

Department of Urology Medical Student Handbook



DEPARTMENT OF
Urology

UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE
AND PUBLIC HEALTH

Innovative Research, Outstanding Care.

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Urology Log

Student Name: _____

M3 M4 Dates of Rotation: _____

A faculty or NP/PA observed me performing:	Instructor name(s)/date(s)
Digital rectal exam	
Testicular exam	
Female genital exam	

I have:	Date(s)
Watched the video & inserted a Foley into a male patient	
Watched the video & inserted a Foley into a female patient	
Sutured in the operating room	

INTRODUCTION

Hello, and welcome to Urology! You have chosen a great selective during your Surgical and Procedural Care rotation. Most of the students who take this subspecialty course enjoy themselves and learn more than they thought they would when they signed up for it.

During your rotation you will meet a group of urologists who are excited about their medical specialty and feel privileged to work in it. Urology is a rapidly evolving technological specialty that requires surgical and diagnostic skills. Watch the video “**Why Urology?**” for a brief introduction to the field from the American Urological Association (AUA). <https://youtu.be/kyvDMz9MEFA>

Urology at UW

Urology is a specialty that treats patients with many different kinds of problems. At the UW you will see:

- patients with kidney problems including kidney cancer and kidney stones
- patients with bladder problems such as bladder cancer and urinary incontinence
- men with prostate cancer
- men with benign prostatic enlargement and its subsequent symptom of difficult urination (often cared for by urologists as well as primary care physicians)
- men with erectile dysfunction and male-factor infertility
- Pediatric Urology patients with an array of congenital problems with the kidneys, bladder, penis and testicles

The majority of the patients at UW require surgery, but other patients have problems that only require medication or reassurance. For this reason, you will spend half of your urology rotation in the OR and half with faculty in clinic.

The majority of you will not choose a career in Urology so this rotation is based on the AUA National Medical Student Curriculum. The AUA conducted a survey of a broad assortment of physicians around the country and asked, “*What do you think every medical student should know about Urology before finishing medical school?*” Based on the results, the curriculum includes the 10 core topics and two skills below.

1. Kidney Stones
2. Hematuria
3. Adult UTI’s
4. Pediatric UTI’s
5. The Acute Scrotum
6. Urinary Incontinence
7. Benign Prostatic Hyperplasia (BPH)
8. Prostate Cancer Management

9. Prostate Cancer Screening
10. Erectile Dysfunction
11. How to insert a Foley catheter
12. How to perform a digital rectal exam

You can find the curriculum here in this handbook as well as at the Department of Urology's website and on Canvas. In addition, you will find links to two videos which demonstrate the proper technique for Foley catheter insertion in men and women as well as videos that illustrate proper technique for performing female and male genital exams. There are also links to some patient clinical scenarios that are fun and allow you to do more interactive computer-based learning.

In addition to learning through participation in the operating room and seeing patients in clinic, there will also be several small group learning sessions with the Urology faculty in the Department. Lastly, portions of the General Surgery Core Discussion sessions are mentored by some of the Urology faculty and cover several of the core topics that the UW Urology faculty and the AUA feel are important for all medical students to learn.

Before you start, our Educational Programs Manager, Denise Mussehl, will email you a copy of your schedule with information about where you should be on your first day of the rotation.

Denise will meet with you for orientation during the first day or two of your Urology rotation. She will discuss learning objectives, give you a few suggestions and let you know how faculty provide feedback throughout the rotation. You will also meet with the Department Chairman, Dr. Nakada.

CONTACT INFORMATION

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Welcome to Urology

1. Discussion content, Dr. Nakada

- Intro to rotation
- Urinalysis review, be prepared to discuss:
 - specific gravity
 - WBCs
 - RBCs
 - Squamous cells
 - Urinary sediment
 - Micro
 - Hematuria history taking

2. Feedback, concerns

1. Denise Mussehl, Coordinator
2. Tracy Downs, Director
3. Stephen Nakada, Chairman, 608-215-5990, nakada@urology.wisc.edu

WHAT IS UROLOGY?

The following contains excerpts from What Is Urology: Information for Medical Students and Prospective Urology Residents, prepared by the AUA Graduate Medical Education Committee.

Urology is a surgical specialty that deals with diseases of the male and female urinary tract and the male reproductive organs. Although urology is classified as a surgical specialty, knowledge of internal medicine, pediatrics, gynecology, and other specialties is required by the urologist because of the wide variety of clinical problems encountered. In recognition of the wide scope of urology, the American Urological Association has identified seven subspecialty areas:

1. Pediatric Urology
2. Urologic Oncology (cancer)
3. Renal Transplantation
4. Male Infertility
5. Calculi (urinary tract stones)
6. Female Urology (urinary incontinence and pelvic outlet relaxation disorders)
7. Neurourology (voiding disorders, urodynamic evaluation of patients and erectile dysfunction or impotence)

Historically, the subject, which clearly established the specialty of urology as being distinct from general surgery, was the treatment of obstructive uropathy. This treatment ranges from the correction of obstructing posterior urethral valves or ureteropelvic junction obstruction in the infant to the correction of bladder outlet obstruction from benign prostatic hyperplasia in the older male. Through the decades, we have witnessed a tremendous increase in our general understanding of the diverse functional disorders of urine transport associated with various overt and covert forms of neuromuscular dysfunction. The rapidly evolving discipline of urodynamics has established itself as a major resource in the diagnosis and therapy of such disturbances.

Stone disease of the urinary tract has always provided a substantial portion of general urologic practice. The recent introduction of rigid and flexible ureteroscopy has greatly improved the capacity of the urologist to deal with the problem while the management of stones in the kidney has been revolutionized twice in the immediate past: first with the introduction of percutaneous methods for stone disintegration and extraction, and secondly by the application of shockwave lithotripsy. Collectively these techniques have largely rendered open surgical procedures for dealing with kidney and ureteral stones obsolete. These new technologies remain under urological stewardship. In addition, advances in the diagnosis and metabolic management of recurrent nephrolithiasis allow urologists to reduce the risk of recurrent stone formation.

Another area of major urologic concern is that of congenital anomalies. The urinary tract is affected by congenital anomalies more than any other organ system. These congenital abnormalities run the gamut from the relatively common problem of cryptorchidism to the complex area of intersexuality. These patients are usually cared for by Pediatric Urologists.

Involvement of the urologist in the problems of renal insufficiency and end-stage renal disease has been necessitated by an enormous increase in the number of patients on dialysis and requiring transplantation. In a number of centers, urologists are the prime surgical arm for renal transplantation and, in others, serve as members of the surgical team. This practice has tended to increase the experience of the urologist in vascular surgery, which has been beneficially incorporated into other areas such as renal vascular reconstruction and in the new microvascular surgical procedures performed for certain cases of impotence. The enhanced communication between nephrologist and urologist often leads to involvement in the general area of hypertension and adrenal disorders.

The treatment of malignant disease is a very large portion of urologic practice. Some of the most encouraging results in the medical and surgical management of solid tumors have involved genitourinary tumors, namely testis tumors and Wilms tumors. The development of multimodal therapy, in which chemotherapy, radiation therapy, and surgical treatment are used in conjunction, will hopefully improve the results of the treatment of other genitourinary malignancies. Newer diagnostic methods for the detection of prostate cancer have recently emerged and currently the diagnosis and treatment of prostate cancer occupies much of many urologists' time.

Urinary tract infections affecting every age group in both sexes comprise a significant fraction of urological practice. While urinary tract infection may be the obvious and definitive clinical symptom at presentation, it may also reflect other disorders of the urinary tract such as obstructive uropathy. Much recent interest has been focused on the characterization of pathogenic bacteria that are particularly prone to cause persistent urinary tract infections, specifically pyelonephritis. Bacteriuria is such a common clinical problem that there is inevitably a large cross-disciplinary approach to this problem. Urologists often interact with internists, pediatricians, and gynecologists in the management of patients with bacteriuria.

The importance of urologic problems seen primarily in women (stress urinary incontinence, interstitial cystitis, urethral diverticuli, etc.) is being increasingly recognized. The diagnosis and therapy of urinary incontinence constitute a significant portion of most urology practices. New therapies, both surgical and non-surgical, are being constantly developed. The number of female patients treated by urologists is substantial, and urologists need to understand gender differences in the medical and surgical approaches to these patients.

Male sexual dysfunction and infertility have become virtual subspecialties. The management of impotence has been revolutionized first by the introduction of

prosthetic devices in urology. The area of prosthetics in urology has gradually expanded to encompass not only the various forms of penile prostheses, but also the use of the artificial urinary sphincter. The management of infertility in the male has generally focused on the surgical correction of various acquired and congenital obstructions within the genital system, and increasingly sophisticated efforts to diagnose and treat the problem of coexisting male subfertility and varicocele. Continued improvements in the medical management of male infertility require a high level of expertise in the area of reproductive physiology and endocrinology.

Trauma to the genitourinary system involves the urologist as one member of the trauma team during the initial evaluation of the multiply injured patient. Recent improvements in imaging techniques for the evaluation of renal trauma and standardization of approaches to the problem of lower urinary tract trauma have significantly improved the care of such patients. There are a vast number of operative approaches to the problem of the late correction of injuries to the lower urinary tract, which fall under the general heading of reconstructive surgery.

The specialty of urology is constantly changing. Much of this change has been the result of improved technology. Refinements in the area of ureteral and renal endoscopic surgery have already revolutionized the therapy of urinary tract stones and, working in conjunction with the new generation of extracorporeal lithotriptors, many of the traditional surgical and even endoscopic approaches to the problem of renal and ureteral calculi are now largely obsolete. Other traditional urologic procedures, specifically vasovasostomy and hypospadias repair have improved results in selected cases with the use of the surgical microscope. Skill and experience using the surgical microscope will undoubtedly be an important part of urologic practice in the future. Lasers are in their infancy, but will influence the practice of urology in the management of neoplasms and, in a somewhat different context, the management of ureteral calculi. Much recent research effort has evolved in the area of laparoscopic surgery. Many urologic operations, which have been done by open surgery in the past, can now be performed through the laparoscope. The development of new cancer chemotherapeutic agents has significantly altered therapy for some urologic cancers. In summary, urology is a rapidly changing and exciting area of medicine, which requires practicing urologists to be actively involved in continuing education. (Borrowed from the AUA website 04-01-2013: <http://www.auanet.org/about/what-is-urology.cfm>)



WHY UROLOGY?

American Urological Association
Advancing Urology®

Healthy **WORK-LIFE BALANCE** with a robust income and opportunity for growth

There's a great need for **MORE UROLOGISTS** throughout the country!

"There is no other specialty that has this combination of medicine, surgery and advances in technology."
— John Lynch, MD
PROFESSOR OF UROLOGY,
GEORGETOWN UNIVERSITY

3 out of 4 medical students get matched with a urology residency

"There are things you can do in Urology that can't be done in other specialties!"
— Lindsay Menchen, MD
UROLOGY RESIDENT,
UNIVERSITY OF PENNSYLVANIA

Offers a diverse mix of
CLINICAL — & — SURGICAL opportunities

WHAT SUBSPECIALTIES ARE PRACTICED BY UROLOGISTS?
Calculi
Female Urology
Male Infertility
Neurourology
Pediatric Urology
Renal Transplantation
Urologic Oncology

YOUR RELATIONSHIP WITH AUA DOESN'T END IN MEDICAL SCHOOL. HERE'S HOW WE CONTINUE TO SUPPORT YOU IN YOUR MEDICAL CAREER:

- Clinical Guidelines
- AUAUniversity and e-learning
- Professional Development & Leadership Opportunities
- News and Publications
- Legislative and Regulatory Advocacy
- Patient Education
- Resources for your medical practice

There are approximately **12,000** practicing urologists in the United States

WHAT CONDITIONS DO UROLOGISTS TREAT?

- Kidney Stones
- Prostate Cancer
- Male infertility and sexual health
- Urinary Tract Infections
- Overactive Bladder
- ...and many more!

HOW AUA SUPPORTS MEDICAL STUDENTS

- Medical Student Curriculum
- Research and fellowship opportunities

UROLOGY ROTATION OVERVIEW

We realize that most of you will choose a career in one of the primary care fields. Therefore, our main teaching objective for this rotation is for you to identify and integrate a core of basic urologic knowledge in a manner so that when you practice in your future career, you will be able to recognize the signs and symptoms of a urologic disease and either treat it, or when appropriate, refer the patient to a urologist.

CLINICAL LEARNING EXPERIENCES

During your Urology rotation you will see both children and adults and a mix of both inpatient and outpatient procedures. As such, your time on the Urology rotation will be divided amongst the Operating Rooms, both Inpatient and Ambulatory, as well as the Outpatient Clinic and Inpatient Hospital care. In a short 2-week rotation, it will be difficult to experience everything in urology. Therefore, we strongly advise that you read and prepare prior to your time in clinic and OR to optimize your learning from each experience (the UWHC Urology Clinic is located at C7/2).

To try to maximize your educational opportunities, we will divide the students on service between clinic and the operating room. All students will spend equal amounts

of time in clinic and OR during their 2 weeks. If you find that there is something taking place in the OR that you really want to see, or if there is an Attending in clinic with whom you really want to work, you can apply a small amount of flexibility to the schedule; but in general, try to adhere to the schedule to maximize your experience.

All of our faculty and residents are happy to work with students as we see our patients in clinic. However, clinic is often very busy. Therefore, it will be important for you to be proactive in order to maximize your learning experience. Please talk to each staff Urologist prior to starting in clinic to see how they would like you to work with them. For the most part, we encourage you to see the patients and introduce yourself as a medical student working with Dr. X, and give the name of the physician that you are working with so the patients are not confused by your presence. Obtain a focused history, then examine the patient with the faculty and devise an assessment and plan. This part of your rotation is extremely vital and usually a lot of fun for the students.

TEACHING CONFERENCES

In addition to learning through clinical experiences with patients, we have also created learning opportunities through teaching conferences. Some of these conferences are held with the entire faculty, residents and students. There are also multidisciplinary conferences that concern our patients or practices. In addition, we have quite a few conferences that are focused primarily on student education. These are called Small Group Learning Sessions and they will be held at locations throughout the Department (check weekly schedule for detailed information). If there are any changes to the schedule, we will do our best to inform you of them. Please refer to the weekly schedule to learn where and when the teaching sessions take place.

WHAT TO READ

As mentioned earlier, we know that most of you will choose a career in a field other than Urology. Therefore, some of the reading suggestions may seem overwhelming. At the very least, we expect you to read the modules included in this handbook. However, if you are interested in exceeding expectations during this rotation, you will need to demonstrate that you have read and understood more than just the core modules through thoughtful, illustrative discussions with the faculty and residents.

Additional texts:

Campbell-Walsh-Wein Urology, 12th ed. (2021)

<https://www-clinicalkey-com.ezproxy.library.wisc.edu/#!/browse/book/3-s2.0-C20161048666>

Smith & Tanagho's General Urology - 19th Ed. (2020)

<https://accessmedicine-mhmedical-com.ezproxy.library.wisc.edu/book.aspx?bookid=2840>

ONLINE TEACHING VIDEOS

One of the learning objectives for this course is for you to learn the proper technique for insertion of a urethral catheter into both male and female patients. This skill may be used in the clinic or operating room. Please watch the online videos from the New England Journal of Medicine that illustrate the proper technique for catheter insertion in preparation prior to doing it yourself. They can be found online through the Department of Urology's website, <http://www.urology.wisc.edu/>, under Residency & Fellowship.

You will also find interactive case based clinical scenarios after each of the BPH, Prostate Cancer, and ED modules. These reinforce some of the principle learning objectives for those modules and they are fun to do. They are also found at the Department of Urology website.

There is also a video, which demonstrates a technique for doing a thorough female pelvic exam and a module for the male genital exam.

Female Urethral Catheterization:

<http://www.nejm.org/doi/full/10.1056/NEJMvcm0706671>

Male Urethral Catheterization:

<http://www.nejm.org/doi/full/10.1056/NEJMvcm054648>

Female Genital Exam:

<http://www.nejm.org/doi/full/10.1056/NEJMvcm061320>

Male Genital Exam:

<http://www.auanet.org/education/medical-student/gu-exam/index.cfm>

Don't forget to watch the "Why Urology?" Video!

<http://www.youtube.com/watch?v=kyvDMz9MEFA>

REQUIRED READINGS

Prior to seeing patients with each faculty member, you should read the modules listed next to their name.

Dr. Abel	Module 5 Module 8	Hematuria Prostate Cancer
Dr. Best	Module 6	Kidney Stones
Dr. Borza	Module 5 Module 8	Hematuria Prostate Cancer
Dr. Downs	Module 5	Hematuria
Dr. Farhat	Module 7	Pediatric UTI
Dr. Gralnek	Module 9 Module 2 Module 3	Urinary Incontinence Adult UTI BPH
Dr. Grimes	Module 9	Urinary Incontinence
Dr. Hedican	Module 5 Module 3	Hematuria BPH
Dr. Jarrard	Module 5 Module 8	Hematuria Prostate Cancer
Dr. Le	Module 4	ED
Dr. Lin	Module 9	Urinary Incontinence
Dr. McAchran	Module 9 Module 2	Urinary Incontinence Adult UTI
Dr. Nakada	Module 6	Kidney Stones
Dr. Paolone	Module 4 Module 3	ED BPH
Dr. Richards	Module 8	Prostate Cancer
Dr. Su	Module 7	Pediatric UTI
Dr. Williams	Module 4 Module 3 Module 10	ED BPH Male Infertility

STAFF

Dr. Abel
Dr. Best
Dr. Borza
Dr. Downs
Dr. Farhat
Dr. Gralnek
Dr. Grimes
Dr. Hedican
Dr. Jarrard
Dr. Le
Dr. Lin
Dr. McAchran
Dr. Nakada
Dr. Paolone
Dr. Richards
Dr. Su
Dr. Williams

SPECIAL INTEREST

Urologic Oncology - Kidney Cancer
Kidney Stones and Laparoscopy, Minimally Invasive Surgery
Urologic Oncology - Bladder Cancer, Kidney Cancer
Urologic Oncology - Bladder Cancer
Pediatric Urology
General Urology, Voiding Dysfunction
Reconstructive Urology
Laparoscopy and Prostate Diseases
Urologic Oncology - Prostate Cancer
Male Infertility, Erectile Dysfunction
Female Pelvic Medicine and Reconstructive Surgery
Female Urology and Voiding Dysfunction
Kidney Stones and Laparoscopy
Male Infertility, Erectile Dysfunction, BPH
Urologic Oncology
Pediatric Urology
Male Infertility, Erectile Dysfunction, BPH

MODULE 1: THE ACUTE SCROTUM

KEY WORDS: Testis, epididymis, torsion, epididymitis, ischemia, tumor, infection, hernia

LEARNING OBJECTIVES

At the end of this rotation, the student should be able to:

1. Describe six conditions that may produce acute scrotal pain or swelling.
2. Distinguish, through the history, physical examination and laboratory testing, testicular torsion, torsion of testicular appendices, epididymitis, testicular tumor, scrotal trauma, and hernia.
3. Appropriately order imaging studies to make the diagnosis of the acute scrotum.
4. Determine which acute scrotal conditions require emergent surgery and which may be handled less emergently or electively.

INTRODUCTION

The “acute scrotum” may be viewed as the urologist’s equivalent to the general surgeon’s “acute abdomen.” Both conditions are guided by similar management principles:

- The patient history and physical examination are key to the diagnosis and often guide decision making regarding whether or not surgical intervention is appropriate.
- Imaging studies should complement, but not replace, sound clinical judgment.
- When making a decision for conservative, non-surgical care, the provider must balance the potential morbidity of surgical exploration against the potential cost of missing a surgical diagnosis.
- A small but real, negative exploration rate is acceptable to minimize the risk of missing a critical surgical diagnosis.

DIFFERENTIAL DIAGNOSIS OF THE ACUTE SCROTUM

A list of potential medical conditions that can present as acute pain or swelling of the scrotum is found in Table 1.

Table 1: Causes of Acute Scrotal Pain and Swelling

Ischemia:
Torsion of the testis (synonymous with torsion of the spermatic cord) Intravaginal; extravaginal (prenatal or neonatal)
Appendiceal torsion, testis, or epididymis
Testicular infarction due to other vascular insult (cord injury, thrombosis)
Trauma:
Testicular rupture
Intratesticular hematoma, testicular contusion
Hematocele
Infectious conditions:
Acute epididymitis
Acute epididymoorchitis
Acute orchitis
Abscess (intratesticular, intravaginal, scrotal skin, cutaneous cysts)
Gangrenous infections (Fournier's gangrene)
Inflammatory conditions:
Henoch-Schonlein purpura (HSP) vasculitis of scrotal wall
Fat necrosis, scrotal wall
Hernia:
Incarcerated, strangulated inguinal hernia, with or without associated testicular ischemia
Acute on chronic events:
Spermatocele, rupture or hemorrhage
Hydrocele, rupture, hemorrhage, or infection
Testicular tumor with rupture, hemorrhage, infarction, or infection
Varicocele

While the differential diagnosis is broad, an accurate history and physical examination can frequently precisely define the condition. Often, carefully chosen imaging studies can complement clinical judgment and expedite therapeutic decisions. A discussion of the most important and common conditions that cause acute scrotal pain or swelling follows.

TORSION

Testicular torsion

The testicle is typically covered by the tunica vaginalis, creating a potential space around the testis. Normally, the tunica vaginalis attaches to the posterior surface of the testicle and allows for very little mobility of the testicle within the scrotum. Some patients have an inappropriately high attachment of the tunica vaginalis, such that the testicle can rotate freely on the spermatic cord within the tunica vaginalis (intravaginal testicular torsion) (Figure 1). This congenital anomaly, called the “bell

clapper deformity,” consists of a transverse as opposed to longitudinal lie of the affected testis; it can be unilateral or bilateral and is a risk factor for a torsion event. This congenital abnormality is present in approximately 12% of human males.

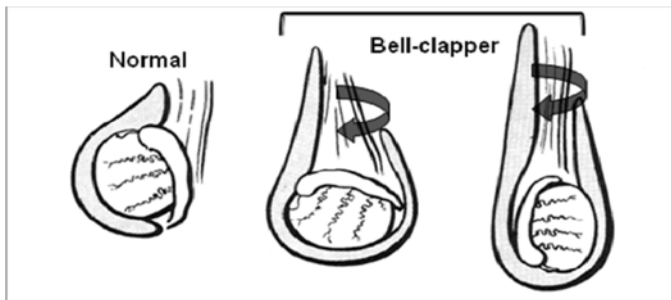


Figure 1: Bell clapper deformity. Normal testis lie is on the left and the classic “bell clapper” lie is in the middle. The right side shows a bell clapper variation.

During testis torsion, the testicle twists spontaneously on the spermatic cord, causing venous occlusion and engorgement, with subsequent arterial ischemia and infarction. Experimental evidence indicates that 720° twist is required to compromise flow through the testicular artery and result in ischemia. In neonates, the testicle frequently has not yet descended into the scrotum, after which it becomes attached within the tunica vaginalis. This increased mobility of the testicle predisposes it to torsion (extravaginal testicular torsion).

Testis torsion is the most common cause of testis loss in the US. The incidence in males <25 years old is approximately 1:4000. Torsion more often involves the left testicle. Among neonatal testicular torsion cases, 70% occur prenatally and 30% occur postnatally. The testis salvage rate approaches 100% in patients who undergo detorsion within 6 hours of the start of pain. However there is only a 20% viability rate if detorsion occurs >12 hours; and virtually no viability if detorsion is delayed >24 hours (Figure 2).

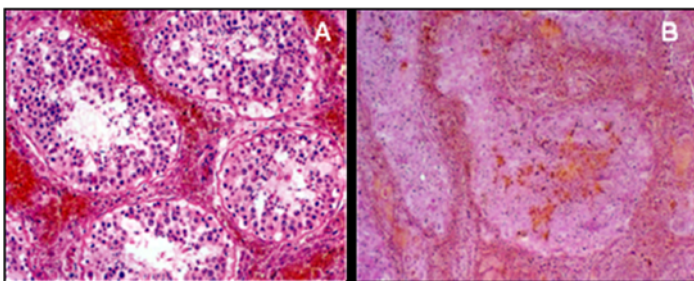


Figure 2. Testis histology during early (A) hemorrhagic phase and chronic late (B) phases of testis torsion. Note the decreased seminiferous tubule diameter and loss of germ cells in late relative to early phases.

Testicular torsion presents with the rapid onset of severe testicular pain and swelling. The onset of pain may be preceded trauma, physical activity, or by no activity (e.g. during sleep). It most often occurs in children or adolescents, but this diagnosis should be considered in evaluating men with scrotal pain of any age, as it may occasionally occur in men 40-50 years old. In this age group, the diagnosis is often delayed or missed due to a low suspicion because of age. Torsion should be in the differential for any sudden acute scrotal pain or swelling.

The classic physical examination findings with testis torsion are an exquisitely tender testicle with a high, horizontal lie. Normally the testicle has a vertical lie within the tunica vaginalis of the scrotum - that is, the longitudinal axis of the testis is oriented vertically. With torsion and twisting of the spermatic cord, the testis may assume an altered lie based on the degree of twisting. After venous outflow is occluded, there is swelling and occlusion of arterial flow. Early on, one may be able to palpate the torsed cord and the testis below it; later in the course, however, progressive edema and inflammation ensues, such that after 12-24 hours, the entire hemiscrotum appears as a confluent mass without identifiable landmarks. At this stage, the physical examination may be indistinguishable from that seen with epididymoorchitis. Importantly, with torsion, signs of infection are usually absent: patients are usually afebrile, free of irritative voiding symptoms such as dysuria, and harbor a normal urinalysis and normal white blood cell count. (In later torsion, however, an elevated WBC may be seen in response to the inflammation).

With a high degree of suspicion, one may reasonably recommend surgical exploration without delay. If scrotal ultrasonography is readily available, and especially if the diagnosis is questionable, this test is the single most useful adjunct to the history and physical examination in the diagnosis of torsion. The ultra-sonographer should use Doppler flow to assess arterial flow within the affected testis; if arterial flow is absent, torsion is highly likely. It is helpful to compare the flow patterns between both testes to help make this diagnosis. Ultrasonography may also exclude significant testicular trauma, show a hernia extending into the scrotum, and can distinguish epididymitis from torsion by demonstrating increased flow to the epididymis and adnexal structures along with preserved testicular perfusion. Beware of the ultra-sonographer who suggests that a “complex mass” exists above the testis that might represent an inflamed epididymis; the torsed cord with edema and inflammation is difficult to distinguish from an inflamed epididymis in torsion. Remember, testicular perfusion is the key to the ultrasound diagnosis of torsion. Tests such as nuclear testicular scans, CT or MRI, have essentially no role in the contemporary management of the acute scrotum.

When torsion is diagnosed, urgent surgical exploration and detorsion is mandated, as testicular torsion is a true vascular emergency. Testicular preservation is excellent when corrected within 4-6 hours of onset. Beyond 12 hours, the risk of subsequent testis atrophy is significant with detorsion. Testis salvage is often still appropriate if the testicular appearance at exploration improves with observation following detorsion. The alternative to detorsion is scrotal orchiectomy for pain relief in affected patients. After sharply entering the scrotum, the tunica vaginalis is opened. Then the testis detorsed and wrapped in a warm, moist gauze. The contralateral side then undergoes orchidopexy to prevent torsion on that side. The affected testis is reinspected for signs of improved perfusion (“pinking up”) (Figure 3). If the testis appears viable, or the timeframe suggests that salvage is reasonable then orchidopexy is performed by anchoring the tunica albuginea of the testis to the overlying parietal tunica vaginalis and scrotal dartos muscle.



Figure 3: Exploration of torsed testis. Note dark, cyanotic color of testis following 30 minutes of detorsion suggesting nonviability.

In general, scrotal exploration is a procedure of low morbidity. A negative exploration seldom results in long-term complications. When weighing conservative treatment with the loss of a potentially salvageable testis, it is best to err on the side of exploration. In cases of “late torsion” or “established torsion” exploration generally reveals a hemorrhagic, frankly necrotic testis for which orchiectomy should be performed.

“Intermittent” testicular torsion is a well-recognized entity in which a classic torsion history is obtained, but physical examination and ultrasound findings are normal. In such cases, it is reasonable to offer an elective bilateral scrotal orchiopexy for the possibility of intermittent symptoms becoming full-fledged torsion.

Torsion of testicular or epididymal appendages

Small polypoid appendages are often found attached to the testis or epididymis and are either Mullerian or Wolffian duct remnants (Figure 4). Similar to testis torsion, torsion of the appendix testis or appendix epididymis can also present with the acute onset of scrotal pain and mass. In most cases, however, the testis is palpable and has a normal lie. If encountered early, the edematous, torsed appendage can often be palpated at the upper pole of the testis. If the torsed appendage is ecchymotic, it can usually be seen through the skin and represents the “blue-dot sign.” Doppler ultrasound will demonstrate a normally perfused testis, often with hypervascularity in the area of the appendage. This process is often self-limited, with the infarcted appendage undergoing atrophy with time. If exploration is pursued, the appendage is simply excised and no orchidopexy is needed. Later in its course, it can be more difficult to distinguish this entity from testicular torsion or epididymitis, as global enlargement and edema of the scrotal compartment may occur. Ultrasound is valuable here to identify normal blood flow to the testis.

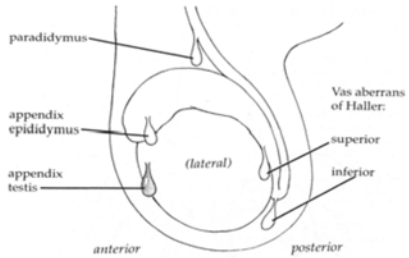


Figure 4: Illustration of the common appendices of the testis and epididymis. The appendix testis is most commonly affected by torsion.

TRAUMA

Penetrating and blunt testicular injury

Testicular rupture results when there is laceration of the tunica albuginea of the testis, such that testicular parenchyma may extrude. It may occur from either blunt or penetrating trauma. As a general principle, penetrating injuries to the scrotum should be surgically explored. The risk of testicular injury is quite high with these injuries. Even penetrating injuries with a tangential trajectory have a high likelihood of injuring the testis. In cases of blunt trauma, however, the incidence of testicular rupture varies widely, and depends on the forces exerted, the mechanism of injury, and testis mobility. Following blunt injury, the physical examination findings may include swelling, tenderness or ecchymosis. If one can clearly palpate the testis and it is entirely normal to palpation, rupture is unlikely. If there is significant scrotal wall thickening from edema or hematoma, testicular palpation may be difficult or impossible, and scrotal ultrasonography can determine the degree of testis injury. In addition to demonstrating a break in the continuity of the tunica albuginea or evidence of extruded parenchyma, ultrasound evidence of a marked loss of internal homogeneity of the testis is highly predictive of testicular rupture and warrants surgical exploration. Blunt injury may result in testicular rupture, intratesticular hematoma, testicular contusion (bruising) or hematocele (blood collection within the tunica vaginalis space). Among these, only testicular rupture requires surgical repair. Large or painful hematoceles may benefit from drainage. For intratesticular hematoma (intact tunica albuginea, localized hematoma within an otherwise intact testis) or local tenderness (contusion), observation, rest, cold packs and analgesics are appropriate therapy.

Surgical exploration for trauma is performed through incisions that anticipate the structures at risk. For penetrating trauma, a vertical incision may be easily extended into the groin to expose the spermatic cord. For blunt trauma, a transverse incision over the injured scrotal compartment is effective. After inspecting and draining the tunica vaginalis space, any extruded testicular parenchyma is inspected, irrigated and resected or retained and tunical lacerations repaired. The testicular compartment may be drained, generally with a small Penrose drain. With trauma, most testicular injuries are amenable to repair. Orchiectomy is indicated when there is major injury

to the spermatic cord with organ devitalization, and destruction of parenchyma is so extensive that no significant tissue can be salvaged.

INFECTIONS

Epididymitis and epididymoorchitis

Although they may be difficult to distinguish on physical examination from scrotal trauma or testis torsion, it is important to accurately diagnosis epididymitis and orchitis, as their management is entirely nonsurgical. Epididymitis is usually caused by infections. In men <35 years old with a history of sexually transmitted infection (STI) exposure, recent sexual activity, epididymitis is often caused by Chlamydia or gonococcal infection, and is amendable to standard antibiotic treatment. In older men and those with problems such as significant benign prostatic hypertrophy (BPH), a history of UTI's, or urethral stricture disease, enteric, gram negative bacteria related to ascending urinary infection are much more likely causes. In either case, initial broad spectrum antibiotics are used with therapy further directed based on culture results. There are also noninfectious or inflammatory forms of epididymitis. These are due to the adverse effects of medications, urinary reflux within the ejaculatory ducts, and sperm and fluid extravasation after vasectomy. When epididymitis extends into the testis and causes testicular tenderness and enlargement, it is termed epididymoorchitis.

There are several features in the patient history that may indicate epididymitis, such as a history of previous STI, recent sexual activity, irritative voiding symptoms, BPH/incomplete emptying of the bladder, or UTI. The very sudden onset of pain and swelling is more typical of torsion, while a more gradual, progressive onset pain (often greater than 24 hours) suggests epididymitis. On physical examination, epididymitis presents with tenderness posterior and lateral to the testis (the usual location of the epididymis). Scrotal ultrasound may show an enlarged, hyper vascular epididymis with normal or increased blood flow to the testis, which will distinguish this condition from torsion or trauma. Abscess formation within the epididymis or in the peri-epididymal tissues, can also be detected by ultrasound. The diagnostic challenge occurs when trying to distinguish advanced epididymoorchitis from late torsion. In both entities, there is typically a confluent mass in the scrotum with edema and fixation of the overlying scrotal wall that obliterate normal anatomic landmarks. Furthermore, advanced epididymoorchitis can result in testicular ischemia and infarction due to compression of the testicular vasculature from epididymal inflammation. On ultrasound, this may present in a very similar manner to testis torsion. In either case, the lack of testis blood flow on Doppler ultrasound requires surgical exploration which allows these conditions to be differentiated.

When diagnosed, epididymitis and orchitis are managed conservatively with antibiotics, anti-inflammatory, analgesics, rest and scrotal elevation. If abscess formation occurs, surgical drainage and/or orchiectomy may be necessary.

SCROTAL WALL INFECTIONS

Infectious conditions within the scrotal wall are also classified under the acute scrotum and include cellulitis and fasciitis (gangrene). Scrotal wall cellulitides and abscess formation are distinguishable testicular conditions on physical examination, as the testis is usually palpably normal and nontender, if it can be palpated without compressing the inflamed scrotal wall. Scrotal wall infections may result from infected sebaceous cysts, folliculitis, or other dermatologic conditions. Incision and drainage with gauze packing and broad-spectrum antibiotics are prescribed for these superficial conditions. Fasciitis of scrotum and groin, termed Fournier's gangrene, involves a rapidly progressive, life threatening infection of the genital soft tissues. It is associated with predisposing issues including urethral perforation and periurethral abscess and is most often seen in the immunocompromised or diabetic patient. On physical examination, there can be diffuse enlargement, thickening and erythema of the scrotal wall, groin and perineum. There may be necrotic black or ecchymotic patches of genital skin present (Figure 5).



Figure 5: Fournier's gangrene of the scrotum. Note necrotic, black patch of scrotal skin with large ulceration. (From: Aho T et al. (2006) Fournier's gangrene Nat Clin Pract Urol 3: 54-57)

The most diagnostic is the finding of crepitus, a spongy, cracking feeling within the skin that indicates gas-producing microorganisms underneath that can be felt in the scrotum or perineum. When left untreated, genital gangrene will progress over hours and result in overwhelming bacterial sepsis with an associated high mortality rate. Therefore, broad spectrum antibiotics that cover aerobic and anaerobic organisms, and urgent and repeated surgical drainage and debridement are required to control the infection. At the time of surgical treatment, cystoscopy and proctoscopy may be performed to exclude urethral and rectal abnormalities.

SCROTAL WALL INFLAMMATION

Henoch-Schonlein purpura (HSP) is a vasculitis of scrotal wall that causes thickening and erythema in the absence of infection. Idiopathic scrotal edema and filarial infections (rare in the US) can also cause chronic, relatively painless, scrotal swelling. Lastly, scrotal edema secondary to hypoalbuminemia, portal hypertension and lymphadenopathy are also rare but significant conditions that may occur under the aegis of the acute scrotum. In most of these conditions, the history of a slowly

progressive disease process helps differentiate them from more classically acute conditions. Treatment of the underlying, non-scrotal cause is most effective to relieve the scrotal symptoms.

INGUINAL HERNIA

An acute inguinal hernia may also present as an acute scrotum. In this case, pain and swelling involve both the scrotal contents and the groin area. Although important to differentiate, it may be difficult to distinguish an incarcerated inguinal hernia from other, less emergent, scrotal issues such as hydrocele, scrotal trauma, or scrotal abscess. An incarcerated inguinal hernia involves bowel that is obstructed and is a true surgical emergency. In selected, less acute cases, groin and scrotal ultrasound or pelvic CT scans can clarify the diagnosis before surgical exploration. Hernia repairs that use polypropylene mesh for correction may be associated with vas deferens obstruction and infertility later on.

ACUTE ON CHRONIC EVENTS

Other scrotal conditions that are chronic in nature can also present with acute symptoms and include testicular neoplasms, spermatoceles and hydroceles. In the case of testis tumors, patients may only become aware of the mass after it has been present for many months, after it affects the appearance of the scrotum. However, testicular tumors can present precipitously if they undergo hemorrhage or necrosis, and produce swelling, pain and soreness. In this case, a scrotal physical examination reveals a firm, intratesticular mass and scrotal ultrasound demonstrates a solid intratesticular mass which has a > 90% likelihood of being a germ cell tumor. The suspicion of tumor is important for the approach to exploratory surgery in the acute scrotum, as the correct surgical approach to testis cancer is through an inguinal incision and not transcrotally. In addition, the testis and its investments are dissected out intact, to minimize tumor spillage during surgery and spermatic cord ligation is done in the inguinal region to further contain the spread of cancer.

Other chronic scrotal lesions which can present acutely include hydroceles (increased fluid within the tunical vaginalis space) and spermatoceles (cystic dilation of the fine ducts that lead from the rete testis to the epididymal head) that hemorrhage after trauma, or become infected. In addition, a scrotal varicocele, a condition characterized by dilated pampiniform plexus veins and that occurs in 15% of men at puberty, can be present for years but become acutely symptomatic. These dilated veins surround the spermatic cord. If the varicocele has acute onset, is only right-sided, or persists in the supine position, then inferior vena caval (IVC) obstruction must be excluded (i.e., IVC thrombus, abdominal mass, etc.). A careful history, physical examination and ultrasound examination is usually sufficient to diagnose these usually benign acute on chronic events. Urgent surgical intervention is rarely needed for drainage of a loculated infection or for a persistent hemorrhage associated with hydroceles or spermatoceles.

SUMMARY

- A full range of scrotal pathology must be considered in acute scrotum cases.
- Several conditions that result in acute scrotum require surgical exploration, making this a very time sensitive condition.
- A high value is place on the history, physical examination and ultrasound imaging for acute scrotum diagnoses.

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(Updated August 2018)

MODULE 2: ADULT URINARY TRACT INFECTIONS

KEYWORDS: Urinary tract infection (UTI); cystitis; pyelonephritis; uropathogens; antibiotics

LEARNING OBJECTIVES

At the end of this clerkship, the learner will be able to:

1. Outline the prevalence and socioeconomic impact of adult UTI.
2. List the distinctions between urinary infection, contamination and colonization in diagnosing a UTI.
3. List the important host and bacterial characteristics associated with a clinically important UTI.
4. Name the most common gram negative and gram positive bacteria associated with adult UTI.
5. Name the predominant organisms constituting normal perineal flora.
6. List methods of urine collection and the advantages of each.
7. Describe the different signs and symptoms associated with upper tract and lower tract adult UTIs.
8. Describe and perform chemical and microscopic urinalysis, and its limits in the diagnosis of adult UTI.
9. Name dominant pathogens or disease entities that need to be considered in the differential diagnosis of UTI.
10. Describe the differences between complicated and uncomplicated adult UTI.
11. List indications and use of imaging modalities in the diagnosis of adult UTI.
12. Outline treatment principles of both complicated and uncomplicated adult UTIs including cystitis, pyelonephritis, epididymitis, and prostatitis.

Introduction

Urinary tract infections are a troubling and increasingly dangerous condition treated by physicians from a number of specialties, including Urology. The landscape of diagnosis and management is changing as new resistance patterns emerge. In this section of the Medical Student Curriculum, we discuss epidemiology, diagnosis, and management of both complex and non-complex urinary tract infections.

EPIDEMIOLOGY/SOCIOECONOMICS/EDUCATION

Urinary tract infection (UTI) is a significant health problem in both community and hospital-based settings. It is estimated that 150 million UTIs occur yearly world-wide, accounting for \$6 billion in health care expenditures. In premenopausal women in the

U.S., an annual estimated incidence of UTI is 0.5 - 0.7/person/year. In Medicare beneficiaries 65 years or older, UTIs account for 1.8 million office visits per year.

The majority of community-acquired UTIs manifest as uncomplicated bacterial cystitis, and occur mainly in females. In the health-care setting, approximately 40% of all nosocomial infections are UTIs, and most are associated with the use of urinary catheters. There are more than 1 million catheter-associated UTIs/year in the U.S., and up to 40% of hospital gram negative bacteremias/year originate as UTIs. Urinary infections are treated with antibiotics and removal of predisposing factors when possible, including indwelling catheters. Antibiotic use should be reserved for symptomatic infections and the decision to proceed with treatment requires thoughtful consideration of collateral impact and antimicrobial resistance patterns.

ETIOLOGY/PATHOGENESIS

Definitions:

Urine is generally considered sterile. The urinary system can be divided into the upper tract, which consists of the kidneys (renal parenchyma and collecting system) and the ureters, and the lower urinary tract, which includes the bladder (responsible for storage and elimination of urine), the urethra (tube through which urine exits the bladder to the outside world), and prostate in men. In the female, the urethra exits the bladder near the vaginal area, the vagina could contribute to contamination of urine specimens. In the male, the urethra exits the bladder, passes through the prostate, and then through the penile urethra. The foreskin when present may contribute to infection in select instances. When discussing UTI's it is important to distinguish among the following terms:

- **Contamination** - organisms are introduced during collection or processing of urine. No health care concerns.
- **Asymptomatic bacteriuria (Colonization)** - organisms are present in the urine but are causing no illness or symptoms. Depending on the circumstances, significance is variable, and the patient often does not require treatment.
- **Infection (UTI)** - the combination of a pathogen(s) within the urinary system and symptoms and/or inflammatory response to the pathogen(s) requiring treatment.
- **Uncomplicated UTI** - infection in a healthy, non-pregnant, pre-menopausal female patient with anatomically and functionally normal urinary tract.
- **Complicated UTI** - infection associated with factors increasing colonization and decreasing efficacy of therapy.
- **Recurrent UTI** - occurs after documented infection that had resolved. Defined as 2 or more infections in 6 months, or ≥ 3 infections in 12 months (JAMA article).
- **Reinfection UTI** - a new event with reintroduction of bacteria into urinary tract or by different bacteria.
- **Persistent UTI** - UTI caused by same bacteria from focus of infection.

Factors Important for the Genesis of UTIs

Bacterial entry:

Bacteria ascending into the bladder through the urethra is the most common cause of UTIs. There are several risk factors that may promote or encourage bacterial ascent.

Risk factors for UTIs

- Reduced urine flow
 - outflow obstruction with incomplete bladder emptying (prostatic hyperplasia, prostatic carcinoma, urethral stricture, pelvic organ prolapse or foreign body)
 - neurogenic bladder
 - inadequate fluid uptake
 - voiding dysfunction
- Promote colonization
 - sexual activity - increased inoculation
 - spermicide - increased binding
 - estrogen depletion - increased binding
 - antimicrobial agents - decreased indigenous flora
- Facilitate Ascent
 - catheterization (chronic or intermittent)
 - urinary incontinence
 - fecal incontinence
 - residual urine with ischemia of bladder wall

Hematogenous spread is an uncommon cause of UTIs. The organisms most commonly involved with hematogenous spread are *Staphylococcus aureus*, *Candida* species and *Mycobacterium tuberculosis*. Hematogenous infection develops most often in immunocompromised patients, elderly, or neonates. Relapsing hematogenous infections can be secondary to incompletely treated prostatic or kidney parenchymal infections (e.g. emphysematous pyelonephritis).

Bacterial uropathogenic factors:

A limited number of *E. coli* serotypes are responsible for the majority of UTIs. Bacteria that cause infection have increased adhesion, colonization and tissue invasion properties relative to nonpathogenic bacteria. The mediators of these pathogenic features include pili, cell surface structures responsible for adhesion to host tissues, which promote colonization and increase resistance to bacteriocidal host activity. Specifically, Type 1 pili adhere to mannose receptors on in the urinary epithelial mucopolysaccharide lining as well as polymorphonuclear leukocytes (PMNs); Uropathogenic *E. coli* with Type I pili are often associated with cystitis (bladder infection). P pili are mannose resistant and adhere to renal glycolipid receptors. P pili do not bind PMNs and are therefore relatively resistant to phagocytosis and clearing by the host immune system thus most often associated with kidney infections

(pyelonephritis). One characteristic of *E. coli* that allows it to ascend to the kidney is the phasic variation of Type 1 pili. Intermittent pili expression decreases opportunity for PMN binding making phagocytosis is less effective. One of the significant factors in resistance to bactericidal activity involves the expression of K antigen (capsular polysaccharide) on bacteria. Another mediator, hemolysin, produced by select bacteria, can augment tissue invasiveness and predispose to infection.

Host defenses:

Several factors relating to host defenses determine susceptibility to UTIs. Mechanical issues such as urethral length (female shorter than male), completeness of bladder emptying (leading to residual urine in the bladder) and the integrity of the natural ureterovesical junction "valve" (leading to vesicoureteral reflux; VUR) are important anatomic issues that predispose to UTIs. Biochemical properties are normally important in making bacterial survival difficult in urine: acid pH, high urea content, and high osmolality. In addition, mucosal mucopolysaccharide within the lining of the urinary tract as well as systemic and local antibody production may be protective for UTIs. Finally, there may be a genetic predisposition to UTIs, as certain HLA and Lewis blood group (non-secretor status) factors may put patients at higher risk due to increased colonization ability or increased adherence by bacteria to the urinary tract epithelium.

Natural Defenses of Urinary Tract

1. Periurethral and urethral region - Normal flora in these areas contain: lactobacilli, coagulase negative staph, corynebacterium and streptococci that form barriers against colonization. Changes in estrogen, low vaginal pH and cervical IgA affect colonization by normal flora.
2. Urine - High osmolality, high urea concentration, low pH, high organic acid are protective. Glucose in urine may facilitate infections. Tamm Horsfall proteins may be protective.
3. Bladder - Epithelium expresses Toll-like receptors (TLRs) that recognize bacteria and initiate immune/inflammatory response (PMNs, neutrophils, macrophages, eosinophils, NK cells, mast cells and dendritic cells). Adaptive immune response then predominates (T and B lymphocytes). Induced exfoliation of cells also occurs to allow excretion of bacterial colonization.
4. Kidney - Local immunoglobulin/antibody synthesis in the kidney occurs in response to infections (IgG, IgA).

Alterations in Host Defense Mechanisms

- **Obstruction** - Key factor in increasing susceptibility to UTI but does not necessarily predispose to infection.
- **VUR** - Hodson and Edwards (1960) described association of VUR, UTI, and eventual renal scarring.
- **Underlying Disease** - Diabetes mellitus (DM), sickle cell disease (SCD), nephrocalcinosis, gout, analgesic abuse, aging, hyperphosphatemia, hypokalemia.

- DM: Glycosuria may contribute to severity of infections due to immune compromise. Majority of infections (80%) are in the upper tracts.
- Papillary necrosis: due to DM, pyelonephritis, obstruction, analgesics, SCD, transplant rejections, cirrhosis, dehydration, contrast media, renal vein thrombosis.
- HIV: UTIs 5x more prevalent in this population and they recur more frequently.
- **Pregnancy** - Bacteriuria in pregnancy = 4-7% and incidence of acute clinical pyelonephritis = 25-35% in untreated patients.
- **Spinal Cord injury with high pressure bladder** - High morbidity and mortality from bacteriuria

DIAGNOSIS OF UTI

Clinical symptoms: Symptoms are very helpful in the diagnosis of a UTI, but may not accurately localize the infection within the urinary tract. In many cases, however, colonization of the urinary tract can be asymptomatic. The most generic form of UTI is cystitis (bladder infection) characterized by irritative symptoms (urinary urgency, frequency, dysuria) hematuria, foul- smelling urine, and suprapubic pain. These symptoms are also common for urethritis and prostatitis. Epididymitis can be associated with cystitis and diagnosed reliably by physical examination in men. Symptoms associated with "upper urinary tract" infections, exemplified by pyelonephritis, may include those typical of cystitis, as well as fever, rigors, flank or abdominal pain, and frequently associated with nausea and vomiting. In a female patient with recurrent urinary tract infection, a thorough abdominal and pelvic exam should be performed.

Collection method: Analysis of the urine is critical in determining the likelihood of infection. The method of urine collection is important to distinguish between contamination and true colonization. There are 3 commonly used methods of collection: a) clean catch midstream voided urine, b) catheterized urine and c) suprapubically aspirated urine. The most variable of these three is the midstream voided urine, especially in females, where contamination of urine by vaginal or perineal organisms is common during collection. Voided urines that are sterile or contain high colony counts (>100,000) of single bacteria correlate well with urine obtained by other more invasive methods.

Contamination should be suspected when the following factors are noted: growth of normal vaginal flora such as lactobacillus, mixed cultures with more than one organism, or low quantities of pathogenic organisms in an asymptomatic patient. The clinician should also review the urinalysis and may be suspicious of contamination in the presence of epithelial cells or mucus. If a contaminated specimen is suspected, a straight catheterization can be more reliable in obtaining an accurate specimen. Suprapubic aspirate can also be performed but is more invasive and less frequently utilized in clinical practice.

Techniques to improve the accuracy of urine culture include preparation of the urethral meatus and periurethral vaginal epithelium, though this is not been definitively proven as beneficial from an evidence-based standpoint. Avoiding contact of the collection cup with the perineum, labial spreading, and discarding the initial urinary stream in favor of the midstream sample can help prevent contamination of the specimen.

Urinalysis: A chemical analysis (dipstick) is suggestive for UTI if leukocyte esterase and/or nitrite are positive. Detection of leukocyte esterase means that there are white blood cells present in the urine. Leukocyte esterase has a 73-84% specificity and has a 80-92% sensitivity for UTI. The finding of nitrite positivity on urine dipstick, indicates the conversion of nitrate to nitrite by certain gram negative bacteria (not gram positive), is very specific (96-99%) but due to conversion only by Gram negative bacteria, not very sensitive.

Urine Microscopy: Urine microscopy is an important adjunct to the urinalysis. The finding of elevated white blood cells in the urine (pyuria) is the most reliable indicator of infection (>10 WBC/hpf on spun specimen) is 95% sensitive but much like the LE on chemical analysis, less specific for a UTI. Pyuria in the absence of urinary symptoms does not mean UTI is present. Urine microscopy is important for identification of the presence of squamous epithelial cells. More than 15-20 squamous epithelial cells/hpf on microscopy is suggestive of a contaminated specimen and sterile straight catheterized specimen may be desired. In addition, bacteria or yeast species may be seen. UTI can often have associated gross or microscopic hematuria, the number of RBC/hpf should be quantified and documented; if a patient has a negative culture a hematuria evaluation would need to be performed.

Table 1: Sensitivity and Specificity of Indicators of Possible Infections Found on Urinalysis and Microscopy

Test	Sensitivity (%)	Specificity (%)
LE	79 (73-84)	87 (80-92)
N	49 (41-57)	98 (96-99)

LE or N	88 (82-91)	79 (69-87)
LE+N	43 (30-61)	98 (96-99)
WBC	74 (67-80)	86 (82-90)
Bacteria	88 (75-94)	92 (83-96)

Quantitative urine culture: In general, > 100K colonies/mL on urine culture is considered diagnostic for UTI. However, as mentioned above, the probability of a UTI also depends on the method of collection. In general, lower colony counts obtained by sterile urethral catheterization or by suprapubic aspiration can represent true infection, but clean catch, mid-stream urine that harbors < 100K colonies/mL in a female requires further verification or repeat sampling to confirm a UTI.

Potentially Infective Pathogens in the Urinary Tract

Common Causative Pathogens in Adult UTIs

- E coli (80% of outpatient UTIs)
- Staphylococcus saprophyticus (5-15% of outpatient UTIs)
- Klebsiella
- Proteus
- Pseudomonas
- Enterobacter
- Enterococcus
- Candida
- Adenovirus type 11

Normal Perineal Flora

- Lactobacillus
- Corynebacterium
- Staphylococcus
- Streptococcus

Anaerobes

Methods to localize infection: For patients who have recurrent UTI, localization may be desired to identify a possible source if not clear with imaging and cystoscopy. Upper urinary tract infections may be isolated using the Stamey test in which a patient is catheterized and urine cultures both before and after a thorough saline wash. If the second, post-wash bladder culture is positive, this may indicate upper tract bacteria entering the bladder.

Combining bladder washing with selective ureteral catheterization is a more precise way to localize the laterality of the upper tract infection.

Used historically to diagnose chronic bacterial prostatitis, several localization methods have been described, but are otherwise uncommonly used. To diagnose chronic prostatitis, a "four glass" quantitative culture test can be used. With this method, urine is collected in four separate containers:

- 1) an initial voided urine that reflects bacterial activity within the urethra (urethral pathogens)
- 2) a subsequent, mid-stream urine to evaluate bacteria within the bladder
- 3) collection of expressed prostatic secretions, captured from the penile urethra while massaging the prostate with a rectal exam
- 4) a post-massage voided urine collection that may reflect prostatic bacteria.

Significantly increased bacterial colony counts in the third (expressed prostatic secretion) and fourth (post-prostatic secretion) cultures are diagnostic of chronic prostatitis. If acute bacterial prostatitis is suspected a prostatic massage should NOT be performed for concern of bacteremia.

INDICATIONS FOR RADIOLOGIC IMAGING WITH UTI

Patients with uncomplicated cystitis or uncomplicated pyelonephritis generally do not benefit from imaging studies or endoscopic evaluation. In patients who do not respond to treatment, or in patients with complicated UTIs or recurrent UTIs, imaging with either a kidney and bladder ultrasound or a non-contrast CT scan of the abdomen and pelvis may be useful for identification of potential causes. Cystoscopy or ureteroscopy of the urinary tract may be performed for cases of recurrent UTI to exclude bladder or upper tract pathology.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for recurrent UTI is expansive and includes consideration of other types of non-bacterial infection as well as causes of recurrent UTIs. In addition, it is important to consider the differential diagnosis for non-infectious causes of the same symptoms, specifically urgency, frequency, and dysuria.

DDx of infectious causes:

- STI (Herpes genitalis (HSV), N. Gonorrhoea, Chlamydia, Trichomonas)
- Urethritis
- Prostatitis
- Vaginal Infection/PID
- Candida Infection
- Urinary Tuberculosis
- Intra-abdominal Abscess
- Sepsis - source other than GU

DDx for Recurrent UTIs/Persistent UTI:

- Lower Urinary Tract Neoplasm (bladder cancer or CIS of the bladder)
- Bladder Outlet Obstruction
- Diverticulum (Bladder or Urethral)
- Skene's Gland Abscess
- Urinary Fistula (Vesicovaginal, Enterovaginal, Urethrovaginal)
- VUR or Ureteral anomalies
- Infected stones (Renal, Ureteral, Bladder)
- Foreign Body
- Voiding Dysfunction
- Infected Urachal Cyst
- Chronic Bacterial Prostatitis
- Abnormality of Renal Unit (Medullary Sponge Kidney, Infected Cysts, Atrophic Kidney)

DDx for symptoms:

- Lower Urinary Tract Neoplasm (bladder cancer or CIS of the bladder)
- Bladder Outlet Obstruction
- Interstitial cystitis
- Overactive bladder
- Vaginal Atrophy
- Vaginal Contact Dermatitis
- Distal Ureteral or Bladder stones
- Foreign Body (i.e. mesh)
- Voiding Dysfunction
- Pelvic Floor Muscle Dysfunction

MANAGEMENT OF UTI

Each symptomatic episode of acute cystitis should be evaluated first with a urinalysis and urine culture with sensitivity prior to treating with antibiotics. The combination of clinical findings and urine evaluation is essential for diagnosis of UTI. Treatment is based upon pathogen identification and the type and degree of clinical illness, as well as the presence or absence of predisposing host factors. In general, the treatment consists of hydration, relief of urinary tract obstruction if present, removal of foreign body or catheter if feasible, and judicious use of antibiotics. The type and duration of antibiotic treatment is dependent on site of infection (pyelonephritis, cystitis, prostatitis, epididymitis, orchitis), host factors, and severity of illness. Most antibiotics are highly concentrated in the urine and therefore are very effective at clearing bacteria from the urinary tract. However, in cases of pyelonephritis, prostatitis, epididymitis, or orchitis, selection of antibiotic with proper tissue penetration is important.

When considering treatment, first determine whether the UTI is complicated or uncomplicated in nature. Uncomplicated infections include acute cystitis in a non-

pregnant, premenopausal female, and acute pyelonephritis in an otherwise healthy patient. Young post-pubertal females are susceptible to uncomplicated UTIs because of sexual intercourse in combination with delayed post-coital bladder emptying. Use of diaphragm and spermicidal contraceptives alter the normal vaginal flora and may allow colonization by pathogenic *E. coli*.

Complicated UTIs are those that occur when certain predisposing factors are present, but in general should be considered in pregnant or post-menopausal females and men. Patients with complicated UTIs are more likely to have medical co-morbidities or conditions with require special consideration. In addition, they may have a greater variety of pathogenic bacteria, more drug resistance, and require a longer duration of antibiotic therapy.

Complicated UTIs requires one or more of following:

- Anatomic or functional abnormality of urinary tract (outlet obstruction, stone disease, diverticulum, neurogenic bladder, VUR etc.)
- Urinary instrumentation or foreign bodies in the urinary tract (i.e. catheters, stents, nephrostomy tubes)
- Systemic disease (renal insufficiency, diabetes, immunodeficiency, organ transplantation)
- Pregnancy
- Multi-drug resistant bacteria

The mainstay of treatment of acute UTI, either non-complicated or complicated infections, is antibiotics. Local antibiograms are useful for determining the prevalence of local resistance patterns and determining optimal antibiotic strategies for patients with complicated UTIs and particularly for nosocomial infections. Additionally, use of antibiotics in pregnancy should be tailored according to the American Board of Obstetrics and Gynecology committee opinion and local consultation with the treating obstetrician is often necessary to determine an optimal and safe strategy for therapy: <http://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co494.pdf?dmc=1>.

If asymptomatic bacteriuria is suspected, it does not necessarily need to be treated. Clinical signs and symptoms of acute cystitis should prompt treatment rather than the presence of bacteria on urine culture. There are some groups of patients, notably patients undergoing urologic surgery and pregnant women, who should be treated for asymptomatic bacteriuria. Routine surveillance urine cultures for asymptomatic bacteriuria in healthy, uncomplicated patients should not be performed.

Uncomplicated Cystitis

▫ Preferred:

- o Fosfomicin, 3 gram single po dose
- o Nitrofurantoin, 100 mg po bid x 5 days
- o Trimethoprim-sulfamethoxazole DS, 1 pill po bid x 3 days

- Alternative when bacteria are resistant to the preferred antibiotics
 - Ciprofloxacin, 250 mg bid x 3 days - fluoroquinolone antibiotics should not be the first line treatment of uncomplicated cystitis.

Complicated Cystitis in Women

- Urine culture and susceptibility should be performed
- Prior cultures should be reviewed and empiric selection of those results
- Patients who are candidates for outpatient therapy
 - Oral ciprofloxacin 500 mg BID x 7 days
 - Once daily oral fluoroquinolone (ciprofloxacin 1000 mg ER x 7 days or levofloxacin 750 mg x 5 days)
 - Oral TMP-SMX DS BID x 14 days (not for Enterococcus or Pseudomonas)
 - Use of initial one-time IV agent (ceftriaxone 1 g, aminoglycoside, fluoroquinolone)
 - Treat for 14 days
- Failure to respond after 24-72 hours of appropriate antibiotics need further investigation

Cystitis in Men

- Urine culture and susceptibility should be performed
- Preferred:
 - Trimethoprim/sulfamethoxazole 160/800 mg po BID
 - Levofloxacin 500 mg po daily
 - Ciprofloxacin 500 mg po BID
 - Ciprofloxacin ER 1000 mg po daily
- Treatment is generally for 7-14 days, optimal duration is not know

Uncomplicated Pyelonephritis in a Healthy Patient

- Urine culture and susceptibility should be performed
- Preferred:
 - Ciprofloxacin 500 mg po BID x 7 days ± initial Ciprofloxacin 400 mg IV x 1
 - Ciprofloxacin 1000 mg po daily x 7days
 - Levofloxacin 750 mg po daily x 5 days **if fluoroquinolone resistance > 10% initial dose of ceftriaxone 1gm or aminoglycoside 24-hour dose recommended
 - Trimethoprim-Sulfamethoxazole DS (160/800mg) po BID x 14 days **if susceptibility to TMP-SMX is not known, initial dose of ceftriaxone 1gm or aminoglycoside 24-hour dose recommended

Complicated Pyelonephritis (requiring hospital admission)

- Urine culture and susceptibility should be performed
- Adjust antibiotics according to culture results
- For inpatient management of Pyelonephritis
 - IV fluoroquinolone
 - Aminoglycoside +/- ampicillin
 - 3rd generation cephalosporin

- o Extended spectrum penicillin+/- aminoglycoside
- o Carbapenem
- Switch from parenteral to oral therapy at 48 hours after clinically well
- Treat for 14 days

Acute Pyelonephritis with Intrarenal, Perirenal or Pararenal Abscess

- Treatment for complicated UTI and appropriate drainage.

Bacterial Prostatitis

- Acute (*E coli*, *Enterobacteria*, *Pseudomonas*, *Enterococci*)
 - o Treat for 2 weeks duration
 - o 1st Line: Trimethoprim/Sulfamethoxazole or Fluoroquinolone
 - o 2nd Line: 2nd generation cephalosporin
 - o 3rd Line: 3rd generation cephalosporin

New Antimicrobials

- Cefiderocol
 - o Approved by FDA in 2019 for specific urinary infections
 - o Similar to other antibiotics, action is related to inhibition of gram negative bacterial cell wall

Exhibits enhanced stability against β -lactamase

- o Role in treatment of carbapenem resistant and ESBL producing organisms

Special Considerations:

Recurrent UTI

Recurrent UTI is defined as 2 or more infection in a 6-month period or ≥ 3 culture proven infections in 12 months. Both re-infection and relapsing infection contribute to the development of recurrent UTIs. Re-infection is the recurrence of a UTI with the same or different organisms rapidly after cure has been documented. In patients that have re-infection a test of cure after treatment should be performed to establish clearance of the pathogen. If there is concern for a relapsing infection, or failure to eradicate the pathogen despite reasonable treatment course a urologic referral should be made.

With the push towards antibiotic stewardship increased consideration is be given to non-antibiotic options for UTI prevention. Vaginal estrogen may be useful for post-menopausal women who have recurrent UTIs. It is established that after menopause there is thinning of the vaginal epithelium and alkalization; use of vaginal estrogen preparations may reverse these changes. There is low systemic absorption of vaginal estrogen preparation, but consideration should be given to individual patients, risks, and patient preference. There are numerous supplements that may be used for the prevention of UTIs in some patients, though for many of these there is little supporting evidence and recommendation is based more anecdotally. The 2012 Cochrane review concluded that cranberry juice can no longer be recommended, and other cranberry preparations need to be quantified prior to use in clinical studies. The

active ingredient of cranberries is proanthocyanidins (PAC) specifically type A. It has been determined that 36mg of PAC are needed to prevent the binding of E coli to urothelial cells. Methenamine hippurate is metabolized to formaldehyde in acidic urine and bacteriostatic. The 2012 Cochrane review concluded that there is evidence that methenamine may be useful for short-term prophylaxis. Vitamin C can be added to acidify urine alone or in combination with methenamine; it may have a bacteriostatic effect. Finally, both D-Mannose and Probiotics may be useful in the prevention of infections, but evidence is limited.

However, at times, despite attempts at preventative measures prophylactic antibiotics are required for management of recurrent UTIs. Any prior cultures should be reviewed to determine if antibiotic resistance exists. Options for prophylaxis include a post coital or continuous form. If daily prophylaxis is considered the best option for the patient, it should be continued for a minimum of 6 months.

Table 4: Antibiotic Prophylaxis Regimens for Recurrent Cystitis

Long Term Daily Prophylaxis	Post-coital Prophylaxis
Fosfomycin 3 gm every 10 days	Nitrofurantoin 50-100 mg single dose
Nitrofurantoin 50-100 mg daily	Trimethoprim/sulfamethoxazole 80/400mg single dose
Cephalexin 125-250 mg daily	Cefixime 400 mg single dose

**FDA warnings are posted for use of Nitrofurantoin long term due to severe pulmonary and hepatic long term effects

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is defined as a specific number of bacteria isolated from urine in individuals without symptoms or signs of a UTI. In women the Infectious Diseases Society of American has defined this as > 10(5) cfu/ml of the same organism on 2 consecutive clean catch urine samples, and in men is a > 10(5) cfu/ml in a single clean-catch urine. The presence or absence of pyuria does not differentiate symptomatic from asymptomatic bacteriuria. Screening and treatment is recommended for patients who are pregnant and patients with planned urology procedures where mucosal bleeding is anticipated (ISDA ref) or ureteroscopy (my opinion). For patient preparing for joint arthroplasty there is no consensus on screening and treatment.

Catheter associated UTI (CAUTI)

Patients with indwelling urethral catheter will universally develop bacteriuria over time; 10-25% of these will develop symptoms. Risk factors included female gender, elderly, DM, error in catheter care and bacterial colonization of the drainage bag. Pyuria, cloudy appearance, and foul odor has not been demonstrated to associated with bacteriuria or UTI (uptodate.com/contents/catheter-associated-urinary-tract-infection-in-adults)

CAUTI has multiple definitions.

- The IDSA in patient with an indwelling catheter (urethral or suprapubic) or CIC or culture within 48 hours of catheter removal positive for $>10^3$ cfu/ml of uropathogenic bacteria with the following any of the following symptoms: fevers, suprapubic/CVA tenderness, unexplained systemic symptoms of mental status change, hypotension, systemic inflammatory response syndrome without other identifiable cause or source of those symptoms and signs
- The National Health Safety Network (NHSN) defines it as $>10^5$ cfu/ml of no more than 2 organisms with symptoms of fever, suprapubic tenderness or CVA pain

Prevention of recurrent urinary tract infections

Historically, suppressive antibiotic therapy has been utilized for the prevention of recurrent urinary tract infections. Prophylactic antibiotic use has been shown to decrease the likelihood of experiencing recurrent urinary tract infections compared to no antibiotic prophylaxis. However, appropriate antibiotic stewardship remains a concern when long-term antibiotic prophylaxis is utilized. There is also a risk of side effects associated with antibiotic suppressive therapy. Antibiotics that have been studied for the prevention of recurrent urinary tract infections include nitrofurantoin, fosfomicin, trimethoprim, trimethoprim with sulfamethoxazole, and cephalosporins. Fluoroquinolones have also been utilized for prophylaxis, but the FDA has issued warnings regarding the complications associated with fluoroquinolone use. These can include cardiac effects such as QT interval prolongation, seizures, aneurysm rupture, tendon rupture, tendonitis, and neurological side effects.

The American Urological Association Guidelines for recurrent urinary tract infections in female patients acknowledges these concerns and recommends that clinicians prescribing antibiotic prophylaxis discuss the risks and benefits as well as the alternatives to antibiotic prophylaxis in this patient population.

Cranberry supplementation in the diet may be utilized to help reduce the risk of recurrent urinary tract infections as per the American Urological Association Guidelines. The challenges of applying this recommendation is that cranberry supplementation may come in various forms, including juice, tablets, and cocktails. It is believed that the proanthocyanidins help prevent bacterial adhesion to the urothelium.

Increased fluid intake in healthy patients may help reduce the risk of recurrent UTIs. Research on other non-antibiotic prophylaxis options is not robust enough to make strong recommendations in favor of their routine use. Nonetheless, many of these options are utilized by patients and practitioners, including lactobacillus, methenamine, and D-mannose. Healthy female peri- or post-menopausal women with recurrent UTIs can be prescribed intravaginal (not oral) estrogen to decrease the risk of infection, assuming there are no contraindications to estrogen supplementation.

SUMMARY

- Urinary tract infections are both prevalent and costly.
- Bacterial UTIs (different from urinary colonization or asymptomatic bacteriuria) results from the interaction of multiple host and bacterial factors.
- The diagnosis of UTI is made by urine examination and a clinical picture of illness.
- A broad differential diagnosis can exist with urinary tract symptoms that include nonbacterial pathogens and non-infectious conditions.
- Effective treatment of bacterial UTI depends on the pathogen, severity and site of illness, and other complicating patient factors.

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(Updated August 2020)

MODULE 3: BENIGN PROSTATIC HYPERPLASIA

KEYWORDS: Prostatic hypertrophy, prostatic hyperplasia, PSA, voiding dysfunction, lower urinary tract symptoms (LUTS)

At the end of this clerkship, the medical student will be able to:

1. Identify and name the major anatomic and histologic features of the prostate gland
2. Identify the predominant location in the prostate where BPH develops and describe how this fact relates to the symptoms and signs of BPH
3. Define BPH
4. Describe the distinctive epidemiological features and natural history of BPH
5. List the symptoms and signs of BPH
6. List the important components of the history when interviewing a patient with BPH
7. List the important components of the physical exam of a patient with BPH
8. Summarize the laboratory, radiologic, or urodynamic tests, if any, that should be ordered in a patient with BPH
9. List the indications for treatment of BPH
10. List the medical and surgical treatment options for BPH.
11. Describe when a patient with BPH should be referred to a urologist

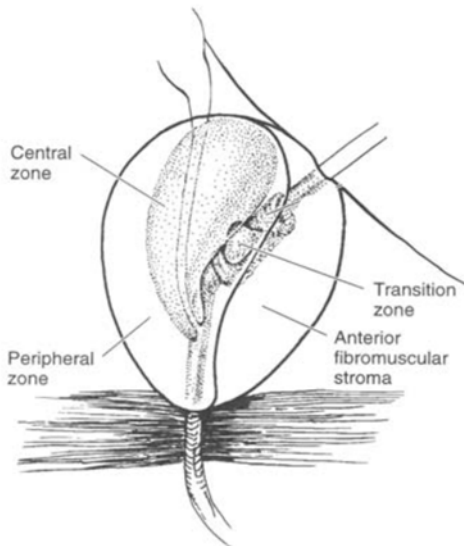
PROSTATE ANATOMY

There are 4 basic anatomic zones of the prostate, as illustrated in **Figure 1**: the anterior zone, the peripheral zone, the central zone, and the transition zone. The anterior zone is entirely fibromuscular and non-glandular, and it appears to have little significance in prostatic function or pathology. This area comprises approximately 20% of the bulk of prostatic tissue. The peripheral zone is composed entirely of acinar tissue. It comprises the posterior surface of the prostate, including the apical, lateral, posterolateral and anterolateral portions of the prostate. The peripheral zone and anterior zone, together, represent approximately 70% of glandular volume in the normal adult prostate. The vast majority of prostatic carcinomas arise in the peripheral zone of the prostate. The central gland is composed of the proximal urethra, the prostate tissue around the posterior urethra and the smooth muscle of the internal urethral sphincter. It forms the central portion of the prostate and extends from the base of the prostate to the verumontanum. The transition zone surrounds the urethra, and although this region accounts for only 10% of prostate glandular tissue in young men, it exhibits significant growth with age. Indeed, it is in the transition zone is where benign prostatic hyperplasia (BPH) develops.

BENIGN PROSTATIC HYPERPLASIA DEFINITION

Benign prostatic hyperplasia (BPH) refers to the proliferation of epithelial and smooth muscle cells within the transition zone of the prostate. Other terms for BPH include benign prostatic hypertrophy and benign prostatic enlargement (BPE). The term has been used to describe a constellation of voiding symptoms that occurs in men with aging. These symptoms are generally referred to as obstructive in nature, as the hyperplastic tissue leads to a narrowing of the prostatic urethra. Such symptoms include decreased force of stream, hesitancy, straining, incomplete bladder emptying, and nocturia. Irritative symptoms are also associated with BPH and include urinary frequency, urgency, and occasionally dysuria.

BPH has been used synonymously with “prostatism” and “bladder outlet obstruction”, implying that obstruction to urinary outflow, secondary to prostatic enlargement, is the cause of such symptoms. More recently, it has been recognized that prostatic enlargement is not necessary for such symptoms. Furthermore, women may experience similar symptoms with age. Thus, “lower urinary tract symptoms” (LUTS) is currently the preferred term to describe this complex of obstructive and irritative urinary symptoms that occur in both sexes with age.



Voiding dysfunction in the aging male may be due to a variety of factors including changes in the bladder, prostate and/or urethra. Intrinsic changes in the bladder, such as bladder instability, decreased bladder compliance and decreased bladder capacity may all lead to LUTS. However, in many men these symptoms are due to BPH. With age, the prostate exhibits glandular enlargement, increased smooth muscle tone and decreased compliance secondary to altered collagen deposition; these changes can lead to altered urinary symptoms due to outlet obstruction. Urethral stricture and bladder neck contracture are other forms of obstruction or blockage that can present with similar symptoms.

Figure 1. The zones of the normal prostate.

BPH is one of the most frequent diagnoses leading to urology referral. It begins to develop before age 30 with almost 10% of men having histologic evidence of BPH by 40 years of age, and 50% of men showing evidence by age 60. Overall, nearly 80% of men will develop BPH, and as many as 30% will receive treatment for it. In studies that examine the natural history of BPH, the incidence of acute urinary retention or the development of a significant post-void residual urinary volume is 2% per year. Although BPH is seldom life-threatening, it significantly impacts patient quality of life. Thus, the burden of BPH on the healthcare system is substantial.

BENIGN PROSTATIC HYPERPLASIA-DIAGNOSIS

After excluding other causes of LUTS, both objective and subjective parameters are used to decide whether or not treatment is indicated. Objective parameters include determination of prostate size, measurement of urinary flow rate and determination of the post-void residual urine volume. Although several subjective instruments are available to quantify the severity of LUTS, the American Urological Association Symptom Score Index (AUASI) also known as the International Prostatic Symptom Score (IPSS) is used by most clinicians (**Figure 2**). This questionnaire consists of 7 items that determines the severity of irritative and obstructive voiding symptoms.

International Prostate Symptom Score (I-PSS)							
Patient's Name		Date of Birth		Date Completed			
	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times or more	
7. Nocturia Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
Total IPSS Score							
Quality of Life Due to Urinary Symptoms							
	Delighted	Pleased	Mostly satisfied	Mixed about some satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Figure 2: The validated AUA Symptom Score tool for voiding symptoms.

Symptom severity related to urinary frequency, nocturia, weak urinary stream, hesitancy, intermittency, incomplete bladder emptying and urinary urgency is assessed, as well as its effect on quality of life. On a scale of 0-35, mild symptoms exist with scores of 0-7, moderate symptoms with scores of 7-15 and severe symptoms with a score of >15. This index demonstrates predictive validity, reliability and

internal consistency. There is some correlation between the objective and subjective measures in that the lower the peak urinary flow rate, the more severe the urinary symptoms and the larger the prostate. Using the AUA Symptom score and the information from the clinical evaluation, treatment options can be reviewed, as outlined in Figure 3.

Importantly, there are several signs or symptoms that may coexist with voiding symptoms that can alter the treatment algorithm. If the patient has urinary retention, an acute condition in which urine is unable to be voluntarily voided, then immediate treatment is indicated, and may include surgical intervention. A trial of Foley catheter or clean intermittent catheterization (CIC) and alpha blocker medication may avoid surgical treatment in the future in about 80% of cases in which urinary retention coexists with LUTS. Recurrent urinary tract infections, persistent or recurrent gross hematuria, and bladder stones are also coexisting conditions that may necessitate surgical rather than medical treatment.

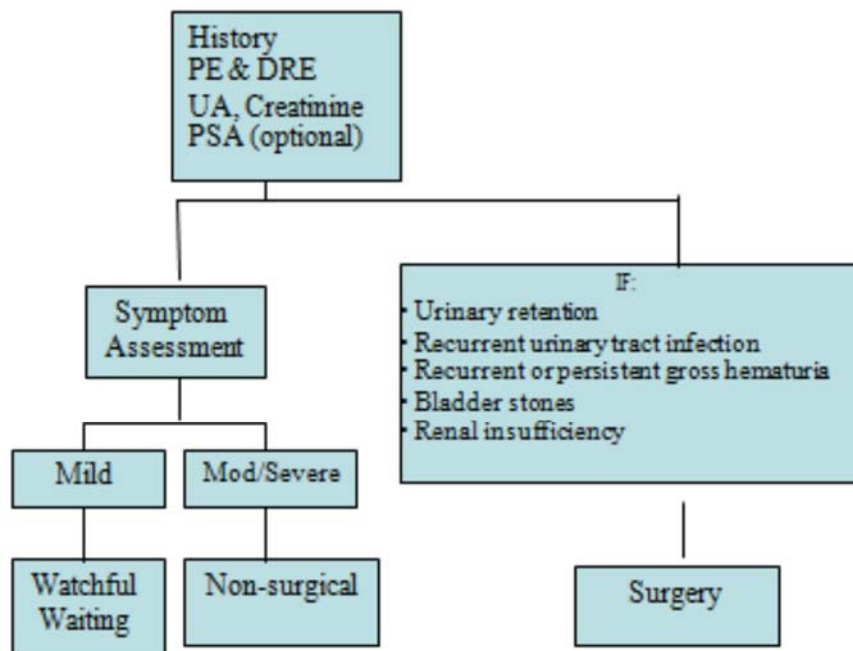


Figure 3.
Diagnostic and
treatment
algorithm for
BPH.

BENIGN PROSTATIC HYPERTROPHY-TREATMENT

Drug Therapy

Medical therapy for BPH attempts to shrink or stop the growth of the prostate or open the urethral channel within the prostate, without using surgery. The FDA has currently approved multiple drugs to relieve the symptoms associated with an enlarged prostate.

Medications in the class known as 5-alpha-reductase inhibitors (5-ARIs) result in decreased production of the hormone dihydrotestosterone (DHT), which is responsible for growth of the acinar glands of the prostate. These include Finasteride, FDA approved in 1992, and dutasteride, FDA-approved in 2001. The 5-ARIs may either prevent progression of growth of the prostate or actually shrink the prostate in some men.

Another class of drugs used for treating BPH is the alpha-1-adrenergic receptor blockers (alpha blockers), which act by relaxing the smooth muscle of the prostate and bladder neck to improve urine flow and reduce bladder outlet obstruction. This class includes terazosin, doxazosin, tamsulosin, and alfuzosin. Terazosin and doxazosin were developed as blood pressure pills, but tamsulosin and alfuzosin were developed specifically to treat BPH. There is excellent clinical trial data that shows that combination therapy with a 5-ARI and an alpha blocker (finasteride and doxazosin) together is more effective than using either drug alone to relieve symptoms and prevent BPH progression. The dual-drug regimen reduced the risk of BPH progression by 67 percent, compared with 39 percent for doxazosin alone and 34 percent for finasteride alone.

Conventional Surgical Therapy

Transurethral resection of the prostate (TURP): Surgical therapy with transurethral resection of the prostate (TURP) has traditionally been the “gold standard” treatment for men with BPH. In 1986, it was estimated that TURP accounted for 24% of the professional workload for practicing urologists in the U.S. In this type of surgery, no external incision is needed. After giving anesthesia, the surgeon reaches the prostate by inserting an instrument called a resectoscope through the urethra. The resectoscope is about 12 inches long and 1/2 inch in diameter, contains a light, valves for controlling irrigating fluid, and an electrical loop that cuts tissue and seals blood vessels. During the 60-90-minute operation, the surgeon uses the scope's wire loop to remove the obstructing tissue one piece at a time. The pieces of tissue are carried by the fluid into the bladder and then flushed out at the end of the operation. A TURP is used for approximately 90% of all prostate surgeries for BPH. In most patients, before TURP is performed, consideration has already been given to medical therapy. In general, TURP is reserved for very symptomatic men or those who develop complications including urinary tract infection, bladder stones, or gross hematuria as mentioned above.

A variation of the TURP procedure is called transurethral incision of the prostate (TUIP). Instead of removing tissue, as with TURP, this procedure widens the urethra by making a few small cuts in the bladder neck, where the urethra joins the bladder, and in the prostate gland itself. Although some people believe that TUIP gives the same relief as TURP with less risk of side effects such as retrograde ejaculation, its advantages and long-term side effects have not been clearly established.

Surgical “open” prostatectomy: In the few cases when a transurethral procedure is not able to be done, because the prostate is too large, the bladder has been damaged or contains bladder stones, or important identifying landmarks are not visible for TURP, open prostatic surgery is indicated. With all open surgical procedures, anesthesia is given and an incision is made. Once the surgeon reaches the prostate capsule, he or she scoops out the enlarged tissue from inside the gland. Importantly, as with other types of surgery and procedures for BPH, the part of the prostate at risk for prostate cancer development is not removed and therefore men who have procedures for BPH are still at risk for developing prostate cancer.

Transurethral laser surgery: Surgical procedures that employ side-firing laser fibers and Nd: YAG lasers to vaporize obstructing prostate tissue are also used to treat BPH. A laser fiber is passed into the urethra near the prostate using a cystoscope and then several bursts of energy lasting 30 to 60 seconds are delivered through the laser fiber. The laser energy destroys prostate tissue and causes shrinkage. As with TURP, laser surgery requires anesthesia and a hospital stay. One advantage of laser surgery over TURP is that laser surgery causes less blood loss and allows for a quicker recovery. But laser surgery may not be effective on larger prostates and the long-term effectiveness of laser surgery is unclear. There are two variations of laser surgery for BPH: Photoselective Vaporization of the Prostate (PVP) uses a high-energy laser to destroy prostate tissue and seal the treated area, and Interstitial Laser Coagulation involves placing the tip of the fiberoptic probe directly into the prostate tissue to destroy it.

Laser enucleation. Holmium laser enucleation of the prostate (HoLEP) or thulium laser enucleation of the prostate (ThuLEP) is a minimally invasive technique that can be offered to patients with larger prostate glands.

Although these approaches are often successful, some adverse effects may occur. The cutting of prostatic tissue may result in significant bleeding and the absorption of irrigation fluid into veins that are cut open may result in a life-threatening syndrome of fluid overload and dilutional hyponatremia known as “TUR syndrome”. In addition, electrical energy may damage important surrounding structures. Damage to the internal urethral sphincter may cause retrograde ejaculation and possible incontinence, whereas damage to the nerves responsible for erection (which run along the outer rim of the prostate) may result in impotence.

Minimally Invasive Therapy

A number of minimally invasive procedures have been developed to relieve BPH symptoms, while avoiding general anesthesia and the potential adverse effects listed above. In general, these procedures are less invasive than conventional surgery for BPH.

Transurethral microwave procedures: This device uses microwaves to heat and destroy excess prostate tissue. In the procedure called transurethral microwave thermotherapy (TUMT), the device sends microwaves through a catheter to heat selected portions of the prostate to at least 111 degrees Fahrenheit. A cooling system protects the urinary tract during the procedure. The procedure is performed on an outpatient basis in an hour without general anesthesia. TUMT has not been reported to lead to erectile dysfunction or incontinence. Although microwave therapy does not cure BPH, it reduces urinary frequency, urgency, straining, and intermittent flow. It does not correct the problem of incomplete emptying of the bladder. The long-term effects of microwave therapy are still not clear however.

Transurethral needle ablation (TUNA): The TUNA system delivers low-level radiofrequency energy through twin needles to burn away selected regions of the enlarged prostate. Shields protect the urethra from heat damage. The TUNA system improves urine flow and relieves symptoms with fewer side effects when compared with conventional surgery, transurethral resection of the prostate (TURP). No incontinence or impotence has been observed with this procedure.

Water-induced thermotherapy: This therapy uses heated water to destroy excess tissue in the prostate. A catheter containing multiple shafts is positioned in the urethra so that a treatment balloon rests in the middle of the prostate. A computer controls the temperature of the water, which flows into the balloon and heats the surrounding prostate tissue. The system focuses the heat in precise regions of the prostate, while surrounding tissues in the urethra and bladder are protected. Destroyed tissue either escapes with urine through the urethra or is reabsorbed by the body. This therapy may be offered to patients who are desirous of preserving erectile and ejaculatory function.

High-intensity focused ultrasound (HIFU): The use of low frequency ultrasound waves to destroy prostate tissue is the youngest of the minimally invasive therapies developed for BPH. It appears as safe as other minimally invasive methods but long term outcome data is not available as of yet.

Prostatic urethral lift. Prostatic urethra lift is a transurethral procedure that can be office-based whereby implants are delivered to retract the obstructing prostatic lobes. Symptoms reduction and flow rates for this procedure are less significant as compared to TURP, but this procedure can be offered to patients who are concerned with preservation of ejaculatory and erectile function.

BENIGN PROSTATIC HYPERPLASIA AND PSA

Prostate Specific Antigen (PSA) is a serine protease produced by benign and malignant prostate tissue. Functionally, PSA is the enzyme responsible for liquefaction of the seminal fluid after ejaculation. Although produced in small amounts in other tissues, it should be considered to be prostate specific. PSA circulates in the serum in both free (unbound) and complexed (bound) forms. In addition to being elevated by BPH and prostate cancer, PSA may also be transiently elevated in cases of prostatic inflammation (prostatitis) or infarction, and after prostatic manipulation by biopsy. However, routine digital rectal examination (DRE) usually has little effect on serum PSA levels. The half-life of serum PSA is 2.2 to 3.2 days. Therefore, one should wait 4 to 8 weeks after prostate manipulation and inflammation (cystoscopy, prostate biopsy, and prostatitis) before obtaining a PSA.

A flawless and standardized interpretation of elevated PSA values has yet to be determined. Although it has been well demonstrated that patients with elevated serum PSA levels are more likely to be harboring aggressive disease serum PSA screening **interpreted outside the context of important patient-specific variables** carries with it a significant risk of what has been called over diagnosis: the identification and treatment of patients who might otherwise have lived out the rest of their lives without experiencing any of the terrible symptoms associated with advanced prostate cancer. Since the treatment of prostate cancer is associated with a significant level of patient morbidity (including bowel dysfunction, urinary dysfunction, and impotence), the use of serum PSA as a screening tool has been a topic of significant controversy. In May of 2012, the United States Preventative Services Task Force (USPSTF), released their recommendation against routine PSA screening, stating they have found "fair evidence that [PSA screening] is ineffective or that harms outweigh the benefits." Nevertheless, the AUA recognizes that the interpretation of an asymptomatic patient's PSA level is a nuanced exercise that must be tailored to the patient in question.

Potential screening should be preceded by an informed discussion of the risks and benefits of screening, early diagnosis and treatment. Given the added cost and anxiety associated with PSA screening, in combination with a lack of randomized trials showing that screening decreases morbidity and mortality, such screening is not recommended for everyone. With such information, the patient can make an individual decision regarding PSA screening.

SUMMARY

- The prostate is composed of several regions and zones: two zones of interest are the peripheral zone, where most cancers arise, and the transition zone, where BPH arises.
- The diagnosis of voiding dysfunction due to BPH is made based on both subjective and objective findings on clinical evaluation.

- Medical treatment of BPH involves treatment that relaxes the muscular stromal tissue of the bladder neck and prostatic urethra (alpha-blockers) and reduction in the acinar-glandular volume of the prostate through reduced DHT production (5-alpha-reductase inhibitors).
- Indications for surgical intervention with BPH include urinary retention, gross hematuria, bladder stones, and urinary tract infection.
- Serum PSA, a serine protease that liquefies the ejaculate, increases over time with both BPH and prostate cancer, which makes it a difficult diagnostic marker for cancer alone.

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(Updated April 2020)

MODULE 4: ERECTILE DYSFUNCTION

KEYWORDS: Erectile dysfunction, phosphodiesterase inhibitors, sexual dysfunction

LEARNING OBJECTIVES

At the end of this clerkship, the medical student will be able to:

1. Draw, identify and name the major anatomic regions of the penis involved with erections
2. Describe the physiology of the normal penile erection
3. List and briefly describe the major causes of erectile dysfunction (ED)
4. List the important components of the history when interviewing a patient with ED
5. Outline the important components of the physical exam of a patient with ED
6. List the treatment options for erectile dysfunction and describe the mechanisms by which they work
7. Describe the contra-indications and side-effects of phosphodiesterase inhibition for ED
8. Describe when a patient with ED should be referred to a urologist

DEFINITION

Erectile dysfunction is defined as the inability to achieve and maintain an erection sufficient for satisfactory sexual intercourse. It is estimated to affect 20 to 30 million men in the US. ED may result from impairment of one or most commonly, a combination of factors: psychological, neurologic, hormonal, arterial, and venous. More recently it has become clear that, in many cases, ED may be a “silent marker” for the later development of endothelial dysfunction and eventually, cardiovascular disease.

THE PENILE ERECTION

Penile erection is a neurovascular event subject to psychological and hormonal modulation. Upon sexual stimulation, nerve impulses release neurotransmitters from the cavernous nerve terminals and relaxing factors from the endothelial cells in the penis. Resultant smooth muscle relaxation in the arteries and arterioles supplying the erectile tissue results in a several-fold increase in blood flow. Concomitantly, there is (b) relaxation of the sinusoidal smooth muscle within the paired corporeal bodies, facilitating rapid filling and expansion of the sinusoidal system (Figure 1). As a result, (c) venous plexuses located between the sinusoids and rigid tunic covering the penis

are compressed resulting in almost total occlusion of venous outflow. These events effectively trap the blood within the corpora cavernosa and raise the penis from flaccid to erect position. During full erection, the intracavernous pressure of 100 mmHg is achieved. Sensory stimulation triggers the bulbocavernosus reflex, causing the ischiocavernosus muscles to forcefully compress the blood-filled corpora cavernosa. During ejaculation, penile intracavernous pressures reach several hundred mm Hg. During this phase, vascular inflow and outflow temporarily cease. Detumescence results when erectile neurotransmitter release stops, when there is breakdown of second messengers by phosphodiesterases, or due to sympathetic discharge during ejaculation.

The penis is innervated by autonomic and somatic nerves. In the pelvis, the sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa, corpus spongiosum and glans penis to regulate the blood flow during erection. The pudendal nerve, the somatic component, is responsible for penile sensation and the contraction and relaxation of the bulbocavernosus and ischiocavernosus muscles that surround the penis.

Nitric oxide released from nonadrenergic-noncholinergic neurotransmission and the endothelium is likely the principal neurotransmitter for penile erection. Within the muscle, nitric oxide activates a guanylyl cyclase that raises intracellular concentrations of cyclic guanosine monophosphate (GMP). Cyclic GMP in turn activates a specific protein kinase, which results in the opening of the potassium channels and hyperpolarization and causes sequestration of intracellular calcium and blocks calcium influx. As a result of this drop in cytosolic calcium, smooth muscle relaxation occurs leading to erection. On return to the flaccid state, cyclic GMP is hydrolyzed to guanosine monophosphate by phosphodiesterase type 5. Sildenafil, vardenafil and tadalafil are drugs currently FDA approved to treat erection dysfunction and they work by blocking phosphodiesterase enzyme activity.

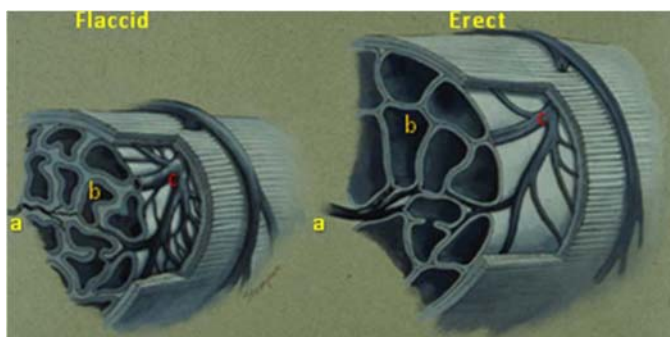


Figure 1. Anatomy of the penis. The penile erection occurs as a result of 3 processes: a) smooth muscle relaxation among arteries and trabecular tissue increases blood flow, which b) lengthens and enlarges penis through sinusoidal filling, and c) expanded sinusoids compress the subtunical venous plexus, reducing venous outflow.

CAUSES OF ERECTILE DYSFUNCTION

Erectile dysfunction can be classified as psychogenic, organic (neurogenic, hormonal, arterial, venous or cavernosal and drug-induced), and mixed psychogenic and organic (Table 1). Mixed etiologies for ED are the most common. Typical causes of psychogenic erectile dysfunction include performance anxiety, strained relationship, lack of sexual arousability, and overt psychiatric disorders such as depression and schizophrenia. Neurologic disorders such as Parkinson's and Alzheimer's diseases, stroke, and cerebral trauma often cause erectile dysfunction by decreasing libido or causing inability to initiate the erectile process. In men with spinal cord injuries, the degree of erectile function depends largely on the nature, location and extent of the lesion. Hormonally, androgen deficiency results in a decrease in nocturnal erections and decreases libido. However, erection in response to visual sexual stimulation is preserved in men with hypogonadism, suggesting that androgen is not essential for erection. Hyperprolactinemia of any cause results in both reproductive and sexual dysfunction due to the inhibitory action of prolactin on gonadotropin-releasing hormone secretion, resulting in hypogonadotropic hypogonadism.

TABLE 1: CLASSIFICATION AND CAUSES OF ERECTILE DYSFUNCTION

Category	Disorders	Problem
Psychogenic	Performance anxiety, Depression	Loss of libido, overinhibition, Impaired nitric oxide release
Neurogenic	Stroke, Spinal cord injury, Diabetic retinopathy	Lack of nerve impulse, or Interrupted transmission
Hormonal	Hypogonadism, Hyperprolactinoma	Inadequate nitric oxide release
Vasculogenic (arterial or venous)	Atherosclerosis, Hypertension	Impaired arterial or venous flow
Medication-induced	Antihypertensives, Antidepressants, Alcohol, Tobacco use	Central suppression, Vascular insufficiency

Due to the intricate relationship between vascular function and erections as outlines above, vascular deficiencies often manifest with compromised erectile function. Common risk factors associated with generalized penile arterial insufficiency include hypertension, hyperlipidemia, cigarette smoking, diabetes mellitus, and pelvic irradiation. Focal stenosis of the common penile artery most often occurs in men who have sustained blunt pelvic or perineal trauma (e.g., biking accidents). Poor venous occlusion during erection (veno-occlusive dysfunction) can also result with erectile dysfunction. This can result from degenerative changes (Peyronie's disease, aging, and diabetes mellitus) or traumatic injury (penile fracture) to the tunica albuginea and structural alterations of the cavernous smooth muscle and endothelium.

Many drugs have been associated with erectile dysfunction. Central neurotransmitter pathways, including serotonergic, noradrenergic, and dopaminergic pathways involved in sexual function, may be disturbed by antipsychotics, antidepressants and centrally acting antihypertensive drugs. Beta-adrenergic blocking drugs may cause erectile dysfunction by potentiating alpha-1 adrenergic activity in the penis. Thiazide diuretics have been reported to cause erectile dysfunction, but the cause is unknown. Spironolactone can cause erectile failure as well as decrease in libido and gynecomastia. Cigarette smoking may induce vasoconstriction and penile venous leakage because of its contractile effect on the cavernous smooth muscle. Alcohol in small amounts improves erection and increases libido because of its vasodilatory effect and the suppression of anxiety; however, large quantities may result in central sedation, decreased libido and transient erectile dysfunction. Cimetidine, a histamine-H2 receptor antagonist, has been reported to decrease libido and cause erectile failure via its role as an antiandrogen. Other drugs known to cause erectile dysfunction are estrogens and drugs with antiandrogenic action such as ketoconazole and cyproterone acetate.

Sexual function progressively declines in "healthy" aging men. For example, the latent period between sexual stimulation and erection increases, erections are less turgid, ejaculation is less forceful, ejaculatory volume decreases, and the refractory period between erections lengthens. Comorbid medical conditions demonstrate significant impact on the development of erectile dysfunction. About 50% of men with diabetes mellitus have erectile dysfunction due to compromise to small vessels which may affect both blood flow and neurotransmitter delivery. Chronic renal failure has frequently been associated with diminished erectile function, impaired libido, and infertility. Men with angina, myocardial infarction, or heart failure may have erectile dysfunction from anxiety, depression, or concomitant penile arterial insufficiency.

ERECTILE DYSFUNCTION-DIAGNOSIS

Erectile dysfunction can be the presenting symptom of a variety of diseases such as cardiovascular disease, diabetes mellitus, hyperlipidemia, hypertension, spinal-cord compression, and pituitary tumor. Therefore, a thorough history (medical, sexual and psychosocial), physical examination and appropriate laboratory tests aimed at detecting these diseases should be performed. A detailed psychosocial history may reveal chronic issues or acute relationship conflicts optimally treated by mental health professionals. Standardized, validated survey instruments such as the Sexual Health Inventory for Men (SHIM) are valuable to assess erectile dysfunction in affected individuals and track response to therapy (Figure 2). Often, the particular characteristics of the erectile problem can help with the diagnosis: in cases of arterial problems, prolonged stimulation may be required to achieve an erection; with venous leak an erection is easily achieved but lost very quickly. Physical examination should include evaluation of the breasts, hair distribution, penis and testis, palpation of the femoral and pedal pulses and testing of genital and perineal sensation. Recommended laboratory tests include urinalysis, complete blood count, and measurement of fasting

blood glucose, creatinine, and in select instances augmented by laboratory evaluation of cholesterol and triglycerides, and testosterone.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence that you could get and keep an erection?		VERY LOW	LOW	MODERATE	HIGH	VERY HIGH
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No SEXUAL ACTIVITY	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	DID NOT ATTEMPT INTERCOURSE	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	DID NOT ATTEMPT INTERCOURSE	EXTREMELY DIFFICULT	VERY DIFFICULT	DIFFICULT	SLIGHTLY DIFFICULT	NOT DIFFICULT
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	DID NOT ATTEMPT INTERCOURSE	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5

Add the numbers corresponding to questions 1-5. TOTAL: _____

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:

1-7 Severe ED 8-11 Moderate ED 12-16 Mild to Moderate ED 17-21 Mild ED

Figure 2: Sexual Health Inventory for Men (SHIM) that is used clinically to assess the degree of erectile dysfunction.

It is critical once a thorough history and physical is conducted to inquire regarding the goals and preferences of the man (and his partner), and discuss further diagnostic and therapeutic options. If the patient is utilizing a pharmaceutical known to cause erectile dysfunction or recreational drugs, or has vascular risk factors, a change in medication or life-style may be helpful. If primary hypogonadism is detected, androgen therapy may be indicated in select instances. Importantly, PDE5 inhibitors are contraindicated in those taking nitrate medication and also in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors. This goal-directed approach to diagnosis and treatment of erectile dysfunction, tailored to the individual’s health status and goals, is outlined in Figure 3.

Importantly, erectile dysfunction not just a sexual health issue. In many men, ED may be a serious harbinger of life-threatening cardiovascular conditions. A landmark study followed men age 55 and older over for 7 years and assessed them for both erectile

dysfunction and cardiovascular disease, including heart attack and stroke. In patients with a new onset of erectile dysfunction there was an associated 25% increased risk for heart attacks, strokes, angina, or mini-strokes, compared to men with no erectile dysfunction. If men already had ED at the onset of the study, the risk for cardiovascular disease was 45% higher than those with no ED. In fact, ED is as important a cardiovascular disease risk factor as is smoking or a family history of heart disease.

Physiologically, this kind of associated risk makes sense, as the cells that form plaques in the arteries of the penis are the same cells that form plaques the arteries anywhere else in the body. Indeed, previous research has shown that among patients who seek help for ED, nearly 20% had undiagnosed high blood pressure, 15% had diabetes, and 5% already had significant coronary artery disease. Particularly for younger patients presenting with ED, evaluation with preventional cardiology may uncover occult cardiovascular disease and should be considered by the clinician.

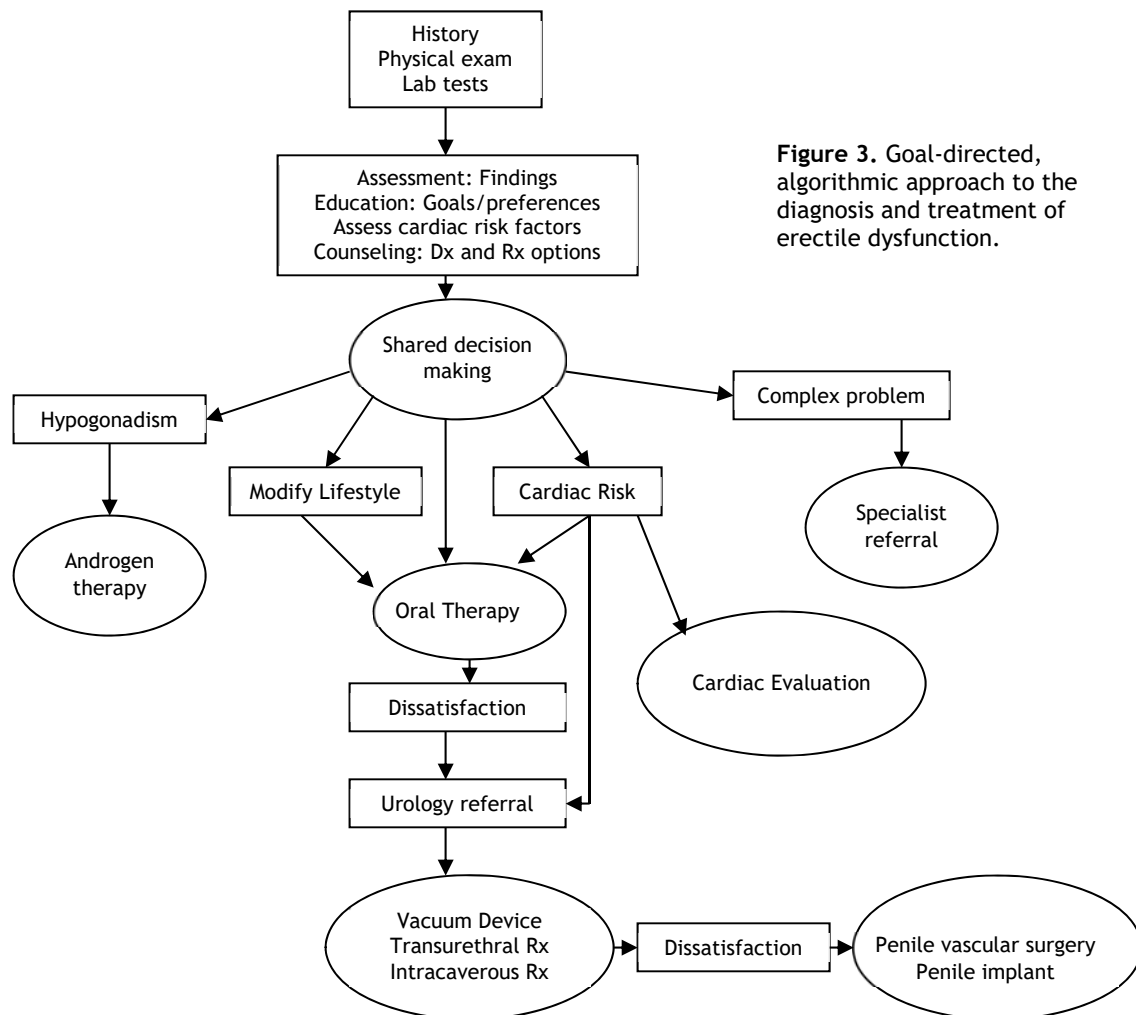


Figure 3. Goal-directed, algorithmic approach to the diagnosis and treatment of erectile dysfunction.

ERECTILE DYSFUNCTION - TREATMENT

Life style changes. In general, most physicians suggest treatments that proceed from least to most invasive. Healthy lifestyle changes like quitting smoking, losing excess weight, and increasing physical activity may help some men regain sexual function. Discontinuing drugs with harmful side effects is another effective treatment.

Psychotherapy. Until other treatments became more popular in the 1980s and 1990s, psychotherapy was the mainstay of ED treatment. Psychotherapy attempts to treat ED by decreasing the anxiety associated with intercourse. The patient's partner can help by gradually developing better intimacy and stimulation. Psychotherapy remains an option for select patients identified with chronic or situational conditions that may benefit.

Pharmaceutical Therapy. Drugs for treating ED can be taken orally, injected directly into the penis, or inserted into the urethra. In March 1998, the FDA approved sildenafil, the first oral therapy for ED treatment. Since that time, multiple additional phosphodiesterase (PDE) inhibitors have been approved. Taken before sexual activity, PDE inhibitors work by enhancing the effects of nitric oxide, relaxing penile smooth muscle during sexual stimulation and allows increased blood flow. While these medications improve the response to sexual stimulation, they do not trigger an automatic erection. The majority of men with ED will respond to these drugs and for this reason, they are considered first line therapy for ED.

No PDE inhibitor should be used more than once a day. Men who take nitrate-based drugs such as nitroglycerin for heart problems should not use these drugs because the combination can cause a sudden drop in blood pressure. Additionally, clearance by cardiology may be required to approve therapy for men with significant cardiovascular disease for sexual activity. Caution as several members of this class of medications may cause a sudden drop in blood pressure when taken with an alpha-blocker.

Oral testosterone can improve libido in some men with low natural testosterone levels, but it is often ineffective for erections and may cause significant collateral damage. . Other drugs—including yohimbine hydrochloride, dopamine and serotonin agonists, and trazodone—may be effective for ED, but studies to substantiate these claims are inconsistent.

Intracavernosal Injections. Many men achieve stronger erections by injecting medications directly into the cavernous bodies of the penis, resulting in smooth muscle relaxation and engorgement with blood. Drugs such as papaverine hydrochloride, phentolamine, and alprostadil (a prostaglandin E2) all modulation endothelial function and can help induce and maintain erections. These drugs may create unwanted side effects, however, including persistent erection (known as priapism) and scarring.

Intraurethral Injection. A system for inserting a pellet of alprostadil into the urethra is marketed as MUSE. The system uses a prefilled applicator to deliver the pellet about an inch deep into the urethra. An erection will begin within 8 to 10 minutes and may last 30 to 60 minutes. The most common side effects are penile pain, warmth or burning sensation in the urethra; redness from increased blood flow to the penis; and minor urethral bleeding or spotting.

Vacuum Erection Devices. Mechanical vacuum devices induce erections by creating a partial vacuum, which draws blood into the penis, engorging and expanding it. The devices have three components: a plastic cylinder, into which the penis is placed; a pump, which draws air out of the cylinder; and an elastic band, which is placed around the base of the penis to maintain the erection after the cylinder is removed and during intercourse by preventing venous return.

Penile Surgery. Surgical procedures to improve erections are performed for 3 reasons: to implant a device that can cause the penis to become erect, to reconstruct arteries and increase penile blood flow, and to occlude veins that allow blood to leak out of the penis and cause ED. Implanted devices, known as penile prostheses, are excellent at restoring erections in men with medication refractory ED. Implants are devices, however and have complications that include mechanical breakdown, erosion and infection. Malleable implants consist of paired solid rods, which are inserted surgically into the corpora cavernosa. The user manually adjusts the position of the penis and, therefore, the rods. Adjustment does not affect the width or length of the penis. Inflatable implants consist of paired cylinders that are surgically inserted inside the penis and then expanded using pressurized fluid from a co-implanted fluid reservoir and a pump. The cylinders are inflated by pressing on the scrotal pump and reproduce a more natural erection with expansion of both the width and length of the penis.

Surgery to repair arteries can reduce ED caused by blockages. The best candidates for such surgery are young men with localized blockage of an artery due to pelvic injury or fracture. The procedure is almost never successful in older men with diffuse vascular disease. Surgery to ligate veins permitting blood to leak from the penis has the opposite goal: to reduce venous leak which results in poor erectile sustain. Given the complexity of the venous drainage patterns from the penis, this type or penile surgery is rarely performed.

SUMMARY

- The normal penile erection involves relaxation of cavernous arteries, filling of venous sinusoidal spaces within the corpora cavernosal bodies and constriction of the subtunical venous plexus system.
- Nitric oxide released from nonadrenergic-noncholinergic neurotransmission and the endothelium is the principal neurotransmitter for penile erection.

- Erectile dysfunction is a common, age related and very treatable urologic condition that can have psychogenic, arterial, venous neurogenic and hormonal causes.
- The clinical evaluation of ED involves a patient and goal-directed approach that incorporates the use of validated survey tools and laboratory testing for testosterone, cholesterol and lipids as appropriate.
- Treatment with oral PDE5 inhibitors is effective for most men with mild to moderate ED.

For expanded information refer to the AUA guideline on erectile dysfunction: (<https://www.auanet.org/education/guidelines/erectile-dysfunction.cfm>) and the AUA guideline on Peyronie's disease: ([https://www.auanet.org/guidelines/peyronies-disease-\(2015\)](https://www.auanet.org/guidelines/peyronies-disease-(2015)))

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(Updated September 2020)

MODULE 5: HEMATURIA

KEY WORDS: Hematuria, Cystoscopy, Urothelial carcinoma, CT Urography

LEARNING OBJECTIVES

At the end of this clerkship, the learner will be able to:

1. Define microscopic hematuria.
2. Describe the proper technique for performing microscopic urinalysis.
3. Identify risk factors that increase the likelihood of diagnosing urologic malignancy during evaluation of hematuria.
4. Explain the significance of finding red cell casts in patients with microscopic hematuria.
5. Discuss the evaluation of hematuria.

DEFINITION

Hematuria is defined as the presence of red blood cells in the urine. When visible to the naked eye, it is termed gross hematuria. When detected by the microscopic examination of the urinary sediment, it is termed microscopic hematuria.

The dipstick method to detect hematuria depends on the ability of hemoglobin to oxidize a chromogen indicator with the degree of the indicator color change proportional to the degree of hematuria. Urine dipstick testing has a sensitivity of 95% and a specificity of 75% for detecting microscopic hematuria. False positive readings can be due to free hemoglobin (e.g. menstrual blood), myoglobin due to exercise, dehydration and certain antiseptic solutions (povidone- iodine). Knowing the serum myoglobin level and results of the microscopic urinalysis will help differentiate these confounders. Thus, positive dipstick results should be confirmed with microscopic evaluation. The presence of significant proteinuria (2+ or greater) suggests a nephrologic origin for hematuria. The presence of many epithelial cells suggests skin or vaginal contamination, and another sample should be collected.

Microscopic examination of urine is performed on 10 mL of a midstream, clean-catch specimen that has been centrifuged for 10 minutes at 2000 rpm or for 5 minutes at 3000 rpm. The sediment is re-suspended and examined under high power magnification. With this method, microscopic hematuria is defined as > 3 red blood cells per high powered field (rbc/hpf) on a single specimen.

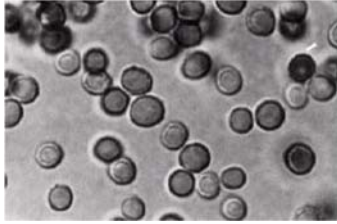


Figure 1: Red blood cells observed on high power microscopy of urine sediment.

The presence of red cell casts, dysmorphic red blood cells, leukocytes, bacteria and crystals should also be included in the urinalysis report.

EPIDEMIOLOGY

Hematuria is one of the most common urologic diagnoses accounting for 20% of urology consultations. The prevalence of microscopic hematuria ranges from 2-31% depending on the population studied. The likelihood of finding significant urologic oncologic disease varies with associated risk factors which include:

Table 1 - Risk Factors for Malignancy in Patients with Hematuria

- Older age
- Male gender
- History of cigarette smoking
- History of occupational chemical benzene or aromatic amines exposure (e.g. dyes, rubber, petrochemicals)
- History of cyclophosphamide/ifosfamide chemotherapy
- History of pelvic radiation
- Irritative voiding symptoms (urgency, frequency, dysuria)
- History of chronic indwelling catheters
- Family history of urothelial cancers

Even though the likelihood of documenting a urologic malignancy in patients referred for microscopic hematuria is less than 5%, no major health organization currently recommends routine screening for microhematuria in asymptomatic patients. Instead, the decision to obtain a urinalysis (dipstick or microscopic) is based on the interpretation of clinical findings by the evaluating physician.

ETIOLOGY

The source of red blood cells in the urine can be from anywhere in the urinary tract between the kidney glomerulus and the urethral meatus.

When considering the evaluation of hematuria, hematuria should be separated into glomerular or non-glomerular etiologies. Glomerular causes arise from the kidney itself. In general, glomerular hematuria is the purview of nephrologists, whereas urologists are concerned with structural and pathologic conditions that are visible on imaging and/or endoscopic examination. The presence of dysmorphic RBC, proteinuria, cellular casts, and/or renal insufficiency warrant concurrent nephrological and urologic evaluation.

Urinary findings suggestive of a glomerular source for the patient's hematuria include dysmorphic red blood cells (Figure 2), significant proteinuria, and red cell casts (Figure 3). The presence of red cell casts in the urinary sediment is strong evidence for glomerular hematuria.

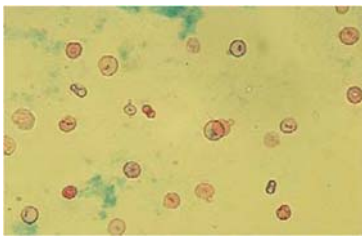


Figure 2: Example of dysmorphic red blood cells consistent with renal or glomerular hematuria.



Figure 3: Example of a red cell cast (arrow) in the urinary sediment.

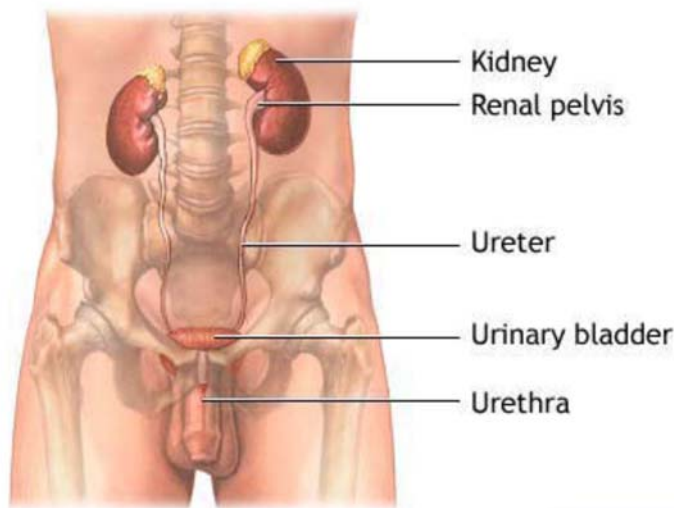
Although protein may enter the urine along with the red blood cells regardless of the origin of the hematuria, significant proteinuria (>1,000 mg/24 hours) likely indicates a renal parenchymal process and should prompt consultation with a nephrologist. The more common causes of glomerular hematuria are listed in Table 2.

Table 2 - Common Causes of Glomerular Hematuria

- IgA nephropathy (Berger's disease)
- Thin glomerular basement membrane disease
- Hereditary nephritis (Alport's syndrome)

Berger's disease is the most common cause of asymptomatic glomerular microhematuria and, in the absence of significant proteinuria, typically follows a benign course. There is no proven treatment for the condition although fish oils may benefit patients with progressive disease.

Nonglomerular etiologies can be subdivided by location: the upper urinary tract (kidney and ureter) or the lower urinary tract (bladder and urethra) (Figure 4). The



more commonly encountered upper and lower urinary tract etiologies are listed in Table 3. Although urothelial carcinoma involving the urinary bladder is the most common malignancy discovered in patients with asymptomatic microhematuria, benign processes are far more common than cancer. In particular, urinary tract infection (UTI), urinary tract stones, and benign prostatic hyperplasia (BPH) occur more frequently than urologic malignancies.

Figure 4: Human urinary tract anatomy that is at risk when hematuria is found. From: Nlm.nih.gov

Table 3 - Common Causes of Non-Glomerular Hematuria

Upper Tract

- Urolithiasis
- Pyelonephritis
- Renal cell carcinomas or other malignant/benign renal tumors
- Upper tract urothelial carcinoma
- Urinary obstruction (e.g. ureteropelvic junction obstruction, ureteral strictures)
- Trauma

Lower Tract

- Bacterial cystitis (UTI)
- Prostatitis
- Benign prostatic hyperplasia
- Strenuous exercise (“marathon runner’s hematuria”)
- Urothelial carcinoma of bladder/urethra
- Prostate cancer
- Instrumentation
- Trauma
- Radiation cystitis
- Benign hematuria (e.g. interstitial cystitis, trigonitis)

Oral anticoagulation therapy does not lead to *de novo* hematuria. However, the degree and duration of hematuria from another cause may be influenced by such therapy. The American Urologic Association guidelines require the same hematuria evaluation in patients on anticoagulation therapy as those without anticoagulation.

EVALUATION

As the differential for hematuria is quite broad, a thorough medical history and directed physical examination are necessary. It is imperative to determine if the patient has experienced gross hematuria or if the hematuria is purely microscopic, as the evaluation for these conditions may be different. The patient should be asked about the onset, duration, and associated symptoms of hematuria. The presence of flank pain, fever or urinary symptoms such as dysuria, frequency and urgency should be noted. Lower urinary tract symptoms in men, such as straining to void or nocturnal enuresis, may be indicative of BPH. Association with other activities (menses, physical exertion, etc.) may suggest an etiology for the patient's hematuria. Pelvic irradiation and certain chemotherapeutic agents, in particular cyclophosphamide and mitotane, have been associated with hemorrhagic cystitis. Both cigarette smoking and occupational exposures to aniline dyes and aromatic amines used in certain manufacturing processes increase the risk of bladder cancer, as does any sort of chronic irritation of the bladder (e.g. indwelling catheter, stones, and recurrent infections). Additionally, any prior history of urologic disease or interventions is an important aspect to discuss. The physical examination of patients with hematuria is invaluable. The presence of edema and cardiac arrhythmias may suggest the nephrotic syndrome. Costovertebral angle tenderness is suggestive of ureteral obstruction, often secondary to stone disease, in the afebrile patient. When fever and flank tenderness are both present the diagnosis of pyelonephritis should be entertained.

If the patient has not had a formal microscopic urinalysis this should also be part of the initial evaluation. As noted earlier, the dipstick urinalysis may yield false-positive results in patients with myoglobinuria. Also, some patients may present with "red urine" relating to dietary intake or medication use (phenazopyridine) and these cases of spurious hematuria may reveal a normal microscopic urinalysis. Understand, however, that hematuria may be intermittent in patients with significant urologic disease. In addition to identifying the number of red blood cells per high powered field, the presence of white blood cells, bacteria, nitrites, and leukocyte esterase may suggest infection. If infection is suspected, a confirmatory urine culture should be obtained and a repeat urinalysis performed after the infection has been treated. A urine microscopy demonstrating microhematuria after appropriate treatment of a culture proven urinary tract infection mandates an evaluation. Patients with findings consistent with glomerular hematuria should be referred to nephrology for further evaluation.

All patients with hematuria should be evaluated by a urologist. Blood tests including renal function tests, complete blood count, and coagulation parameters can be

useful, and PSA may be checked in men depending on their age, risk factors, and desire for PSA screening.

If patients have a history of gross hematuria, they require a comprehensive evaluation with cystoscopy, upper tract imaging (CT urography or MR urography), and urine cytology. To provide clarity for the evaluation of patients with microscopic hematuria, the AUA recently published the updated guideline which stratifies patients into low, intermediate, and high risk based on based on age, smoking history, and quality/quantity of hematuria (Table 4). Those categorized as low-risk should be engaged in shared decision-making with their urologists about the risks and benefits of further testing. At a minimum, they should have a repeat urinalysis in 6 months. Intermediate and high-risk patients should undergo a thorough urologic evaluation. Currently, urine cytology or other tumor markers are not routinely recommended in the evaluation of microscopic hematuria, but may be considered in patients who have persistent hematuria after a negative evaluation.

Table 4 - AUA Microhematuria Risk Stratification

Low Risk

- Age: Women <50 years old; Men <40 years old
- Smoking History: Never or <10 pack year history
- Urinalysis: 3-10 RBC/HPF

Intermediate Risk

- Age: Women 50-59 years old; Men 40-59 years old
- Smoking History: 10-30 pack year history
- Urinalysis: 11-25 RBC/HPF

High Risk

- Age: 60+ years old
- Smoking History: >30 pack year history
- Urinalysis: >25 RBC/HPF
- Gross hematuria

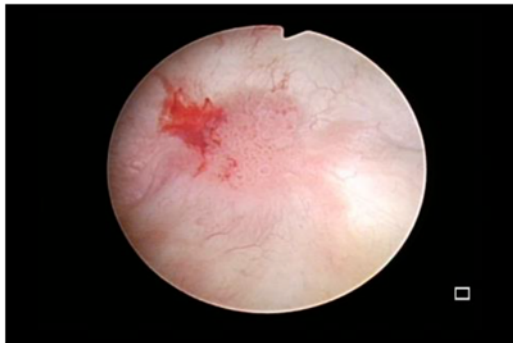
Because of the broad differential of urologic diagnoses that can cause hematuria, a complete evaluation of the urinary tract is indicated. Imaging studies are used to evaluate the upper urinary tract (kidneys and ureters) whereas the lower urinary tract is evaluated via direct endoscopy (Figure 5).



Figure 5: Flexible cystoscopy is used to examine the lower urinary tract in hematuria cases.

Imaging such as ultrasound or CT scans have limited sensitivity in diagnosing bladder masses and cannot identify urothelial erythema or carcinoma in situ, thus necessitating cystoscopy. Cystoscopy is an office-based procedure that does not require sedation. A flexible digital endoscopic camera is inserted into the bladder through the urethra. The entire urethra and bladder are viewed which includes the ureteral orifices and the intraurethral component of the prostate in men. This can allow for the diagnosis bladder tumors concerning for malignancy (Figure 6), urethral strictures, bladder stones, or prostatic enlargement.

Figure 6. Bladder tumor concerning for urothelial carcinoma found on cystoscopy. From: <https://university.auanet.org>



The upper urinary tract including the ureters and kidneys are evaluated with imaging. Renal ultrasound can be utilized in intermediate risk patients to evaluate for renal masses and intra-renal stones; however, ultrasound cannot fully evaluate ureteral anatomy and may fail to identify all upper tract stones. A multiphasic contrasted CT scan of the abdomen and pelvis is utilized to evaluate the entire upper urinary

tract. Also known as CT urography, this scan includes three phases (Figure 7). The first, non-contrasted phase, allows for the identification of renal or ureteral stones. The second, a contrast arterial/venous phase, can characterize renal masses. The third is a delayed phase which is obtained ~15 min after contrast administration. Delayed imaging allows for contrast excretion by the kidneys which then opacifies the urinary collecting system (renal calyces, renal pelvis, and ureters; Figure 7). Any filling defects in the collecting system may be concerning for upper tract urothelial carcinoma. If renal function or iodine allergies preclude the ability for the patient to receive contrast with their CT scan, then MR urography can be performed.

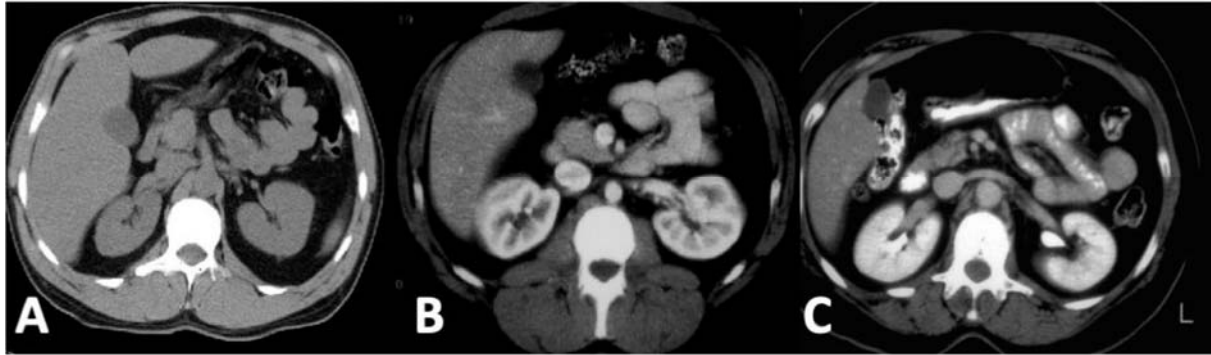


Figure 7. Tri-phasic CT Urography with non-contrasted (A), contrasted (B), and delayed (C) phases. From: <https://university.auanet.org>

With this evaluation strategy, a cause for hematuria is identified in roughly 57% of patients with asymptomatic microhematuria and 92% of patients with gross hematuria. Malignancy is identified in approximately 3-5% of patients presenting with asymptomatic microhematuria and 23% of patients presenting with gross hematuria. Following an unrevealing work-up for hematuria, a urinalysis should be repeated in a year. If repeat urinalysis is negative, no further workup is required.. Patients with persistent asymptomatic hematuria after a negative initial evaluation, physicians and patients discuss the merits of a repeat workup as some patients may benefit or request further evaluation.

SUMMARY:

1. Hematuria is categorized as either gross (visible to naked eye) or microscopic (diagnosed on microscopic urinalysis).
2. A positive dipstick for hematuria requires confirmatory midstream microscopic urinalysis.
3. The differential for hematuria is broad and includes glomerular and non-glomerular etiologies, the latter of which can be divided into upper and lower urinary tract origins.
4. A thorough history and physical examination, which should include risk factors for urothelial carcinoma, are utilized for risk stratification.
5. A complete urologic workup for hematuria includes cystoscopy and imaging of the upper urinary tracts.

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(Updated October 2020)

MODULE 6: KIDNEY STONES

KEYWORDS: Nephrolithiasis, Urinary Stones, Urolithiasis, Hypercalciuria, Hyperoxaluria, Hypocitraturia, Hyperuricosuria, Cystinuria

LEARNING OBJECTIVES

At the end of this clerkship, the medical student will be able to:

1. List the major risk factors for the most common types of kidney stones.
2. Contrast differences between the clinical presentations of acute renal colic versus an acute abdomen.
3. Name the five most common kidney stone chemical compositions and describe the recommended medical prophylaxis options for each of them.
4. Describe the best imaging study to diagnose kidney and ureteral stones.
5. Describe three types of medications that are effective for relief of renal colic pain.
6. List three clinical situations that warrant urgent surgical decompression of a ureteral stone.
7. List two types of medications that may help medical expulsion therapy of a distal ureteral stone.
8. List the three common surgical techniques to manage renal and ureteral stones that fail to pass with observation.
9. Identify the factors that help predict the likelihood of spontaneous stone passage.

INTRODUCTION

Urinary stone prevalence is estimated at 3% in all individuals, and it affects up to 12% of the population during their lifetime. Urinary stone recurrence rates approach 50% at 10 years and white males have the highest incidence in the U.S. The incidence of stones in women is increasing and approaches 50% of the male rate. The overall incidence of nephrolithiasis is also increasing. There is traditionally a high incidence of urinary stones in the Southeastern and South Central United States, termed the “Stone Belt”, which probably reflects the hot weather climate and relative dehydration that occurs in these areas. Prior to the development of modern urologic techniques for treatment, mortality from untreated staghorn (infection) calculi was 27%. Currently, overall mortality from stone disease is rare, although there is still a significant rate (28%) of renal deterioration with certain stone types.

PATHOPHYSIOLOGY

Urinary calculi may have various compositions which include, in order of decreasing frequency: calcium oxalate, uric acid, struvite or infection (triple phosphate = magnesium ammonium calcium phosphate), calcium phosphate and cystine. There are other less common stones, such as xanthine and drug-related stones, as well. Calculi are typically composed of urinary chemicals that are usually soluble but occur in amounts too high to stay dissolved in the urine. As a result of changes in supersaturation, some of the solutes tend to precipitate and aggregate to form crystalline concretions or stones.

Calcium oxalate stones

Calcium oxalate is by far the most common renal stone material. These stones typically form from an initial calcium phosphate concretion that originates near the renal papilla's epithelium in the highly concentrated, alkaline environment of the distal terminal collecting duct. This calcium phosphate concretion (called a Randall's plaque) eventually erodes through the urothelium in the renal papilla and forms a nidus for eventual calcium oxalate deposition when it is directly exposed to urine. (Figure 1).

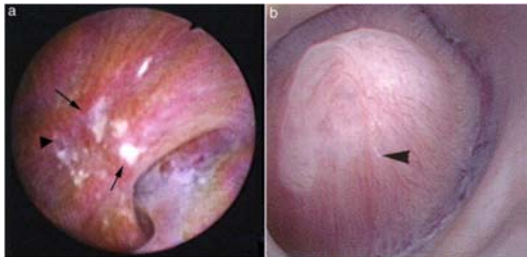


Figure 1: Intrarenal view of renal papillae. (A) stone former showing many Randall's plaques (arrows), and (B) non-stone former with far fewer lesions. (From: Matlaga et al. J Urol 2007; 177: 31-38)

The calcium oxalate deposition continues and grows until the stone becomes large enough to break free of its urothelial “anchor” and passes into the collecting system where it can cause obstruction and pain. Calcium oxalate monohydrate crystals appear as ovals or dumbbells under microscopy, while calcium oxalate dihydrate crystals look like little envelopes or octohedrons.

The most important factors that promote calcium oxalate supersaturation and precipitation are dehydration, hypercalciuria, hyperoxaluria, hypernatrituria, hypocitraturia and hyperuricosuria.

Uric acid stones

Uric acid is a product of purine metabolism and forms 7 - 10% of all urinary calculi. Uric acid is 100 times more soluble at a pH > 6 compared to a pH < 5.5. The most common risk factor for uric acid lithiasis is persistently acidic urine including the lack of a normal postprandial alkaline tide. Gout or hyperuricemia is only associated with about 20% of cases of pure uric acid lithiasis. Hyperuricosuria is also associated with

diseases such as insulin resistance, diabetes mellitus and Lesch-Nyhan syndrome. Chemotherapy treatment of lymphoma or leukemia causes the sudden lysis of millions of cells which releases a large quantity of purines into the circulation and urine that may then precipitate in the renal tubules causing uric acid stones. Uric acid crystals appear as rounded parallelograms under microscopy. As will be discussed later, urinary alkalinization is the cornerstone of uric acid stone management.

Struvite (Triple Phosphate, Infection) Stones

Struvite stones are caused by urinary infections with urease producing organisms, the most common being *Proteus mirabilis*. Less common pathogens include *Klebsiella*, *Enterobacter*, or *Pseudomonas*. (*E. coli* is **not** a urease producing organism!) Urease cleaves each mole of (soluble) urea into two moles of (relatively insoluble) ammonium. As this cleavage occurs, free H⁺ is bound to NH₃ to produce NH₄⁺, yielding free OH ions from water, ultimately making the urine more alkaline. Phosphate is less soluble at alkaline than acidic pH, so phosphate precipitates onto the insoluble ammonium products, yielding calcium ammonium magnesium phosphate (hence the name “triple phosphate”). As the bacteria that produce urease remain within the stone and in the urine, the urease they produce continues to cleave urea resulting in persistently alkaline urine. Under these conditions, very large staghorn shaped stones may develop quite rapidly, filling the entire renal pelvis and all the calyceal spaces of the kidney (Figure 2). A urease inhibitor is available (Lithostat or acetohydroxamic acid) and can be useful as an adjunct to definitive treatment which requires culture-specific antibiotic therapy and complete surgical removal of the stone and all its fragments.



Figure 2: Example of a staghorn calculus (struvite stone) that has molded to the shape of the calyceal space in the kidney.

Calcium Phosphate Stones

Most calcium stones will have a nidus or core of calcium phosphate which originally came from Randall's plaques. Stones that are substantially or primarily calcium phosphate suggest an underlying metabolic disorder such as renal tubular acidosis, primary hyperparathyroidism or medullary sponge kidney, so patients should be screened for these disorders. (For example, renal tubular acidosis will demonstrate severe hypocitraturia; hyperparathyroidism can be identified by elevated parathyroid hormone levels together with hypercalcemia.) Calcium phosphate stones typically

form in an alkaline pH of 7.2 or higher which is a good reason to avoid prolonged overtreatment with urinary alkalinizing agents.

Cystine stones

Cystine stones are produced in patients with a homozygous recessive gene for cystine transport resulting in excessive urinary cystine levels. Cystine is a dibasic non-essential amino acid composed of cysteine-S-S-cysteine. (The four dibasic amino acids are cystine, ornithine, lysine and arginine, hence the mnemonic: COLA.) Under microscopy, cystine urinary crystals appear as perfect hexagons. Normal individuals generally have urinary excretion of < 100 mg cystine/day whereas the majority of homozygous cystinurics excrete > 600 mg/day. Cystine solubility and precipitation depends greatly on urinary cystine concentration and pH as there are no known inhibitors of cystine production. Cystine is much more soluble at a pH of 9.6 and higher compared to lower pH's, but it is practically impossible to achieve such a high urinary pH by oral alkalinizing agents alone (and certainly not without the risk of calcium phosphate stone formation).

Renal Physiology with Obstruction

All stones may produce obstruction and pain. Pain is thought to occur from ureteral dilation from the obstruction and/or renal capsular distension. With acute unilateral obstruction, in the setting of a normal contralateral kidney, the affected kidney responds in two phases to the blockage:

- Initial 2 hours: There is increased renal pelvic pressures and renal blood flow. As renal pelvic pressure increases, glomerular filtration rate (GFR) decreases, as GFR represents the sum of net hydrostatic and oncotic pressures across the glomerulus.
- At 6-24 hours: Renal pelvic pressures remain elevated, but renal blood flow diminishes.
- After 24 hours: Renal pelvic pressures trend down towards baseline (but remain elevated) and renal blood flow continues to diminish. If persistent, the obstruction eventually leads to renal ischemia.

Thus, obstruction from urinary stones threatens GFR, reduces renal blood flow and, if the obstruction is not relieved, renal ischemia which leads eventually to irreversible renal impairment. In general, with high-grade obstruction, renal impairment will occur within two weeks.

CLINICAL PRESENTATION

The classic presentation of a renal stone is acute, colicky flank pain radiating to the groin or scrotum, often associated with nausea and vomiting. As the stone descends in the ureter, pain may localize to the abdomen overlying the stone. Renal and ureteral colic are often considered the most severe pain ever experienced by patients, and

many female stone patients describe the pain as even more intense than that of childbirth. As the stone approaches the ureterovesical junction, lower quadrant pain, urinary urgency, frequency and dysuria are common, mimicking bacterial cystitis. A family history of renal calculi is present in 55% of patients with recurrent stones. Stones occur three times more frequently in men with a family history of stones.

The physical exam typically shows a distressed patient, often writhing and constantly moving while trying to find a comfortable position. In contrast, patients with an acute abdomen typically have board-like abdominal rigidity and do not wish to move at all. Costovertebral angle or lower quadrant tenderness may be present. A distal ureteral calculus at the ureterovesical junction in a woman may sometimes be palpated directly on vaginal exam. Gross or microscopic hematuria is present in approximately 85% of patients. Importantly, the absence of hematuria with acute flank pain does not preclude renal or ureteral calculi as there may be complete obstruction. Hydronephrosis and renal capsular distension may also produce nausea and vomiting. Thus, the typical symptoms of urinary stones producing acute renal colic may mimic other acute abdominal conditions (Table 1), making rapid and accurate diagnosis important.

TABLE 1: DIFFERENTIAL DIAGNOSIS of ACUTE RENAL COLIC in ADULTS

-
- Renal or ureteral stone
 - Hydronephrosis (ureteropelvic junction obstruction, sloughed papilla)
 - Bacterial cystitis or pyelonephritis
 - Lobar pneumonia
 - Rib fractures
 - Acute abdomen (bowel, biliary, pancreas or aortic abdominal aneurysm sources)
 - Gynecologic (ectopic pregnancy, ovarian cyst, torsion or rupture)
 - Radicular pain (L1 herpes zoster, sciatica)
 - Referred pain (orchitis)
-

DIAGNOSTIC EVALUATION

The current gold standard for confirming urinary stones in the setting of acute flank pain is an unenhanced, non-contrast helical computed tomography (CT) scan of the abdomen and pelvis. This study surpasses the intravenous pyelogram (IVP) which had been the standard imaging test for decades. A prospective trial of 106 adult patients with acute flank pain imaged all patients with both an unenhanced helical CT and IVP. CT and IVP showed a ureteral stone in 96% vs. 87% of patients, respectively, which was significantly different. Of those patients without stones, the CT and IVP were negative in 100% versus 94% of cases, also significant. Thus, the positive and negative predictive values for CT were 100% and 91%, and for IVP, 97% and 74%, respectively. In ambulatory settings where CT is not available, a plain abdominal radiograph (KUB) is useful as approximately 75 - 90% of urinary stones are radiopaque. A KUB is also recommended as an adjunct to any initial CT scan positive for urinary stones. The KUB

provides an easy way to track progress of the stone over time, quickly establishes its radio-opacity when its location is known and is usually better than CT for determining stone shape.

Ultrasound appears to be vastly inferior to unenhanced CT for stones and is insensitive for ureteral calculi. However, ultrasound is the recommended first imaging test when a urinary calculus is suspected in a pregnant woman. Ultrasound is also useful when done together with the KUB to help identify non-calcified stones that the KUB alone might miss, to estimate the degree of urinary obstruction/hydronephrosis and to measure the Renal Resistive Index which is elevated when the kidney is obstructed. (Renal Resistive Index = (Peak Systolic Velocity - End Diastolic Velocity)/Peak Systolic Velocity. Normal = <0.65 while readings >0.70 suggest medical renal disease or obstruction.) An IVP or contrast CT is now recommended only when medication metabolite stones are suspected, such as with some HIV medications like Crixivan (Indinivir), as these stones would not otherwise be visible.

INITIAL ASSESSMENT AND MANAGEMENT

The most pressing issue in managing patients with urinary stones is determining whether or not urgent intervention is needed. Table 2 outlines the indications for immediate intervention.

TABLE 2: INDICATIONS FOR URGENT INTERVENTION WITH URINARY STONES

-
- Obstructed upper tract with infection
 - Impending renal deterioration
 - Pain refractory to analgesics
 - Intractable nausea/vomiting
 - Patient preference
-

In addition, Figure 3 presents a clinical algorithm for patients with urinary stones. In general, fully obstructed or infected collecting systems should be surgically decompressed either by percutaneous nephrostomy or ureteral stent placement. If the patient is unstable or septic, drainage of the blocked collecting system is urgent and should be done emergently. Definitive treatment of the obstructing stone should be delayed until any infection is well controlled. Infection is suggested by fever and elevated WBC count as well as a urinalysis showing pyuria and bacteriuria. Acute pyelonephritis cannot be reliably differentiated clinically from an infected kidney with an obstructing urinary calculus, so some type of urological imaging (KUB, ultrasound or CT scan) is recommended in these cases to avoid misdiagnosis and a potentially dangerous delay in surgical intervention. Infection proximal to an obstructing stone differs from an infection (struvite) renal stone. In the absence of obstruction, most struvite calculi may be temporized with antibiotics without decompression, pending definitive treatment.

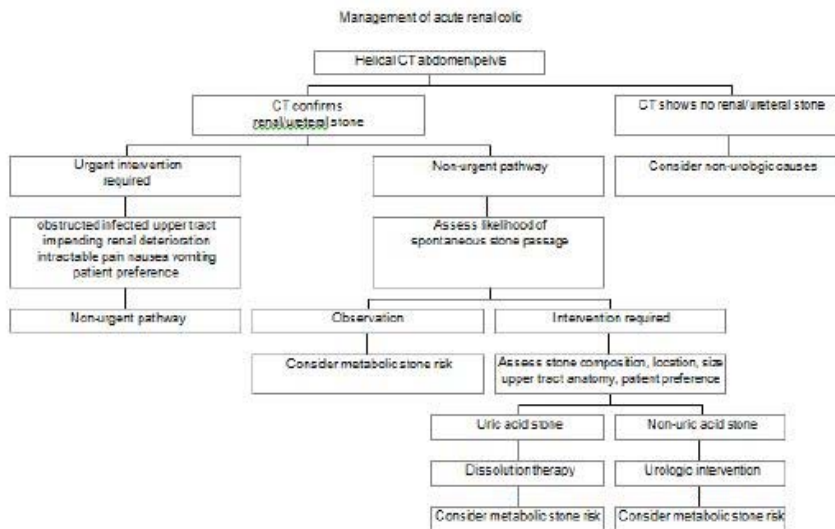


Figure 3. Algorithm for management of acute renal colic

High-grade obstruction (moderate or severe hydronephrosis) in a solitary or transplanted kidney is an example of impending renal deterioration and requires rapid resolution of the blockage with drainage or surgery. Patient preference is a relative indication for urgent intervention.

Pain

Since most stone patients present with pain, analgesia must also be addressed. Traditionally, narcotics and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain relief. In most randomized, blinded studies of NSAIDs versus narcotics, NSAIDs have shown equal or greater efficacy of pain relief and a shorter time to reach adequate analgesia with equal or fewer side effects. NSAIDs may pose a threat to renal function with decreased blood flow from obstruction, particularly if patients have pre-existing renal impairment. Also, if surgical intervention is warranted, NSAIDs cause platelet inhibition and risk increased surgical bleeding. Renal colic may also be managed with antidiuretic hormone (desmopressin, DDAVP) and intravenous acetaminophen. Intractable renal colic pain is effectively controlled by decompressing the obstruction via percutaneous nephrostomy or ureteral stenting.

Expectant management

When urgent intervention is unnecessary, the next clinical decision is whether patients may be followed expectantly in anticipation of passing their stone spontaneously versus elective intervention. Stone size and location are key determinants to predict spontaneous passage. The ureter is the smallest diameter structure of the urinary tract and is the area most prone to obstruction by a stone; especially the ureterovesical junction or UVJ. The majority of stones < 5 mm in diameter are likely to pass spontaneously but the likelihood of spontaneous stone passage decreases as stone size increases (Table 3).

TABLE 3: CHANCE OF PASSING URETERAL STONES

Stone size (mm)	Number of days to pass stone (mean)	% Likelihood of eventual need for intervention
2 or less	8	3
3	12	14
4-6	22	50
> 6	--	99%

Two-thirds of ureteral stones pass spontaneously within four weeks of the onset of symptoms. Spontaneous stone passage within the distal ureter may be facilitated with drugs that enhance expulsion and reduce ureteral spasm. Such medical expulsive therapy (MET) includes calcium channel blockers and alpha blockers like tamsulosin which are typically used in combination with NSAIDs. MET is most effective for small, distal ureteral stones where it appears to shorten the duration of ureteral obstruction and increases the likelihood of spontaneous stone passage by about 30%. Corticosteroids (e.g., prednisone) have also been studied in combination with alpha blockers and may help with stone expulsion; however, anecdotal reports of avascular necrosis of the hip limit its clinical use.

Patients rarely have complete obstruction and thus the risk of renal deterioration from observation for a small stone is presumed low. However, a ureteral stone that has not passed or moved within 1 - 2 months is unlikely to pass spontaneously with further observation alone. An observation period of 2 - 4 weeks is reasonable in most circumstances even in symptomatic patients. With observation, close follow-up is needed to ensure stone passage, to follow stone growth and to watch for new infections. Asymptomatic patients who have stones < 5 mm in size may be followed unless symptoms, infection, impending renal deterioration or stone growth warrant intervention. As precise stone chemical composition is typically not known on initial presentation, it is important to encourage patients to catch and submit their stone or fragments for chemical analysis so that recurrent stone episodes may be more efficiently managed with knowledge of prior stone composition.

Medical and Surgical Management

For those in whom intervention is warranted, treatment is based on stone characteristics such as chemical composition, intra-renal location, number and size as well as upper tract anatomy and other factors such as patient risk factors and comorbidities, patient size and body habitus, equipment availability, surgeon's judgment and patient preference (Table 4).

TABLE 4: OPTIONS FOR STONE INTERVENTION

Oral stone dissolution (Uric acid stones only)
Extracorporeal Shock Wave Lithotripsy (ESWL)
Ureteroscopy
Percutaneous Nephrolithotomy (PCNL)
Open or Laparoscopic Lithotomy

Uric acid calculi are unique in that they may be completely managed and dissolved medically. Urinary alkalinization with potassium citrate (or alternatively sodium citrate or sodium bicarbonate) will dissolve uric acid stones. Sufficient alkalinization therapy should be given to increase the pH to at least 6.5. Maintaining the pH at this level usually results in dissolution of pure uric acid stones in 2 - 6 weeks. Progress can be followed with ultrasound.

Renal calculi < 3 cm in maximal diameter that are visible on KUB are generally best treated by Extracorporeal Shock Wave Lithotripsy (ESWL) (Figure 3). ESWL generates shock waves extra corporeally, focuses them on the stone and then fragments it. The patient then passes these very small fragments painlessly in their urine. Success varies based on the number and density of the stones being treated, the specific ESWL machine used, the total number and rate of shocks given, stone size, chemical composition and the stone's precise intra-renal location. ESWL is less successful for renal calculi located in the lower pole compared to all other renal locations, likely from the effects of gravity on fragment clearance. Patients with lower pole stones are more likely to be stone-free if treated by ureteroscopy or percutaneous nephrolithotomy (PCNL) than by ESWL (Figure 4). Renal calculi in all other locations > 3 cm are best treated by percutaneous nephrolithotomy (PCNL), with or without adjunctive ESWL.

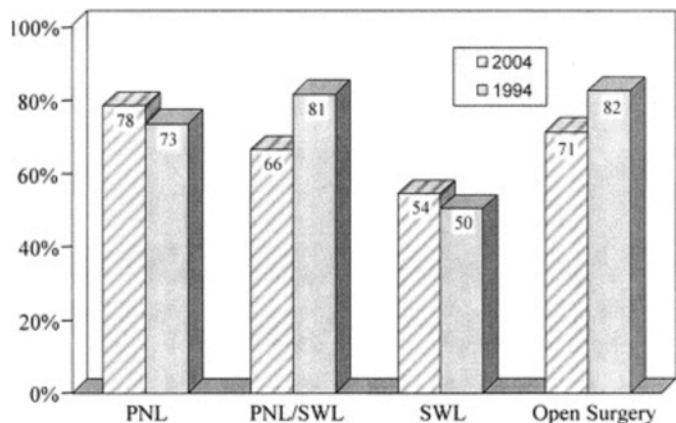


Figure 4. Stone-free rates after various urological procedures. Note: PNL-percutaneous nephrolithotomy; SWL-shock wave lithotripsy. (From: Preminger et al, J Urol 2005;173:1991-2000).

PCNL involves initial placement of a small caliber nephrostomy catheter, under radiographic guidance, through the flank into the renal collecting system. The tract is then dilated and a larger sheath is placed to allow passage of either a rigid or flexible nephroscope into the collecting system. Various working instruments and graspers including lasers, ultrasonic probes and pneumatic devices may then be passed through

the nephroscope to fragment the stone, evacuate fragments or grasp and remove them. PCNL is generally more invasive (and morbid) than ESWL, with a greater likelihood of prolonged oral analgesic use, higher narcotic equivalents required for pain control, greater risk of significant bleeding and higher transfusion rates so it is used only for these larger stones.

It is also feasible to use retrograde ureteroscopy (i.e., passing a flexible digital ureteroscope from the bladder, up the ureter and into the renal collecting system) to treat renal calculi. With sophisticated laser lithotripsy devices and digital ureteroscopic imaging, most stones can be located and removed or fragmented into tiny pieces (< 1 mm) that can pass painlessly. Stone-free outcomes result in over 90% of cases of ureteral calculi after a single ureteroscopy procedure.

Performing nephroscopy for renal calculi is technically a little more challenging, with stone-free outcomes of 60 - 84% after a single procedure. In general, the success rate diminishes as stone size increases and multiple procedures are usually required for renal calculi > 2 cm.

The optimal treatment of ureteral calculi is with ESWL or ureteroscopy. Proximal ureteral calculi are generally treated by ESWL, but ureteral stones located over the bony pelvis may be problematic for ESWL as they are difficult to identify and target with shock waves. For distal ureteral calculi, the preferred treatment is controversial as a randomized study comparing ESWL with ureteroscopy found no difference in stone-free rates but many variables, including patient preference, are considered when treating individual patients. However, in general, the trend has been to favor ureteroscopy for distal ureteral stones and ESWL for proximal calculi.

STONE PROPHYLAXIS

Any patient with recurrent stones warrants metabolic evaluation as renal deterioration is more likely to occur from recurrent compared to solitary stone episodes. Metabolic stone prophylactic evaluations are also recommended for all stone formers with high risk factors such as solitary or transplanted kidneys, GI bypass surgery or significant medical co-morbidities. It is also recommended for all children with kidney stones. The typical metabolic evaluation includes stone composition analysis, 24-hour urine collection and serum studies as described in Table 5.

TABLE 5: METABOLIC STONE EVALUATION

- 24 hour urine for total volume, pH, calcium, oxalate, sodium, uric acid, citrate, phosphate, magnesium, sulfate, creatinine, quantitative cystine (optional).
 - Serum calcium, phosphorus, uric acid, HCO₃, BUN, creatinine, albumin, alkaline phosphate, intact PTH (optional but recommended in hypercalcemia) and 1.25-dihydroxyvitamin D₃ (optional).
 - Stone composition analysis. All urinary stones (except for prostatic calculi) should be chemically analyzed.
-

The most common metabolic factors identified are low urine volume, hypercalciuria, hyperoxaluria, hypocitraturia and hyperuricosuria. We will also briefly review hypercystinuria.

Low Urine Volume increases urinary supersaturation. A simple way to reduce urinary supersaturation is to instruct patients to increase their oral fluid intake sufficiently to generate a 24 hour urinary volume of 2,000 - 2500 mL. Increased urinary volumes beyond 2500 mL are not usually recommended (except for cystine stone formers) as the increased urinary frequency this produces may discourage long term compliance.

Hypercalciuria is best managed with thiazide diuretics which increase calcium reabsorption from the distal renal tubule. Dietary calcium restriction alone is no longer recommended due to decreased intestinal oxalate binding which contributes to hyperoxaluria, particularly in patients with GI bypass surgery or irritable bowel syndromes and chronic diarrheal states (such patients tend to have **Enteric Hyperoxaluria** characterized by severe hyperoxaluria, hypocalciuria and hypocitraturia). Excessive dietary calcium intake in hypercalciuric patients without hyperoxaluria can be moderated safely but severe restrictions should be avoided. Fewer calcium stone recurrences occur in hypercalciuric patients with dietary restriction of animal protein (purines, uric acid) and salt.

Hyperoxaluria can be a difficult metabolic abnormality to manage as there is no specific medication for this condition. Preventive treatment usually consists of dietary oxalate restriction. High oxalate foods include green leafy vegetables like spinach, chocolate and nuts but actual oxalate content of food varies significantly. Vitamin B-6 can help some hyperoxaluric patients by modifying hepatic oxalate metabolism. Oral calcium supplementation (calcium citrate is preferred) given with any high oxalate meal (usually lunch and/or dinner) can be effective in increasing intestinal oxalate binding which limits GI absorption of free oxalate thereby reducing urinary oxalate excretion which otherwise can be difficult to manage with dietary oxalate reduction alone.

Hypocitraturia is an important risk factor for both calcium and uric acid stone disease. It is usually best treated with citrate supplementation sufficient to reach optimal 24 hour urine levels of 500 - 600 mg and/or urine pH of 6.5 if possible. Potassium citrate is usually the preferred citrate supplement and urinary alkalinizing agent, but serum potassium and urine pH levels should be monitored periodically when giving significant potassium citrate supplementation. Dietary methods to increase urinary citrate require very large amounts of lemonade and similar measures which are usually quite difficult for patients to sustain long term. Distal renal tubular acidosis, enteric hyperoxaluria, chronic diarrheal states and the use of carbonic anhydrase inhibitors like topiramate (Topamax) and acetazolamide (Diamox) lead to metabolic acidosis and hypocitraturia, but the specific cause of low urinary citrate in most stone formers is unknown.

Hyperuricosuria contributes to both calcium oxalate and uric acid stones. Potassium citrate supplements are the recommended treatment for uric acid stones unless hyperuricemia or hyperuricosuria are present. Probenecid for gout is discouraged in stone formers as it increases urinary uric acid excretion which increases both uric acid and calcium stone production. Allopurinol is therefore recommended for both uric acid and calcium stone formers when high serum or urinary uric acid is identified.

Cystinuria patients are encouraged to increase their fluid intake enough to generate 3,000 mL of urine daily or more. This may require waking up in the middle of the night specifically to drink more water. Up to 1/3 of cystinuric patients can control their stone production with increased fluid intake alone. Citrate supplements are also recommended with the goal of reaching and maintaining a urinary pH of 7.5 if possible. Cystine solubility is generally 250 - 300 mg/liter at a pH of 6.5 - 7, but at a pH of 7.5, the solubility is doubled to 600 mg/liter which is reasonably obtainable in clinical practice with available oral urinary alkalinizers like potassium citrate and sodium bicarbonate. When these measures fail, tiopronin (Thiola) can be utilized. This medication forms a soluble complex with cystine and effectively reduces cystinuria, but it needs to be taken three times daily and has several potential side effects so its dosage should be titrated carefully.

When other metabolic abnormalities are uncovered (distal renal tubular acidosis, primary hyperparathyroidism, sarcoidosis) specific therapy is warranted. Regardless, patient compliance with long-term stone preventive therapy is no better than 70 - 80%. Moreover, medical prophylaxis may not be cost-effective for all patients with only a single stone episode unless they have high risk factors such as a solitary or transplanted kidney, or have significant co-morbidities making possible surgical intervention inadvisable. Patient motivation is critical to the success of any long-term preventive treatment plan.

SUMMARY

- Urinary calculi typically present with renal colic and hematuria frequently accompanied by nausea and vomiting.
- Gross or microscopic hematuria frequently accompanies renal colic but may be absent in 15% of cases.
- The unenhanced CT is the single best initial diagnostic imaging test. If positive, an immediate KUB is very helpful for determining stone shape and density as well as for follow-up and tracking.
- Clinicians should initially assess the need for urgent intervention as well as the likelihood of spontaneous stone passage.
- Urologic intervention must be individualized.
- Metabolic risk of stone recurrences should be addressed in repeat stone formers, children and in some motivated first-time stone formers.

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(Updated February 2019)

MODULE 7: PEDIATRIC URINARY TRACT INFECTIONS

KEY WORDS: Cystitis, vesicoureteral reflux (VUR), dysuria, hematuria, pyelonephritis, hydronephrosis, UTI

LEARNING OBJECTIVES

At the end of this clerkship, the medical student will be able to:

1. Describe the differences in clinical presentation of UTIs in infants and older children
2. Describe the differences in clinical presentation of cystitis and pyelonephritis
3. Identify modifiable and non-modifiable risk factors associated with bacterial, viral, and fungal UTIs in children
4. Describe variations in urologic anatomy that are associated with pediatric UTIs
5. Describe the anatomic, physiologic, and clinical sequelae of repeated and untreated pediatric UTIs
6. Summarize the diagnostic evaluation of pediatric UTIs
7. Outline the operative and non-operative management options for pediatric UTIs

EPIDEMIOLOGY

Pediatric urinary tract infections are common, accounting for over 1.5 million visits to health care providers annually, and over \$180 million in spending directed toward diagnosis and treatment. About 2% of males and 7% of females will have at least one UTI by the age of 6 years. Although overall females are more likely to develop UTIs, infant males (particularly those with an intact foreskin) are at increased risk in the first year of life.

CLINICAL PRESENTATION

Children, particularly infants, may present with nonspecific UTI symptoms. Infants in particular may present with fever, lethargy, decreased oral intake, or signs of dehydration. Older children may complain of dysuria, irritative bladder symptoms (urinary urgency and frequency, with or without incontinence), a sensation of incomplete emptying, and flank or abdominal pain. Children of any age may also present with blood in the urine (hematuria), vomiting, or with changes in bowel habits (constipation and/or diarrhea). Importantly, while the presence of fever and systemic symptoms raises concern for pyelonephritis, a fever is not pathognomonic for

kidney infection: in some cases, children may present with cystitis and fever, while others may have renal involvement and present with normo- or even hypothermia.

Children who are immunosuppressed may also have atypical presentations.

PATHOPHYSIOLOGY

Bacteria or fungi (including yeast) can enter the urinary tract through ascending (urethra or bladder) or hematogenous (bloodborne) routes. The most common bacterium isolated in pediatric UTIs is *E. Coli*, which is commonly found in stool. The ascent of bacteria from the bladder to the kidneys may be mediated by anatomic abnormalities such as vesicoureteral reflux, or by bacterial virulence factors such as pili that enable the bacteria to “climb” toward the kidneys even in the absence of anatomic anomalies.

Fungal UTIs are common in immunosuppressed children, in those with indwelling catheters, and in those with prolonged antibiotic exposure. Fungal UTIs classically occur in children who are immunosuppressed, or those in the Neonatal Intensive Care Unit (NICU), as patients in the NICU often have multiple invasive lines and tubes and have received broad-spectrum antibiotics for prolonged periods. “Fungal balls” may obstruct the collecting system and necessitate percutaneous drainage. Fungal UTIs may not have significant pyuria, but catheterized urine samples will show fungal growth; this can make the clinical differentiation of fungal colonization and infection difficult. Treatment consists of limiting risk factors (removing or changing indwelling lines and tubes, limiting antibiotic use when possible) and administering antifungal agents (fluconazole or amphotericin B).

Like fungal UTIs, viral UTIs typically occur in immunocompromised children in whom normally dormant viruses are activated. Viral UTIs are common in children following organ transplantation or oncology-related immunosuppression, and viral infection can also be associated with hemorrhagic cystitis. Common viruses include BK virus, adenovirus, and cytomegalovirus (CMV). Limiting immunosuppression when possible, and considering antiviral therapy (e.g. ribavirin, cidofovir) can be helpful.

Sterile pyuria is often seen with UTIs caused by acid-fast bacilli such as *Mycobacterium tuberculosis*.

TABLE 1. Uropathogen Prevalence by Sex and Visit Setting

Table 1
Uropathogen Prevalence by Sex and Visit Setting*

Organism	Male		Female	
	Outpatient	Inpatient	Outpatient	Inpatient
E. Coli	50%(48–52)	37%(35–39)	83%(83–84)	64%(63–66)
Enterobacter	5% (5–6)	10% (8–11)	1% (1-1)	4% (4–5)
Enterococcus	17% (16–18)	27%(25–29)	5% (5-5)	13%(12–14)
Klebsiella	10% (9–11)	12%(10–13)	4% (4–5)	10% (9–11)
P. aeruginosa	7% (6–8)	10% (8–11)	2% (2-2)	6% (5–7)
P. Mirabilis	11% (10–12)	5% (4–6)	4% (4-4)	2% (2–3)

*Based on national data from TSN (The Surveillance Network). Prevalence will vary based on region.

The Table above (Copp 2015) shows nationwide data on the most common bacterial pathogens causing UTI in the inpatient and outpatient settings.

SEQUELAE

Untreated, UTIs may develop into systemic illness (sepsis), damage organs, or have late effects on general health. Examples of spread into adjacent organs include epididymitis and orchitis. Chronic infection of the renal parenchyma (pyelonephritis) has been associated with late effects including renal scarring, poor renal function, and high blood pressure. Renal scarring is most likely in young children with pyelonephritis, and is often seen in children with vesicoureteral reflux. Renal scans using DMSA (dimercaptosuccinic acid) can show differential uptake within the renal parenchyma consistent with renal scarring or dysplasia. One study following children with pyelonephritis-associated scarring for 27 years found a 21% prevalence of hypertension and 10% prevalence of end-stage renal disease. Prompt treatment of suspected UTI in children has been shown to decrease the likelihood of renal involvement, although the data supporting effects on renal scarring are less robust. Treatment should be started as early as possible, and ideally within 24-72 hours of symptom onset.

Xanthogranulomatous pyelonephritis (XGP) is uncommon in children, and develops in the setting of chronic renal obstruction and infection. Nephrectomy is often necessary.

EVALUATION AND MANAGEMENT OF THE CHILD WITH SUSPECTED UTI

A full history and physical examination should be performed. Onset and duration of symptoms, as well as the presence or absence of systemic symptoms (e.g. fever, vomiting, diarrhea) should be recorded. Caregivers should be asked about the child's pre- and post-natal history as well as any family history of urogenital anomalies, current medications, and ill contacts. In children with suspected urinary tract infection, urine should be collected and evaluated for infection. Urine collection using bags in infants is discouraged because of the high risk of contamination; suspected infection on a bagged specimen should be confirmed by collecting urine through suprapubic aspiration or urethral catheterization. In older, toilet-trained children, midstream urine specimens are acceptable options, though care must be taken to adequately cleanse the perineum before voiding and to ensure that midstream urine is collected. Laboratory tests such as complete blood count, basic metabolic panel, C-reactive protein, erythrocyte sedimentation rate, and blood cultures should be performed at the physician's discretion.

In children aged 2-24 months of age, the current AAP UTI Clinical Practice Guideline supports the diagnosis of UTI in children with $>50,000$ cfu/cc of a single pathogen on appropriately collected urine, in conjunction with findings of inflammation (e.g. pyuria: 10 WBC/hpf on an "enhanced urinalysis" or 5 WBC/hpf on a centrifuged specimen). A 2016 study showed that about one in ten children with symptoms of UTI and bacterial growth on urine culture had no pyuria; in those children, *Enterococcus*, *Klebsiella*, and *Pseudomonas* were more likely to be identified as the causative organism. Fungal UTIs may also present with relatively few white cells in the urine. The presence of nitrites supports the diagnosis of a UTI, although nitrites are more common in urine that has been stored in the bladder for >2 hours.

In children in whom the urine suggests infection, early initiation of antibiotic therapy is critical to minimizing the deleterious effects of infection on the upper tracts. Empiric antibiotic selection is based on the suspected pathogen and local resistance patterns, although it is noteworthy that many hospitals do not have antibiograms specific to pediatric patients. Factors such as ease of use (e.g. taste and number of daily doses) as well as cost should also be considered in efforts to increase adherence. Families should be made aware that antibiotics may be changed based on final culture growth and antibiotic sensitivity; these data are typically available 48-72 hours following urine collection. The duration of antimicrobial therapy is dictated by the age and medical complexity of the child: in general, treatment courses of 7-14 days for most children, although the SCOUT trial is investigating the efficacy of shorter antibiotic courses. When nitrofurantoin is selected as the antibiotic of choice, the minimum duration of therapy should be 7 days. Parents and caregivers should be made aware that, in the setting of pyelonephritis, fevers may persist even in the setting of observed clinical improvement.

The 2011 AAP Clinical Practice Guidelines support obtaining a renal-bladder ultrasound in all children 2-24 months after the first febrile UTI. Recent literature suggests that the cost-effectiveness of screening with a renal-bladder ultrasound may

be increased if sonography is limited to children with a second febrile UTI. Additional testing, such as voiding cystourethrogram, should be obtained if the screening ultrasound demonstrates evidence of collecting system dilatation or renal parenchymal abnormality.

The role of antibiotic prophylaxis in the management of urinary tract infections remains a source of debate. In the setting of high-grade (grade 4-5) vesicoureteral reflux, prophylactic antibiotics appear to decrease the risk of recurrent urinary tract infection. The benefit of antibiotic prophylaxis in lower-grade, “nondilating” (grades 1-3) reflux is less clear. The RIVUR study found that antibiotic prophylaxis was associated with a decreased risk of developing a recurrent UTI, although the number needed to treat was over 5000 doses. Even less clear is the role of antibiotic prophylaxis in the setting of voiding dysfunction: while children on antibiotic prophylaxis had lower rates of renal scarring, bladder-bowel dysfunction was an independent predictor of decreased adherence with medication administration. If antibiotic prophylaxis is considered as an option, a clear endpoint for prophylaxis should be planned and families should be counseled on the risks and benefits of antibiotic prophylaxis, including the possible need for periodic laboratory tests.

Antibiotic stewardship is critical to limit the adverse effects of antibiotic for both individual patients and the community at large; 3.5 million people die in the United States each year from antibiotic-resistant infections. The choice of prophylactic antibiotic should be based on the child’s age, any comorbidities, local resistance patterns, and ease of use (e.g. cost, number of daily doses, taste, need for refrigeration). In otherwise healthy term infants, amoxicillin 20 mg/kg daily is frequently used; in infants older than two months, trimethoprim (TMP)-sulfamethoxazole at a dose of 2 mg TMP/kg once daily may be used.

ASSOCIATED CONDITIONS

Anatomic

VUR

Vesicoureteral reflux (VUR), or the retrograde flow of urine toward the kidney, facilitates the exposure of the upper tracts to bacterial pathogens. In high grade (grades 4 and 5) VUR, the risk of UTI may also be increased in part due to the presence of a pseudoresidual volume of urine that arises when the refluxed urine drains from the ureters back into the bladder. Low grade VUR is generally not associated with an increased risk of urinary tract infections in the absence of other anomalies.

In 2011, the AAP released a recommendation (reaffirmed in 2016) that voiding cystourethrogram (VCUG) should be reserved for children with a second febrile urinary tract infection or those in whom the screening ultrasound found sonographic abnormalities in the renal parenchyma or collecting system. In older children with afebrile UTIs, VCUG is generally considered low-yield for the identification of anatomic abnormalities in the absence of other sonographic or physical findings.

A VCUG (see figure) delineates the anatomy within the collecting system, inclusive of the ureters, bladder, and urethra. Thus, it can be used to identify children with VUR and posterior urethral valves; in some cases, ureteroceles and ureteral ectopia may be diagnosed as filling defects and contour abnormalities. Variations in VCUG technique may be associated with differences in radiographic findings, although one multi-institutional study found that the most significant observed difference was in observed bladder capacity rather than in the proportion of children in whom VUR was detected. Nonetheless, as the timing of VUR onset during the filling/voiding cycle is one prognostic factor to be considered when calculating the likelihood of spontaneous resolution, differences in technique should be acknowledged. While the likelihood of spontaneous resolution of VUR has classically been associated with grade (extent of distension of the upper tracts by retrograde contrast), more recent research has identified that the timing of the VUR consent within the filling/voiding cycle as well as the distal ureteral diameter (normalized to the height of a vertebral body) are also important predictive factors.

The AUA Guideline: Management and Screening of Primary Vesicoureteral Reflux in Children is a detailed resource for clinicians.

Posterior Urethral Valves/Myogenic Bladder

Posterior urethral valves are excess tissue in the membranous urethra, just distal to the verumontanum, creating obstruction during voiding and contributing to the development of secondary vesicoureteral reflux and upper tract damage. Improvements in antenatal screening have enabled many of these boys to be identified prenatally, and therapy (bladder decompression followed by endoscopic valve ablation) to be performed fetoscopically or early in the postnatal period. Despite these advancements, half of boys will develop renal insufficiency within the first decade and one in six will develop end stage renal disease. While these data suggest that the baseline risk of renal dysplasia may not be altered by early intervention, optimization of lower tract function and reduction in UTI risk are critical to limit further renal damage in this population.

In the setting of outlet obstruction, the voiding and storage dynamics will be altered by differences in the composition and function of the bladder (specifically collagen and muscle components). Collectively termed the “myogenic bladder,” these variations span a wide spectrum and should be managed according to the underlying abnormalities in bladder function.

Ectopic Ureter/Ureterocele

Ureteral ectopia is present in about 0.05% of children, and occurs when the ureteric bud emerges too proximally in the Wolffian system. As a result, the ureteral orifice opens not in an orthotopic position in the bladder but at or distal to the bladder neck. In girls, the ureter may also drain to the perineum or into the vagina (via a ruptured Gartner’s duct cyst). In boys, the ureter may drain into any remnant of the Wolffian system, such as the vas deferens or seminal vesicle, but does not drain to the perineum. Ureteral ectopia can expose the upper tract to bacteria because of the

absence of the antireflux mechanism generated by tunneling the ureter at the ureterovesical junction, and also because of the relative proximity of the ectopic ureteral orifice to the perineum.

Ureterocele is a cystic dilatation of the distal ureter, and may be associated with obstruction of or less commonly reflux into the affected ureter. Ureterocele may predispose children to the development of urinary tract infections by obstructing the bladder outlet during voiding, with resulting elevated post-void residuals, or by trapping infected urine in the obstructed ureterocele.

Both ectopic ureters and ureterocele are definitively treated surgically.

Neurogenic Bladder

Patients with damage to the nerves that innervate the bladder, the pelvic floor, or the external sphincter often have abnormal bladder capacity, difficulty voiding at low pressures, and incomplete bladder emptying. In the pediatric population, children with spinal dysraphism (e.g. myelomeningocele, sacral agenesis) comprise the majority of children with neurogenic bladders, although neurogenic bladder can be seen with spinal cord injury from trauma, surgery, tumor, and vascular accidents. Children with neurogenic bladder may have functional deficits such as difficulty ambulating, lower extremity pain, and abnormal voiding and stooling habits; in some cases, skin abnormalities, such as variable pigmentation or hair distribution over the lower spine, deep sacral dimples, or deviations in the gluteal cleft, may be seen. The exact functional abnormalities associated with neurogenic bladder vary by the nerves involved. Since abnormalities in lower tract function can be associated with an increased risk of damage to the upper tracts, children with neurogenic bladders must be followed carefully.

Urolithiasis

While renal and ureteral stones were once unusual in children, the cumulative incidence has increased in recent years. While kidney stones are generally not independently a risk factor for the development of urinary tract infections, stones traveling down the ureter can cause obstruction and prevent the antegrade flow of infected urine. Urea-splitting bacteria (e.g., *Proteus* spp) are associated with the development of struvite stones. Bladder stones may serve as a nidus for bacteria and should be considered in children who present with bacterial recurrence or persistence despite appropriate therapy. Bladder stones are most commonly seen in children with concentrated urine and in those who do not completely empty the bladder, such as children who perform intermittent catheterization and those with a bladder augmented with a mucus-producing bowel patch.

Although upper tract urolithiasis is not directly implicated in the development of urinary tract infections, there is considerable overlap in the risk factors (decreased fluid intake, increased dietary salt intake) for the two conditions. More recent research has suggested a possible role for abnormalities in the bowel flora

(microbiome) in children with urinary tract infections as well as those with urolithiasis.

Ureteropelvic Junction Obstruction

Ureteropelvic junction obstruction (UPJO) develops when the flow of urine from the renal pelvis to the ureter is blocked. Obstructions may be “intrinsic” (associated with a defect in the muscular or intimal layers of the ureter or a “high insertion” wherein the ureteropelvic junction is not dependent) or “extrinsic” (usually associated with vascular compression from a lower pole accessory renal artery). Prior to the widespread use of prenatal ultrasonography, UPJO were commonly diagnosed when patients presented with hematuria, UTI, intermittent flank pain, nausea, and vomiting, often after increased fluid intake or diuresis. Persistent pressure on the renal parenchyma from the dilated renal pelvis may be associated with an ipsilateral decrease in renal function. Renal function (estimated renal plasma flow) and drainage can be assessed using MAG-3 nuclear medicine renal scans. Symptomatic patients and those with demonstrated obstruction may be considered for surgical intervention with open or minimally invasive pyeloplasty.

Eagle-Barrett (Prune Belly or Triad) Syndrome

Eagle-Barrett syndrome consists of the triad of deficient or absent anterior abdominal wall musculature (giving the abdomen its characteristic wrinkled appearance), dilated and tortuous ureters, and intra-abdominal undescended testes typically located at the level of the iliac vessels. Even after abdominal wall and urinary tract reconstruction, children with this condition often have urinary stasis, and so instrumentation of the urinary tract should be limited to reduce the risk of introducing bacteria.

Functional

Voiding Dysfunction and Constipation

The relationship between bladder-bowel dysfunction and urinary tract infections is well documented in toilet-trained children. Changes in urodynamic and rectal manometric parameters have been described, including increased voiding pressures and increased post-void residual urine in the setting of increased rectal distension. Additionally, the stool serves as a reservoir of bacteria, and functional constipation is associated with lower urinary tract symptoms. Frequent (every 2-3 hours) voiding, management of constipation, and increased fluid intake may help to decrease lower urinary tract symptoms and UTIs in these children. Children with symptoms refractory to behavioral modification should be evaluated for pelvic floor dysfunction, and may benefit from biofeedback or physical therapy.

Sexual Abuse

Estimates of the prevalence of pediatric sexual abuse vary widely, with some series finding that nearly four in ten children have experienced sexual violence. The signs and symptoms of sexual abuse may be subtle, and physicians must maintain a high index of suspicion for abnormal physical examination findings (e.g. genital abrasions or lacerations), inappropriate demeanor (unexplained fear of the examiner), or

patient statements. Physicians must report suspected sexual abuse to Child Protective Services.

SUMMARY

1. UTIs are common in children and have substantial clinical and economic sequelae.
2. Children with bacterial UTIs may have structural abnormalities of the urinary tract, elimination disorders, or sexual abuse.
3. Risk factors for fungal UTIs include immunosuppression, broad spectrum antibiotics, and invasive vascular and urinary devices.
4. Bacterial pyelonephritis is associated with renal scarring and later renal insufficiency and hypertension.
5. The most common radiologic study for children with UTI is renal and bladder ultrasound. Some children may benefit from VCUG.
6. Antibiotic stewardship, including selection of the proper treatment spectrum and duration, is critical for both treatment and prophylactic antibiotic regimens.
7. Prompt treatment for presumed or proven UTI may decrease renal scarring and late sequelae.

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(Updated April 2020)

MODULE 8: PROSTATE CANCER/PSA: SCREENING & MANAGEMENT

KEYWORDS: Prostate cancer, PSA, Screening, Radical Prostatectomy

LEARNING OBJECTIVES

At the end of this clerkship, the medical student will be able to:

1. Identify and name the basic anatomic zones of the prostate gland, including the locations where prostate cancer develops
2. Describe the physiologic role of the prostate - “what does the prostate do?”
3. Describe the distinctive epidemiological features of prostate cancer
4. Understand the controversy surrounding the use of serum PSA as a screening tool for prostate cancer
5. List the signs & symptoms of prostate cancer
6. Describe the natural history and the common patterns of progression of prostate cancer
7. List the major components in the staging of prostate cancer
8. Briefly describe the treatment options for localized and metastatic prostate cancer
9. Describe when prostate cancer does NOT need to be treated

INTRODUCTION

The prostate is a male sex accessory gland located within the pelvis below the bladder and above the urogenital diaphragm. The prostate encircles the urethra like a doughnut and is derived from the urogenital sinus. There are 4 basic anatomic zones of the prostate: the anterior zone, the peripheral zone, the central zone, and the transition zone. The vast majority of prostatic carcinomas arise in the peripheral zone of the prostate, whereas benign prostatic hyperplasia (BPH) occurs in the transition zone. The role of the prostate is to secrete fluid into the ejaculate that accompanies sperm and seminal vesicle fluid to make up the semen. The contributions of the prostate to the ejaculate include; acid, zinc and a serine protease known as PSA (prostate specific antigen) that is an enzyme responsible for the liquefaction of semen. The prostate continues to grow (hyperplasia) with age and may cause voiding dysfunction. Prostate cancer is the most common solid organ cancer in men and is currently the second leading cause of cancer death in men after lung cancer. Studies suggest that this cancer is much more common than observed clinically and thus any screening strategy must take care not to diagnose cancer in patients that will not suffer clinically from the disease—e.g. autopsy studies have shown about 70% of men deceased in their seventies have prostate cancer present. The incidence of clinically

diagnosed prostate cancer and mortality is highest in Blacks, intermediate in Caucasians and least in Asians. Being derived from a sex accessory gland, most prostate cancers are hormone sensitive and respond favorably to androgen hormonal ablation but the effect is short-lived due to either the development of or selection for hormone insensitive clones within the malignancy. Thus, the treatment stratagem for prostate cancer today is early detection whilst the tumor is confined to the prostate or surrounding tissues and can be cured by either removal or treatments aimed at the primary. Although there are low response rates to currently available chemotherapies and immunotherapies and a palliative effect of hormonal therapy, there are no cures for metastatic prostate cancer.

PROSTATE CANCER SCREENING

While there are no symptoms with early stages of prostate cancer; early detection, including PSA screening, has played a part in decreasing prostate cancer mortality. The serum PSA test and the digital rectal exam are complimentary tests that, along with other key variables including patient ethnicity, age and family history, should serve as a strategic fund of knowledge to be used when deciding whether or not to proceed with biopsy.

A flawless and standardized interpretation of elevated PSA values has yet to be determined. Although it has been well demonstrated that patients with elevated serum PSA levels are more likely to be harboring aggressive disease, elevated PSA levels can also be seen in less biologically aggressive prostate cancers. Other potential causes of elevated PSA values include benign prostatic hypertrophy, infection, urogenital tract instrumentation (i.e. catheter placement) and anything that can cause inflammation within the prostate gland. As such, serum PSA screening **interpreted outside the context of important patient-specific variables** carries with it a significant risk of what has been called over diagnosis: the identification and treatment of patients who might otherwise have lived out the rest of their lives without experiencing any of the terrible symptoms associated with advanced prostate cancer. Since the treatment of prostate cancer is associated with a significant level of patient morbidity (including bowel dysfunction, urinary dysfunction, and impotence), the use of serum PSA as a screening tool has been a topic of significant controversy.

In May of 2012, the United States Preventative Services Task Force (USPSTF), a federally appointed group of 16 individuals commissioned to make recommendations concerning clinical preventative services, issued a Class D recommendation regarding the use of serum PSA in prostate cancer screening. This means they believe that they have found "fair evidence that [PSA screening] is ineffective or that harms outweigh the benefits." They argue that the use of PSA screening and digital rectal exam in asymptomatic patients will cause more harm in the form of treatment morbidity than benefit. It should be noted that while the board includes members with both primary care and nursing backgrounds, none of them are board certified urologists.

The AUA strongly disagrees with the USPSTF's recommendation and has taken steps to better educate both the public and the health profession at large regarding the role of serum PSA and digital rectal exam in prostate cancer screening. Since the introduction of PSA as a screening tool in 1986, the number of total prostate cancer deaths has decreased by approximately 30%. Also, the number of patients suffering from the dire consequences of advanced prostate cancer (to include severe bone pain and bulky tumors that obstruct the urinary tract) has decreased an important victory that the USPSTF's recommendation fails to take into account. The American Cancer Society and the American Society of Clinical Oncologists agree with the AUA's stance. Consequently, the AUA has worked with other patient and physician advocacy groups to introduce legislature that will allow for specialist input into the USPSTF's recommendations and prevent the issuing of sweeping mandates that could potentially confuse patients and compromise care.

Nevertheless, the AUA recognizes that the interpretation of an asymptomatic patient's PSA level is a nuanced exercise that must be tailored to the patient in question. Therefore, the AUA no longer recommends one single PSA threshold for biopsy. Although previous thresholds such as 2.5 and 4.0 ng/mL have been used in the past, the AUA now recommends that the decision to biopsy should take into account the patient's DRE results, age, ethnicity, comorbidities, and prior biopsy history in addition to their serum PSA level.

In order to increase the efficacy of serum PSA interpretation, a number of performance variables are used clinically. These include age-adjusted PSA, density, velocity, and the free-to-complexed PSA ratio:

- a) Age Adjusted PSA: Since PSA normally rises with age, age-adjusted thresholds have been described. Benign growth of the prostate that normally occurs with age is the most common cause of PSA elevation. Roughly 70% of patients with an elevated PSA level between 4 and 10 will have a negative prostate biopsy. Conversely, there is no level of PSA at which you can guarantee a patient that they do not have cancer. Moreover, the absolute PSA level does not predict whether or not prostate cancer is harmful. General age adjusted PSA (ng/dL) thresholds are as follows: age 40-49 = 2.5; age 50-59 = 3.5; 60-69 = 4.5; 70-79 = 6.5.
- b) PSA Density: Another strategy used to improve the results of PSA screening is the calculation of PSA density by measuring prostate volume and dividing the absolute PSA level by the prostate volume (in mL). Prostate volume measurements can be obtained by either transrectal ultrasound or MRI. By these criteria, a PSA density threshold of 0.15 or greater is an indication for prostate biopsy.
- c) PSA Velocity: Since prostate cancer presumably grows faster than normal

prostate, PSA velocity (or change in PSA levels over time) is another strategy to detect prostate cancers in men with "normal" PSA levels. PSA values fluctuate significantly over time due to physiological variation, thus PSA velocity is best determined using at least 3 measurements obtained over a 2-year period. The threshold value for PSA velocity is dependent on the total PSA. The threshold is 0.35 ng/ml/year for PSA values < 4 ng/ml and 0.75 ng/ml/year for patients with total PSA values >4 ng/ml.

- d) Free-Complexed PSA: PSA exists in the serum in two forms, free and complexed to protease inhibitors. Patients with prostate cancer tend to have a higher percentage of PSA complexed to protease inhibitors and thus the percentage of free PSA within the serum is used to add information to the total PSA in patients with PSA levels between 4 and 10 and help determine the degree of suspicion for biopsy. Although there again is no agreement on the best threshold value for free PSA, values above 25% reliably predict the absence of clinically significant prostate cancer.

PROSTATE CANCER STAGING AND TREATMENT

Prostatic anatomy is described in zones. The central and transition zone surround the urethra and are the site of benign prostatic hyperplasia. Prostate cancer most often occurs in the peripheral zone which is closest to the rectum. Prostate cancer is diagnosed by prostate biopsy, as described above, in patients with either an abnormal DRE and/or abnormal PSA. The vast majority of patients who are diagnosed today were identified by prostate cancer screening and have early potentially curable disease. The TNM staging is used for prostate cancer. Prostate cancer has both clinical staging and pathologic staging. The clinical stage is based upon how it was detected. T1 disease is based upon disease discovered by means other than palpable disease. Clinical T1a and T1b stages are when prostate cancer is incidentally found in tissue obtained during surgery for benign disease (T1a involving < 5% and T1b is >5% of tissue obtained), e.g. during transurethral resection of the prostate. Clinical T1c stage are for cancers discovered during biopsy performed on patients with an elevated PSA (T1c). T2 disease is based upon the palpation of cancer in the prostate on digital rectal exam (a: less than half of one side, b: more than half of one side, and c: both sides of the prostate). Patients have T3 disease when cancer is palpable outside the prostate either laterally or involving the seminal vesicles.

Besides clinical stage, the histology of the cancer has a significant impact upon prognosis. The Gleason score (or sum) is the standard measure of the differentiation of prostate cancer. There are five patterns (1 - 5) with 5 being the worst. The biopsy material is examined under low power magnification the most common and second most common patterns are identified. These two numbers are added up to obtain the final Gleason score. The individual numbers and order are just as important in predicting prognosis as the total score since a patient with a Gleason score of 3 + 5 = 8 has a better prognosis as a patient with 5 + 3 = 8.

The management options for localized prostate cancer include radiation therapy, surgery, and active surveillance. The decision on how to manage prostate cancer in a newly diagnosed patient is quite complex and filled with controversy. The age (life expectancy) and health of the patient in addition to the characteristics of the cancer are taken into account. A frequent concern today is whether or not the cancer that is diagnosed is clinically significant. Active surveillance is offered to patients who have very low grade (no Gleason pattern 4 or higher) and low volume disease (< 3 biopsy cores involved) or <10-year life expectancy due to medical illness or age and a reasonable expectation that they will be compliant to the observation protocol. Younger and healthier men or men with more aggressive cancers should undergo therapy with either radiation or surgery. Alternative therapies such as cryosurgery, high intensity focused ultrasound, and herbal therapy have not been fully assessed for the management of clinically localized prostate cancer. There is no clear evidence to suggest that one approach is significantly better than another and the decision is often left to the treating physician and patient.

Radiation therapy may be administered by external beam, brachytherapy or a combination of the two. There are newer radiation modalities that fractionate the radiation differently (e.g. IMRT, cyberknife) that serve to decrease the number of treatments but these are all still different forms of external beam radiotherapy. The major side effects of radiation therapy are erectile dysfunction, in approximately 40%, and radiation proctitis. Stress urinary incontinence does not often occur after radiation therapy, but severe voiding symptoms due to bladder irritation occurs in approximately 15% of patients with significant voiding symptoms (AUA symptom score of > 15 out of 35) who undergo brachytherapy. Brachytherapy cannot be performed in patients with large prostate glands. Side effects from radiation may be minimal at first and tend to increase with time.

Surgical removal of the prostate can be performed either by open surgery or by laparoscopic surgery with or without robotic assistance and via a retropubic or perineal approach. The major risks of surgery are erectile dysfunction and stress urinary incontinence. The results vary based upon patient age, experience of the surgeon and whether or not the patient is a candidate for "nerve-sparing." In general, side effects are greatest immediately after surgery and tend to improve with time.

For non-localized prostate cancer, hormonal therapy is also used. Prostate cancer was the first malignancy to be shown to be hormone dependent and for this discovery, a Nobel Prize was awarded in the mid twentieth century. Hormone therapy involves depriving the prostate cancer of male sex hormones (androgens) to control cancer activity. Hormonal manipulation to decrease androgens in the blood stream by either surgical castration or the use of long acting drugs to suppress pituitary function is used to suppress cancer activity. Forms of androgen deprivation include luteinizing hormone-releasing hormone (LH-RH) agonists (leuprolide acetate, goserelin, triptorelin, and histrelin) that reduce pituitary drive to the testes to make

testosterone (after initial surge or “flare” in pituitary drive); LH-RH antagonists (degarelix) that reduce pituitary drive to the tests to make testosterone without an initial surge in production; antiandrogens (flutamide, bicalutamide, nilutamide, and enzalutamide) that block the action of testosterone on end organs; surgical castration with simple orchiectomy to remove the testicles and reduce natural testosterone levels; and adrenal gland testosterone blockers (ketoconazole and aminoglutethimide) that block the remaining 5% of testosterone that is made by the adrenal gland. When hormonal treatments are combined to bring testosterone levels as low as possible, this is known as total androgen blockade. Studies have not shown whether total androgen blockade is more effective than orchiectomy or an LH-RH agonist alone.

Hormone therapy is most commonly used to control cancer growth after it has metastasized. Since hormone therapy is only palliative and not curative, most prostate cancers will become hormone refractory and grow in the absence of testosterone. Side effects from hormonal therapy include impotence, hot flashes, loss of sexual desire, breast growth or tenderness and osteoporosis. Antiandrogens can cause nausea, diarrhea, or breast growth or tenderness, skin rashes and rarely, liver problems but fewer sexual side effects.

There is no clear “right” answer for the typical patient diagnosed with prostate cancer today. Surgical therapy is generally preferred method of management for the younger patient with a 30-year life expectancy who has localized cancer. Radiation is generally recommended for the patient over 70 years of age with localized cancer. There is an increasing role for active surveillance given the increased diagnosis of prostate cancer in the post-PSA era. The prognosis for most patients with early stage disease is quite good but some patients have metastases at the time of diagnosis. For further information about the management of clinically localized prostate cancer, please refer to the AUA clinical practice guidelines (<http://www.auanet.org/education/guidelines/prostate-cancer.cfm>). The management of metastatic disease today is palliative with hormonal manipulation in the absence of a cure.

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MODULE 9: URINARY INCONTINENCE

KEYWORDS: Urinary incontinence, urgency urinary incontinence, stress urinary incontinence, mixed urinary incontinence, overflow urinary incontinence

Learning Objectives

At the end of this clerkship, the medical student will be able to...

1. Define the causes of transient urinary incontinence.
2. Describe the 4 types of urinary incontinence (stress, urgency, mixed, and overflow) including signs and symptoms.
3. Compare and contrast incontinence as a result of bladder dysfunction verses urethral dysfunction.
4. Demonstrate how to take a comprehensive urologic history for assessment of urinary incontinence.
5. Predict the type of incontinence a patient is experiencing after obtaining comprehensive history for incontinence.
6. Describe the components of the physical examination in a male or female patient with urinary incontinence.
7. Recommend appropriate testing required for a patient with urinary incontinence
8. Be familiar with the treatment strategy for a patient with stress urinary incontinence.
9. Be familiar with the treatment strategy for urgency urinary incontinence/overactive bladder, progressing through first, second, and third line therapies

Urinary Incontinence

Urinary incontinence is a significant quality of life challenge, affecting tens of millions of patients, women and men. Patients may not report incontinence to their primary care providers due to embarrassment or misconceptions regarding treatment. Since incontinence is often treatable and can result in significant impairment in quality of life, it is imperative the health care professional be adept at identifying patients who might benefit from treatment. Treatment of urinary incontinence is dependent on the underlying type of incontinence.

Etiology

Incontinence can be related to non-urologic or urologic causes. Non-urologic causes of incontinence are usually reversible when the underlying issue is identified and

corrected. These transient causes of incontinence can be remembered with the mnemonic “DIAPPERS” (Table 1).

TABLE 1: Transient Causes of Incontinence (DIAPPERS)

Cause	Comment
Delirium	Incontinence may be secondary to delirium and will often stop when acute delirium resolves.
Infection	Symptomatic infection may increase urinary tract irritation and resulting incontinence
Atrophy of vaginal tissues	Vaginitis may result in the same symptoms of an infection.
Psychological	Depression may be occasionally associated with incontinence.
Excessive urine production	Excessive intake, diabetes, hypercalcemia, congestive heart failure and peripheral edema can all lead to polyuria, which can exacerbate incontinence.
Restricted mobility	Incontinence may be precipitated or aggravated if the patient is unable to toilet in a timely fashion.
Stool impaction	Patients with impacted stool can have urge or overflow urinary incontinence and may also have concomitant fecal incontinence.
Pharmacologic	
• Sedatives	Alcohol and long-acting benzodiazepines may cause confusion and secondary incontinence.
• Diuretics	A brisk diuresis may overwhelm the bladder's capacity and cause uninhibited detrusor contractions, resulting in urge incontinence.
• Anticholinergics	Many nonprescription and prescription medications have anticholinergic properties. Side effects of anticholinergics include urinary retention with associated frequency and overflow incontinence.
• Alpha-adrenergics	Tone in the bladder neck and proximal sphincter is increased by alpha adrenergic agonists and can manifest with urinary retention, particularly in men with prostatism.
• Alpha-antagonists	Tone in the smooth muscles of the bladder neck and proximal sphincter is decreased with alpha adrenergic antagonists. Women treated with these drugs for hypertension may develop or have an exacerbation of stress incontinence.

There are 4 broad categories for urologic causes of incontinence that account for most incontinent patients: urgency, stress, mixed, and overflow incontinence. These are the result of urethral and/or bladder dysfunction (Table 2). Less common urologic causes of incontinence include anatomic abnormalities such as urinary fistula or ectopic ureteral orifices.

TABLE 2: Etiologies of Incontinence

<p>Urethral Dysfunction</p> <p>1. Stress Incontinence</p> <ul style="list-style-type: none"> • anatomic (due to mobility of the bladder neck) • intrinsic sphincter deficiency
<p>Bladder Dysfunction</p> <p>2. Urge Incontinence</p> <p style="padding-left: 40px;">Detrusor overactivity:</p> <ul style="list-style-type: none"> • of nonneurogenic origin • of neurogenic origin <p style="padding-left: 40px;">Poor Compliance</p> <p>3. Overflow Incontinence</p>

Urethral Dysfunction

Urethral related incontinence, or stress urinary incontinence (SUI), occurs because of either urethral hypermobility or intrinsic sphincter deficiency (ISD) or a combination of both. Incontinence associated with urethral hypermobility has been called anatomic incontinence, since the incontinence is due to malposition of the sphincter unit. Displacement of the proximal urethra below the level of the pelvic floor does not allow for the appropriate transmission of abdominal pressure that normally aids in closing the urethra. ISD refers to a dysfunction of the proximal smooth muscle sphincter at the bladder neck and is often correlated with more severe stress incontinence. The clinical utility of these terms revolves around complex decisions for optimal treatment and quantification for research, however it is likely that patients who demonstrate stress leakage manifest a combination of pathologies.

Bladder Dysfunction

Bladder dysfunction, either related to storage or emptying, can provoke urgency or overflow incontinence, respectively. Urgency incontinence occurs when the bladder pressure overcomes the sphincter mechanism. Elevation in detrusor pressure may occur from due to an incremental rise in pressure with increased bladder volume (poor compliance) or intermittent abnormal bladder contractions (detrusor overactivity). Poor bladder compliance results from loss of the vesico-elastic features of the bladder or because of a change in neural-regulatory activity. Detrusor overactivity (DO) may be idiopathic or associated with a neurologic disease (neurogenic DO). DO is exceedingly common in the elderly and may be associated with bladder outlet obstruction. Overactive bladder (OAB) has become the popularized term for describing patients with frequency and urgency with or without urgency urinary incontinence (UUI).

Overflow incontinence occurs at extreme bladder volumes or when the bladder volume reaches the limit of the urethral mechanism or the bladder's viscoelastic properties. The loss of urine is driven by an elevation in detrusor pressure which overcomes the outlet resistance but not due to contraction of the detrusor muscle. Overflow incontinence is associated with incomplete bladder emptying caused either by bladder outlet obstruction (BOO) or poor bladder contractility. BOO is more common in men and due to enlargement of the prostate (BPH). It is less common in women but can result from severe pelvic prolapse or following surgery for stress incontinence.

Female Stress Urinary Incontinence

Please refer to the AUA SUI guidelines for reference materials including treatment algorithm:

[https://www.auanet.org/guidelines/stress-urinary-incontinence-\(sui\)-guideline](https://www.auanet.org/guidelines/stress-urinary-incontinence-(sui)-guideline)

Case Presentation:

Chief complaint: 57 y/o woman presents to your clinic with complaints of leakage of urine with activity, particularly when she is playing with her grandchildren or gardening.

To guide your history-taking, physical exam, and additional analysis, this initial information should place stress urinary incontinence high on your differential diagnosis. Stress urinary incontinence (SUI), defined by the International Continence Society (ICS) as the involuntary loss of urine on effort or exertion, remains an astonishingly common urologic condition associated with striking clinical and economic sequelae. Despite increasing public recognition, as well as appreciation by the medical community of the impact of SUI, the projected prevalence between 26% to 44% of adult women is likely substantially underestimated secondary to social factors such as embarrassment and fear that preclude open discussion of incontinence symptoms.

What are some important questions to ask this patient regarding their leakage?

The differential diagnosis of SUI included urgency incontinence, overflow incontinence due to urinary retention, fistula or mixed incontinence with both urgency and stress components. Careful history should include the onset, frequency, severity and pattern of incontinence, as well as any triggers and associated symptoms such as frequency, dysuria, urgency or nocturia. Incontinence may be quantified by asking the patient if she wears a pad and how often the pad is changed. Obstructive symptoms, such as a feeling of incomplete emptying, hesitancy, straining or weak stream, may coexist with incontinence, particularly in female patients with previous pelvic surgery, pelvic organ prolapse or poor bladder contractility. Female patients should be asked about symptoms of pelvic organ prolapse, such as recurrent urinary tract infection, a sensation of vaginal fullness or pressure, or the observation of a bulge in the vagina. All incontinent patients should be asked about bowel function and neurologic symptoms. Response to previous treatments, including pharmaceutical agents, should be noted. Important features of the history include previous gynecologic or urologic procedures, neurologic problems and past medical problems. A list of the patient's current medications, including use of over-the-counter medications, should be obtained.

Although seemingly intuitive, it is important to point out that the history should include subjective bother and treatment goals.

Although the history may define the patient's problem, it may also be misleading. Urgency incontinence may be triggered by activities such as coughing, so that according to the patient's history, he or she would suggest symptoms consistent with stress incontinence. A patient who complains only of urgency incontinence may often have comorbid stress incontinence, termed mixed incontinence.

What are important components of the physical exam for SUI?

Complete physical examination is performed with emphasis on the abdominal, pelvic and rectal examination. In females, the condition of the vaginal epithelium and the degree of urethral mobility is determined. Simple pelvic examination with the patient supine is sufficient to determine if the urethra moves substantially with straining or coughing. A supine or standing stress test should be performed to demonstrate urinary leakage. The most straightforward for of the stress test is asking the patient to cough during the pelvic exam. Negative office stress tests require further analysis for some objective confirmation of SUI prior to invasive treatment. The presence of associated pelvic organ prolapse should be noted as it can contribute to the patient's voiding problems and may have an impact on diagnosis and treatment. A rectal exam includes the evaluation of sphincter tone and perineal sensation.

Any additional office testing indicated for this patient?

Urinalysis: Urinalysis is performed to determine if there is any evidence of hematuria, pyuria, glucosuria, or proteinuria. Post-void residual (PVR): PVR is frequently useful to guide

treatment and may be measured either with bladder ultrasound or directly with a catheter. A normal PVR is dependent on the capacity of the bladder and the individual circumstances of the patient, however in most cases, volumes in excess of 200 mL when associated with urinary symptoms should raise concern. A significant PVR urine may reflect either BOO or poor bladder contractility. The only way to distinguish outlet obstruction from poor contractility is with functional urodynamic testing.

What are some optional test which may assist in making the diagnosis or ruling out other causes of this patient's incontinence?

A voiding diary may be used to quantitate the amount of fluid taken in, the amount of urine per void, the number of voids and the number of incontinent episodes.

A pad weight test may be performed in select instances to quantitate the amount of incontinence but is most often reserved for research endeavors.

A uroflow measure the flow that urine is expelled from the bladder. Like a PVR if abnormal it reflects either BOO or poor bladder contractility but does not differentiate between the two.

Urodynamic testing (UDS) is used to accurately diagnose the etiology of patient's incontinence, however current guidelines for both stress and urgency incontinence indicate many patients can be successfully treated without such functional testing. The purpose of urodynamic testing is to examine bladder compliance, detrusor overactivity, urethral function, and to rule out obstruction as a cause of either overflow or urgency incontinence. Urodynamics are often performed prior to invasive therapies and are indicated in patients undergoing repeat procedures following failed treatments. For expanded information, refer to the AUA guidelines on urodynamics: <https://auanet.org/guidelines/urodynamics-guideline>

Cystoscopy is not routinely required for the diagnosis of incontinence but may be utilized in complex cases where the patient demonstrates hematuria, pyuria, or in the setting of prior surgery.

What are risk factors for development of SUI in women?

Although a diverse suite of pathophysiologic processes contribute to the symptoms of SUI, loss of pelvic floor anatomic support combined with dysfunction of the external urethral sphincter due to both structural and neuromuscular compromise often represent primary etiologies. A delicate orchestration of defects from genetic, anatomic, metabolic, hormonal, environmental, and neurologic realms inevitably combine to dictate patient symptoms. Prominent factors in women are childbirth, aging, abdominal straining such as chronic cough, obesity, and estrogen loss. Defining reversible pathology for any of these components with certainty is currently limited and therefore the treatment strategies available are designed to temporize the symptom complex. Understanding these expectations assists the surgeons' efforts in counseling patients regarding potential outcomes.

What are treatment options for women with SUI?

Strategies for treatment of stress urinary incontinence are tailored to the amount of incontinence and how it affects the patient. The patient who is severely restricted because of severe leakage with minimal movement may not want to try medical therapy but may opt for surgical treatment, whereas the patient who leaks small amounts infrequently may choose conservative treatment. In most cases, patients move from conservative to invasive measures in a stepwise fashion. Women should be counseled on the risks and benefits of all surgical and non-surgical treatment options. An excellent resource for patients regarding SUI and many other Urologic conditions are materials available online from the Urology Care Foundation: <https://www.urologyhealth.org/>

Behavioral modification

A variety of strategies to manage fluid and timed voiding, particularly before provocative activities, may assist with the patient's SUI symptoms. Pelvic floor exercises can improve anatomic stress urinary incontinence by augmenting closure of the external urethral sphincter and by preventing descent and rotation of the bladder neck and urethra. To benefit from the exercises, women must be taught to do them properly and they must do them consistently. Adjuncts to learning pelvic floor exercises include pelvic floor physical therapy, weighted vaginal cones, a perineometer or electrical stimulation.

Devices

Vaginal inserts including continence pessaries or commercially available tampon-like devices are options to promote continence by support of the anterior vaginal wall. These are often employed in situations where patients only leak with certain activities (i.e. running) or for women desirous of avoiding more invasive interventions.

Medications

There are currently no FDA-approved medications for treatment of SUI. Topical transvaginal estrogen has been demonstrated to improve SUI symptoms, but evidence suggests that oral estrogens worsen incontinence.

Alpha-agonists such as pseudoephedrine (Sudafed) have been used for the treatment of stress incontinence. The bladder neck and proximal urethra have abundant alpha receptors. Activation of these receptors by alpha-agonists leads to an increase in smooth muscle tone. Tricyclic antidepressants, such as imipramine (Tofranil), although not approved for incontinence, have both alpha-agonist and anticholinergic properties.

Surgical treatment

Surgical therapy for stress incontinence is indicated when a patient doesn't wish to pursue non-surgical therapy or when other treatments have failed. In general, interventions are grouped into the following categories: cystoscopic injection of urethral bulking agents, retropubic suspensions, and sling procedures. Choosing a surgical procedure is a complex decision and there is substantial heterogeneity in the definitions of success between therapies. Patients should be informed of the level of invasiveness, operative risks, and expectations. The most common procedures performed are slings. Pubovaginal slings, often employed in complex situations or for prior failed interventions, most often utilize a patient's own fascia as a graft. Synthetic mesh mid-urethral slings are employed in patients with urethral hypermobility. For expanded information, refer to the AUA guidelines on the surgical treatment of female SUI: [https://auanet.org/guidelines/stress-urinary-incontinence-\(sui\)-guideline](https://auanet.org/guidelines/stress-urinary-incontinence-(sui)-guideline). Nuances of counseling regarding use of mesh slings is provided by the American Urological Association (AUA) at <https://www.auanet.org/guidelines/use-of-vaginal-mesh-for-the-surgical-treatment-of-stress-urinary-incontinence>.

How is Stress Urinary Incontinence Different in Male Patients?

Men who are experiencing symptoms suggestive of SUI will have a history of neurologic condition such as spinal cord injury affecting the bladder neck or more likely will have had a history of surgery for treatment of prostate cancer or BPH. The history will have a similar focus as in a female patient with emphasis on onset, frequency, severity, assessing for obstructive symptoms and irritative symptoms. Evaluation would include cough stress test, PVR/Uroflow and when appropriate UDS and cystoscopy. Male patients with stress incontinence can be treated with an artificial urinary sphincter or a variety of sling procedures. An artificial urinary sphincter provides continence because a cuff compresses the bulbar urethra. It is considered the gold standard treatment. Male slings provide compression under the urethra and elevate the urethra to a more retropubic position. Slings are best suited for men with lesser degrees of incontinence as determined by a pad weight test. Further information regarding male stress urinary incontinence is provided by the AUA at <https://www.auanet.org/guidelines/incontience-after-prostate-treatment>.

Case Presentation:

Chief Complaint: 57 y/o female presents to your clinic with complaints having to urinate frequently due to a strong urge to void with occasional incontinence on the way to the bathroom. This is particularly embarrassing for her as she works in a large corporate office and has had to leave meetings.

Urinary urgency, frequency, nocturia, with or without urgency incontinence are the symptoms that define overactive bladder (OAB). It is important to recognize that OAB is a symptom complex or clinical diagnosis but does not represent a specific discrete pathological condition and affects both men and women. Understanding the terminology will help assist in your history taking. As defined by the International Continence Society (ICS):

Urinary urgency is described as the sudden and compelling urge to urinate which is difficult to delay

Urinary frequency is an increase in the number of times a person voids during the wake hours; 7 or less voids is often considered normal, however there is substantial variability in frequency due to sleep habits, fluid intake, medications, and other comorbid conditions

Nocturia is interruption of sleep due to the need to void on or more times during the person's normal sleep period

Urgency urinary incontinence (UUI) is the leakage of urine associated with a strong urge or desire to urinate.

OAB is estimated to affect 7%-27% of men and 9%-34% of women, however it is more common for women to experience UUI than men. The prevalence and severity of OAB appears to increase with age. OAB can pose a significant burden to the patient not just in terms of costs for management of the condition, but also in impairment of employment, activities of daily living, psychosocial function and quality of life.

What are the important components of the HPI?

In taking a history for patients with complaints of urinary frequency or urgency, or urgency urinary incontinence any standard mnemonic such as "OLDCARTS" (onset, location, duration, characteristics, aggravating factors, radiation, treatment) can be employed to guide your history taking, starting with open-ended questions that encourage the patient to tell their story. In general information from the patient that should be elucidating includes irritative or

storage symptoms (i.e. urgency, urgency incontinence, frequency, nocturia), obstructive or emptying symptoms (i.e. hesitancy, straining to void, decrease or interrupted stream, history of retention of urine or incomplete bladder emptying), and symptoms of stress urinary incontinence. Fluid habits can be implicated as an underlying cause of OAB and therefore it is important to assess the quantity, type, and timing of fluid intake.

Symptoms of OAB are subjective and difficult to quantify. It is ideal to try and quantify the number of day and night time voids, degree of urgency, number of leaks, and assess degree of bother. Below are some suggestions you could consider asking a patient:

On average how often do you go to the bathroom (i.e. every hour, etc.)?

Are you able to delay urination once you have the urge to go to the bathroom?

Are you able to get to the bathroom without leaking once you have urge to go to the bathroom?

Do your bladder symptoms keep you from doing things that you want to do?

What are the other important considerations that should be obtained in the past medical history, past surgical history, social history, and medications?

During the history screening questions should be asked to assess for co-morbid conditions that impact bladder function directly. Patients with confounding medical conditions are considered complicated OAB patients or may fall into the category of neurogenic bladder. Neurogenic bladder refers to bladder dysfunction related to storage or emptying due to a brain, spinal cord, or nerve condition. Other comorbidities that can affect bladder function include mobility issues, complicated or poorly controlled diabetes, bowel issues (i.e. constipation), prior pelvic surgeries, and history of prior pelvic malignancies treated with radiation to the pelvis.

Other specific aspects that are important and should be assessed specifically are the use of diuretics, prior non-pharmacologic or pharmacologic management strategies tried by the patient (i.e. anti-muscarinic medications, Kegel exercises, timed voiding).

What are the important components of the physical exam (Male and Female) for evaluation of OAB?

Physical examination should include abdominal exam, rectal/genitourinary exam including a focused neurologic exam, assessment of lower extremity edema, and assessment of cognitive or functional impairments. The abdominal examination is to assess for scars, masses, hernias, and areas of tenderness or possible palpable distended bladder. During the genitourinary exam of men this includes assessment for penile pathology, perineal breakdown, and digital rectal examination to assess for prostate pathology or tightness of the pelvic floor muscles, assess for possible impaction/constipation, sensation and sphincter tone. In the female genitourinary exam includes vaginal examination to assess for pelvic organ prolapse, vaginal atrophy and digital assessment of pelvic floor for pain, muscle tone, or ability to perform a Kegel. Vulvar and perineal skin should be inspected, and sensation assessed. Videos of the genitourinary exams can be found on the AUA Medical Student Education website (<https://www.auanet.org/education/auauniversity/for-medical-students/male-gu-exam>, <https://www.auanet.org/education/auauniversity/for-medical-students/female-gu-exam>). The AUA/SUFU guidelines for diagnosis and treatment of overactive bladder (non-neurogenic) in adults recommends assessment for cognitive impairment as it has implications in management of OAB ([https://www.auanet.org/guidelines/overactive-bladder-\(oab\)-guideline](https://www.auanet.org/guidelines/overactive-bladder-(oab)-guideline)).

What is in the differential diagnosis for OAB symptoms (urgency, frequency, urgency urinary incontinence)?

The differential diagnosis for urinary urgency, frequency with or without urgency urinary incontinence is extensive and includes conditions outside the bladder as well as primary bladder related issues. Conditions such as polydipsia of any cause, constipation, pelvic floor muscle dysfunction, poorly controlled diabetes, use of diuretics, congestive heart failure. Primary bladder conditions included IC/PBS, UTI, bladder outlet obstruction due to BPH, urethral stricture or prior incontinence procedures, decrease bladder compliance for example in a patient with prior radiation to the pelvis, bladder cancer, and foreign body in the bladder.

What office testing should be considered in the initial management of this patient?

UA/microscopy/urine culture: Urinalysis with microscopy is important in ruling out the presence of hematuria or infection. In a patient with irritative bladder symptoms, bladder cancer or carcinoma in situ is a critical diagnosis. The presence of microscopic hematuria (> then 3 RBC/hpf) necessitates a hematuria evaluation (<https://www.auanet.org/guidelines/microhematuria>). High levels of glucose in the urine could suggest undiagnosed or poorly controlled diabetes mellitus contributing to polyuria and possible polydipsia, Urine culture is only needed if the UA is suggestive of infection, further assessment and intervention should be deferred until the infection has resolved.

Post void residual (PVR): PVR is an assessment of bladder emptying and can be performed with a small ultrasound scanner or via catheterization following the patient urinating. Normal PVR is considered < 50 ml, >200 ml is often considered abnormal and may be related to BOO or poor contractility. In patients with urgency urinary incontinence and OAB the absolute value should be considered in relation to the patient's total bladder capacity. A PVR is not required prior to initiation of behavioral interventions or in non-complicated OAB starting medications. PVR should be assess when a patient has obstructive symptoms, neurologic diagnosis, prolapse, of history of incontinence or prostate surgery prior to medication intervention or if a patient develops obstructive symptoms while on medication therapies or not responding to standard treatment.

Voiding Diary: There are many different types of voiding diaries, but the essence of a voiding diary is that it captures normal intake and voiding behaviors of a patient. Minimum data includes documentation of the time of each void and details surrounding incontinence episodes. Rating the degree of urgency, measuring voided volume, and measuring fluid intake is useful but not required. Diaries are useful to document baseline symptoms, to assess for voided volumes and fluid intake, and assess treatment impact, and patients may use the diaries for self-monitoring.

A voiding diary is a very useful tool in establishing if a patient has urinary frequency with small or large volume voids. The differential diagnosis and management will differ based on the underlying cause. Normal to large volume voids may indicate nocturnal polyuria if isolated at night or polydipsia. Small volume voids may indicate possible interstitial cystitis (IC), painful bladder syndrome (PBS), genitourinary symptoms of menopause.

What advanced testing may be indicated for the evaluation of OAB/UII?

Advanced diagnostic tests such as UDS, cystoscopy, or renal ultrasound are not needed in the uncomplicated OAB patient. In patients with complicated histories or patients failing to respond to multiple OAB treatments these tests can then be considered. Which tests are needed are left to the discretion of the treating provider dependent on patient parameters.

Renal/bladder ultrasound: imaging of the kidneys and bladder

Urodynamics: this is an invasive procedure in which a small catheter is placed into the bladder and possibly the rectum to assess bladder function and dysfunction. The catheters are designed to record the pressure in the bladder with filling and voiding. Urodynamics are complex tests which require training in for performance and interpretation. For expanded information, refer to the AUA guidelines on urodynamics:

<https://auanet.org/guidelines/urodynamics-guideline>

Cystoscopy: evaluation of the bladder in which a camera scope is passed through the urethra and into the bladder. It provides direct visualization of the bladder mucosa and urethra. It may be used to assess for the presence of cancer, foreign bodies, urethral strictures, prostatic architecture, and changes within the bladder suggestive of chronic bladder obstruction.

What are important concepts to remember in discussing treatment options for OAB?

When we consider treatment options for the management of OAB it is important to remember that this is clinical syndrome that typically carries very low morbidity or mortality but can have profound impact on overall quality of life for patients. However, the patient must be motivated and have a desire to achieve improvement in symptoms. It is acceptable for a patient or caregiver to not pursue treatment or to abort further treatment options when improvements are not being achieved. UUI is treated similar to OAB, however it is important to identify patients with risk factors for poor compliance because left untreated this can have detrimental effects on renal function and the primary goal is decreasing bladder pressure. It is useful for patients to have a basic understanding of bladder function, what is considered normal bladder volume (300-500 ml), the concept of the warning time (time from when one senses the urge to when the bladder contracts to empty), that behavioral interventions are an important component of treatment at all levels in the algorithm, and that it may take trials of multiple medications or intervention to achieve the desired degree of improvement. It is critical to have a discussion with the patient or caregiver early on to manage expectations and to set realistic goals for improvement.

Failure to a treatment may be considered if there is an absence of symptomatic improvement or if the side effects are intolerable.

What are the treatment options for OAB/UUI?

The treatment options for OAB are clearly separated into 1st, 2nd, 3rd line etc. therapies with progression of increasing risk/benefit ratios and degrees of invasiveness. Though treatment ideally progresses in a hierarchical fashion through the treatments, the clinical framework is not intended to be a rigid algorithm in which patients may only progress with failure of the preceding treatments.

First line therapies: behavioral therapies

There are two approaches to behavioral modifications, one focuses on changing bladder function, the other focuses on the pelvic floor or bladder outlet. Simple approaches that can be provided to patients are things such as modification of fluid intake, timed or scheduled voiding prior to the feeling the sensation of urge, reduction of bladder irritants, weight loss, urge control techniques (i.e. distractions). More complex behavioral interventions such as electrical stimulation, biofeedback, pelvic floor exercises may require specialized training and equipment.

There are numerous behavioral therapies and techniques, however they all require participation of the patient or caregiver, and time from the clinician to explain and assess for understanding. Without these two components, behavioral therapies will be less successful. In addition, behavioral therapies can be utilized in combination with 2nd and 3rd line therapies.

Second line therapies: medications

Medications are the mainstay of second line therapy. There are 2 classes of medication available for use in the treatment of OAB/UUI. Anti-muscarinic medications were the mainstay of treatment for decades until the release of the first B3 adrenergic agonist in 2012. Combination therapy using an anti-muscarinic and B3 adrenoreceptor agonist is appropriate with single drug failure.

Anti-muscarinic medications:

Mechanism of action: work by binding the muscarinic receptor on the detrusor muscle this results in decrease in contractility of the detrusor muscle.

Medications: There are many different anti-muscarinic medications available in the US including: oxybutynin (Ditropan), fesoterodine (Toviaz), tolterodine (Detrol), solifenacin (Vesicare), darifenacin (Enablex), trospium (Sanctura). Oxybutynin, Detrol and trospium have both an immediate release (IR) formulation as well as extended release formulation (ER).

Side effects: dry mouth, dry/itchy eyes, constipation, blurred vision are common. Dyspepsia, urinary retention, UTI, tachycardia, drowsiness, and impaired cognitive function are possible. Use in older individuals should be done with extreme caution as these medications can result in decrease memory recall and altered mentation. Anticholinergic medications may also be linked to development of dementia. Life threatening arrhythmias are rare.

Special Considerations: contra-indicated in patients with narrow or closed-angle glaucoma and should be used with caution in patients with history of impaired gastric emptying or history of urinary retention.

Principles: ER formulations are preferred when feasible over IR formulations due to improved compliance and decrease adverse side effects. There is no compelling data that one medication is superior to others regarding therapeutic efficacy. Differences in dry mouth and constipation may exist. It is not unreasonable to consider an alternative anti-muscarinic or dose adjustment when a patient fails to have therapeutic improvement. In the event of intolerance to a drug switching to another anti-muscarinic or B-3 agonist is reasonable.

B-3 adrenoreceptor agonist:

Mechanism of action: works by binding the B-3 adrenergic receptor on the bladder signaling relaxation of the detrusor muscle.

Medication: Mirabegron (Mybetriq)

Side effects: hypertension, headaches, and UTI. Common side effects reported with anti-muscarinic medications such as dry mouth, dry eyes, urinary retention occur less frequently with Mirabegron.

Special considerations: use is contraindicated in patients with uncontrolled hypertension. Contraindicated in patients on metoprolol and select antiarrhythmic medications

Principles: Currently available in 25 and 50 mg dosage with therapy initiated in most instances at lowest dose.

Third line therapies: procedural interventions

There are three third line therapies for treatment of medication refractory OAB. These can be classified into neuromodulation and end organ treatment. There is not a specific order in which to progress through the treatment options, each treatment has a unique set of risks and benefits. In addition, failure of one 3rd line therapy does not prohibit trial of an alternative 3rd line therapy.

Neuromodulation:

Percutaneous tibial nerve stimulation (PTNS): this is a non-surgical treatment option.

PTNS involves stimulations of the posterior tibial nerve to provide effect on the nerves responsible for the bladder and pelvic floor. The patients present to the office weekly for 12 weeks for a 30- minute stimulation session. It carries a very low risk and is considered a non-surgical treatment option. Patients are not required to be off anticoagulation for the procedure to be done.

Sacral nerve stimulation (SNS): SNS is a surgical procedure in which a lead with electrodes placed through the S3 foramen and sits near the nerves that are responsible for bladder function. The lead will generate an electrical current to affect the nerve. Patients will have a “test” phase prior to implantation of the battery (implantable generator). The biggest risk are device infection and malfunction. Except for the brain MRIs, MRI are contraindicated. SNS has added FDA approved for fecal incontinence, and non-obstructive urinary retention.

End Organ:

Intradetrusor botulinum toxin (Botox): Botox works by preventing the release of acetylcholine at the nerve terminals; with a decrease in acetylcholine in the nerve terminals the detrusor muscle is not stimulated and remains flaccid. Generally, it is an office-based procedure in with the bladder is anesthetized with intravesical lidocaine and then the Botox is injected into the detrusor muscle via a cystoscopy.

Alternative management strategies:

When an uncomplicated patient has failed conservative treatment strategies as outline in the 1st, 2nd, and 3rd line therapies, or for some complicated patients’ treatments such as urinary diversion or augmentation cystoplasty could be considered. Urinary diversion is when a piece of bowel (typically small bowel) is isolated from the bowel tract and used as a conduit to bring urine to the skin via a stoma. The ureters can be left attached to the bladder or inserted directly into the bowel segment. Augmentation cystoplasty is where a piece of bowel (preferentially small bowel) is separated from the bowel tract and de-tubularized and used to expand the bladder. Both of these types of procedures are highly specialized procedures that are invasive and have considerable associated risks.

It should also be noted that insertion of a chronic indwelling urethral catheter or suprapubic catheter (SPT) should be considered last resort and reserved for those that are at risk for skin break down or institutionalization due to their urinary incontinence. Urethral catheters carry a risk of irreversible damage to the urethra such as erosion or formation of a patulous incompetent urethra. And both urethral catheters and SPT are at increased risk for catheter-associated infections (CAUTI).

What are the special considerations for patient with poor compliance?

Patients that experience UUI due to a decrease in bladder compliance need early identification and an aggressive approach to management to protect the kidneys for damage. These patients will often have a history of neurologic conditions such as spinal cord injury or myelomeningocele, or history of pelvic radiation. Poor compliance should be considered in any patient with deterioration of renal function or evidence of unilateral or bilateral hydronephrosis on renal ultrasound. Urodynamic is required to make the diagnosis of decreased bladder compliance. In patients with incomplete bladder emptying or elevated PVR either at baseline or with treatment, clean intermittent catheterization will be required to facilitate bladder emptying and lower bladder storage pressures.

Summary:

OAB with or without urgency urinary incontinence are prevalent conditions. The effect to each patient is individual and will vary accordingly. Taking a thorough history and physical examination are the cornerstones for the diagnosis of OAB. Except for UA/microscopy and urine culture, further testing is not essential to diagnosis and management but assist in establishing the diagnosis or help to exclude other possible causes of similar symptoms. There are a wide variety of treatments, and treatment of the patient should be individualized to that patient.

Mixed Incontinence

Stress and urge incontinence often coexist. Mixed incontinence is very common with at least 65% of patients with stress incontinence reporting associated urgency or urgency incontinence. Behavioral therapy, including pelvic floor therapy, can result in a reduction in incontinence episodes and a patient perceived improvement. Approximately half of patients with combined incontinence (stress and urge) will be relieved of urge incontinence following a procedure for stress incontinence. Patients whose urge incontinence does not respond to anticholinergics preoperatively may have a good response to anticholinergics once their stress incontinence is treated. It is critical to remember that SUI or OAB/UUI without impaired compliance has low mortality and that treatment is not required, but degree of bother is varied, and treatment should be adjusted accordingly.

Overflow Incontinence

Treatment of overflow incontinence is geared towards emptying the bladder and is dependent on the causes, anatomic or poor detrusor function. Anatomic cause of obstruction in males is from either urethral stricture disease or prostatic obstruction. Depending on the severity of urethral stricture disease the patient may require a urethral dilation, internal urethrotomy, or an urethroplasty. Prostatic obstruction may be treated with medications or surgical intervention. There are many newer approaches to surgical management of BPH, however transurethral resection remains the "gold standard." When a female is obstructed from previous surgery or from pelvic prolapse, she may benefit from an urethrolisis, removal of the prior sling, or surgical correction of the prolapse. Clean intermittent catheterization is an option in the obstructed patient who does not want or could not tolerate further surgery.

The patient with overflow incontinence secondary to poor detrusor contractility is best treated with clean intermittent catheterization as chronic indwelling catheters are not optimum in the long-term. Indwelling catheters are associated with chronic bacteriuria which predisposes them to bladder calculi and ultimately to squamous cell carcinoma of the bladder. Any foreign object in the bladder can cause or exacerbate elevated bladder pressure which then causes hydronephrosis, ureteral obstruction, renal stones and eventually renal failure.

Indications to Refer to Urology

The main indication to refer the patient with incontinence to urology is failure to respond to behavioral or medical therapies. There is no reason that an internist or family doctor can't do a basic work-up (history, physical, urinalysis, +/- PVR) and counsel the patient on behavioral therapies or consider medical therapy. If the patient fails to respond adequately to medical therapy then referral is warranted. The presence of hematuria, recurrent infections or complicated incontinence, such as following radical prostatectomy in a male, or that thought to be neurogenic, should always prompt a referral.

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Table 3: Comparison of Stress Urinary Incontinence and Overactive Bladder/Urgency Urinary Incontinence

	Stress Urinary Incontinence (SUI)	Overactive Bladder (OAB)/ Urgency Urinary Incontinence (UUI)
Definition	Leakage with activity Bladder pressure > Urethral pressure	OAB: urgency, frequency ± UUI UUI: Leakage that is preceded by a strong urge to void Urgency: sudden and compelling urge to void Frequency: increased number of times voiding in a day
Pathophysiology	1. Urethral hypermobility 2. Intrinsic sphincter deficiency (ISD)	1. Hypersensitivity 2. Detrusor overactivity 3. Poor compliance
Differential Diagnosis	Urgency urinary incontinence, overflow incontinence, fistula, urethral diverticulum, mixed urinary incontinence	Neurogenic bladder, UTI, bladder cancer, vulvar irritation, pelvic floor dysfunction, bladder outlet obstruction (BPH (men), prior sling, pelvic organ prolapse), idiopathic
Evaluation	1. Urinalysis 2. Cough stress test 3. Assessment of post-void residual 4. Voiding diary 5. Pad weight test 6. Urodynamics testing (UDS) 7. Cystoscopy	1. Urinalysis 2. Assessment of post-void residual 3. Voiding Diary 4. Urodynamics (UDS) 5. Cystoscopy 6. Creatinine (if decreased compliance)
Treatment		
1 st Line therapy	Behavioral Therapy/Conservative Therapy 1. PT/Kegel exercises 2. Devices (Pessary, Tampons, Impressa Device) 3. Pads/Protection	Behavioral Therapy/Conservative Therapy 1. Pelvic floor physical therapy 2. Timed or Prompted Voiding 3. Fluid modification (volume and type) 4. Pads/Protection
2 nd Line Therapy	Medications: No FDA approved medications for treatment of SUI 1. Vaginal estrogen 2. α -agonists (pseudoephedrine) 3. Imipramine (Tofranil)	Medications: 1. Anti-Muscarinics 2. β -3 Adrenoceptor Agonists
3 rd Line Therapy	1. Urethral Bulking Agents 2. Sling (mesh or autologous tissue) 3. Retropubic Suspensions	1. Posterior Tibial Nerve Stimulation 2. Sacral Nerve Stimulation 3. Botulinum Toxin Injection

(Updated October 2019)

MODULE 10: MALE INFERTILITY

KEYWORDS: INFERTILITY, AZOOSPERMIA, OLIGOSPERMIA, SEMEN ANALYSIS, VARICOCELE

LEARNING OBJECTIVES:

At the end of medical school, the medical student will be able to...

1. Describe the hypothalamus-pituitary-gonadal (HPG) axis
2. Describe the workup for male infertility, including the importance of the physical exam
3. Restate the limitations of the semen analysis
4. List some common reversible causes of infertility and their treatments
5. Recognize when to refer a patient for ART

Introduction

Approximately 15% of couples will be unable to conceive after attempting unprotected intercourse for one year. Of these couples, about 50% of them will have some male factor to that is contributing to their infertility (a male factor is the sole reason in approximately 20% of infertile couples). (Thonneau P, 1991) Male infertility can be due to a variety of genetic, anatomic, and environmental conditions, many of which will be briefly discussed below. When a cause for an abnormal semen analysis cannot be found, it is termed idiopathic. When a man is infertile with a normal semen analysis and workup, the term unexplained infertility is used. As the word suggests, these men do not have a known cause for their infertility but it is thought to likely be due genetic defects that have not been described yet. The purpose of evaluation is to identify possible conditions causing infertility and treating reversible conditions which may improve a man's fertility potential. These treatments can include, medication, vitamin supplementation, surgery, and/or assisted reproductive technologies (ART).

Workup and Evaluation

History and physical exam are incredibly important in the workup of the infertile male. In fact, the decision to offer certain surgeries to these patients can be based solely on physical exam findings such as the presence of a varicocele.

A thorough and complete history should include:

- Male infertility risk factors such as a history of bilateral cryptorchidism, vasectomy, chemotherapy or radiation treatments
- Female infertility risk factors, including advanced female age (over 35 years)
- Reproductive history
 - coital frequency and timing
 - duration of infertility and prior fertility
 - childhood illnesses and developmental history
 - systemic medical illnesses (e.g., diabetes mellitus and upper respiratory diseases)
 - sexual history including sexually transmitted infections;
 - gonadal toxin exposure including heat and testosterone
- Surgical history (with a focus on GU and inguinal surgery)
- A review of medications (prescription and non- prescription) as many drugs can contribute to infertility
- Lifestyle exposures such as alcohol, marijuana, and tobacco use as well as vocational exposures
- Family reproductive history

As mentioned before, the physical exam is very important in the workup of a man with infertility, with particular focus on the GU (genitourinary) exam. This should include:

- Examination of the penis including the location and size of the urethral meatus
- Palpation of the testes and measurement of their size
- Presence and consistency of both the vas deferens and epididymides
- Presence of a varicocele
- Secondary sex characteristics including body habitus, hair distribution and breast development;

When a varicocele is palpated it is graded as follows:

- Grade 0 (subclinical): seen on ultrasound only but not physically palpable
- Grade I: palpable when the patient is performing the Valsalva maneuver
- Grade II: palpable without Valsalva
- Grade III: able to visualize varicocele through scrotum (“bag of worms”)

The diagnosis of congenital bilateral absence of the vasa deferens (CBAVD) and varicocele is established by physical examination. Scrotal exploration and imaging is not needed to make these diagnoses so make sure a good physical exam is part of your work up for any man who complains of infertility!

Semen Analysis

The cornerstone of a male infertility workup is the semen analysis. The most current guidelines for this are published by the WHO (World Health Organization) and are on their 5th edition. (World Health Organization, 2010) There are several important

things to know about a semen analysis to be able to properly interpret the results. First, it should be examined under the microscope within one hour of collection and should the sample should be given after 2-3 days of abstinence. A proper semen analysis takes time and very specialized training by the andrologist so ideally these this test is done at a center that does a lot of them. While many routine laboratory tests have a relatively set cut off point between normal and abnormal (white blood cell count, troponins, creatinine, etc.), semen analysis do not really have this kind of differentiation despite what the “normal” lab values you will see listed net to most semen values. This is because of how the data was originally designed. Essentially, the original studies involved taking a bunch of men who had conceived with their partner within the last year and having them perform a semen analysis. A large bell curve distribution was noted and the authors somewhat arbitrarily decided that anything better then the *5th percentile* would be considered “normal”. This means that a patient with a barely “normal” semen analysis still has worse semen parameters then 95% of fertile men! (Cooper TG, 2010) This is an important fact to consider when interpreting results and counseling patients. Despite these limitations, it is still the single best test we have when evaluating these patients. Below are the “normal” values based on the most recent data.

Semen Parameter	WHO 5th Ed. (2010)
Volume	1.5 ml
Appearance	Grey and opaque
pH	> 7.2
Concentration	> 15 million/ml
Motility	> 40% (> 32% progressive)
Morphology	> 4% normal forms (strict criteria)
Leukocytes	< 1 million/ml

Blood Tests

Blood tests focus on testing for hormonal and genetic causes of infertility. The figure below shows the important hormones involved in the hypothalamus-pituitary-gonadal (HPG) axis (figure 1). The hypothalamus makes GnRH (gonadotropin releasing hormone) to stimulate the pituitary gland. This in turn causes the pituitary to release FSH (follicle stimulating hormone) and LH (luteinizing hormone). FSH Acts on Sertoli cells to initiate meiosis and spermatogenesis. It also causes the Sertoli cells to release Inhibin, a molecule that causes negative feedback inhibition. LH acts on Leydig cells to stimulate the production of testosterone which also acts as a potent negative inhibitor of FSH and LH release from the pituitary. Estradiol is made from conversion of testosterone by aromatase. Derangement of one or more of these hormones can lead to fertility problems. Some of the common abnormalities will be described in the next section.

Genetic testing (karyotype and Y-chromosome microdeletion) should be performed on any patient with severe oligospermia. More advanced testing such as sperm DNA fragmentation can also be done but is outside the scope of this discussion.

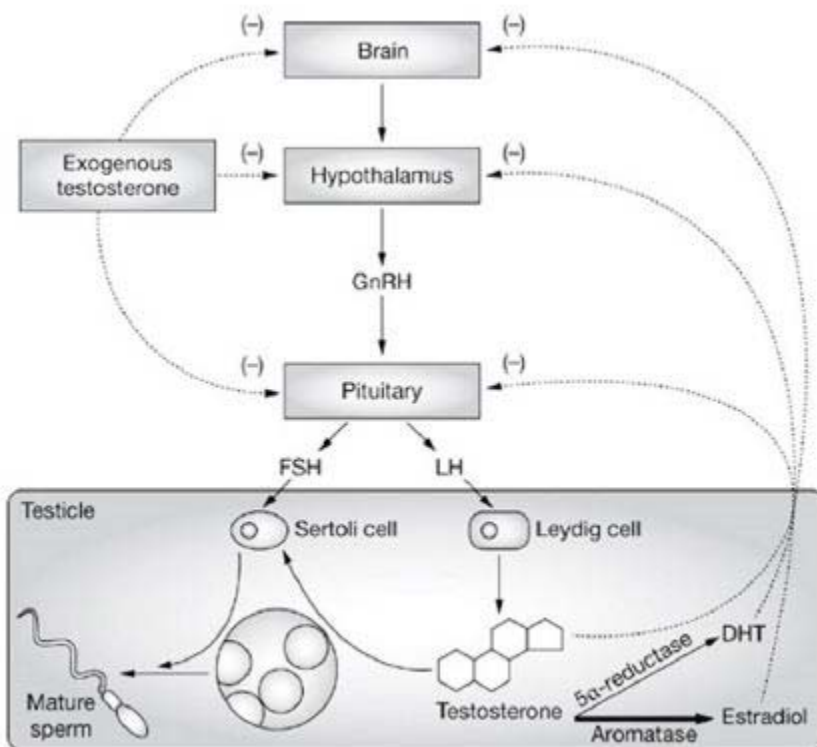


Figure 1: hypothalamus-pituitary-gonadal (HPG) axis

Imaging

Scrotal ultrasound, transrectal ultrasound, brain MRIs, and CT scans are all indicated depending on the diagnosis and work up. Scrotal ultrasound is good for diagnosing testicular tumors and confirming the presence of a varicocele in obese or otherwise difficult to examine patients. A transrectal ultrasound can help diagnose ejaculatory duct obstruction and a brain MRI can rule out a prolactinoma as a cause of infertility if their prolactin is elevated.

Pathology

Many anatomic, hormonal, and genetic abnormalities can cause male infertility. Primary infertility describes a man who has never fathered a child while secondary infertility is the term used when a man has previously fathered a child but is now having trouble conceiving. Below is a short description of some of the most commonly seen diagnoses and their treatments. A few more important terms to know when discussing abnormal fertility findings include:

- Azoospermia: absence of sperm
- Oligozoospermia: low sperm count

- Severe Oligospermia: very low sperm count (<5 million/ml)
- Asthenozoospermia: poor sperm motility
- Teratozoospermia: abnormal sperm morphology

Obstructive Azoospermia

Azoospermia can come in two flavors, *non-obstructive* and *obstructive*, and they are treated very differently.

Obstructive azoospermia is due to an obstruction/blockage somewhere between the testicle and the seminal vesicles and may occur in up to 7% of the infertile population. An obstruction between the seminal vesicles and prostate is called an ejaculatory duct obstruction (EDO) and will be discussed later. Patients with obstructive azoospermia will have a semen analysis with no sperm, but normal pH and volume. A common cause of obstructive azoospermia is a previous vasectomy. There are 3.6 million vasectomized men in the United States alone, which represents an overall vasectomy prevalence of 6-8% based on several large national cohorts. (Eisenberg ML, 2010) Up to 7% of these men desire restoration of fertility and at least 2% undergo a vasectomy reversal. Other causes of obstruction include hernia repair. Damage to the vas deferens during adult hernia repair is uncommon, but patients who have undergone bilateral hernia repair as children have vasal obstruction rates as high as 40%. (Matsuda T, 1998) Sexually transmitted infections, previous groin/GU surgery, and trauma can also cause obstruction. These obstructions can often times be fixed with a vasovasostomy or a vasoepididymostomy with excellent results. Using small sutures (9-0 and 10-0) the obstruction can be bypassed. When the obstruction is in the vas and one is able to sew the vas directly back to the vas, success rates are around 90%. When the vas must be connected to the epididymis, rates of sperm return drop to around 60-70%.

Finally, obstructive azoospermia can be caused by congenital bilateral absence of the vas deferens. This is seen when a patient is a carrier of the CFTR (cystic fibrosis) gene. These patients will have low volume azoospermia and no palpable vas on examination. Fortunately, they usually do not have a problem with sperm production and their sperm can be harvested with a small surgical procedure such as a PESA (*Percutaneous Epididymal Sperm Aspiration*) or TESE (*Testicular Sperm Extraction*). When seeing a patient with this diagnosis, it is imperative to have the partner checked for their CFTR carrier status as well.

Nonobstructive azoospermia is a failure of the testis to produce sperm. This is classically diagnosed with an elevated FSH, small testis on exam and normal volume azoospermia seen on semen analysis. The causes of this are multifactorial and can include genetic abnormalities, medications (chemotherapy, testosterone, radiation), infections, and idiopathic causes. The most common genetic cause is Klinefelter's disease (a phenotypic male with 47, XYY). Other genetic syndromes include primary ciliary dyskinesia (Kartagener's Syndrome) which can be treated with in-vitro fertilization and Kallmann Syndrome (absence of GnRH production) which can be

treated with exogenous replacement of LH and FSH. Until recently, there were no treatments for the other causes of nonobstructive azoospermia until it was determined that there may be small pockets of sperm production within a testis despite not making enough sperm to make it into the ejaculate. In this setting, a microscopic testicular sperm extraction (microTESE) can be offered to these patients. In this procedure, an operating microscope is used to carefully dissect a large portion of the testis. The goal is to find testicular tubules that seem healthy and plump. These are then resected and examined under a regular light field microscope for the presence of sperm that can then be used for invitro fertilization. Depending on the etiology, this procedure is successful 20-60% of the time.

Ejaculatory Duct Obstruction

Another form of obstruction is when the seminal vesicles (SV) are unable to drain into the prostate due to ejaculatory duct obstruction (EDO). Semen analysis will show minimal volume (the majority of ejaculate volume is produced by the seminal vesicles), acidic pH (prostatic fluid is acidic and seminal vesicle fluid is basic) and severe oligospermia. Usually there will be severe oligospermia or azoospermia. Further diagnosis can be made with a transrectal ultrasound of the prostate that will reveal dilated SVs and aspiration will often times reveal sperm. Occasionally, enough sperm can be obtained from this aspiration to be used for in-vitro fertilization (IVF) but usually a transurethral resection of the ejaculatory ducts (TURED) is needed. This is similar to a TURP or other transurethral resection, but just the area just lateral to the verumontanum is resected. When this is successful the ejaculatory ducts will be resected, and patients will often have return of normal semen parameters. Sterile epididymitis is the most common side effect from the procedure because the one way valve effect of the ejaculatory duct is removed allowing urine to flow in a retrograde fashion down the vas and into the epididymis.

Varicocele

Varicoceles, an abnormal dilation of the veins of the pampiniform plexus, are the most common cause of secondary infertility. They are also incredibly common in the general population with a prevalence around 20% with the vast majority of varicoceles forming on the left side due to venous anatomy. Not all varicoceles are symptomatic though and only those causing semen analysis abnormalities or discomfort should be fixed. The exact etiology of how a varicocele can cause infertility is still debated, but it is most likely due to thermal dysregulation. (Tadros & Sabanegh Jr., 2017) The dilated veins cause blood to pool around the testis which causes the intratesticular temperature to increase. Since optimal spermatogenesis occurs at a temperature lower than body temperature (hence why the testes are located outside the body and in the scrotum), the increased blood pooling will cause a decrease in sperm production and quality. On semen analysis, one can see oligospermia, asthenozoospermia, and/or teratozoospermia.

Treatment is relatively straight forward and involves ligation of the abnormal veins. This can be done via multiple approaches, but the gold standard is a sub-inguinal

microscopic varicocelectomy. This procedure is done through a small incision below the external inguinal ring. The Spermatic cord is brought up through the incision and an operating microscope is used to identify and ligate large veins. Care is taken to not damage the arterial supply (with use of intraoperative doppler) and the vas.

Idiopathic Male Infertility

Unfortunately, many men seen for infertility and abnormal semen analyses have no obvious cause for their condition. This frustrating for both the physician and patient. While we may not know the cause of their problem, there are still some treatments that can help these men. First line therapy includes behavioral modification including quitting smoking, weight loss if needed, avoiding activities with scrotal/perineal pressure (bike riding), and avoiding long exposure to wet heat (sauna, hot tub). In addition there is some medical therapy available. The most common medication used is clomiphene citrate. This medication is a selective estrogen receptor modulator (SERM). It acts by blocking the negative feedback of estrogen on the hypothalamus and pituitary which causes a downstream increase of FSH and LH. This in turn can stimulate spermatogenesis within the testis. Many of these patients also have low testosterone and the increase in LH will also increase their testosterone without harming sperm production. Another commonly used class of medications are the aromatase inhibitors, anastrozole being the most common in the United States. This medication acts by blocking the conversion of testosterone to estradiol in the adipose tissue. It is most effective when there is a greater than 10:1 ratio of estrogen to testosterone.

An increasingly recognized cause of idiopathic infertility is oxidative stress. This may be the common pathway of many insults. In fact, a new term has been proposed, Male Oxidative Stress Infertility (MOSI). (Agarwal A, 2019) Treatment of this condition as well as many others is with antioxidants. Which antioxidants as well as the correct dose is still hotly debated and the focus of multiple research studies. (Smits RM, 2019) Commonly used antioxidants include vitamin C, vitamin E, zinc, l-carnitine, co-enzyme Q10, and many others. The jury is out on whether or not these antioxidants improve fertility outcomes, but the cost and side effect risk is so low that many physicians routinely recommend them to their infertile men.

Finally, assisted reproductive technologies such as intrauterine insemination (IUI) and IVF can overcome many potential causes of idiopathic infertility. This is also the treatment of choice for *unexplained infertility* which is infertility despite a completely normal workup of both the man and female partner.

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- Thonneau P, M. S. (1991). Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988-1989). *Hum Reprod, 6*, 811.
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(Updated October 2020)

UROLOGIC ABBREVIATIONS

PUV	posterior urethral valves
PVP	photoselective vaporization of the prostate (laser)
PVR	post void residual
RCC	renal cell carcinoma
RPLND	retroperitoneal lymph node dissection
RPP	radical perineal prostatectomy
RRP	radical retropubic prostatectomy
TRUS	transrectal ultrasound
TUIP	transurethral incision of the prostate
TURBT	transurethral resection of bladder tumor
TURP	transurethral resection of the prostate
UPJ	ureteropelvic junction
URS	ureteroscopy
UVJ	ureterovesical junction
VCUG	voiding cystourethrogram
VUR	vesicoureteral reflux
XGP	xanthogranulomatous pyelonephritis

SUGGESTED READINGS

FROM *SMITH AND TANAGHO'S GENERAL UROLOGY* TEXTBOOK
(19TH ED.)

PRIOR TO STARTING YOUR UROLOGY ROTATION:

- Chapter 1, “**Anatomy of the Genitourinary Tract**” to refresh your memory on urologic anatomy. Also skim through Chapter 3, “**Symptoms of Disorders of the Genitourinary Tract**” to learn why urologic problems cause the symptoms they cause.

PRIOR TO SCRUBBING IN THE OPERATING ROOM:

- It would be beneficial to read Chapter 10, “**Laparoscopic Surgery**” prior to scrubbing for any laparoscopic surgical procedures such as laparoscopic nephrectomies, prostatectomies or pyeloplasties.
- It would be beneficial to read Chapter 8, “**Retrograde Instrumentation of the Urinary Tract**” prior to scrubbing for outpatient cystoscopic or ureteroscopic cases in B2 Ambulatory Surgery.
- It would be beneficial to read Chapter 11, “**Robotic Surgery in Urology**” prior to scrubbing for a robotic case.
- It would be beneficial to review Chapter 13 “**Vesicoureteral Reflux**” prior to scrubbing in on ureteral reimplantation surgery or endoscopic management of pediatric vesicoureteral reflux.
- It would be beneficial to review Chapter 23, “**Urinary Diversion & Bladder Substitutions**” prior to scrubbing in for a cystectomy or bladder augmentation.
- It would be beneficial to read Chapter 37, “**Disorders of the Ureter & Ureteropelvic Junction**” prior to scrubbing in on a ureterocele repair, a pyeloplasty or a megaureter repair.
- It would be beneficial to read Chapter 41, “**Disorders of the Penis & Male Urethra**” prior to scrubbing in on a hypospadias repair.

IF YOU ARE LOOKING FOR ADDITIONAL INFORMATION ABOUT THE DISEASE PROCESSES YOU MAY ENCOUNTER WHILE SEEING PATIENTS IN CLINIC:

- You may wish to skim through Chapter 12, “**Urinary Obstruction & Stasis**” prior to joining **Dr. Hedican** in clinic.
- You may wish to skim through Chapter 13 on “**Vesicoureteral Reflux**” as well as Chapter 37, “**Disorders of the Ureter & Ureteropelvic Junction**” and Chapter 41, “**Disorders of the Penis & Male Urethra**” prior to seeing patients in the Pediatric Urology clinic.
- You may wish to skim through Chapter 17, “**Urinary Stone Disease**” prior to seeing patients with **Dr. Nakada** or **Dr. Best**.
- You may wish to skim through Chapter 19, “**Urothelial Carcinoma: Cancers of the Bladder, Ureter, & Renal Pelvis**” prior to seeing patients with **Dr. Jarrard** or **Dr. Downs**.
- You may wish to skim through Chapter 20, “**Renal Parenchymal Neoplasms**” prior to seeing patients with **Dr. Hedican** or **Dr. Abel**.
- You may wish to skim through Chapter 21, “**Cancer of the Prostate Gland**” prior to seeing patients with **Dr. Jarrard**.
- You may wish to skim through Chapter 29, “**Urodynamics**” and Chapter 30, “**Urinary Incontinence**” prior to seeing patients with **Dr. McAchrn**.
- You may wish to skim through Chapter 39, “**Male Sexual Dysfunction**” and Chapter 44, “**Male Infertility**” prior to seeing patients with **Dr. Williams**.

EVALUATION PROCESS

Being evaluated and receiving feedback are important components to every educational process. While you are rotating with us, your performance will be evaluated and you will receive feedback from attendings and residents. Some of it will be as a written evaluation at the conclusion of your rotation. But some will be informal through discussion in the operating room, in clinic, or while rounding with the team. We will comment on the strengths you exhibit while working with us. We will also offer feedback with suggestions for how you can improve your performance. Grading will be performed by our faculty and residents

Your evaluations will be reviewed and summarized and a grade of Outstanding, Exceeds Expectations, Meets Expectations, Needs Improvement, or Unacceptable will be awarded. Grades are determined as a group by all of the faculty and residents that you work with. Clinical grading is somewhat subjective and there is no “point system” for earning Outstanding, which is given only to the top 5% of students. Therefore, meeting all obligations and doing a solid job does not necessarily equal an Outstanding grade. You must clearly stand out in your performance, either by knowledge, your patient care, your work ethic, or a combination of all of these factors.

Your grades will then be forwarded to the Department of Surgery Medical Student Education Office, posted on OASIS and included as part of your overall SPC clerkship grade. Your performance will also be evaluated in part by the successes you have answering urologic questions on the SHELF exam.

We welcome your feedback. Please complete the electronic evaluation form on OASIS. These are anonymous and we receive collated results every six months. If you have specific feedback or comments, please share those directly with us as you feel comfortable. Your feedback, evaluations and comments are taken seriously and used to improve our educational program.

Phase II Grading Guidelines

Outstanding (5%) Must have BOTH superior knowledge/skills and superior effort. Always puts forth an outstanding effort. Routinely goes above and beyond. Great team player. Effort, knowledge base and clinical skills significantly above peers. Stands out as one of the top students.

Exceeds Expectations (Top 25%) Has EITHER superior knowledge/skills or superior effort, but not both. Outstanding effort, routinely goes above and beyond. Great team player. Knowledge base and skills above average. OR Good effort, does what is expected, but doesn't routinely go above and beyond. Knowledge base and skills are outstanding.

Meets Expectations (Majority of students): Has BOTH good effort and good knowledge/skills. Puts forth a good effort, meets all requirements. Demonstrates a good fund of knowledge/skills.

Needs Improvement: Lacks either effort or knowledge/skills. Does not meet expectations for effort (shows up late, skips cases/clinics), does not follow patients routinely. Clinical knowledge/skills below expected level.

Department of Urology Mistreatment and Harassment Policy

The University of Wisconsin Department of Urology strives to maintain a learning environment of the highest professional and ethical repute that does not tolerate mistreatment or harassment of students by faculty, residents, staff or patients.

Students are encouraged to raise questions or concerns about mistreatment, harassment or unsafe or unhealthy work environments. Students should discuss these concerns with the Department of Urology Medical Student Education Director or Coordinator. If the concern(s) cannot be resolved in this manner, the student should contact the Department of Surgery Medical Student Education Director or Coordinator. Additional support is available through the UWSMPH Office of Student Services, Director of Student Services or Dean for Students.

For further information regarding definitions of mistreatment or harassment, confidential reporting of incidents, and links to campus resources, please consult Section 16 of the MD Program Student Handbook found at:

<https://www.med.wisc.edu/media/medwiscedu/documents/education/md-program/medical-student-handbook-2020-21.pdf>

Incidents of hate and bias can also be reported through the following secure and confidential mechanisms:

<https://doso.students.wisc.edu/report-an-issue/bias-or-hate-reporting/>

RESEARCH OPPORTUNITIES

The Department of Urology always has several ongoing research projects that could use the assistance of an independent and enthusiastic medical student. Please see “Department Research Programs” on the Department of Urology’s website at <http://www.urology.wisc.edu/>.