Urology Practice Review™

Making Education Easy

Issue 10 - 2023

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **ARTG** = Australian Register of Therapeutic Goods; **AUA** = American Urological Association; **BPH** = benign prostatic hyperplasia; **CT** = computed tomography; **DFS** = disease-free survival; **EAU** = European Association of Urology; **EFS** = event-free survival; **IPSS** = International Prostate Symptom Score; **MIBC** = muscle invasive bladder cancer; **PBAC** = Pharmaceutical Benefits Advisory Committee; **PBS** = Pharmaceutical Benefits Scheme; **PD-(L)1** = programmed death-(ligand) 1; **RPLND** = retroperitoneal lymph node dissection; **SUI** = stress urinary incontinence; **TGA** = Therapeutic Goods Administration; **UTI** = urinary tract infection.

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Welcome to the 10th issue of Urology Practice Review.

This Review covers news and issues relevant to clinical practice in urology. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, professional body news and more. And finally, on the back cover you will find our COVID-19 resources for Urologists and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

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Clinical Practice

EAU Guidelines: Urological infections

A 2023 update to the European Association of Urology (EAU) Urological Infections Guidelines has been published. Based on a comprehensive literature review of publications in Medline, EMBASE and the Cochrane Libraries, the update was collated by a panel comprised of specialist urologists plus an infectious disease specialist and a clinical microbiologist and provides evidence-based recommendations for the prevention and treatment of infections of the urinary tract (UTIs) and male accessory gland. Changes from the 2022 iteration of the guidelines have been made in the sections covering recurrent UTIs, and peri-procedural antibiotic prophylaxis. An inaugural section titled, "Genitourinary Tuberculosis" debuts in the 2023 update. Sections with advice for asymptomatic bacteriuria, uncomplicated cystitis, uncomplicated pyelonephritis, complicated UTIs, catheter-associated UTIs, urosepsis, urethritis, bacterial prostatitis, acute infective epididymitis, Fournier's gangrene and the management of Human papilloma virus in men have not been modernised since the 2022 refurbish.

The novel genitourinary tuberculosis section covers epidemiology, aetiology and pathophysiology, diagnosis and medical treatment. A dearth of high-quality evidence regarding surgical treatment and imaging diagnostics for genitourinary tuberculosis precludes the formation of practical advice in these areas. Two recommendations for diagnosis and three for treatment are provided that are supported by a strong evidence base as follows:

Diagnosis

- A full medical history, including history of previous pulmonary and extrapulmonary tuberculosis infection, should be obtained for all patients presenting with persistent non-specific genitourinary symptoms and no identifiable cause
- In the absence of a single diagnostic test, acid-fast bacilli culture is the reference standard and should be performed preferentially over smear microscopy to isolate *M. tuberculosis*. Culturing of three midstream first-void urine samples should be conducted. Disadvantages of this method include the long lag in results and low sensitivity for urine culture in renal specimens

Weak recommendations regarding the diagnosis of genitourinary tuberculosis advocate for the use of a nucleic acid amplification test (the WHO conditionally recommends Xpert MTB/RIF for use in patients suspected of extrapulmonary tuberculosis), in addition to the microbiological test and/or use of an imaging modality such as ultrasound, intravenous urography, computed tomography or magnetic resonance imaging to identify infectious loci and evaluate the extent of damage.

Treatment

- Medical treatment should be used as the first-line therapeutic
- Treatment for newly diagnosed genitourinary tuberculosis should consist of a six-month regimen including daily isoniazid plus rifampicin (5 and 10 mg/kg every 24 hours, respectively), administered in combination with pyrazinamide (25 mg/kg every 24 hours) and ethambutol (15–20 mg/kg every 24 hours) for the first two months.
- Multi-drug resistant tuberculosis requires a personalised strategy with a pyrazinamide-based quintuplet regimen including one fluoroquinolone (levofloxacin, moxifloxacin or gatifloxacin), one second-line injectable (amikacin, capreomycin, kanamycin or streptomycin) plus at least two other second-line agents such as ethionamide/ prothionamide, cycloserine/terizidone, linezolid or clofazimine.

Both the full comprehensive guidelines plus an abridged pocket version are available on the EAU website here

Updated testicular cancer guidelines

Recent updates to both the American Urological Association (AUA) and the EAU guidelines on diagnosing and treating testicular cancer, a rare malignancy comprising 5% of urological tumours but the most common solid malignancy among young men, have been published. The recommendations encapsulate the most up-to-date evidence to aid clinicians in providing the highest standard of clinical care for patients with this condition and optimise outcomes. Both guidelines were informed by systematic reviews of the latest evidence regarding risk stratification, recurrence, survival, therapy efficacy and treatment-related toxicity, with authorship attributed to a multidisciplinary panel comprised of experts in the fields of urology, oncology, radiology and pathology.

Following is a synopsis of the salient amendments in the 2023 guideline iterations:

EUA guideline update

Counsel is provided in this guideline for the management of germ cell neoplasia *in situ*, seminoma germ cell tumours and nonseminoma germ cell tumours, according to TNM stage and metastatic status. The guideline covers diagnosis and initial management - including clinical assessment, imaging with ultrasound, contrast-enhanced computed tomography (CT) ± brain imaging in select patients and evaluation of serum tumour markers such as serum α-fetoprotein (AFP), hCG and lactate dehydrogenase plus microRNAs (particularly miR-371a-3p). Advice is provided regarding determination of prognostic class, prognostic factors for progression and recurrence, as well as surgical and medical treatments for locoregional and metastatic disease including radical orchidectomy with/without retroperitoneal lymph node dissection (RPLND), testis-sparing surgery and adjuvant treatments. A pivotal change in the 2023 iteration of the guidelines is an inaugural oncology treatment protocols section that covers the main principles of toxicity and emergency management particular to germ cell tumours, corresponding to the reference chemotherapy protocols section. Other key alterations included the provision of information concerning venous thromboembolism prophylaxis in patients with metastatic tumours undergoing chemotherapy; quality of life after treatment; an update of the histological classifications and inclusion of the World Health Organization 2022 pathological classification; and inclusion of the revalidation of the 1997 International Germ Cell Cancer Collaborative Group prognostic risk factors.

In 2024 a full update to the EAU guideline is expected to incorporate all novel evidence, with creation of novel online sections.

AUA guideline update

Of the 43 statements in the 2019 guidelines on the diagnosis and treatment of early-stage testicular cancer changes were made to five, namely:

Imaging

The strong recommendation for contrast-enhanced CT peritoneal and pelvic imaging for staging and treatment selection purposes in newly diagnosed patients has been modernised to suggest magnetic resonance imaging in cases of contraindication to CT (Evidence Level: Grade C)

Management of seminoma

Moderate strength advice advocates for RPLND as a less toxic alternative to multi-agent cisplatin-based chemotherapy or radiation in patients with stage 2A/B seminoma with a lymph node diameter of 3 cm or less (Evidence Level: Grade B)

Management of non-seminoma

The decision between surveillance and adjuvant therapy following a primary RPLND should be guided by pathology findings, with surveillance directed for pN1 and pN1-3 pure teratoma and two cycles of cisplatin-etoposide chemotherapy without bleomycin for pN2-3 disease at RPLND (Moderate Recommendation; Evidence Level: Grade B)

Surveillance of stage 1 disease

The recommendation regarding regular physical examination and cross-sectional abdominal ± pelvic imaging for patients undergoing surveillance for clinical stage 1 seminoma has been strengthened from moderate to strong. The modernised timing of the surveillance protocol is six monthly follow-up for two years followed by annual or bi-annual follow-up up to year 5 (Evidence Level: Grade B)

Survivorship

The expert opinion advice regarding survivorship has been condensed into a single section (statement 43). The pertinent consideration in this regard concerned the need for a long-term comprehensive survivorship program that screens for potential concomitant conditions and development of treatment-related sequelae.

Full versions of the guidelines are available on the EAU and AUA websites

Eur Urol. 2023;84(3):289-301

J Urol. 2023; Sep 14. Online ahead of print

What are the short-term benefits and potential harms of therapeutic modalities for the management of overactive bladder syndrome in women?

A review of evidence under the auspices of the European Association of Urology, Female Non-neurogenic Lower Urinary Tract Symptoms Guidelines panel finds that overactive bladder syndrome in females is a manageable condition that requires employment of conservative, pharmacological and/or surgical modalities, according to individual patient factors. Analysis of acute efficacy, safety and adverse events for each therapy was based on literature published in online databases such as Medline, Embase and Cochrane *inter alia* with a cut-off date of May 2022. In the first-line setting both antimuscarinics and beta-3 agonists outperformed placebo for amelioration of symptoms, with beta-3 agonists having a safer profile and outranking antimuscarinics for mitigation of nocturia episodes. Of the second-line therapy options, onabotulinumtoxin-A bladder injections and sacral nerve stimulation had comparable efficacy outcomes, with improved rates of cure of urgency urinary incontinence and higher success rates with the former and the latter, respectively, compared to antimuscarinics. The removal and revision rate for sacral nerve stimulation were 9% and 3%, respectively.

Eur Urol. 2023;84(3):302-12

Evaluation of sensitive urine DNA-based *PENK* methylation test for detecting bladder cancer in patients with hematuria

A urine-based molecular tool may be a novel diagnostic test for bladder cancer in patients with haematuria, offering an economical, sensitive and non-invasive diagnostic alternative to cystoscopy, with positive results reported by a South Korean research group. The DNA methylation test employs linear target enrichment followed by quantitative methylation-specific PCR to identify *PENK* methylation in urine. In a case-control study of over 300 individuals with/without bladder cancer and a prospective validation clinical study of almost 400 patients with haematuria, the test demonstrated high overall sensitivity and specificity (86.9%/84.2% and 91.6%/95.7%, respectively) with a diagnostic accuracy of approximately 90%. Negative and positive predictive values of 98.2% and 68.7%, respectively, were reported. The greatest sensitivity was found in malignancy of Ta high-grade or higher stage (92.3%).

J Mol Diagn. 2023;25(9):646-54

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FURTHER INFORMATION AVAILABLE ON REQUEST FROM ASTRAZENECA.

References: 1. Zoladex 10.8mg Approved Product Information. **2.** Zoladex 3.6mg Approved Product Information.

The PINNACLE study: A double-blind, randomized, sham-controlled study evaluating the Optilume BPH catheter system for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia

The multi-centre North American PINNACLE trial evaluated the efficacy of the Optilume™ BPH Prostatic Dilation DCB Catheter system - a novel dual-action minimally invasive prostatic urethra commissurotomy device that achieves mechanical prostate lob separation through the use of a double-lobe drug-coated balloon and pharmacological inhibition of further growth plus refusion of the lateral lobes with paclitaxel - for lower urinary tract symptoms secondary to benign prostatic hyperplasia (BHP). A total of 148 men at least 50 years of age with moderate-to-severe symptomatic BHP (International Prostate Symptom Score [IPSS] ≥ 13; prostate volume, 20-80 g), an obstructed urinary tract impeding urine flow (peak urinary flow ≥ 5 ml/sec and ≤ 12 ml/sec) and a history of an inadequate response to medical intervention were enrolled from sites in the US and Canada. Random allocation assigned patients to undergo surgery with the Optilume BPH Catheter System or a sham device modified to prevent inflation in a 2:1 ratio, with the same analgesia, anaesthesia and catherization protocols.

Analysis in the intention-to-treat population revealed that the Optilume BPH elicited significantly greater improvements in symptom severity versus sham, with a roughly 11-point reduction in mean IPSS at three-months that was durable at 12-month follow-up - an average improvement of 49% that exceeded the prespecified performance goal of 30%. The same metric in the sham cohort was -8 points at three-months (p=0.008), an improvement that was not sustained, with continual worsening of symptoms over time (12-months, mean IPSS- 4.8). Durable improvements in urine flow rate were also significantly greater in the patients who underwent surgery with the Optilume BPH Catheter System (mean change in peak urinary flow, +9.7 vs +5.5 mL/s; p=0.009). Relief from symptoms in the intervention arm were reported immediately with minimal adverse events and no compromise of sexual function. According to the study authors the procedure is suitable for use in outpatient or ambulatory settings.

These data, along with findings from the EVEREST-1 randomised trial, led to the US Food and Drug Administration approval of the Optilume™ BPH Catheter System for this indication in June this year and to roll-out of the procedure commercially in Canada. In Australia, a similar device – the Optilume® Urethral Drug Coated Balloon - has TGA approval for the treatment of anterior urethral stricture.

J Urol. 2023;210(3):500-09

Antibiotic prophylaxis in infants with grade III, IV, or V vesicoureteral reflux

PREDICT aimed to elucidate whether long-term antibiotic prophylaxis mitigates the risk of bacterial UTIs in children with congenital malformations of kidney or urinary tract resulting in vesicoureteral reflux. The trial also investigated if renal damage caused by acute UTI-associated pyrexia influences the development of chronic kidney failure. Infants between one and five months of age (n=292) with grade 3, 4 or 5 vesicoureteral reflux and a low glomerular filtration rate (> 15 ml/min/1.73 m2) who had no history of prior symptomatic UTI were accrued from 39 European centres and randomised 1:1 to receive two-years of continuous antibody prophylaxis or clinical surveillance without prophylaxis. Patients in the intervention arm received physician's choice of nitrofurantoin, amoxicillin-potassium clavulanate combination, cefixime or trimethoprim/sulfamethoxazole, according to the spectrum of UTI-causing bacteria in their region. Intention-to-treat analysis at the conclusion of the treatment period found a 14.4% lower rate of first UTI development in the antibiotic prophylaxis arm versus the surveillance arm, a difference that was statistically significant with a hazard ratio of 0.55 (21.2% vs 35.6%). The study authors reported that seven children needed to be treated for two years to prevent one UTI. Secondary outcomes, including the incidence of new renal scars and kidney function, were comparable between treatment cohorts. Although serious adverse events were not higher in the antibiotic prophylaxis arm compared to the surveillance arm, antibiotic resistance and non-*Escherichia coli* organisms were more common in children who developed a UTI while on antibiotic prophylaxis. Follow-up with assessment of renal function is ongoing for a further three years.

N Engl J Med. 2023;389(11):987-97

Perioperative chemoimmunotherapy with durvalumab for muscle-invasive urothelial carcinoma: Primary analysis of the single-arm phase II trial SAKK 06/17

Data from this Swiss single-arm trial support the perioperative use of chemoimmunotherapy in patients with resectable muscle-invasive bladder cancer (MIBC), reporting high event-free survival (EFS) rates with the integration of the anti-programmed death-ligand 1 (PD-L1) antibody durvalumab to a standard neoadjuvant chemotherapy regimen plus single-agent durvalumab adjuvant therapy. Adult patients (n=61) with histologically proven urothelial cell carcinoma, predominantly of the bladder, that has penetrated to the superficial or deep muscle of the bladder (stage T2-4a and ≤ N1), with one or no solitary small lymph node lesions and no distant metastasis considered amenable to curative radical surgery were enrolled. Treatment consisted of four cycles of durvalumab plus cisplatin/gemcitabine chemotherapy prior to radical surgery and 10 cycles of single-agent durvalumab administered in the adjuvant setting. The trial met its primary efficacy endpoint, finding an EFS rate of 76% at two years. Rates of overall survival at two and three years were 85% and 81%, respectively. One-third of patients who underwent surgery attained a complete pathological response. A favourable side event profile was reported with low rates of severe adverse events. The phase 3 NIAGARA trial further evaluated this treatment strategy.

J Clin Oncol. 2023; Aug 17. Online ahead of print

Commencement of trials of automated artificial sphincters for SUI

A press release from the French mechatronics technology company UroMems reports that both female and male patients with stress urinary incontinence (SUI) have been implanted with automated artificial sphincters in the TRANSITION and SOPHIA trials, respectively. Named UroActive™, the devices are powered by a MyoElectroMechanical System and are "smart", automatically adjusting urethral pressure according to patient activity as measured by microsensors. The data from these initial trials will inform the design of pivotal studies with patient accrual planned in the US and Europe. UroActive is supported by an FDA Safer Technologies Program (STeP) designation to expedite development and commercialisation.

The full press release can be read here and more information is reported in the *Urology Times*

Regulatory News

PBAC recommendations

At its July 2023 meeting the Pharmaceutical Benefits Advisory Committee (PBAC) made the following recommendations for Pharmaceutical Benefits Scheme (PBS) listings:

- to change the existing listing for of the composite pack of abiraterone acetate with 30 methylprednisolone (Yonsa Mpred®) for metastatic hormone sensitive prostate cancer to a General Schedule Authority Required listing.

Read more here

PBS listings

In 2023 several new or expanded PBS listings have been made including:

- A composite pack of oral abiraterone and methylprednisolone (Yonsa® MPRED) tablets for the treatment of patients with metastatic castration resistant prostate cancer
- Apalutamide (Erlyand®) will be subsided for hormone-sensitive prostate cancer effective 1 June 2023, joining androgen deprivation therapy (ADT) and chemotherapy for this indication
- Following the PBAC recommendation to list enzalutamide (Xtandi®) for the treatment of metastatic hormone-sensitive prostate cancer in combination with ADT, irrespective of disease volume or suitability for docetaxel, subsidy became effective from 1 August 2023. Clinicians can apply for authority in real-time via the Online PBS Authorities system or over the phone
- Indications for subsidy of chlorogonatrophin alfa (Ovidrel®) will be extended beyond artificial reproductive techniques for ovarian stimulation and initiation of ovulation from the 1st July to include the following applications in males:
  - Treatment of acquired hypogonadotropic hypogonadism
  - Puberty induction in males with congenital hypogonadotropic hypogonadism
  - Promotion of testicular descent not due to anatomic obstruction
  - Stimulation of spermatogenesis in infertility caused by hypogonadotrophic hypogonadism

TGA registrations

New medical devices listed on ARTG

Several new listings for medical devices have received Therapeutic Goods Administration (TGA) approval and been added to the Australian Register of Therapeutic Goods (ARTG) including:

- The iSR'obot Mona Lisa 2.0 - Prostate stereotactic biopsy/ablation system. This stereotaxic accessory is designed to aid positioning of probes or needles during image-guided diagnostic and interventional procedures such as biopsies, and soft tissue ablations.
- The CT3000 Pro Console - Urodynamic measurement system. This device is used to measure urinary flow rate, urethral pressure, bladder capacity and response and measurement of sphincter and other muscle activity and is utilised in the diagnosis of abnormal voiding conditions such as neurogenic bladder diseases, stress incontinence, urinary path obstruction or deficient sphincters.
- The InterStim X Model 97800 - Implantable incontinence-control electrical stimulation system pulse generator. Used for sacral neuromodulation therapy

Relevant ARTG listings and links to public summary documents for these devices can be found here, here and here.

News in Brief

Early bird registration for EAU 2024 open

Registration for the 39th Annual EAU Congress, to be held in France in April 2024, opened on the 1st October with the lowest-price early fee available until the 5th February 2024. The four-day scientific programme will include live surgery, lectures, case discussions and debates. An inaugural Research Forum will put a spotlight on translational and basic research, providing a Urological Research section in abstract selections and expanding the allocated time for relevant presentations.

Registrations can be made through the online registration system here.

World continence week 2023

In recognition of the significant burden of bladder and bowel incontinence and to promote awareness, available therapies and proactive management strategies, the Continence Foundation of Australia celebrated World Continence Week in June. The occasion was marked with a series of podcasts called "My Story" and a special feature on the Brownlow medallist Robert "Dipper" DiPeirdomenico's experience with incontinence in the winter edition of the Bridge magazine.

Podcasts are available to download at no cost here

First results from AMBASSADOR show a DFS benefit to adjuvant pembrolizumab localised urothelial cancer

Adjuvant immunotherapy with pembrolizumab prevents disease recurrence after radical surgery in patients with localised MIBC and locally advanced urothelial carcinoma, according to a prespecified interim analysis from the multicentre US AMBASSADOR trial (KEYNOTE-123). Per a press release from the trial sponsor, a significant disease-free survival (DFS) benefit was found in patients who received the PD-1 inhibitor after surgical resection compared to patients who received post-surgical observation only. Data is expected to be presented at an upcoming medical conference. Data regarding the dual primary outcome measure of overall survival is immature.

The press release from Merck can be read here

Gemcitabine and cisplatin plus nivolumab as organ-sparing treatment for muscle-invasive bladder cancer: a phase 2 trial

Results from this phase 2 trial suggest that a novel bladder-sparing treatment paradigm may be appropriate for select patients with MIBC who attain a stringent clinical complete response to cisplatin-based chemotherapy plus PD-1 blockade. Patients (n=76) enrolled to the study received four cycles of gemcitabine, cisplatin and nivolumab followed by either cystectomy or eight doses of nivolumab monotherapy, according to clinical complete response status on restaging. Data showed that 43% of patients achieved a clinical complete response to chemoimmunotherapy with no evidence of malignancy on biopsy, urine cytology or imaging. Finally, a positive predictive value of 0.97 was reported for a composite outcome of two-year metastasis-free survival in patients forgoing immediate cystectomy or <ypT1N0 in patients electing to receive immediate cystectomy.

Nat Med. 2023; Oct 2. Online ahead of print

COVID-19 Resources for Urologists

Royal Australasian College of Surgeons
European Urology Journal
British Association of Urological Surgeons

Conferences, Workshops, and CPD

Please click on the links below for upcoming local and international urology meetings, workshops and CPD.
USANZ – Events
COMS – Conferences and Meetings on Urology

Research Review Publications

Genitourinary Cancer Research Review with Associate Professor Andrew Weickhardt

Prostate Cancer Research Review with Associate Professor Niall Corcoran and Professor Nathan Lawrentschuk

Urology Research Review with Professor Eric Chung

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