site-specific infections including urethritis, prostatitis, and epididymitis.

Acute uncomplicated lower UTI (cystitis): guideline recommendations

Definitions of uncomplicated cystitis vary between guidelines. The 2018 European Association of Urology (EAU) guidelines define uncomplicated UTI as acute, sporadic, or recurrent cystitis limited to nonpregnant, premenopausal women with no relevant anatomical or functional abnormalities in the urinary tract.[12] The relevance of any urinary tract abnormality is the key factor in whether a UTI should be treated as complicated or uncomplicated. This is emphasized in the current German S3 guidelines, which define uncomplicated UTI on the basis of no relevant functional and anatomical abnormalities, no relevant renal dysfunctions, or no relevant comorbidities/differential diagnoses favoring UTI or more serious outcomes.[13] From the perspective of the German S3 guidelines, infection in pregnant women, postmenopausal women, young men, and diabetics with stable glycemic control can receive the same categorization as uncomplicated when patients are otherwise healthy and without relevant comorbidities.[13]

When treating acute uncomplicated cystitis, physicians should target rapid resolution of symptoms, reduction of morbidity, and prophylaxis against reinfection. Treatment goals can be achieved *via* short-term antibiotic therapy without a focus on eliminating the presence of potentially pathogenic microbes in the urinary tract. The advantages of short-term therapy include: good compliance; low costs; fewer adverse events; and low impact on periurethral, vaginal, and rectal flora. Current EAU and German S3 guidelines recommend short courses of older antibiotics (fosfomycin trometamol, nitrofurantoin, nitroxoline, or pivmecillinam) for uncomplicated cystitis.[12,13] The minimal inhibitory concentration of nitroxoline (introduced in 1962) displays a wildtype-like distribution, indicating a lack of resistance markers in UPEC.[14]

Guidelines state that co-trimoxazole, fluoroquinolones, or cephalosporins should not be considered as first-line antibiotics for uncomplicated cystitis both due to the rise of resistance in the urinary tract, and collateral damage such as selecting for resistance in other compartments including the skin and fecal flora.[12,13] In addition, the United States Food and Drug Administration (US FDA) recently released a warning that the burden of fluoroquinolone side effects outweigh the benefits for uncomplicated infections of the urinary and respiratory tract.[15–17] Despite these myriad problems, the message on fluoroquinolones does not appear to have reached those treating uncomplicated acute cystitis in the community.

So, how should physicians treat asymptomatic bacteriuria (ABU)? The weight of evidence suggests that ABU is benign in the majority of cases and may in fact be protective.[18] In cases of significant ABU ($>10^5$ colony-forming units/ml in two urine cultures >24h apart), antibiotic treatment is only indicated during pregnancy and before invasive urological interventions. Studies have demonstrated that treatment of ABU has no beneficial effect in patients with diabetes, and antibiotic therapy has a detrimental effect on recurrent UTI, likely due to disruption of the urinary tract microbiota.[19,20] Additional evidence for this protective effect comes from a small phase I study ($n = 20$) in which UTI episodes were reduced following the introduction of *E. coli* 83972 into patients with neurogenic bladder.[21]

Diagnostics and symptom scoring

Classical diagnostics in acute uncomplicated cystitis involve: taking history to determine experience of recurrence and complicating factors; determining symptoms including frequency, urgency, and dysuria; physical examination of the genitals and assessment of suprapubic and flank pain; urinalysis using test strips, flow cytometry or microscopy; and urine culture. The delay involved in urine culture generally makes the test impractical, resulting in empirical treatment of most acute uncomplicated cystitis cases.

Novel data on the sensitivity and specificity of uranalysis and an increased understanding of the benign nature of ABU have led to a refocusing on symptoms scoring as a measure of diagnosis and treatment success.[22,23] The Acute Cystitis Symptom Score is an 18-item, validated, self-reported measure of symptoms that comprises four sections which assess: (1) typical symptoms; (2) symptoms for differential diagnosis; (3) quality of

life; and (4) additional signs and symptoms. With 94% sensitivity and 90% specificity, this system is analogous to microbiological assessments.[24] The Spanish and Portuguese versions of the questionnaire are currently being validated.

Recent data show that targeting symptoms and underlying inflammation using ibuprofen can be almost as effective as antimicrobial therapy. Patients were randomly assigned to receive fosfomycin trometamol 3 g as a single dose (n = 246; 243 analyzed) or ibuprofen 400 mg three times daily (n = 248; 241 analyzed) for 3 days. Symptoms reduced slightly more rapidly in the fosfomycin trometamol group, but after 7 days symptom scores were close to zero in both groups. However, cases of pyelonephritis were somewhat higher in the ibuprofen group. Diagnostic tests that can differentiate between patients who need therapy directed at the host response and those who need antimicrobial therapy could ameliorate the risk of patients developing pyelonephritis.[25]

Recurrent UTI and prophylaxis

Recurrent cystitis is defined as ⩾2 acute episodes in 6 months, or ⩾3 in 1 year. Within 3–4 months of an initial UTI, 20–30% women will experience a recurrence; 10–20% of women are thought to be living with recurrent UTIs at any one time.[26] In these patients, treatment of acute cystitis is not sufficient, and prophylaxis must be considered. There are three tiers of prophylactic measures for recurrent UTI: behavioral modification and counseling should be the first tactics employed to reduce recurrence, followed by nonantibiotic prophylaxis, and finally by low-dose continuous or postcoital antibiotic prophylaxis as a last resort.[12]

In cases where antibiotic prophylaxis is considered, nitrofurantoin (50−100 mg/day or after intercourse) or fosfomycin trometamol (3 g every 10 days) are recommended. However, rare but serious hepatic and pulmonary adverse reactions during long-term prophylaxis with nitrofurantoin must be taken into account and have led to its contraindication in some European countries. In pregnant women, prophylaxis with cephalexin (125−250 mg/day) or cefaclor (250 mg/day) is recommended, though the routine use in nonpregnant women cannot be recommended due to collateral damage to flora.[12]

Effective alternative strategies should avoid the side effects associated with antimicrobial use, avoid collateral damage, prevent resistance, and spare the limited antibiotic armament.[27] Behaviors such as reduced fluid intake, habitual and postcoital delayed urination, wiping from back to front after defecation, douching, and wearing occlusive underwear have been suggested to increase the risk of recurrent UTI.[12,28] However, evidence of the efficacy of most behavioral interventions targeting these risk factors remains weak. An exception to this is reduced sexual intercourse and avoidance of diaphragm/spermicide use, where the evidence of an association with reduced UTI is stronger.[29]

In postmenopausal women with a history of recurrent UTI, data from a randomized controlled trial indicates that use of topical estrogen (estriol 0.5 mg/8 months) led to a reduced incidence of UTI (0.5 *versus* 5.9 episodes per patient-year; $p < 0.001$) in treated patients (n = 50) compared with placebo (n = 43).[30] Use of probiotics containing Lactobacillus strains *L. rhamnosus* GR-1, *L. reuteri* RC-14, and *L. crispatus* CTV-05 may be considered for prevention of recurrent UTIs. Topical use is recommended once or twice weekly for prophylaxis, and daily use of oral products containing these strains can restore the vaginal lactobacilli. Competition of *Lactobacilli* with urogenital pathogens leads to a reduction in bacterial vaginosis, a condition that increases the risk of UTIs. In a randomized placebo-controlled trial of 100 women, those receiving intravaginal capsules containing *L. crispatus* had a relative risk (95% confidence interval) of 0.5 (0.2−1.2).[31] However, the evidence for these products remains weak, and more studies are needed.[12]

A large Cochrane review (n = 4473) including 24 studies on cranberry for UTI prophylaxis found no benefit overall [risk ratio (RR) 0.86 (0.71−1.04)]. Neither was any effect seen in subgroups including women with recurrent UTIs (RR 0.74, 0.42−1.31), the elderly [0.75 (0.39−1.44)], pregnant women [RR 1.04 (0.97−1.17)], children with recurrent UTI [RR 0.48 (0.19−1.22)], cancer patients [RR 1.15 (0.75−1.77)], and people with neuropathic bladder/spinal injury [RR 0.95 (0.75−1.20)].[32] In a randomized study of the fruit-derived sugar D-mannose (2 g daily; n = 103) *versus* nitrofurantoin (50 mg daily; n = 103) or no prophylaxis in women with a history of recurrent UTI, both prophylactic strategies led to a reduction in recurrence (RR 0.239 and 0.335, respectively; $p < 0.0001$). However, more studies are

required before recommendations can be made for D-mannose prophylaxis.[33]

Efficacy data for the oral bacterial lysate OM-89 are available from five 6-month randomized controlled trials and one 12-month randomized controlled trial. In the 6-month trial by Schulman and colleagues, patients with a history of ⩾2 microbiologically confirmed UTIs/year (⩾10^5 bacteria/ml or ⩾10^4 bacterial/ml in a catheterized sample) received 6 mg of OM-89 daily for 3 months (n = 82) or placebo (n = 78). Frequency of UTIs was reduced by 49% for OM-89 *versus* placebo ($p <$ 0.0001). Prophylaxis significantly reduced antibiotic use over the full trial period [mean days (% reduction): 6.3 *versus* 3.0 (−50%); $p <$ 0.0001]. In addition, there was an improvement in typical signs and symptoms, and a favorable risk-benefit profile [2 adverse event in the OM-89 group *versus* 11 with placebo (2% *versus* 6%)].[34]

In the 12-month randomized placebo-controlled trial by Bauer and colleagues, patients with ⩾3 acute UTIs in the previous 12 months (two or three symptoms for 2 days with microbiological urine analysis ⩾10^3 bacteria/ml) received a similar initial 3-month dosing schedule of OM-89 (n = 231) or placebo (n = 222). During months 7−9, patients received a 10-day booster or placebo. OM-89 therapy resulted in a 34% reduction in the cumulative mean rate of acute UTIs (185 *versus* 276; $p <$ 0.003). OM-89 also significantly decreased the mean number of antimicrobial drugs prescriptions by 13% (p = 0.005). The proportion of patients experiencing at least one adverse event was similar in the OM-89 *versus* the placebo group (32.5% *versus* 32.0%, respectively).[35]

These trial results have been confirmed in two meta-analyses: Naber and colleagues included five trials (n = 975) and demonstrated a 36% reduction ($p <$ 0.00001) in the frequency of UTIs over 6 months and a 20% increase in the number of patients who remained UTI free at study end ($p <$ 0.001). Furthermore, in higher risk patients there was a greater benefit of OM-89 prophylaxis. Results in terms of safety and antibiotic sparing were similar to individual trials.[9] Similarly, in a meta-analysis of 17 trials (n = 2165) comparing a number of nonantimicrobial prophylactic strategies, the efficacy of OM-89 was confirmed. Tentative positive results for bacteria-derived vaginal suppository Urovac, cranberry, and acupuncture, require further supporting research (Figure 3).[36]

A number of open-label studies also suggest that OM-89 is effective in higher risk groups.[37–41] In a 12-month study, postmenopausal women with recurrent UTI (n = 55) received a 3-month course of OM-89 with three booster sessions as described above. The mean incidence of recurrences fell by 64.7% ($p <$ 0.0001) during the study compared with the 6-months before study initiation. In a high-risk subgroup (>2 UTI in previous 6 months) the reduction was 66.9% ($p <$ 0.0001).[41] In 62 pregnant women with bacteriuria (>10^5/ml) who received OM-89 during weeks 16−28 of pregnancy, recurrences reduced by 62% compared with pre-initiation frequency, and antibiotic use was reduced by 76% (both $p <$ 0.002). All the newborns were healthy with normal Apgar (Appearance, Pulse, Grimace, Activity, and Respiration) scores, however, further studies are necessary before the safety of OM-89 can be confirmed during pregnancy.[37] Promising results were also found in children and patients with spinal cord injury. OM-89 was well tolerated in all trials.[38–40]

Guidelines recommendations for prophylaxis

The 2018 EAU guidelines give a strong recommendation for OM-89 (level of evidence: 1a; grade of recommendation: strong). All other previously mentioned prophylactic strategies require more data, except for topical estrogen for postmenopausal women, which received a weak recommendation (level of evidence: 1b; grade of recommendation: weak). OM-89 is currently recommended for prophylaxis by the EAU, German, Russian, Korean, and Brazilian guidelines, alongside those of Mexico City.[12,13,42–45]

Latin America: progress towards regional guidelines

Close to one-tenth of the world's population lives in Latin America. The unique ethnic makeup of patients, alongside local variation in the availability of medicines, antibiotic resistance, and health care practices necessitates the creation of regional guidelines on the treatment of UTI. Prescription of antibiotics for recurrent UTI without consideration of preventive measures is common in many Latin American countries. In a global survey of *E. coli* susceptibility in 10 countries, the mean sensitivity to trimethoprim/sulfamethoxazole was 71.2%; in the sole representative Latin American country, Brazil, it was 54.4%.[46]

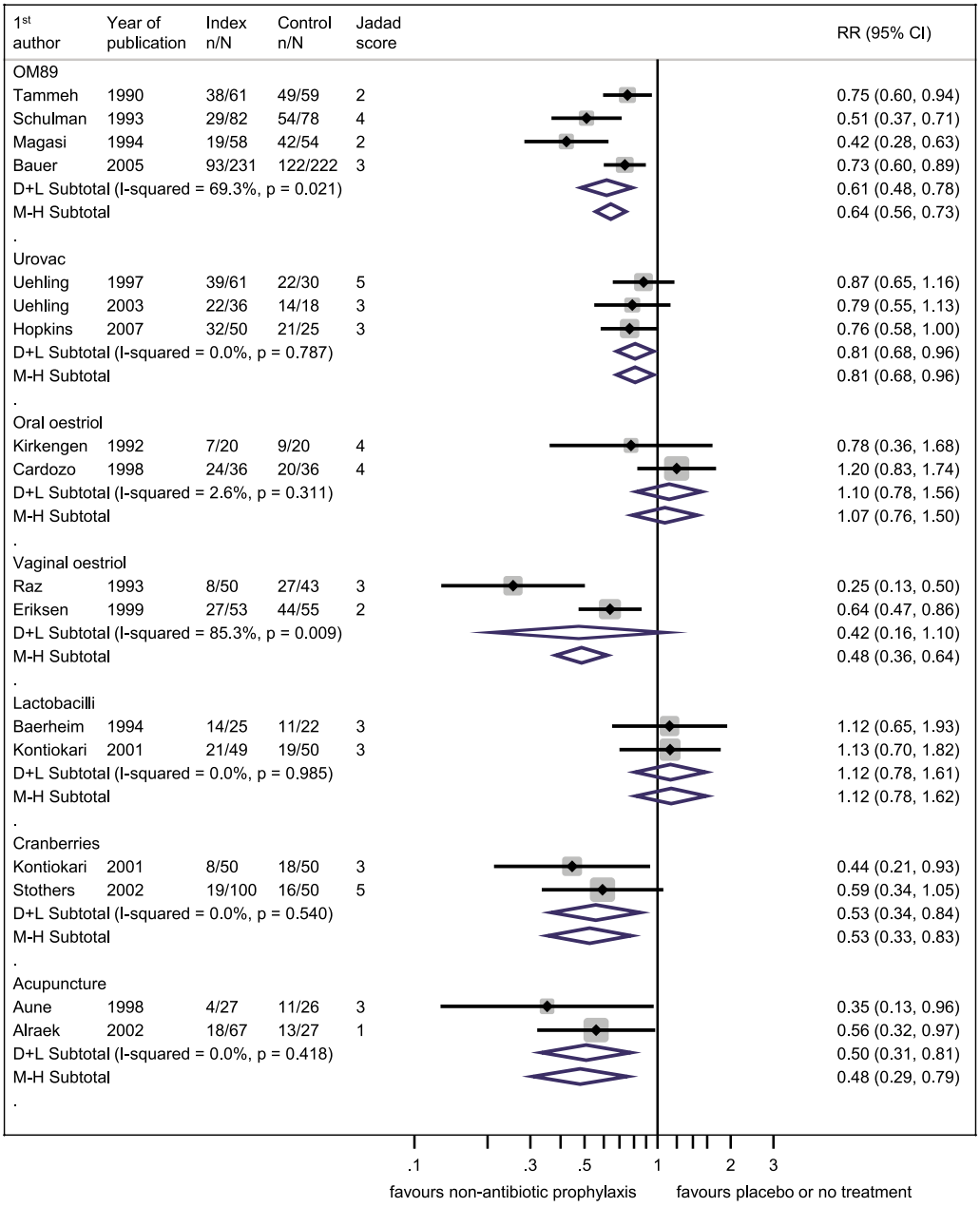

Figure 3. Forest plot of the efficacy of different forms of UTI prophylaxis.[36]
UTI, urinary tract infection; D+L, DerSimonian-Laird (random effects method); M-H, Mantel-Haenszel (fixed effects method). Beerepoot MA, Geerlings SE, van Haarst EP, *et al*. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. *J Urol* 2013; 190: 1981–1989, https://www.jurology.com/. © 2013 by American Urological Association Education and Research, Inc.

The current Brazilian guidelines were based on systematic review and expert opinion, organized by the Urogynecology Committee of the Brazilian Federation of Gynecology and Obstetrics Associations [*Federação Brasileira de Ginecologia e Obstetricia* (FEBRASGO)]. The committee included papers that cover genital prolapse, stress urinary incontinence, overactive bladder, mixed urinary incontinence, painful bladder syndrome, and recurrent UTI. Guideline sections covering genital prolapse and stress urinary incontinence have been published in the Brazilian Journal of Gynecology and Obstetrics.[47,48] The guidelines for recurrent UTI have yet to be published in a peer-reviewed journal, but are available online as a guide for members of FEBRASGO; they recommend behavioral modification, followed by immunomodulatory prophylaxis (in particular

OM-89), and, finally, by either continuous or postcoital antimicrobial prophylaxis.

Although local guidelines from individual countries or regions exist, there is a need for an overarching Latin American consensus.[42,43] The founding of the Brazilian Society of Urogynecology and the Pelvic Floor (*Associação Brasileira de Uroginecologia e Assoalho Pélvico*) in 2017, and the experience of its president, Jorge M. Haddad, as representative to the International Urogynological Association (IUGA) precipitated the formation of the Latin American Board of Urogynecology, in the same year. As well as working towards a unified guideline, the board (which is made up of the presidents of regional societies) will facilitate the work of representatives within both global and regional organizations such as the IUGA, the International Federation of Gynecology and Obstetrics, and the *Federacion Latinoamericana de Sociedades de Obstetricia y Ginecología*. In addition, a database of regional studies is being created to act as a single regional data repository to facilitate multicenter studies and promote high-quality publications.

Following their first meeting, the board defined the parameters of their upcoming consensus statement on the management of recurrent UTI, which will cover diagnostic workup, risk factors and behavioral changes, nonantimicrobial prophylaxis, and antimicrobial prophylaxis. As of summer 2018, the consensus has been drafted, and an English translation is being created in anticipation of publication.

Case series discussions

The following section summarizes cases with special features resulting in difficult treatment choices, which, though unusual, are still seen frequently in urological clinics.

Case 1

A 55-year-old woman presented with an acute uncomplicated UTI and a 3-year history of recurrent UTIs (six episodes per year). Despite receiving multiple treatments from multiple specialists including behavioral interventions, her quality of life was poor at presentation. She underwent abdominal hysterectomy 10 years earlier during which her left ureter was accidentally sectioned, requiring reinsertion into the bladder 1 week after the initial surgery. Recurrent UTIs began following an uneventful recovery and normal urine flow without leakage (confirmed by computed tomography scan). At presentation, the patient was receiving hormone replacement therapy (HRT) with oral estrogens and had an abnormal vaginal flora. Uranalysis results showed 5600 leukocytes/µl, positive bacteria, and positive nitrites.

Her urine culture revealed multi-resistant *E. coli* (10^4 colony-forming units/ml) with susceptibility to amikacin [minimum inhibitory concentration (MIC) $\leqslant$ 16.0 µg/ml], nitrofurantoin (MIC $\leqslant$ 32.0 µg/ml), cefepime (MIC $\leqslant$ 6.0 µg/mL), imipenem (MIC $\leqslant$ 4.0 µg/ml), meropenem, (MIC $\leqslant$ 4.0 µg/ml), and piperacillin/tazobactam (MIC $\leqslant$ 16.0 µg/ml). The patient was started on nitrofurantoin 100 mg/8 h for 7 days to control the acute infection. Vaginal estriol cream was initiated to normalize vaginal flora (1 mg/g every other day for 1 month), and HRT was stopped. Prophylactic therapy with OM-89 was initiated daily for 3 months. The patient was asymptomatic for 18 months before presenting with a mildly symptomatic acute UTI, uranalysis showed 200 leukocytes/µl and bacteria present. Urine culture showed multi-resistance *E. coli* with sensitivity to nitrofurantoin once again. Nitrofurantoin treatment was reinitiated, along with a second course of OM-89 to ensure coverage for the next 18 months.

Case 2

A 54-year-old female patient presented with acute UTI. She had a 4-year history of type 2 diabetes and recurrent vaginal infections caused by *Candida spp.* and *E. coli*. Her glycemic control was poor despite treatment with metformin and a SGLT-2 inhibitor. The patient was allergic to nitrofurantoin following 10 years of chronic treatment for recurrent UTIs. Her vaginal flora was deficient, and she was using combined topical HRT to control her symptoms. Upon presentation she was found to have a *Candida albicans* infection resistant to fluconazole and voriconazole. Leukocytes were negative and bacteria were absent.

Urinalysis revealed glycosuria (>20 g/l) and hematuria, with trace amounts of hemoglobin. The patient was referred to an endocrinologist to address the underlying glycosuria. Prophylaxis with OM-89 for 3 months, along with weekly itraconazole (200 mg) to control the acute infection, were initiated. With improved glycemic control,

prophylaxis, and acute treatment she presented with one UTI caused by *E. coli* and with two episodes of fungal infection in the following year.

Conclusion

The branches of the immune system act in concert to control infection, and under normal circumstances maintain a balance between control of infection and excess inflammation. In the urinary tract, immunomodulatory therapies such as OM-89 have dual modalities, acting both to stimulate the immune response and to regulate excessive inflammation. The integrated mucosal immune system facilitates the immunomodulatory effect of oral therapies at remote sites including the urinary tract.

Current guidelines for the treatment of acute uncomplicated cystitis recommend short-term antibiotic therapy with a focus on symptom resolution rather than elimination of microbes in the urinary tract. Prophylaxis against recurrent UTI should encompass behavioral modification and counseling, followed by nonantibiotic prophylaxis, and, finally, by continuous or postcoital antibiotic prophylaxis. Current EAU guideline recommendations for nonantimicrobial prophylaxis recommend OM-89; in postmenopausal women, topical estrogen is also recommended.

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Conflict of interest statement

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References

1. Karta MR, Broide DH and Doherty TA. Insights into group 2 innate lymphoid cells in human airway disease. *Curr Allergy Asthma Rep* 2016; 16: 8.
2. Flores-Mireles AL, Walker JN, Caparon M, *et al*. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol* 2015; 13: 269–284.
3. Abraham SN and Miao Y. The nature of immune responses to urinary tract infections. *Nat Rev Immunol* 2015; 15: 655–663.
4. Brumbaugh AR and Mobley HL. Preventing urinary tract infection: progress toward an effective Escherichia coli vaccine. *Expert Rev Vaccines* 2012; 11: 663–676.
5. Floyd KA, Mitchell CA, Eberly AR, *et al*. The UbiI (VisC) aerobic ubiquinone synthase is required for expression of type 1 pili, biofilm formation, and pathogenesis in uropathogenic *Escherichia coli*. *J Bacteriol* 2016; 198: 2662–2672.
6. Thomas-White K, Brady M, Wolfe AJ, *et al*. The bladder is not sterile: history and current discoveries on the urinary microbiome. *Curr Bladder Dysfunct Rep* 2016; 11: 18–24.
7. Thomas-White K, Forster SC, Kumar N, *et al*. Culturing of female bladder bacteria reveals an interconnected urogenital microbiota. *Nat Commun* 2018; 9: 1557.
8. Kurts C, Panzer U, Anders HJ, *et al*. The immune system and kidney disease: basic concepts and clinical implications. *Nat Rev Immunol* 2013; 13: 738–753.
9. Naber KG, Cho YH, Matsumoto T, *et al*. Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis. *Int J Antimicrob Agents* 2009; 33: 111–119.

10. Lee SJ, Kim SW, Cho YH, *et al.* Anti-inflammatory effect of an Escherichia coli extract in a mouse model of lipopolysaccharide-induced cystitis. *World J Urol* 2006; 24: 33–38.

11. Meredith M, Chiavaroli C and Bauer HG. Immunotherapy for recurrent urinary tract infections: effects of an escherichia coli extract. *Curr Urol* 2009; 3: 1–8.

12. Bonkat G, Pickard R, Bartoletti R, *et al. EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2018*. ISBN 978-94-92671-01-1, EAU Guidelines Office, Arnhem, The Netherlands, http://uroweb.org/guidelines/compilations-of-all-guidelines/

13. Kranz J, Schmidt S, Lebert C, *et al.* The 2017 Update of the German clinical guideline on epidemiology, diagnostics, therapy, prevention, and management of uncomplicated urinary tract infections in adult patients: part 1. *Urol Int* 2018; 100: 263–270.

14. Kresken M and Korber-Irrgang B. In vitro activity of nitroxoline against Escherichia coli urine isolates from outpatient departments in Germany. *Antimicrob Agents Chemother* 2014; 58: 7019–7020.

15. US Food and Drug Administration. FDA approves safety labeling changes for fluoroquinolones, https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm500325.htm (2016, accessed 26 July 2016).

16. Auwaerter PG. Fluoroquinolones not first line: FDA advisory reinforces standard practice in ambulatory care, https://www.medscape.com/viewarticle/863778?nlid=105987_1842src=WNL_mdplsfeat_160607_mscpedit_wiruac=143664DGspon=17impID=1120486faf=1 (2016, accessed 2 June 2016).

17. Alternatives to fluoroquinolones. *JAMA* 2016; 316: 1404–1405.

18. Wagenlehner FME and Naber KG. Editorial commentary: asymptomatic bacteriuria—shift of paradigm. *Clin Infect Dis* 2012; 55: 778–780.

19. Harding GK, Zhanel GG, Nicolle LE, *et al.* Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. *N Engl J Med* 2002; 347: 1576–1583.

20. Cai T, Nesi G, Mazzoli S, *et al.* Asymptomatic bacteriuria treatment is associated with a higher prevalence of antibiotic resistant strains in women with urinary tract infections. *Clin Infect Dis* 2015; 61: 1655–1661.

21. Sunden F, Hakansson L, Ljunggren E, *et al.* Escherichia coli 83972 bacteriuria protects against recurrent lower urinary tract infections in patients with incomplete bladder emptying. *J Urol* 2010; 184: 179–185.

22. Stamm WE, Counts GW, Running KR, *et al.* Diagnosis of coliform infection in acutely dysuric women. *N Engl J Med* 1982; 307: 463–468.

23. Hooton TM, Roberts PL, Cox ME, *et al.* Voided midstream urine culture and acute cystitis in premenopausal women. *N Engl J Med* 2013; 369: 1883–1891.

24. Alidjanov JF, Abdufattaev UA, Makhsudov SA, *et al.* New self-reporting questionnaire to assess urinary tract infections and differential diagnosis: acute cystitis symptom score. *Urol Int* 2014; 92: 230–236.

25. Gágyor I, Bleidorn J, Kochen MM, *et al.* Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. *BMJ* 2015; 351: h6544.

26. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Am J Med* 2002; 113(Suppl. 1A): 5s–13s.

27. Dethlefsen L, Huse S, Sogin ML, *et al.* The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol* 2008; 6: e280.

28. Wagenlehner FM, Vahlensieck W, Bauer HW, *et al.* Prevention of recurrent urinary tract infections. *Minerva Urol Nefrol* 2013; 65: 9–20.

29. Hooton TM, Scholes D, Hughes JP, *et al.* A prospective study of risk factors for symptomatic urinary tract infection in young women. *N Engl J Med* 1996; 335: 468–474.

30. Raz R and Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med* 1993; 329: 753–756.

31. Stapleton AE, Au-Yeung M, Hooton TM, *et al.* Randomized, placebo-controlled phase 2 trial of a Lactobacillus crispatus probiotic given intravaginally for prevention of recurrent urinary tract infection. *Clin Infect Dis* 2011; 52: 1212–1217.

32. Jepson RG,Williams G and Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev* 2012; 10: Cd001321.

33. Kranjcec B, Papes D and Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol* 2014; 32: 79–84.

34. Schulman CC, Corbusier A, Michiels H, *et al.* Oral immunotherapy of recurrent urinary tract infections: a double-blind placebo-controlled multicenter study. *J Urol* 1993; 150: 917–921.

35. Bauer HW, Alloussi S, Egger G, *et al*. A long-term, multicenter, double-blind study of an Escherichia coli extract (OM-89) in female patients with recurrent urinary tract infections. *Eur Urol* 2005; 47: 542–548; discussion 8.

36. Beerepoot MA, Geerlings SE, van Haarst EP, *et al*. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. *J Urol* 2013; 190: 1981–1989.

37. Baertschi R, Eduah SB, Liechti A, *et al*. Bacterial extract for the prevention of recurrent urinary tract infections in pregnant women: a pilot study. *Int J Immunother* 2003; 19: 25–31.

38. Czerwionka-Szaflarska M and Pawlowska M. Influence of Uro-Vaxom on sIgA level in urine in children with recurrent urinary tract infections. *Arch Immunol Ther Exp (Warsz)* 1996; 44: 195–197.

39. Lettgen B. Prevention of recurrent urinary tract infections in female children: OM-89 Immunotherapy compared with nitrofurantoin prophylaxis in a randomized pilot study. *Curr Ther Res* 1996; 57: 464–475.

40. Hachen HJ. Oral immunotherapy in paraplegic patients with chronic urinary tract infections: a double-blind, placebo-controlled trial. *J Urol* 1990; 143: 759–762; discussion 62–63.

41. Popa GLK, Rothe H and Rugendorff E. Urinary tract infection in the postmenopause. Efficacy of oral immunotherapy with E. coli preparations Article in German. *Muenchener Medizinische Wochenschrif* 1996; 138: 713–716.

42. Tavares W, Lopes HV, Castro R, *et al*. Cistite recorrente: tratamentoe prevenção. *Diretrizes Clínicas na Saúde* 2011.

43. Del Pilar Velazquez M, Romero Nava LE, Lopez de Avalos DR, *et al*. Clinical practice guidelines. Recurrent infection of the urinary tract in women. Colegio Mexicano de Especialistas en Ginecología y Obstetricia. *Ginecol Obstet Mex* 2010; 78: S437–S459.

44. Perepanova TS. The 2015 federal clinical guidelines for antimicrobial therapy and prevention of infections of the kidney, urinary tract, and male genitals. *Ter Arkh* 2016; 88: 100–104. (in Russian).

45. Lee SJ, Choe HS, Na YG, *et al*. 2017 Guidelines of The Korean association of urogenital tract infection and inflammation: recurrent urinary tract infection. *Urogenit Tract Infect* 2017; 12: 7–14.

46. Naber KG, Schito G, Botto H, *et al*. Surveillance study in Europe and Brazil on clinical aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): implications for empiric therapy. *Eur Urol* 2008; 54: 1164–1175.

47. Moroni RM, Magnani PS, Haddad JM, *et al*. Conservative treatment of stress urinary incontinence: a systematic review with meta-analysis of randomized controlled trials. *Rev Bras Ginecol Obstet* 2016; 38: 97–111.

48. Juliato CR, Santos Júnior LC, Haddad JM, *et al*. Mesh surgery for anterior vaginal wall prolapse: a meta-analysis. *Rev Bras Ginecol Obstet* 2016; 38: 356–364.