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# Clinical Care Pathways in Andrology

Springer

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# Preface

Andrology is the medical specialty that deals with male health, especially as it pertains to problems of the male sexual and reproductive system. Andrological issues in urologic practice and indeed in general medical practice are commonly encountered, yet perplexing for many clinicians.

In medical training, urologic or general medicine, there is generally minimal attention focused on these topics. Thus, clinicians are often left under-informed and under-trained. This is the impetus behind this book. It was my vision to develop a series of clinical care algorithms to aid the clinician in their medical practice. Whether you are a urologist or belong to another medical specialty or are a physician in training, a nurse or physician assistant, these algorithms have been designed to assist you in your decision-making regarding patient evaluation and treatment. To the best of our ability, we have designed algorithms that are evidence-based and where such evidence or society guidelines do not exist I have used my substantial clinical experience in sexual and reproductive medicine to generate these clinical care pathways. I have been ably assisted in the development of these pathways by two bright young stars in andrology, both trained by me, Doron Stember MD and Peter Stahl MD, without whose efforts this project would not have been possible.

No doubt, there may be topics that you would have liked to see covered by us that have been omitted. We have tried to focus on the most frequent or important areas for clinical practice. Each chapter is organized in an identical fashion, with the algorithm presented with annotations to text that expands on the point in question. We have attached appendices where we believe these are of value, in particular, specific questionnaires that may be of value to you in your daily practice. We have included numerous tables, listing definitions, key history and examination points, and medication doses and side effects. We have also included suggested reading lists, which are specifically designed not to be comprehensive and overwhelming, but rather functional.

I hope you find this book of clinical utility to you. I welcome comments and suggestions with regard to specific algorithms in this book or future algorithms.

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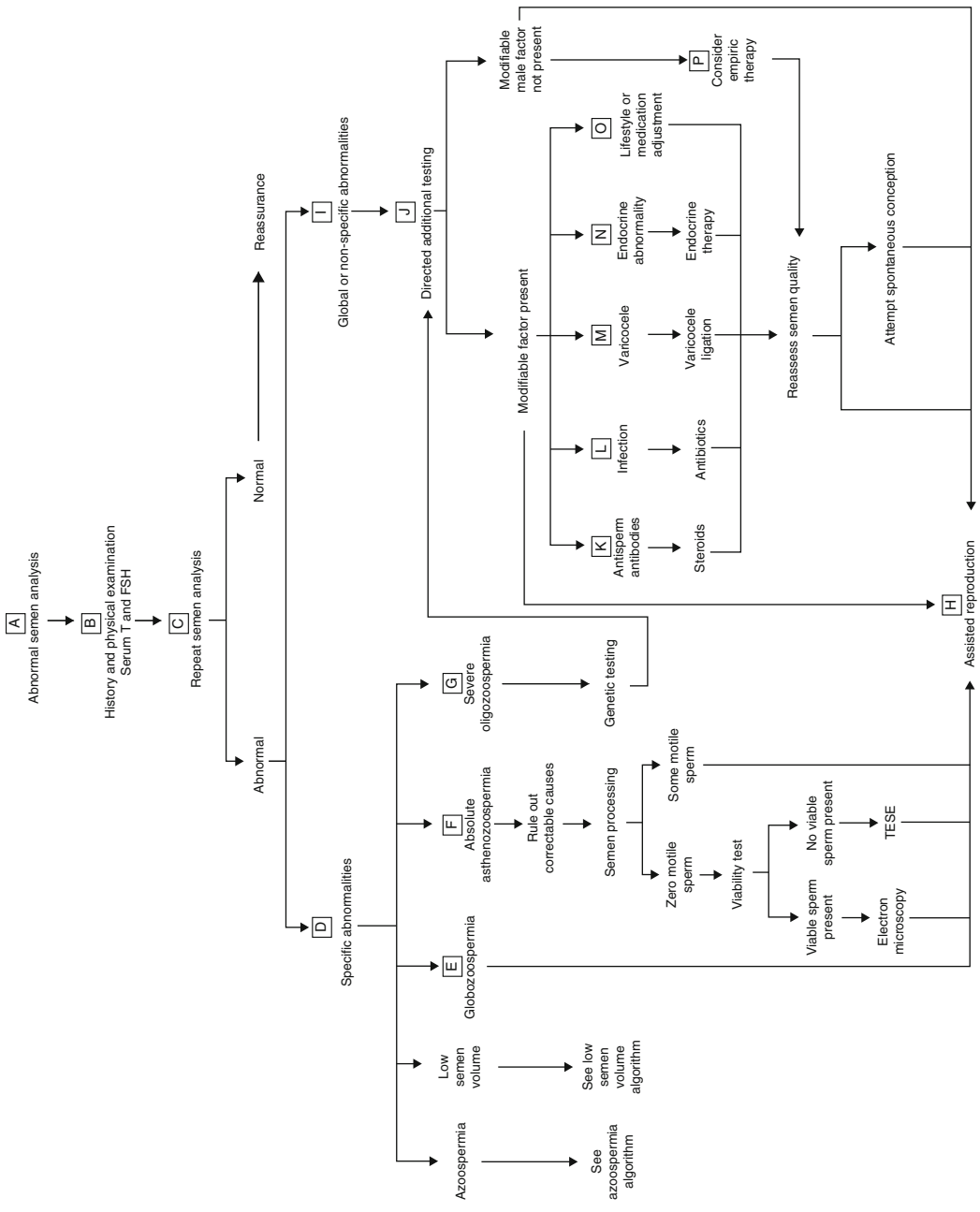
# Chapter 1
# Abnormal Semen Analysis

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Interpretation of semen analysis (SA) results is an important skill for any clinician who cares for men with subfertility or testicular dysfunction. Confirmed SA abnormalities indicate the presence of male factor infertility, which occurs in 40–60% of subfertile couples, and guides subsequent evaluation and management. Male factor infertility is important to identify because it may be amenable to medical or surgical therapy, and because it may be the presenting symptom of occult health-threatening conditions such as hypogonadism or testicular cancer. Moreover, some causes of severe male factor infertility such as Y chromosome microdeletions and chromosomal translocations are genetically transmissible and may threaten the health or fertility of the patient's potential offspring. Semen analysis should be performed according to standard protocol published by the World Health Organization (WHO). Each sample should be collected after an ejaculatory abstinence period of 2–5 days. Samples should be collected in wide-mouthed, sterile containers, maintained as close as possible to body temperature, and analyzed within 1 h. The semen sample is allowed to liquefy and is examined under wet mount light microscopy. The main parameters analyzed are ejaculate volume, pH, sperm concentration (sperm per mL), total sperm number (sperm per total ejaculate), sperm motility (% of sperm with any motility and % of sperm with forward progressive motility), and sperm morphology (% of morphologically normal sperm). Abnormalities of semen parameters are typically described using standard nomenclature (Table 1.1) based upon reference values published by the WHO (Table 1.2).

## (A)

In 1999 and 2010 the WHO published the only widely used, accepted reference limits for interpretation of the semen analysis (Table 1.2). It is important to understand that the WHO reference limits do not reflect "normal" or "average" values and do not have a validated relationship with subfertility. The 1999 reference limits were the result of expert consensus, while the 2010 reference limits were defined as the statistical 5th percentile value for each SA parameter derived from an international population of fertile men. The WHO reference limits should not be used as strict criteria to define the presence or absence of male factor subfertility, but rather should serve as a useful guide during the evaluation of each individual patient. Correctable male factors may be present in some men whose semen parameters are within the WHO 2010 normal reference range, and such men may benefit from treatment.

## (B)

The initial evaluation of men with an abnormal semen analysis should include a detailed medical history (Table 1.3), a directed physical examination (Table 1.4), and measurement of serum testosterone (T), and follicle stimulating hormone (FSH). The serum T and FSH levels may indicate the presence of medically important and treatable endocrine dysfunction. FSH is a crude but reasonable marker of the level of spermatogenesis. The higher the level the more likely spermatogenesis is impaired. FSH levels higher than 8 IU/L are concerning for primary testicular dysfunction.

## (C)

Significant intra-individual variation in semen parameters is common and at least two semen samples should be analyzed for each patient. It is preferable that the samples are collected over more than

1 cycle of spermatogenesis (2 months apart), particularly if systemic illness or gonadotoxin exposure has occurred. Analysis of a third semen sample may be informative if significant discrepancy exists between the two samples.

## (D)

Some semen analysis abnormalities indicate the possibility of specific underlying etiologies and warrant-specific diagnostic testing and clinical management. These abnormalities include azoospermia, low semen volume, globozoospermia, absolute asthenozoospermia, and severe oligozoospermia (sperm concentration <5 million per mL, isolated or in combination with other semen analysis abnormalities).

## (E)

Globozoospermia refers to the very rare (<1 in 1,000 semen analyses) condition in which all sperm are round-headed due to absence of the acrosome. Globozoospermia is easily diagnosed by an experienced andrologist during standard light microscopic evaluation, and may be confirmed if desired by sperm electron microscopy. Fertilization and biological paternity are only possible by intracytoplasmic sperm injection (ICSI), which is thought to be safe but is only effective in some cases.

## (F)

Absolute asthenozoospermia refers to the rare condition (1 in 5,000 semen analyses) in which 100% of sperm in freshly ejaculated semen are immotile. This finding indicates one of the three possible underlying conditions: live sperm that are immotile because of ultrastructural flagellar defects, live sperm with unexplained (idiopathic) immotility, and dead sperm (necrozoospermia). The group of patients with ultrastructural defects includes patients with immotile-cilia syndrome and Kartagener's syndrome (immotile cilia syndrome plus situs inversus). The first step in the evaluation of absolute asthenozoospermia is to search for correctable factors such as genital tract infections, latex condom exposure, prolonged abstinence from ejaculation, and more rare conditions such as partial ejaculatory duct obstruction. If no correctable factors are identified, or if the condition persists after the correctable factor is addressed, the next step is semen processing by centrifugation, density gradient sperm selection, sperm incubation, and extensive sperm search. Identification of any motile sperm obviates the need for further specific testing, and the patient should be evaluated as is suggested for patients with "global or non-specific abnormalities." Sperm viability testing is indicated if motile sperm cannot be identified after semen processing. The commonly used sperm viability assays test sperm membrane function and include the eosin-nigrosin test (live sperm exclude the red eosin dye whereas dead sperm do not) and the hypo-osmotic swelling test (live sperm swell when placed in hypo-osmotic solution whereas dead sperm do not). Sperm electron microscopy may be considered (if available) to evaluate for sperm ultrastructural defects when viable sperm are found. In such cases, reproduction is possible by ICSI, which may be optimized by use of sperm selection techniques to identify viable sperm for oocyte microinjection. Genetic counseling is recommended to inform the patient of the risks of absolute asthenozoospermia, infertility, and associated health problems (such as recurrent pulmonary infections due to immotile cilia syndrome) in potential offspring. If no viable sperm are

found, the diagnosis is necrozoospermia. This condition may result from sperm death that occurs in the testis or epididymis due to infection, oxidative stress, hyperthermia, gonadotoxin exposure, systemic illnesses, or sometimes advancing age. In some cases viable sperm may be surgically retrieved from the testis and used for ICSI.

## (G)

Y chromosome microdeletion testing and peripheral blood karyotyping are indicated in all men with severe oligozoospermia (i.e., sperm concentrations <5 million/mL). Genetic defects are detectable in 10–15% of such patients and are important to identify because of their prognostic relevance, possible overall health implications, and in some cases transmissibility to conceived offspring. The most commonly detected abnormalities in this population are Y chromosome microdeletions involving a region of the Y chromosome known as the AZFc (azoospermic factor C) region. Complete or partial AZFc deletions have variable effects on sperm production that range from severe oligozoospermia to azoospermia, and have no other known clinical sequelae. Diagnosis enables genetic counseling prior to assisted reproduction, which is critical because Y chromosome microdeletions are transmitted to all male offspring who inherit the abnormal Y chromosome. Other genetic abnormalities detected in severely oligozoospermic men include sex chromosome abnormalities (particularly classic or mosaic Klinefelter's syndrome, 47,XXY or 46,XY/47,XXY) and autosomal anomalies such as translocations and inversions. Patients with any karyotype abnormalities should undergo genetic counseling prior to assisted reproduction. Pre-implantation genetic diagnosis is indicated in some cases to reduce the risk of aneuploidy in offspring.

## (H)

Assisted reproduction may be the only option for achievement of biological paternity for men with severe deficits in semen quality. ICSI is an advanced reproductive technology during which a single sperm is directly injected into a single oocyte under microscopic guidance. ICSI is an alternative to conventional in vitro fertilization, during which thousands of sperm are placed in the oocyte's microenvironment (together in a Petri dish) but must fertilize the oocyte without assistance. The development of ICSI in the early 1990s revolutionized the treatment of severe male factor infertility by enabling successful reproduction with surgically retrieved testicular sperm or functionally impaired ejaculated sperm.

## (I)

The majority of subfertile men exhibit mild to moderate abnormalities in one or more semen analysis parameters and can generally be evaluated with the same diagnostic algorithm. This includes patients with isolated or combined oligozoospermia, teratozoospermia, and asthenozoopsermia (absolute asthenozoospermia and globozoospermia, however, require more specific evaluation, see "E" and "F").

## (J)

Additional testing is helpful in some cases of poor semen quality and should be directed by the initial evaluation (history, physical examination, serum T, serum FSH, semen analysis). The goal of additional diagnostic testing is to identify or confirm the presence of treatable male factors that are not readily apparent from the initial evaluation. Indications for commonly used tests and methods for interpretation of their results are presented in Table 1.5.

## (K)

Testing for anti-sperm antibodies should be considered when isolated asthenozoospermia or sperm agglutination (microscopic attachment of motile sperm to one another) are present on semen analysis. Anti-sperm antibodies can inhibit sperm transit through the female reproductive system and may interfere with sperm survival and/or oocyte fertilization. The most clinically important assays examine semen for the presence of antibodies bound to sperm. The clinical significance of serum anti-sperm antibodies in the male is less clear. Some experts advocate treatment of anti-sperm antibodies with systemic corticosteroids. Described protocols include cycled treatment with 40–80 mg of daily methylprednisolone on menstrual cycle days 1–10, and continuous treatment with 2–3 mg of daily dexamethasone for 9–13 weeks. However, this approach has not been prospectively validated and patients must be warned about the rare but serious side effect of aseptic bone necrosis. Other experts advocate treatment of affected subfertile couples with ICSI, which is not significantly affected by anti-sperm antibodies.

## (L)

Infections of the male genital tract may have significant adverse effects on semen quality or sperm function. Although the value of antimicrobial testing in asymptomatic subfertile men is controversial and not supported by robust evidence, many experts advocate treating any positive cultures that are detected. The goals of therapy are to resolve any symptoms of infection that are present, to ameliorate the theoretical adverse effects of infection on semen quality and sperm function, and to avoid transmission of infection to the female partner.

## (M)

Varicocele refers to the presence of abnormally dilated spermatic cord veins and is the most common correctable cause of male subfertility, found in 35–40% of cases. A large body of evidence that includes several meta-analyses and randomized controlled prospective trials has shown that varicocele has a negative impact on male fertility, and that varicocele treatment improves both semen quality and pregnancy outcomes. Nonetheless, considerable controversy persists about the value of varicocele treatment due to significant methodological flaws in most of the existing literature. The American Urological Association and the American Society for Reproductive Medicine advocate varicocele treatment in men with palpable varicoceles, impaired semen quality, and documented subfertility, who have a female partner with normal fertility or correctable infertility. The best treatment modality

is microsurgical varicocelectomy, which has lower recurrence and complication rates and yields greater improvements in semen quality than radiographic embolization or non-microsurgical surgical ligation.

## (N)

Treatable endocrine abnormalities are the cause of only a small percentage of male subfertility cases. In most cases, treatment of the endocrine abnormality yields significant improvements in semen quality and often enables unassisted conception. Hypogonadotropic hypogonadism may be treated with gonadotropin replacement therapy. Deficiences in LH can be corrected by administration of human chorionic gonadotropin (hCG) injections (1,000–3,000 IU IM or subcutaneously three times per week). FSH deficiency is treated with injectable recombinant FSH (100–150 U three times per week). Treatment is typically highly effective but often requires prolonged gonadotropin replacement. Prolactin secreting pituitary tumors may be treated medically (Carbegoline 0.125–1.0 mg twice weekly) or surgically. Finally, although endocrine therapy is largely ineffective for primary testicular failure, patients with abnormally low (<10) serum testoserone:estradiol ratios may benefit from treatment with an aromatase inhibitor (anastrazole 1 mg daily, testalactone 100–200 mg daily, or letrazole 2.5 mg daily).

## (O)

High dietary intake of fruits, vegetables, and whole grains has been recently linked to improve sperm function; and high intake of meat and potatoes may be associated with higher sperm concentrations. Chronic heavy alcohol use can impair the hypothalamic-pituitary axis, and acute alcohol ingestion directly interferes with sperm morphology. Moderate or social alcohol ingestion, however, is not associated with male subfertility. Cigarette smoking and marijuana smoking have been consistently associated with low sperm concentration, low motility, and poor morphology. Chronic scrotal heat exposure, most commonly including frequent use of hot tubs or saunas, impairs testicular function. Medications that may adversely affect semen quality are listed in Table 1.6.

## (P)

Empiric therapy for male subfertility is advocated by some experts when no modifiable male factors are present. Although such treatments are supported only by limited evidence, semen quality and reproductive outcomes may improve significantly in appropriately selected patients. Antioxidant therapy and estrogen receptor modulation are the two most commonly utilized strategies. Oral antioxidants for which at least one study has demonstrated a benefit include coenzyme Q, vitamins C and E, carnitine, glutathione, N-acetylcysteine, and selenium. Clomiphene citrate (CC) is the most commonly used estrogen receptor modulator, which is used to drive testicular function by decreasing negative feedback exerted by estradiol at the pituitary, thereby increasing gonadotropin production. Due to its mechanism of action, CC is thought to work best in patients with low to normal serum LH levels.

**Table 1.1** Semen analysis nomenclature

| Term | Definition |
|---|---|
| Azoospermia | Clinical state in which sperm are not detectable by microscopic analysis of the pellet derived from centrifugation of a semen sample |
| Oligozoospermia | Clinical state in which the sperm concentration or total number of sperm are below the lower reference limits published by the World Health Organization (WHO) |
| Asthenozoospermia | Clinical state in which the percentage of sperm with any motility or the percentage of sperm with forward progressive motility are below the lower reference limits published by the WHO |
| Teratozoospermia | Clinical state in which the percentage of sperm with normal morphology are below the lower reference limits published by the WHO or below reference ranges for strict (Kruger) criteria |
| Oligoasthenoteratozoospermia | Clinical state in which oligozoospermia, asthenozoospermia, and teratozoospermia are simultaneously present |
| Necrozoospermia | Clinical state in which 100% of ejaculated sperm are immotile and proven to be dead by viability testing |
| Globozoospermia | Rare variant of teratozoospermia characterized by round-headed spermatozoa that lack acrosomes and are therefore incapable of fertilization without intracytoplasmic sperm injection |
| Leukocytospermia | Descriptive term indicating the presence of an abnormal concentration (>1 million/mL) of white blood cells in semen |

**Table 1.2** Semen analysis reference limits published by the World Health Organization in 1999 and 2010

| Semen analysis parameter | WHO 1999 reference limits | WHO 2010 reference limits |
|---|---|---|
| Semen volume | ≥2.0 mL | ≥1.5 mL |
| pH | ≥7.2 | ≥7.2 |
| Total sperm number | $\geq 40 \times 10^6$ per ejaculate | $\geq 39 \times 10^6$ per ejaculate |
| Sperm concentration | $\geq 20 \times 10^6$ per mL | $\geq 15 \times 10^6$ per mL |
| Total motility | N/A | ≥40% |
| Progressive motility | ≥50% | ≥32% |
| Sperm morphology | ≥14% normal forms by WHO criteria | ≥4% normal forms by strict criteria |

**Table 1.3** Important points to elicit in the medical history of patients with an abnormal semen analysis

| Medical history | Interpretation |
|---|---|
| Developmental history, including testicular descent | Delayed puberty suggests congenital problems with androgen synthesis or action |
| | Cryptorchidism is often associated with poor sperm quality |
| Fertility history | Prior spontaneous conception suggests acquired (secondary) infertility |
| Partner's reproductive history and status | Guides treatment selection |
| Current or prior medical conditions, including sexually transmitted infections (STI) | Malignancy and hypogonadism may be associated with poor semen quality |
| | STIs may cause semen analysis abnormalities |
| Current or prior gonadotoxin exposure | May impair sperm production |
| Prior scrotal events including epididymitis, orchitis, and testicular torsion | Prior scrotal events may be associated with poor semen quality |
| Prior scrotal, inguinal, retroperitoneal, or pelvic surgery | Raises the possibility of iatrogenic injury to the male excurrent ductal system that could impair sperm transit or delivery |
| Medication use, including anabolic steroids | Current or prior immunosuppressive or antineoplastic therapy (chemotherapy, radiation therapy, hormonal therapy) may cause poor semen quality |
| | Anabolic steroid use is a common cause of poor semen quality |
| Symptoms of hypogonadism | Profound hypogonadism may be associated with poor sperm production |

**Table 1.4** Important points during physical examination of patients with an abnormal semen analysis

| Physical Examination | Interpretation |
|---|---|
| Body habitus and hair distribution | Tall stature and long limbs and/or a gynecoid habitus suggest hypogonadism during development (long limbs result from delayed epiphyseal closure) |
| | Decreased body and/or facial hair suggest hypogonadism |
| | Very large muscles may suggest anabolic steroid use |
| Visual fields | Visual field deficits may be associated with pituitary tumors and hypogonadotropic hypogonadism |
| Gynecomastia | Gynecomastia indicates imbalance in the testosterone:estradiol ratio, which may occur in Klinefelter syndrome, Leydig cell tumors, germ cell tumors, and obesity |
| Spermatic cord examination | Varicoceles are the most commonly identified abnormality in subfertile men and are diagnosed on physical examination |
| Epididymal examination | Epididymal tenderness suggests epididymitis |
| | Epididymal induration suggests obstructive lesion |
| Testicular examination | Small or soft testicles suggest testicular dysfunction |
| | Testicular tumors are more common in sub-fertile men, may cause subfertility, and are detected by physical examination |
| Penile examination | Urethral discharge suggests STI |

**Table 1.5** Explanation of adjunctive tests useful in the evaluation of abnormal semen analysis

| Test type | Specific test | Indications | Interpretation |
|---|---|---|---|
| Blood work | Luteinizing hormone (LH) | Abnormal serum testosterone | Distinguishes between central and testicular hypogonadism |
| | Follicle stimulating hormone (FSH) | Abnormality in sperm concentration | Indicator of spermatogenesis potential of the testes |
| | Estradiol | Abnormal serum testosterone<br>Gynecomastia | Possible benefit of aromatase inhibitor therapy if testosterone:estradiol ratio <10 |
| Microbiological testing | Semen culture, urethral swab, or culture of expressed prostatic secretions | Signs or symptoms of urethritis, prostatitis, or epididymitis<br>Controversial role in asymptomatic patients | Treatment indicated for symptomatic patients with positive cultures |
| Semen testing | Semen peroxidase stain | >1 million round cells per mL on semen analysis | Distinguishes leukocytes in semen from immature germ cells |
| | Anti-sperm antibody testing | Isolated asthenozoospermia<br>Sperm agglutination | Treatment may be indicated for sperm-bound antibodies detected in semen |
| Imaging | Scrotal ultrasonography | Indeterminate or difficult physical examination | May detect varicoceles or testicular pathology |
| | Transrectal ultrasonography | Low semen volume | Detects ejaculatory duct obstruction |
| Urinalysis | Post-orgasm urinalysis | Low semen volume | May detect retrograde ejaculation |

**Table 1.6** Medications associated with male infertility

| Medication | Mechanism |
|---|---|
| Anabolic steroids | Direct gonadotoxicity, endocrine effects |
| Anti-androgens | Endocrine effects, sexual dysfunction |
| Anti-psychotics | Endocrine effects (hyperprolactinemia) |
| Cimetidine | Direct gonadotoxicity, endocrine effects |
| Erythromycin, gentamycin, neomycin | Direct gonadotoxicity |
| Chemotherapeutic agents | Direct gonadotoxicity, endocrine effects |
| Finasteride | Endocrine effects (the 1 mg dose of finasteride used for male pattern baldness has not been shown to affect fertility) |
| Nitrofurantoin | Direct gonadotoxicity, endocrine effects |
| Selective serotonin reuptake inhibitors | Direct gonadotoxicity, endocrine effects |
| Spironolactone | Endocrine effects |
| Testosterone | Direct gonadotoxicity, endocrine effects |

## Suggested Reading

Male Infertility Best Practice Policy Committee of the American Urological Association, Practice Committee of the American Society for Reproductive Medicine. Report on optimal evaluation of the infertile male. Fertil Steril. 2006;86(5 Suppl 1):S202–9.

Male Infertility Best Practice Policy Committee of the American Urological Association, Practice Committee of the American Society for Reproductive Medicine. Report on varicocele and infertility. Fertil Steril. 2004;82 Suppl 1:S142–5.

Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Male Reproduction and Urology. The management of infertility due to obstructive azoospermia. Fertil Steril. 2008;90(5 Suppl):S121–4.

Showell MG, Brown J, Yazdani A, Stankiewicz MT, Hart RJ. Anti-oxidants for male subfertility. Cochrane Database Syst Rev. 2011;1(1):CD007411.

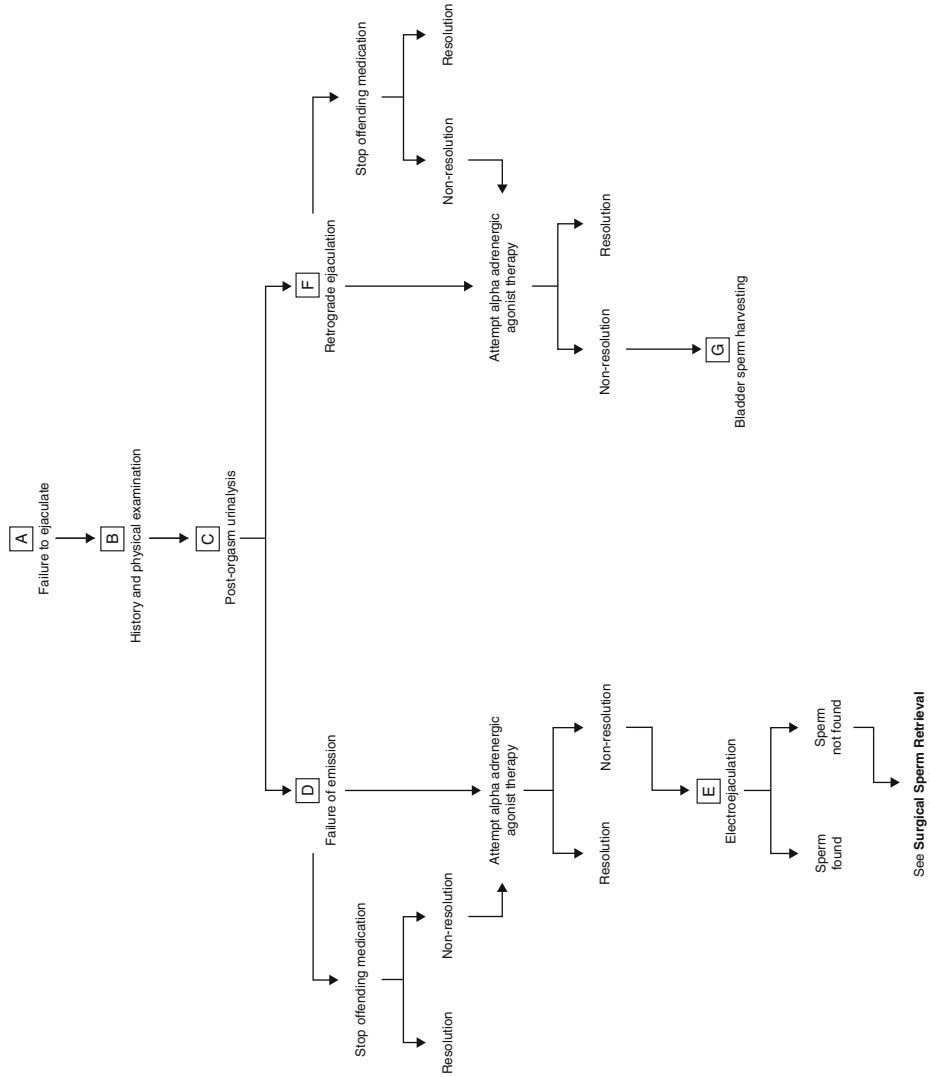
Sokol RZ. Endocrinology of male infertility: evaluation and treatment. Semin Reprod Med. 2009;27(2):149–58.

Stahl PJ, Stember DS, Schlegel PN. Interpretation of the semen analysis and initial male factor management. Clin Obstet Gynecol. 2011;54(4):656–65.

World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: World Health Organization; 2010.

Zini A, Boman JM. Varicocele: red flag or red herring? Semin Reprod Med. 2009;27(2):171–8.

# Chapter 2
# Anejaculation

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## (A)

Anejaculation refers to the failure to ejaculate, a situation in which the patient is usually capable of achieving an orgasm. The absence of orgasm is anorgasmia, and difficulty achieving orgasm is termed delayed orgasm (see *Delayed Orgasm* algorithm). The lack of seminal fluid at the time of orgasm may be due to either retrograde ejaculation (RE) or failure of emission (FOE). RE in which seminal fluid travels into the urinary bladder is due to incompetence of the bladder neck. Thus, with orgasm, little or no seminal fluid is ejaculated. FOE, on the other hand, is the complete absence of seminal fluid deposition into the prostatic urethra. This results from greater impairment of the neural innervation of the seminal vesicles and the prostate. The causes can be subdivided into neurogenic (i.e., autonomic neuropathy or retroperitoneal surgery), medication (alpha-adrenergic blockers), and anatomic (bladder neck surgery or congenital) categories.

## (B)

The history should first focus on why the patient is bothered by the anejaculation. It is important to distinguish whether the absence of antegrade ejaculate is relevant for fertility reasons or whether the patient is psychologically distressed. Men with psychological impairment typically report feeling less masculine or sexual due to the absence of antegrade ejaculation. The next step is identifying factors that may be causative for the anejaculation (Table 2.1). A thorough medical, surgical, sexual, and medication history is essential. Focusing on the onset of the failure to ejaculate and its relationship to medication commencement or dates of surgery may help in the diagnosis and thus the prognosis.

## (C)

The essential test is a post-orgasm urinalysis (also known as a retrograde semen analysis) (Table 2.2). The presence of semen and/or sperm in the first urine collection after orgasm defines retrograde ejaculation, whereas its absence defines FOE. It is important that the patient have little urine in his bladder at the time of masturbation so that only a small volume of urine needs to be centrifuged to find a semen pellet. The patient should not be encouraged to overhydrate himself for this test.

## (D)

FOE results from severe damage to the sympathetic pathways to the bladder neck and ejaculatory apparatus or may be due to the use of the alpha-blocker tamsulosin, which has been shown to cause FOE rather than RE. Discontinuing tamsulosin reverses the problem, provided there are no other causative factors. Alpha-adrenergic agonist medications (Table 2.3) have been shown to promote antegrade ejaculation and may be attempted, but are unlikely to be effective in the setting of neurogenic FOE.

## (E)

In cases when alpha agonist therapy does not work, the patient will require electroejaculation (EEJ) if sperm are required for fertility reasons. This procedure has been used in for animal husbandry for decades but has been FDA approved in humans for fewer than 20 years. For this procedure, other than in spinal cord injured men, general anesthesia is required. The anesthesiologist should be reminded to avoid paralyzing agents. A catheter is used to drain the bladder of urine and then fill it with sperm-friendly transport medium. The use of betadine and standard surgical lubrication is to be avoided since they are toxic to sperm. The urethra should instead be lubricated with mineral oil and/or transport medium. The patient is then placed in the lateral decubitus or lithotomy position. Prior to EEJ, digital rectal examination and anoscopy should be performed to assess for anal lesions and the integrity of the anal mucosa. The probe is then placed in the rectum (Fig. 2.1) with the transmitting plates placed firmly against the anterior wall of the rectum. The probe is chosen based on patient age and anatomy (Fig. 2.2). Low level electrostimulation is applied and the current, voltage, and temperature of the probe are monitored continuously. Typical parameters are 20–25 V and 0.4 A. The probe temperature should be maintained below 37°. We stimulate in cycles of five stimulations, monitoring erectile rigidity continuously as this is a surrogate for the effectiveness of neural stimulation. Over 90% of men ejaculate with this procedure. The ejaculate is collected in a sterile container. After ejaculation, the patient is returned to the supine position after repeat anoscopy. The bladder is re-catheterized to collect the retrograde specimen. The retrograde specimen is placed in a separate sterile container. The specimens can be assessed immediately, using a table microscope in the operating room, for sperm presence and motility. The most common adverse event after EEJ is a urine infection and for this reason we treat the patient with short course of postoperative antibiotics.

## (F)

Retrograde ejaculation can result from partial impairment of the sympathetic nerve fibers to the bladder neck/ejaculatory apparatus, certain medications, or surgery that renders the bladder neck incompetent (Table 2.1). The diagnosis is made on a post-orgasm urinalysis. If the patient has medication-induced RE, withdrawal of the medication is likely to resolve the problem. Neurogenic RE, most commonly secondary to diabetes mellitus or retroperitoneal lymph node dissection for testis cancer, is very amenable to the use of alpha-adrenergic agonist therapy (Table 2.3), with conversion to antegrade ejaculation in more than 50% of such patients. Unfortunately, the patients who have had prior bladder neck surgery cannot be converted to antegrade ejaculation.

## (G)

In men for whom alpha agonist therapy does not work and for whom fertility is a concern, bladder sperm harvesting can be performed. In this process, a man urinates after orgasm and the sperm are retrieved from the urine and used for intrauterine insemination. Due to the acidic pH of urine (which is highly toxic to sperm), the urine needs to be alkalinized prior to harvesting. We usually use oral sodium bicarbonate or potassium citrate for this purpose. Some authorities also attempt to sterilize the urine also through the use of pre-procedure antibiotics.

**Table 2.1** Causes of anejaculation

| | |
|---|---|
| Neurogenic | Diabetes |
| | Multiple sclerosis |
| | Retroperitoneal surgery |
| | Thoracic spinal surgery |
| | Any cause of autonomic neuropathy |
| Medication | Alpha-adrenergic blockers[a] |
| | Anti-psychotics[b] |
| Anatomic | Bladder neck Y-V plasty |
| | Transurethral resection of the prostate |
| | Transurethral bladder neck incision |
| | Pelvic radiation |
| | Radical pelvic surgery |
| | Proximal urethral stricture |
| | Congenital abnormalities[c] |

[a]Tamsulosin, alfuzosin, silodosin, prazosin, doxasosin, terazosin
[b]Thioridazine, isocarboxazid, and phenelzine, fluphenazine, trifluoperazine, tranylcypromine
[c]Posterior urethral valves, utricular cysts, exstrophy

**Table 2.2** Patient instructions for post-orgasm urinalysis and bladder sperm harvesting

1. Select a sperm bank and make an appointment for the analysis. Tell them that you have retrograde ejaculation so they can tell you if they have any special instructions to follow before you come
2. Do not have sexual activity for 2 days, and ideally 4 days, before the appointment. This includes activity with a partner or self-stimulation
3. For 12 h before the appointment, do not drink more fluids than you normally would. If your urine is very watery, it is harder to extract the sperm
4. You will collect your semen at the sperm bank. If the sperm bank does not give you specific instructions on how to do this, follow these steps
   (a) Go to the bathroom and urinate to empty your bladder.
   (b) You will be given two cups for collection, labeled #1 and #2. You will be brought to a private room. You will stimulate to get sexually excited in order to ejaculate
   (c) You can stimulate yourself or your partner can stimulate you. Your hands should be clean and dry. Do not use saliva or lubricants to stimulate yourself. These will destroy the sperm
   (d) Hold collection cup #1 at the tip of your penis and collect any semen you have. Give this cup to the staff
   (e) Return to the waiting area for 10–15 min. Do not drink any fluid during this time
   (f) Go to the bathroom with the collection cup #2. Urinate into the cup. Give this cup to the staff

Retrograde ejaculation is when semen passes into the bladder instead of out through the penis during ejaculation. It occurs if the nerves and muscles that control ejaculation are damaged or removed. Despite this, it might be possible for you to have a child using your own sperm, by removing sperm from your urine. A sample of semen must be analyzed by a sperm bank, and the following instructions explain how to do this

**Table 2.3** Alpha-adrenergic medications used for the treatment of anejaculation

| **Agent** | **Dosing** |
|---|---|
| Pseudoephderine | 60 mg by mouth 4 times daily |
| Imipramine | 25–50 mg daily |
| Midodrine | 7.5–30 mg daily |

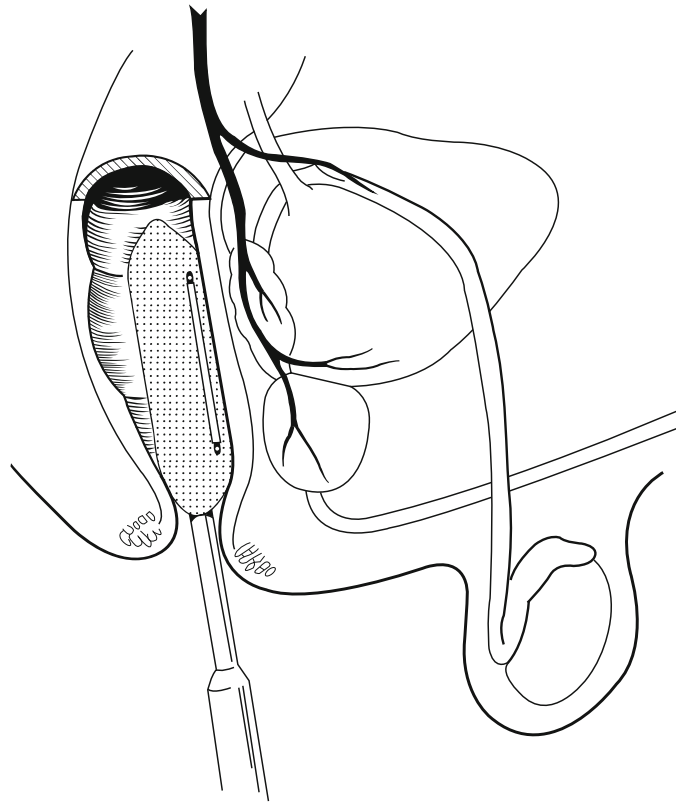


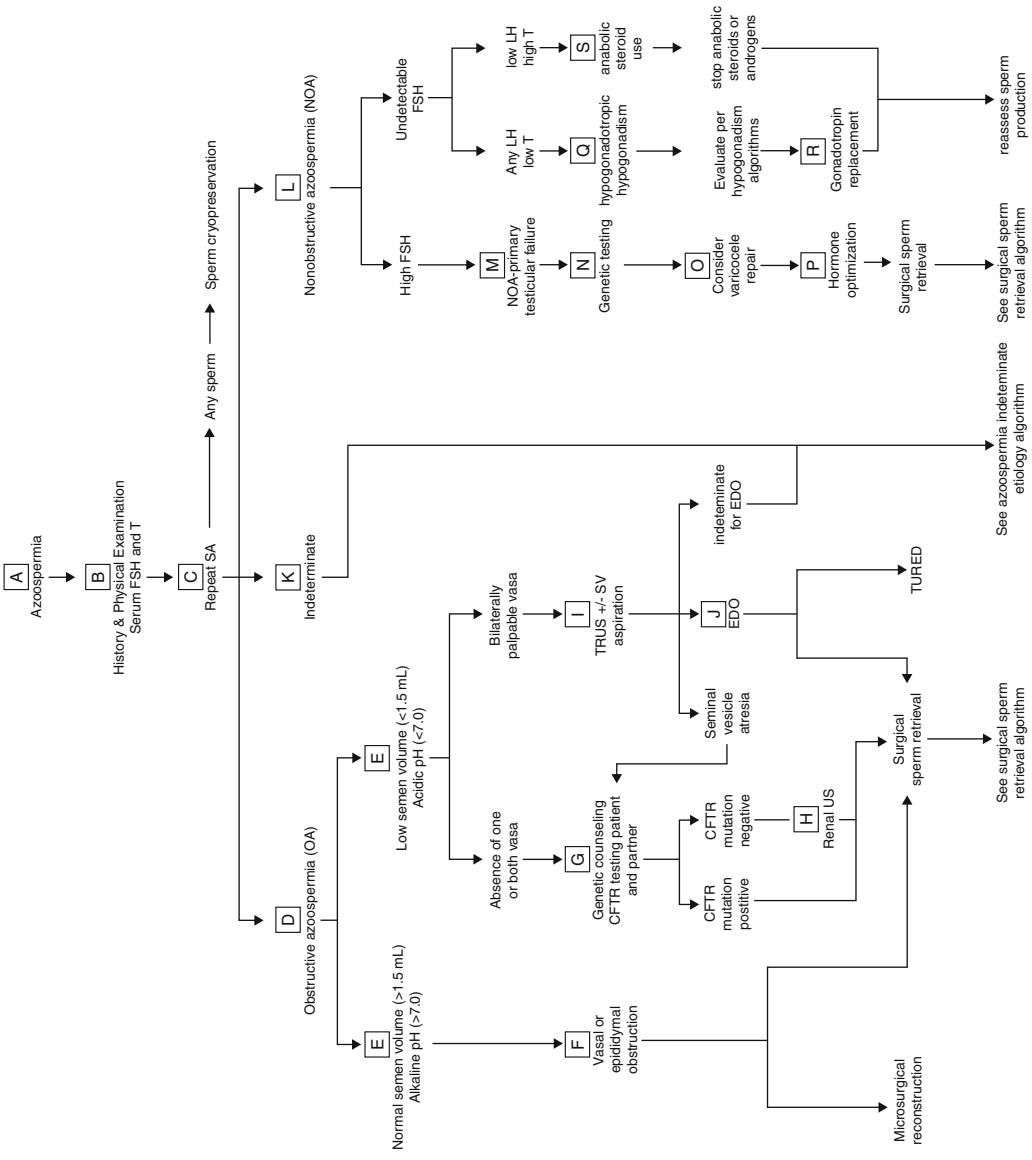
**Fig. 2.1** Electroejaculation probe placement


**Fig. 2.2** Rectal probe electroejaculator (Seager)

## Suggested Reading

Kamischke A, Nieschlag E. Update on medical treatment of ejaculatory disorders. Int J Androl. 2002;25(6):333–44.
Male Infertility Best Practice Policy Committee of the American Urological Association, and Practice Committee of the American Society for Reproductive Medicine. Report on optimal evaluation of the infertile male. Fertil Steril. 2006;86(5 Suppl 1):S202–9.
Meacham R. Management of psychogenic anejaculation. J Androl. 2003;24(2):170–1.
Ohl DA, Quallich SA, Sonksen J, Brackett NL, Lynne CM. Anejaculation: An electrifying approach. Semin Reprod Med. 2009;27(2):179–85.
Rowland D, McMahon CG, Abdo C, Chen J, Jannini E, Waldinger MD, et al. Disorders of orgasm and ejaculation in men. J Sex Med. 2010;7(4 Pt 2):1668–86.

# Chapter 3
# Azoospermia

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Azoospermia refers to the clinical finding that sperm are not detectable in the ejaculate after centrifugation and microscopic analysis of two semen samples. This condition affects approximately 1 % of the general male population and 15 % of subfertile men. Azoospermia is generally indicative of either complete bilateral obstruction of the male excurrent ductal system (obstructive azoospermia) or severely impaired sperm production (nonobstructive azoospermia). Fertility is only possible in affected men through medical or surgical intervention. The goals of the diagnostic evaluation are to identify underlying etiologies that are of medical or prognostic significance, to identify genetic abnormalities that may affect the patient's offspring, and to guide the selection of medical or surgical therapy. The differential diagnosis of azoospermia is listed in Table 3.1.

## (A)

The diagnosis of azoospermia requires the absence of sperm within the centrifuged pellets of two separate semen samples.

## (B)

The initial evaluation of azoospermia should include a detailed medical history (Table 3.2), a directed physical examination (Table 3.3), and measurement of serum testosterone (T), and follicle stimulating hormone (FSH). This simple initial evaluation is usually sufficient to distinguish between suspected obstructive (OA) and nonobstructive azoospermia (NOA). Elevated serum FSH (>8 IU/L) suggests NOA due to testicular failure, which may occur with normal or low serum T. Very low serum FSH suggests NOA due to hypogonadotropic hypogonadism, and usually coexists with T deficiency.

## (C)

Sperm are often intermittently present in the ejaculate of patients with severely impaired sperm production. Rare sperm detected upon repeat semen analysis in a patient who was previously azoospermic should be cryopreserved whenever possible. Ejaculated cryopreserved sperm may be used for assisted reproduction and obviate the need for surgical sperm retrieval. Intermittently azoospermic and severely oligozoospermic men (<5 million sperm/mL) should undergo the same diagnostic evaluation as azoospermic men prior to assisted conception. These men are at risk for transmissible genetic abnormalities that may affect their own health as well as that of any offspring and should undergo appropriately directed genetic testing.

## (D)

OA occurs when testicular sperm production is normal but the male excurrent ductal system is blocked anywhere between the testis and urethra. OA should be suspected when testicular volume is normal (>12 mL per testis) and serum FSH within normal limits (1.5–8 IU/L), as would be expected when sperm production is not impaired.

The working diagnosis of OA is further supported by suggestive factors in the medical history, such as prior inguinal surgery or prior known fertility, and by signs on physical examination, including

epididymal fullness, induration, or non-palpable vasa deferentia. However, it is important to note that testicular volume may be normal and serum FSH may be in the upper range of normal in some cases of NOA. This is often seen in patients with histological maturation arrest, a form of NOA in which germ cell development fails to progress.

## (E)

Approximately 70 % of ejaculated semen is derived from the seminal vesicles, which produce alkaline, fructose positive fluid that is delivered into the posterior urethra via the paired ejaculatory ducts along with a small volume (<5 % of total semen volume) of sperm-containing fluid from the testis. The remaining 20–30 % of the ejaculate comprises acidic fluid produced by the prostate, which does not pass through the ejaculatory ducts but rather enters the posterior urethra via many prostatic ducts. Knowledge of the fluid composition of ejaculated semen enables determination of the anatomic location of obstruction based upon the semen volume and pH. When the semen volume (<1.5 mL) and pH (>7.0) are normal, the alkaline high volume seminal vesicle component of the ejaculate must be present, and the obstruction must therefore be in the epididymis or vas deferens. Conversely, when the semen volume is low (<1.5 mL) and the pH is acidic (<7.0), fluid from the seminal vesicles is absent from the ejaculate. This implies that the seminal vesicles are either obstructed, as is the case in ejaculatory duct obstruction (EDO), or hypoplastic/absent, as is the case in congenital bilateral absence of the vas deferens (CBAVD).

## (F)

For the classic OA patient with vasal or epididymal obstruction, options include bypass of the obstruction (vasoepididymostomy or vasovasostomy) and sperm extraction for intracytoplasmic sperm injection (ICSI). Treatment decisions should be individualized to each couple based upon the number of desired children, the duration of obstruction (if known), the female partner's fertility status, and access to a skilled reconstructive microsurgeon. Microsurgical reconstruction is generally favored when the couple desires multiple children, the obstructed interval is short (<15 years) and the female partner is young (<37 years old) and does not have risk factors for infertility. Sperm retrieval with ICSI is favored when the obstructed interval is long (>15 years), the female partner is older (>37 years old), or the female partner has known or suspected infertility.

## (G)

Men with acidic, low semen volume semen, and absence of one or both vasa deferentia (congenital unilateral or bilateral absence of the vas deferens, CUAVD and CBAVD respectively) on physical examination should undergo genetic counseling and testing for mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which plays a central role in the embryological development of the seminal vesicles and vasa deferentia, and is critical for pulmonary and pancreatic function. More than 1,300 CFTR mutations have now been described that vary considerably in their effect on CFTR protein function. Approximately 1/25 North American Caucasians carries one mutated CFTR allele, but only patients with two mutated alleles are clinically affected. The phenotypic manifestations of disease in an individual patient depend on the severity of the paternal and maternal mutations that they have inherited, and range from overt cystic fibrosis (always associated with CBAVD) to isolated CBAVD with otherwise normal health. The prevalence of detectable CFTR

mutations in men with CBAVD is approximately 70 %, and is lower in men with CUAVD. CFTR mutation screening commonly includes testing for the 30–100 most prevalent point mutations and for a commonly encountered polymorphism known as the 5T allele that, when present, causes decreased production of functional CFTR protein. Negative CFTR mutation testing does not exclude the presence of less commonly detected mutations that are not included in standard mutational screening panels, which should be presumed to be present in all men with CBAVD who test negative for CFTR mutations. Therefore, CFTR testing should be performed in all female partners of men with CBAVD considering assisted reproduction. If the female is positive, genetic counseling and pre-implantation genetic diagnosis may be performed to select unaffected embryos for uterine transfer.

## (H)

Patients with CBAVD who test negative for CFTR mutations and all men with CUAVD should undergo renal ultrasonography to evaluate for potential associated renal anomalies or agenesis. The association of vasal agenesis and renal anomalies is due to the common embryological origin of the vas deferens and kidney from the mesonephric duct. Renal agenesis is found in 26 % of men with CUAVD and 11 % of men with CBAVD.

## (I)

In cases of low volume azoospermia when the vasa deferentia are palpable, EDO should be suspected. In such cases, transrectal ultrasonography (TRUS) is indicated. EDO is suggested by visualization of dilated seminal vesicles (>2 cm in anteroposterior diameter), dilated ejaculatory ducts, and/or the presence of midline prostatic cysts. Some experts advocate TRUS-guided needle aspiration of fluid from the seminal vesicles. Microscopic visualization of many sperm in the aspirated seminal fluid supports the diagnosis.

## (J)

EDO may be treated by either transurethral resection of the ejaculatory ducts (TURED) or ICSI using surgically retrieved sperm. Some experts advocate transurethral laser incision of the ejaculatory ducts as an alternative to TURED. A midline prostatic cyst may cause compressive EDO and may be treatable by unroofing of the cyst alone. Treatment decisions should be individualized to each couple based upon their reproductive goals, the anatomic location of the obstruction relative to the bladder neck, the location of the obstruction within the ejaculatory ducts, and the fertility status of the female partner.

## (K)

The initial evaluation may be indeterminate for the etiology of azoospermia in rare cases in which the history, physical examination, and serum FSH are discrepant. Typical patients have mildly low testicular volumes and/or serum FSH levels in the high normal to slightly elevated range. In such cases, exploratory surgery can be both diagnostic and therapeutic and is recommended. Genetic testing to exclude Karyotype abnormalities and Y chromosome microdeletions should be considered (see “N”).

## (L)

NOA occurs when sperm production is either absent or so impaired that sperm fail to reach the ejaculate. NOA should be suspected when serum FSH is undetectable or elevated (>8 IU/L) and the testicles are small (<12 mL per testis) and/or soft in consistency. However, in some cases of NOA, testicular volume and FSH may be close to normal. The working diagnosis of NOA is further supported by suggestive factors in the medical history, such as a history of bilateral cryptorchidism, lifelong hypogonadism, gonadotoxin exposure, and by signs on physical examination, including flat epididymities or a gynecoid body habitus.

## (M)

Primary testicular failure accounts for the vast majority of NOA and is usually characterized by an elevated serum FSH level. It is sometimes referred to as hypergonadotropic hypogonadism. This condition has many separate etiologies including Klinefelter syndrome (KS), gonadotoxin exposure, cryptorchidism, systemic illness, prior orchitis, testicular tumors, and Y chromosome microdeletions. Testosterone (T) deficiency may also be present.

## (N)

Genetic testing is recommended in all men with NOA. The goals of testing are to identify genetic abnormalities that are medically important, that affect the prognosis for surgical sperm retrieval, or that may affect the health of offspring conceived by assisted reproduction. Karyotype abnormalities are found in 10–15 % of men with NOA, with Klinefelter syndrome (usually 47,XXY) being the most commonly detected abnormality. Men with KS have an excellent prognosis for surgical sperm retrieval, but are at risk for testosterone deficiency and osteoporosis, and may be at increased risk for breast cancer, diabetes, impairments in cognitive processing, and auto-immune disorders. Patients with translocations on inversions identified during Karyotyping should be sent for genetic counseling, as some of these lesions increase the risk for sperm and embryo aneuploidy. Pre-implantation genetic diagnosis should be considered.

Y chromosome microdeletions are found in approximately 10 % of men with NOA. Men with AZFa and AZFb deletions have been shown to have zero chance of sperm retrieval and are not candidates for sperm retrieval surgery and should be counseled towards use of donor sperm or adoption. On the contrary, men with AZFc deletions are excellent candidates for surgical sperm retrieval with retrieval rates of 70 % being consistently reported. Any sons conceived using sperm from a patient with a Y chromosome microdeletion will inherit the abnormal Y chromosome and the infertile phenotype.

## (O)

Repair of grade II or III varicoceles may be beneficial in men with NOA. Rare sperm return to the ejaculate after varicocele repair in approximately one third of cases. This may obviate the need for surgical sperm retrieval. However, in this scenario varicocele repair is unlikely to improve sperm production sufficiently to enable reproduction by natural contraception or with intrauterine insemination.

## (P)

Some experts advocate hormone optimization of men with NOA and coexistent testosterone (T) deficiency prior to surgical sperm retrieval, though this approach is controversial and has not been prospectively validated. The selective estrogen receptor modulator clomiphene citrate may be used to inhibit the negative feedback of estradiol (E) on the hypothalamus and pituitary, thereby increasing pituitary gonadotropin production and potentially driving up intratesticular Leydig and Sertoli cell function. Given its mechanism of action, clomiphene citrate is most likely to be effective when the serum LH level is low or normal. The result is increased intratesticular and peripheral T concentrations, which may be beneficial for sperm production. The typical starting dose is 25–50 mg every other day. Aromatase inhibitors provide an alternative method for hormone optimization. These drugs inhibit the peripheral conversion of T to estradiol, which similarly suppresses the central negative feedback of estradiol and stimulates pituitary production of FSH and LH. Anastrazole (1 mg daily), testalactone (100–200 mg daily), and letrazole (2.5 mg daily) are the most commonly used agents. Optimal candidates for aromatase inhibition are those with Klinefelter syndrome and patients who have serum T:E ratios <10.

## (Q)

Secondary testicular failure (hypogonadotropic hypogonadism) is indicated by very low or undetectable serum FSH, LH, and T. In this condition, both sperm production and testosterone synthesis are insufficient due to inadequate stimulation of the testes by gonadotropins. This rare cause of NOA may be congenital (Kallman's syndrome), acquired (pituitary tumor, surgery or infarct), or idiopathic. Genetic tests for hypogonadotropic hypogonadism are available but are not yet part of routine clinical practice. One important caveat to note is that laboratory evidence of hypogonadotropic hypogonadism in a man who is particularly muscular and androgenized should raise suspicion for anabolic steroid use with an anabolic compound that is not detectable on standard testosterone assays (nandrolone or stanozolol).

## (R)

Sperm production may be restored in hypogonadotropic men by gonadotropin replacement therapy. The first step in gonadotropin replacement therapy is typically stimulation of testicular production of testosterone with human chorionic gonadotropin (hCG) (1,000–3,000 IU 3 times per week), which has a biologically equivalent action to LH on the testis. After 6 months, FSH replacement therapy may be added by administration of recombinant human FSH (100–150 IU 3 times weekly). Sperm production is reassessed every 3 months thereafter. Optimization of sperm production may take up to 2 years.

## (S)

Anabolic steroid abuse should be suspected when the serum T level is elevated with very low levels of serum LH and FSH. In such cases, the patient's sperm production should be serially assessed after cessation of exogenous androgen supplementation. In some cases, recovery may be expedited by gonadotropin replacement therapy.

**Table 3.1** Differential diagnosis of azoospermia

| |
|---|
| Hypogonadotropic hypogonadism (Kallman's syndrome, idiopathic) |
| Pituitary pathology including tumors, infiltrative diseases, and infarction |
| Systemic malignancies |
| Anabolic steroid abuse |
| Klinefelter syndrome |
| Y chromosome microdeletions |
| Testicular cancer |
| Leydig cell or Sertoli cell tumors |
| Idiopathic testicular failure |
| Prior testicular vascular or traumatic insults |
| Prior orchitis |
| Gonadotoxin exposure (chemotherapy, radiation, medications) |
| Congenital bilateral absence of the vas deferens (mutations in the cystic fibrosis transmembrane receptor gene) |
| Congenital, iatrogenic, or post-inflammatory epididymal obstruction |
| Iatrogenic vasal obstruction |
| Ejaculatory duct obstruction |

**Table 3.2** Important points to elicit in the medical history of azoospermic men.

| Medical history | Interpretation |
|---|---|
| Developmental history, including testicular descent | Delayed/absent puberty suggests impaired androgen synthesis or activity and NOA |
| | Cryptorchidism suggests NOA |
| Fertility history | Prior spontaneous conception suggests acquired OA |
| Partner's reproductive history and status | Guides treatment selection, particularly in cases of OA |
| Current or prior medical conditions, including sexually transmitted infections (STI) | Malignancy and hypogonadism may be associated with NOA |
| | STIs may cause epididymal obstruction |
| Current or prior gonadotoxin exposure | Suggests NOA |
| Prior scrotal events including epididymitis, orchitis, and testicular torsion | Prior epididymitis suggests epididymal obstruction |
| | Prior orchitis, torsion, or injury may be associated with NOA |
| Prior scrotal, inguinal, retroperitoneal, or pelvic surgery | Raises the possibility of iatrogenic OA |
| Medication use, including anabolic steroids | Current or prior immunosuppressive or antineoplastic therapy suggest NOA |
| | Anabolic steroid use is a common reversible cause of NOA |
| Symptoms of hypogonadism | Hypogonadism may be associated with NOA |
| Recurrent pulmonary infections | May be associated with inherited causes of OA including CFTR mutations, Young's syndrome, and Kartagener's syndrome |
| Gastrointestinal dysfunction | May be associated with or mutations in the CFTR gene and OA |
| Family medical and fertility history | May suggest genetic causes of azoospermia |

**Table 3.3** Important points to elicit in the physical examination of azoospermic men

| Physical examination | Interpretation |
|---|---|
| Body habitus and hair distribution | Tall stature and long limbs suggest congenital hypogonadal states |
| | Decreased body and/or facial hair suggest hypogonadism and NOA |
| | Very large muscles may suggest anabolic steroid use |
| Visual fields | Visual field deficits associated with pituitary tumors |
| Sense of smell | Smell deficits (hyposmia, anosmia) associated with Kallman's syndrome |
| Gynecomastia | Gynecomastia indicates imbalance in the testosterone:estradiol ratio, may occur in Klinefelter syndrome, Leydig cell tumors, germ cell tumors, or idiopathic NOA |
| Lower abdominal, inguinal, or scrotal surgical scars | Indicate prior surgery and may be associated with OA |
| Spermatic cord examination | Absence of one or both vasa deferentia suggest OA due to CFTR mutations or aberrant embryological development of the Wolffian duct structures |
| | Varicoceles may be associated with NOA, but are also commonly found in men with OA |
| Epididymal examination | Fullness or induration of the epididymis suggest OA |
| | An empty, flat epididymis is consistent with NOA |
| Testicular examination | Very small (< 5 mL) and hard testicles suggest Klinefelter syndrome |
| | Small (<12 mL) and soft testicles suggest NOA |
| | Normal testicular size and consistency suggest OA |

## Suggested Reading

Carpi A, Sabanegh E, Mechanick J. Controversies in the management of non-obstructive azoospermia. Fertil Steril. 2009;91(4):963–70.

Goldstein M, Tanrikut C. Microsurgical management of male infertility. Nat Clin Pract Urol. 2006;3(7):381–9.

Jarow JP, Espeland MA, Lipshultz LI. Evaluation of the azoospermic patient. J Urol. 1989;142(1):62–5.

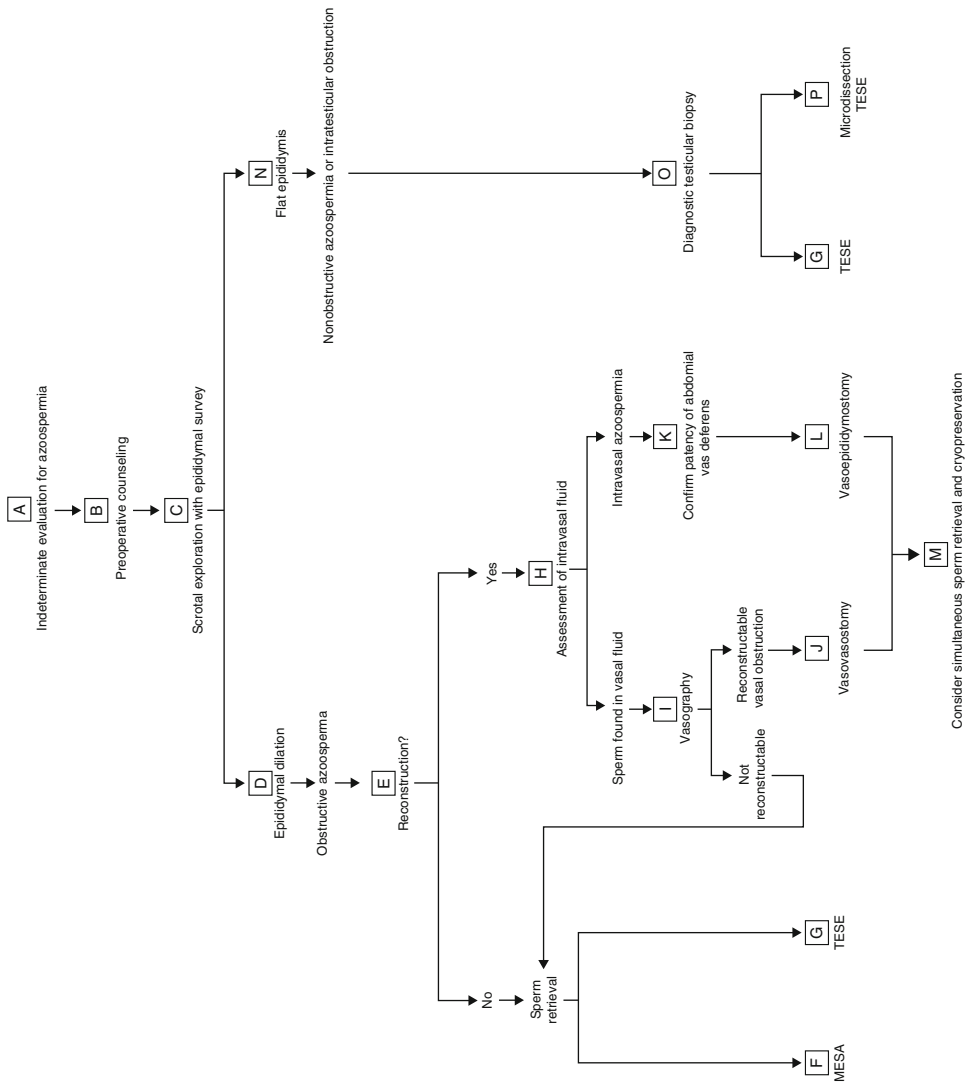
Male Infertility Best Practice Policy Committee of the American Urological Association, and Practice Committee of the American Society for Reproductive Medicine. Report on evaluation of the azoospermic male. Fertil Steril. 2006;86(5 Suppl 1):S210–5.

Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Male Reproduction and Urology. The management of infertility due to obstructive azoospermia. Fertil Steril. 2008;90(5 Suppl):S121–4.

Schlegel PN. Non-obstructive azoospermia: a revolutionary surgical approach and results. Semin Reprod Med. 2009;27(2):165–70.

Stahl PJ, Schlegel PN. Genetic evaluation of the azoospermic or severely oligozoospermic male. Curr Opin Obstet Gynecol. 2012;24(4):221–8.

# Chapter 4
# Azoospermia: Indeterminate Etiology

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## (A)

In some cases it may be difficult to distinguish between obstructive and nonobstructive azoospermia based on the initial clinical evaluation. These indeterminate cases include patients with borderline clinical findings such as mild serum FSH elevations and mildly low testicular volumes, as well as patients in which discrepancies exist between the clinical history, physical examination, and serum hormone evaluation. The classic approach in these cases has been performance of diagnostic testicular biopsy for direct histologic assessment of spermatogenesis and remains the gold standard for diagnostic evaluation. However, most experts (including the authors) advocate directly proceeding to exploratory surgery without performance of a separate testicular biopsy. The advantage of this approach is that it is both diagnostic and therapeutic, allowing for management of the patient with indeterminate azoospermia with a single procedure.

## (B)

Preoperative counseling is critically important prior to exploratory surgery for azoospermia. It is incumbent upon the surgeon to enter the operating room with a clear understanding of the patient's objectives. Each possible intraoperative scenario should be reviewed with the patient and discussed prior to exploratory surgery so that the surgeon can react to the intraoperative findings appropriately and according to the patient's wishes. In particular, the surgeon must know whether the patient prefers vasovasostomy and vasoepididymostomy to sperm retrieval for assisted reproduction. If sperm retrieval is preferred over reconstruction, the surgeon should understand the patient's preferred procedure for sperm retrieval.

## (C)

Scrotal exploration for indeterminate azoospermia should be performed by an experienced surgeon capable of both microsurgical vasovasostomy and vasoepididymostomy. Bilateral vertical high scrotal incisions are preferred because they provide easy access to the vas deferens, testicle, and epididymis and may be extended towards the external inguinal ring if necessary for vasal exploration or mobilization. The testicle is delivered within the tunica vaginalis, which is then opened to expose the tunica albuginea of the testis and the epididymis. At this point the epididymis is palpated and inspected under the operating microscope. Focal or pan-epididymal dilation suggests obstruction. A non-dilated flat epididymis suggests nonobstructive azoospermia, but in rare cases may result from obstruction of the rete testis or efferent ducts.

## (D)

Epididymal dilation is easily appreciated by using an operating microscope. The finding of epididymal dilation strongly suggests obstruction. Pan-epididymal dilation suggests that obstruction is present on the abdominal side of the epididymis (vasal or ejaculatory duct obstruction), whereas focal epididymal dilation suggests epididymal obstruction. Vasal obstructions may occur in the scrotal, inguinal, or retroperitoneal portions of the vas deferens and may be post-inflammatory,

iatrogenic (i.e., surgical ligation of the vas deferens during herniorraphy), or congenital. Epididymal obstruction may be post-inflammatory or iatrogenic, but is often idiopathic without any clear predisposing history.

## (E)

Once the diagnosis of obstructive azoospermia is established, the surgeon must proceed with either reconstruction or surgical sperm retrieval. This decision is based upon the preoperative counseling discussion.

## (F)

Microsurgical epididymal sperm aspiration (MESA) is the gold standard for sperm retrieval techniques in men with obstructive azoospermia. MESA is performed under ×10 magnification. Dilated tubules filled with translucent fluid are selected for aspiration. The targeted tubules are exposed by careful incision of the epididymal sheath and gentle microdissection, after which they are sharply punctured. Epididymal fluid is collected and transferred into collection containers containing sperm transport fluid. Immediate microscopic analysis of the collected fluid enables determination of specimen quality and adequacy. Multiple areas of one or both epididymities may be sampled. MESA typically yields millions of motile sperm, enabling cryopreservation of multiple vials of sperm in nearly all cases.

## (G)

Testicular sperm extraction (TESE) refers to open surgical biopsy of seminiferous tubular tissue and is the most commonly described and performed procedure for sperm retrieval. TESE is effective in virtually all cases of obstructive azoospermia. Reported sperm retrieval rates in nonobstructive azoospermia range from 41 to 58%. The tunica albuginea of the testis is incised in an avascular area that may be easily selected with microsurgical magnification. Seminiferous tubular tissue is extruded through the incision by gently squeezing the testis and sharply excised. Ideally, the excised tissue is immediately mechanically disrupted within sperm transport solution to liberate sperm into solution. Immediate microscopic analysis of the testicular tissue suspension determines specimen quality and adequacy. Multiple specimens may be taken from the same site by repeatedly squeezing the testis to extrude tissue, or from different sites by incising the testis in other locations.

## (H)

Intraoperative assessment of intravasal fluid is indicated in all patients prior to vasal-epididymal reconstruction. Intravasal fluid is collected and placed on a glass slide after transection of the vas deferens. It is important to consider the site of suspected obstruction based on the patient's clinical history and the intraoperative findings prior to vasal transection so as to enable a tension-free anastomosis. If epididymal obstruction is suspected, the vas deferens should be divided near the epididymis;

whereas transection should be in the inguinal region if inguinal vasal obstruction is suspected. The microscopic and macroscopic appearance of the intravasal fluid dictates the reconstructive procedure to be performed. Thick white fluid devoid of sperm indicates that the obstruction is on the testicular side of the vasal transection (usually epididymal obstruction that requires vasoepididymostomy), whereas thinner fluid that contains any sperm with even short tails indicates vasal (or ejaculatory duct) obstruction and is usually amenable to vasovasostomy. Vasovasostomy is also indicated in rare cases of intravasal azoospermia when copious, thin, and watery intravasal fluid is present.

## (I)

Vasography is indicated when sperm are present in the intravasal fluid prior to reconstructive surgery. Vasography should be performed with a Foley catheter on gentle traction in the bladder after inflation of the balloon with air, which prevents retrograde flow of contrast and also marks the location of the bladder neck. The vasa are cannulated simultaneously with 24 gauge angiocatheters for injection of 0.5 mL of water-soluble contrast into the abdominal side of each vas deferens. Fluoroscopy or plain radiographs are obtained and analyzed to determine the location of the obstruction and whether or not it is amenable to surgical correction. Of note, the finding of unilateral or bilateral blind ending vasa indicates atypical vasal agenesis and should prompt cystic fibrosis transmembrane conductance regulator (CFTR) genetic testing prior to attempts at reproduction.

## (J)

The majority of vasal obstruction (excluding vasectomy) discovered during exploratory surgery for azoospermia is the result of iatrogenic vasal injury during prior surgery, most commonly inguinal hernia repair. Reconstruction by vasovasostomy may be possible when the site of obstruction is inguinal or retroperitoneal in close proximity to the internal inguinal ring. Extensive dissection and vasal mobilization may be required to create a tension-free anastomosis. Vasovasostomy is best performed microsurgically in multiple layers.

## (K)

Confirmation of abdominal vasal patency is important when intravasal azoospermia is present and vasoepididymostomy is being considered. In this case formal vasography is unnecessary. The simplest approach is gentle injection of 1 mL of saline into the abdominal end of the vas deferens with a 24-guage angiocatheter attached to a small insulin syringe. The absence of resistance to injection is enough to confirm vasal patency. If there is any doubt, diluted indigo carmine (not methylene blue, which is toxic to sperm) may be injected and the bladder catheterized. The finding of blue urine confirms patency.

## (L)

Epididymal obstruction may be bypassed by vasoepididymostomy. Vasoepididymostomy is technically challenging and should be performed by an experienced microsurgeon. The end to side and intussuscepted techniques for anastomosis are the most commonly utilized. Reported patency and pregnancy rates are approximately 80 and 30% in most series, respectively.

## (M)

Simultaneous cryopreservation of sperm retrieved from the vas deferens or epididymis should be considered for all patients undergoing reconstruction. This approach provides a safety net for the patient in the event of surgical failure.

## (N)

The finding of a flat epididymis upon microsurgical epididymal exploration suggests that sperm are not reaching the epididymis. This implies either poor sperm production (nonobstructive azoospermia) or intratesticular obstruction, such as may occur at the level of the rete testis.

## (O)

Diagnostic testicular biopsy is indicated when the epididymis is discovered to be flat and non-dilated during exploratory surgery for azoospermia. A formal biopsy should be preserved in an appropriate fixative (Bouin, Zenker, or buffered glutaraldehyde solution) and sent for formal histologic evaluation to definitively distinguish between obstructive and nonobstructive azoospermia. Testicular biopsy is informative for the patient, determines the need for genetic testing, and may guide selection of future sperm acquisition procedures. In addition, immediate microscopic evaluation of a wet mount slide prepared from extracted testicular tissue can be used to guide TESE. The absence of sperm from the wet prep slide indicates nonobstructive azoospermia and should prompt either multiple testicular biopsies or testicular microdissection.

## (P)

Microdissection testicular sperm extraction (mTESE) is a novel sperm retrieval technique that utilizes high power optical magnification to optimize the efficiency, safety, and efficacy of TESE. The tunica albuginea of the testis is widely opened and the seminiferous tubular tissue is examined at ×30 magnification. Deep layers of the testis may be accessed by careful dissection. Larger, opaque tubules that are more likely to contain sperm are visually identified and selectively extracted. Microdissection TESE has been shown to be superior to conventional TESE in most comparative studies. Reported sperm retrieval rates range from 33 to 77%.

## Suggested Reading

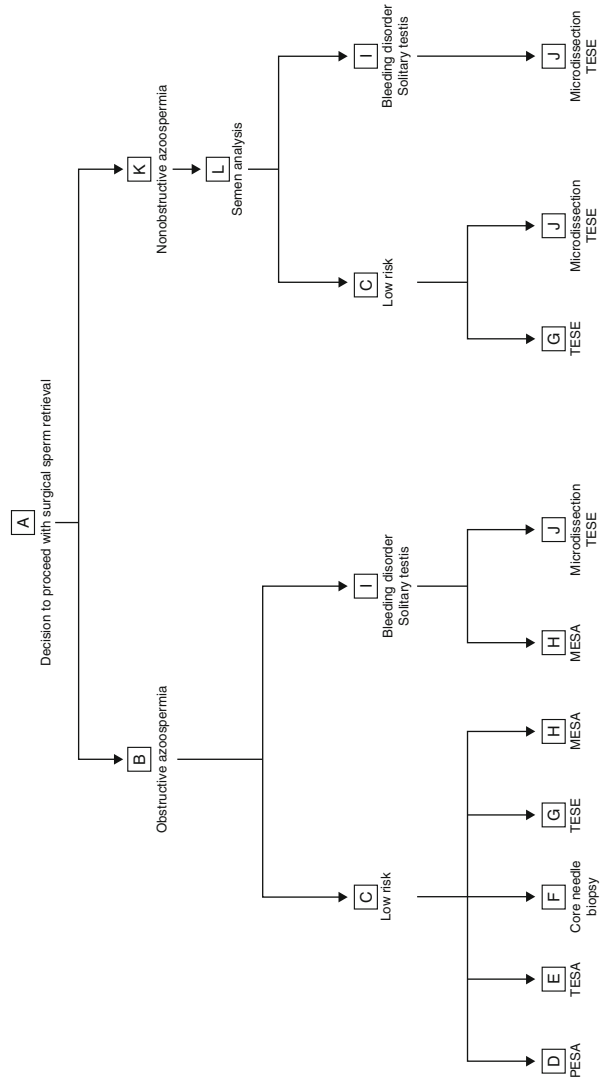
Hsiao W, Goldstein M, Rosoff JS, et al. Nomograms to predict patency after microsurgical vasectomy reversal. J Urol. 2012;187(2):607–12.

Practice Committee of the American Society for Reproductive Medicine. Sperm retrieval for obstructive azoospermia. Fertil Steril. 2006;86(5 Suppl 1):S115–20.

Schlegel PN. Non-obstructive azoospermia: a revolutionary surgical approach and results. Semin Reprod Med. 2009;27(2):165–70.

Tanrikut C, Goldstein M. Obstructive azoospermia: a microsurgical success story. Semin Reprod Med. 2009;27(2):159–64.

# Chapter 5
# Azoospermia: Surgical Sperm Retrieval




J.P. Mulhall et al., *Clinical Care Pathways in Andrology*, DOI 10.1007/978-1-4614-6693-2_5,

Recent advances in techniques for surgical sperm retrieval and the advent of intracytoplasmic sperm injection (ICSI) allow for biological paternity in azoospermic men for whom the only available treatments a mere 20 years ago were use of donor sperm or adoption. Many procedures are available with which sperm may be retrieved from the epididymis and testis. These procedures vary significantly in efficacy, invasiveness, requirement for technical expertise, and indication. Informed procedure selection and proper technical performance are critical for achievement of optimal reproductive outcomes. The least traumatic method that yields sufficient high quality sperm to meet the couple's immediate and future reproductive goals should be selected. Communication with the reproductive endocrinologist is critically important for delivery of optimal care to the couple. Sperm retrieval may either be performed electively with cryopreservation of retrieved sperm for ICSI to be performed at a later date (frozen approach), or it can be coordinated so that fresh sperm are available immediately following oocyte retrieval (fresh approach). The frozen approach has significant logistical advantages and is the preferred approach by most experts for men with obstructive azoospermia, in whom an abundance of sperm are anticipated to be retrieved. Expert consensus varies when the patient has nonobstructive azoospermia. The literature suggests that fertilization rates and pregnancy outcomes of ICSI cycles using cryopreserved sperm are at least equivalent to outcomes in cycles using fresh sperm. However, there is a theoretical chance that no viable sperm will survive the freeze-thaw process, especially when very few sperm are retrieved.

## (A)

The decision to proceed with surgical sperm retrieval should only occur after appropriate evaluation of the azoospermic man and appropriate counseling of the affected couple about the process and risks of surgical sperm retrieval and assisted reproduction with ICSI. In particular, discussion should focus on the risks of ovarian hyperstimulation, possible complications of oocyte and sperm retrieval, the risk of multiple gestations, and the small but statistically significant increase in risk of congenital anomalies in offspring conceived with ICSI compared to children conceived naturally. Patients should also be counseled that there is a risk of transmitting their infertility (and potential disease) to offspring, which emphasizes the importance of preconception genetic testing in select azoospermic men.

## (B)

The clinical characteristics of obstructive azoospermia include prior fertility, known iatrogenic obstruction (vasectomy), normal testicular volume and consistency, epididymal fullness or induration, and normal serum levels of follicle stimulating hormone (FSH). Sperm production is quantitatively and qualitatively normal and distributed widely throughout both testes. Millions of typically motile sperm accumulate in the epididymis and often even in the testes. The wide distribution and abundance of sperm throughout the epididymities and testes make patients with obstructive azoospermia excellent candidates for all available surgical sperm retrieval procedures, though the quality and yield of retrieved sperm varies significantly based on the retrieval technique that is used. No differences in ICSI outcomes are apparent in the literature based on the anatomic sperm source (testis vs. epididymis). Therefore procedure selection is based largely on patient and physician preference.

## (C)

All patients without bleeding disorders and two testes may be considered low risk for significant complications from surgical sperm retrieval. Low risk patients with obstructive azoospermia are candidates for percutaneous epididymal sperm aspiration (PESA), testicular sperm aspiration (TESA), percutaneous testicular core needle biopsy, testicular sperm extraction (TESE), and microsurgical epididymal sperm aspiration (MESA). Low risk patients with nonobstructive azoospermia are candidates for TESE and microdissection TESE.

## (D)

PESA is an office-based procedure performed under local anesthesia that is effective in approximately 80–100 % of men with obstructive azoospermia. After administration of a spermatic cord block with local anesthetic, the epididymis is stabilized between the surgeon's thumb and forefinger. Epididymal fluid is aspirated into the tubing of a butterfly needle that is inserted through the skin into the head of the epididymis. The aspirated epididymal fluid is then flushed with a small amount of sperm transport fluid into a sterile collection container. A droplet of the collected fluid should be immediately examined with a light microscope to determine specimen adequacy and quality. If necessary, multiple or bilateral punctures may be performed. PESA only rarely yields sufficient sperm for cryopreservation and usually therefore necessitates repeat retrieval procedures for each attempted ICSI cycle.

## (E)

TESA is widely considered to be the least technically demanding procedure for surgical sperm retrieval. TESA is a quick, safe, and effective procedure that can be performed in the office under spermatic cord block local anesthesia. Techniques vary based on the size of the needle used, with procedures utilizing 21–23 gauge needles generally referred to as "fine needle aspiration (FNA)" and procedures using 14–20 gauge needles referred to as "large needle aspiration (LNA)." Reported sperm retrieval rates with FNA and LNA in patients with obstructive azoospermia are 52–100 % and 98–100 %, respectively. The testis is manually stabilized within the taut scrotal skin and a straight or butterfly needle is inserted through the relatively avascular anteromedial or anterolateral surfaces of the testicular lower pole. The needle is directed towards the contralateral upper pole while gently aspirating, and may be manipulated without fully removing it to sample multiple areas of the testis through the same puncture in the tunica albuginea. It is important to maintain negative pressure until the needle has been completely withdrawn. The aspirated testicular tissue and fluid is then flushed with a small volume of sperm transport fluid into a sterile container. A droplet of the collected fluid should be immediately examined with a light microscope to determine specimen adequacy and quality. If necessary, multiple or bilateral punctures may be performed. Similar to PESA, TESA only rarely yields sufficient sperm for cryopreservation and usually therefore necessitates repeat retrieval procedures for each attempted ICSI cycle.

## (F)

Testicular core needle biopsy is a simple, office-based percutaneous technique for sperm retrieval that may be performed under spermatic cord block local anesthesia. Core needle biopsy differs from TESA in that large, undisturbed fragments of testicular tissue sufficient for diagnostic histological assessment of sperm production may be retrieved. Reported sperm retrieval rates in men with obstructive azoospermia range from 82 to 100 %.

The testis is manually stabilized as above. After a small puncture wound is made in the skin under local anesthesia, a 14–16 gauge spring loaded biopsy needle with a short (1 cm) automatic excursion is fired either through the anteromedial or anterolateral surface of the testicular lower pole towards the upper pole or through the lower pole aimed at the upper pole. The needle is withdrawn and the trapped testicular tissue fragment is deposited in sterile collection container prefilled with sperm transport solution. The specimen should be mechanically disrupted to liberate sperm from the seminiferous tubules, after which a drop of the sperm containing fluid should be examined microscopically to determine specimen adequacy and quality. Multiple core needle biopsies may be obtained through the same entry points in the skin and testis.

## (G)

TESE refers to open surgical biopsy of seminiferous tubular tissue, and is the most commonly described and performed procedure for sperm retrieval. TESE is effective in virtually all cases of obstructive azoospermia. Reported sperm retrieval rates in nonobstructive azoospermia range from 41 to 58 %. TESE may be performed in the office or operating room under local, regional, or general anesthesia. The testis is surgically exposed by either fashioning a small window in the tunica vaginalis, or by widely incising the tunica vaginalis and delivering the testis into the surgical field. The tunica albuginea of the testis is then incised in an avascular area that may be easily selected with minimal surgical magnification. Seminiferous tubular tissue is extruded through the incision by gently squeezing the testis and sharply excised. Ideally, the excised tissue is immediately mechanically disrupted while bathed in sperm transport solution to liberate sperm into solution. Immediate microscopic analysis of the testicular tissue suspension determines specimen quality and adequacy. Multiple specimens may be taken from the same site by repeatedly squeezing the testis to extrude tissue, or from different sites by incising the testis in other locations.

## (H)

MESA is the gold standard for sperm retrieval techniques in men with obstructive azoospermia. MESA is performed under optical magnification provided by an operating microscope and may be performed under general, regional, or local anesthesia. The epididymis is surgically exposed and inspected at 10–15-fold magnification to select dilated tubules filled with translucent fluid for aspiration. The targeted tubules are exposed by careful incision of the epididymal sheath and gentle microdissection, after which they are sharply punctured. Epididymal fluid is collected using a fine angiocatheter and small syringe and transferred into collection containers containing sperm transport medium. Immediate microscopic analysis of the collected fluid enables determination of specimen quality and adequacy. Multiple areas of one or both epididymities may be sampled. MESA typically yields millions of motile sperm, enabling cryopreservation of multiple vials of sperm in nearly all cases.

## (I)

Patients with bleeding disorders or a solitary testis are at increased risk for testicular complications, which may include testicular loss or postoperative testicular failure requiring androgen replacement therapy. In such patients all possible care should be taken to minimize testicular trauma and the risk of postoperative bleeding. Sperm retrieval is best accomplished by open microsurgical sperm retrieval using optical magnification. The use of the operating microscope enables visualization and precise control of the small blood vessels that supply the epididymis and testis. Both MESA and microdissection TESE are safe and effective options when performed by an experienced microsurgeon.

## (J)

Microdissection TESE is a novel sperm retrieval technique that utilizes high power optical magnification to optimize the efficiency, safety, and efficacy of TESE. Microdissection TESE is effective in nearly all cases of obstructive azoospermia and has been shown to be superior to conventional TESE in most comparative studies of patients with nonobstructive azoospermia, for whom this technique was specifically developed.

Reported sperm retrieval rates range from 33 to 77 %. Nonetheless, microdissection TESE is expensive, time-consuming, and requires specific microsurgical training. Microdissection TESE is performed in an operating room under general or regional anesthesia. The testis is delivered into the surgical field and mobilized from its attachments after wide incision of the tunica vaginalis. The tunica albuginea is bivalved by either a near circumferential incision at the testicular equator or a longitudinal incision in the anterior surface of the testis. Blood vessel-preserving microdissection of the testicular parenchyma under ×30 power enables a visual search for larger, more opaque seminiferous tubules that are selectively excised once they are identified. The small volume of excised tissue is carefully mechanically disrupted within sperm transport solution to liberate sperm into the fluid, which is then microscopically analyzed. The procedure is continued until adequate sperm are identified or the entire volume of both testicles has been microdissected, which may take several hours.

## (K)

The clinical characteristics of nonobstructive azoospermia include the absence of prior fertility, known gonadotoxin exposure, known endocrine or testicular dysfunction (Klinefelter syndrome), decreased testicular volume with soft consistency, flat epididymitis, and elevated serum FSH. Sperm production is so severely impaired that sperm are not produced in sufficient quantities to be detectable in the ejaculate (or are not produced at all). When testicular sperm are present, they are typically heterogeneously distributed throughout one or both testes (termed patchy spermatogenesis) and are often identifiable only by utilization of extensive search or sampling techniques. In these patients, TESE and microdissection TESE are the recommended options for sperm acquisition.

## (L)

It is always prudent to confirm azoospermia by obtaining at least two semen analyses. Azoospermia may only be diagnosed after semen centrifugation and microscopic analysis of the resuspended semen pellet. Because many men with very poor sperm production oscillate unpredictably between azoospermia

and severe oligozoospermia, many experts recommend obtaining a semen analysis on the day of planned sperm retrieval. Often rare sperm are present in the ejaculate, obviating the need either for invasive sperm retrieval (if using a fresh approach) or thawing the cryopreserved sperm (if a frozen approach has been used).

## Suggested Reading

Carpi A, Sabanegh E, Mechanick J. Controversies in the management of nonobstructive azoospermia. Fertil Steril. 2009;91(4):963–70.

Goldstein M, Tanrikut C. Microsurgical management of male infertility. Nat Clin Pract Urol. 2006;3(7):381–91.

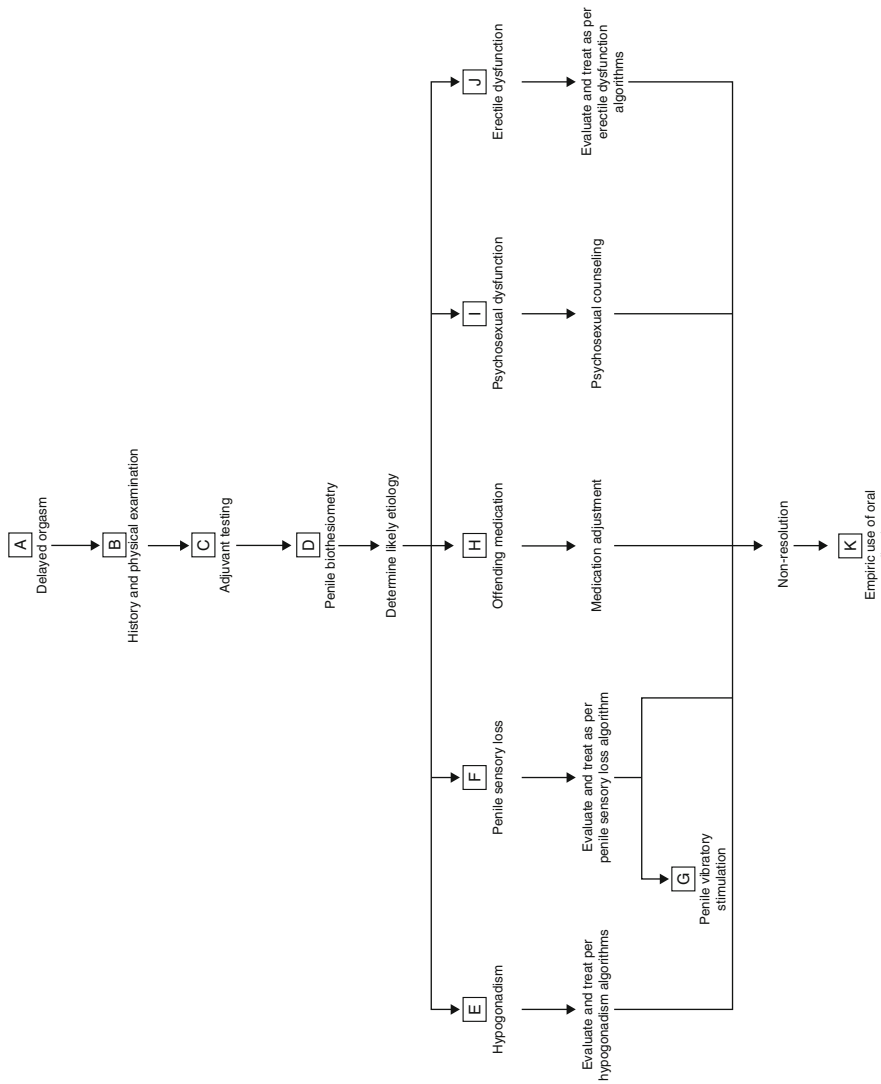
Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Male Reproduction and Urology. The management of infertility due to obstructive azoospermia. Fertil Steril. 2008; 90(5 Suppl):S121–4.

Schlegel PN. Non-obstructive azoospermia: a revolutionary surgical approach and results. Semin Reprod Med. 2009;27(2):165–70.

Stahl PJ, Stember DS, Goldstein M. Contemporary management of male infertility. Annu Rev Med. 2012;63:525–40.

Wald M, Makhlouf AA, Niederberger CS. Therapeutic testis biopsy for sperm retrieval. Curr Opin Urol. 2007;17(6): 431–8.

# Chapter 6
# Delayed Orgasm

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## (A)

While a firm definition exists for premature ejaculation (PE), such does not exist for delayed orgasm, also known as retarded orgasm/ejaculation and inhibited orgasm/ejaculation. Complete failure to achieve orgasm is known as anorgasmia, while complete inability to ejaculate is known as anejaculation (see *Anejeculation* algorithm). Delayed orgasm is one of the most poorly understood and pharmacologically recalcitrant sexual dysfunctions. A reasonable definition is "the persistent or recurrent difficulty, delay in, or absence of attaining orgasm after sufficient sexual stimulation, which causes personal distress." There is no specific time frame, and as is the case with PE, time frame cannot be the sole factor defining the condition. As with PE, the condition can be lifelong (primary) or acquired (secondary). It may be global, that is, occurring in all sexual scenarios or situational, occurring only in specific sexual scenarios (e.g., with partner but not masturbation, or with one partner but not another). The most robust study addressing this condition (US National Health and Social Life Survey) cites an incidence of "inability to achieve orgasm" of 8 %, although this clearly under-represents the incidence of "difficulty achieving orgasm." Delayed orgasm has been associated with significant reduction in health-related quality of life as well as self-esteem, anxiety, and depression and has been linked to reduced sexual satisfaction and relationship dissatisfaction and discord.

## (B)

In history taking, the first point is to ensure that the patient understands the difference between ejaculation and orgasm. Patients are usually not used to thinking of these entities are separate phenomena. Asking about "fluid coming out of the tip of the penis" vs. the "climactic pleasure experienced during sexual activity" will go a long way towards simplifying the diagnosis and management. Men can easily have anejaculation and still be perfectly orgasmic. However, men who say they ejaculate and have no orgasm usually have a psychological sexual problem. Asking whether the patient has the complete inability to achieve or has difficulty (delay) in achieving orgasm is important. The next step in history taking is defining whether the condition is life-long or acquired. In men with life-long anorgasmia, the cause is usually psychological in nature. Sensitive inquisition regarding gender dysphoria, sexual orientation, and prior sexual abuse are useful avenues to follow in men with life-long orgasm problems. In men with acquired difficulty achieving an orgasm, on the other hand, psychological causes play a major role but there is also often an organic etiology.

Five etiologies cause the vast majority of delayed orgasm cases. These are medication use, low serum testosterone, reduced penile sensation, chronic penile hyperstimulation, and psychogenic. In some cases, no identifiable cause can be found and these patients are diagnosed with idiopathic-delayed orgasm. A thorough medication history, especially for selective serotonin reuptake inhibitor (SSRI) type medications is essential. Asking about symptoms consistent with low testosterone (low energy, afternoon fatigue, loss of muscle, increased body fat, loss of body hair, decreased strength and endurance) is also an important step in defining an etiology. Inquiring about reduced penile sensation is important and focusing on conditions associated with neuropathy (see *Penile Sensory Loss* algorithm)—particularly diabetes mellitus—may be very helpful. Chronic vigorous stimulation of the penis, for example in a man who masturbates daily, will make it more difficult for oral, vaginal, or anal sex to bring him to orgasm, given the high level of friction generated by self-stimulation.

Another subgroup of this population includes men who practice idiosyncratic masturbation, that is, self-stimulating in a fashion that is not replicated by oral, vaginal, or anal sex (e.g., laying face down on sheets and rubbing themselves vigorously on the sheets). Psychological factors implicated in

delayed orgasm include first relationship after divorce or being widowed, fear of getting a partner pregnant, and relationship conflict or discord. A simple exploration in this regard is useful. In men with acquired delayed orgasm, defining the onset is useful. Another illuminating question is whether there is a difference in orgasm capability between partner-based sexual relations and self-stimulation. Reported difficulty with a partner, but less with masturbation, suggests a psychological issue or reduced penile sensitivity. Patients with reduced sensitivity may have less difficulty reaching orgasm with masturbation because their condition can be overcome by the more vigorous stimulation achievable during masturbation.

## (C)

There is accumulating evidence that low T (not necessarily in the hypogonadal range) is associated with an increased incidence of delayed orgasm. There are also some, albeit weak, data supporting a link between delayed orgasm and hypothyroidism and hyperprolactinemia. Testing for hypogonadism, thyroid dysfunction, and hyperprolactinemia therefore may be helpful in select patients.

## (D)

Penile vibration sensation testing known as biothesiometry is useful in most patients with delayed orgasm to exclude penile sensory impairment.

## (E)

Anecdotal evidence and data from uncontrolled studies suggest that T replacement may improve orgasm intensity and ease of achieving orgasm in men with HG.

## (F)

If biothesiometry confirms penile sensory loss, further specialized evaluation is warranted (see *Penile Sensory Loss* algorithm).

## (G)

For the patient with sensory neuropathy, we utilize penile vibratory stimulation as a strategy with good efficacy (70 % of men with anorgasmia achieve orgasm on at least some occasions). While there are sophisticated and expensive vibrators available with functions such as variable amplitude and frequency of vibration, we suggest patients start with a basic vibrator. These vary in cost and can be obtained online at stores such as Brookstone (www.brookstone.com) and Adam & Eve (www.adamandeve.com). The vibrator is applied to the frenular area of the penis for 30–60 s with a 30 s relief period. This should be reapplied for several cycles.

## (H)

The ability of SSRIs to delay ejaculation was accidentally discovered when these drugs were being evaluated for the treatment of depression in the 1970s. Although none of these agents have received FDA approval for PE treatment, the current guidelines from AUA and recommendations of the 2009 International Consultation on Sexual Medicine (ICSM) suggest the off-label use of SSRI for managing PE. Men being treated by SSRI agents for anxiety or depression may complain of difficulty achieving orgasm. Delayed orgasm is the most common side effect of SSRI agents and usually occurs a few weeks after commencement of the medication. The first-generation agents (fluoxetine, paroxetine, sertraline) are more likely than other members of the class to cause this problem. Per medication labeling, delayed orgasm occurs in 16–37 % of patients. Upon direct patient questioning, however, the figure is higher at 60–70 %.

## (I)

The most common variants of psychosexual dysfunction found in men with delayed orgasm are partner-specific relationship issues and idiosyncratic masturbatory practices (i.e., self-stimulating in a fashion that cannot replicated by sex with a partner). For men with interpersonal problems or those prone to obsessive-compulsive or idiosyncratic masturbation, referral to a psychosexual counselor is worthwhile.

## (J)

Not commonly, a man with chronic erectile dysfunction (ED) may complain of delayed orgasm, especially if the ED is psychogenically mediated. The first step in the management in this scenario is to treat the underlying ED and its cause.

## (K)

When basic strategies fail, there a number of oral therapies which have been used in an empiric fashion with mixed success. The list of medications includes cabergoline (Dostinex), cyproterone acetate (Cyprostat), yohimbine (Yocon), buproprion (Wellbutrin), modafanil (Provigil). The evidence supporting any of these agents is generally anecdotal at best and based on small case series.

## Suggested Reading

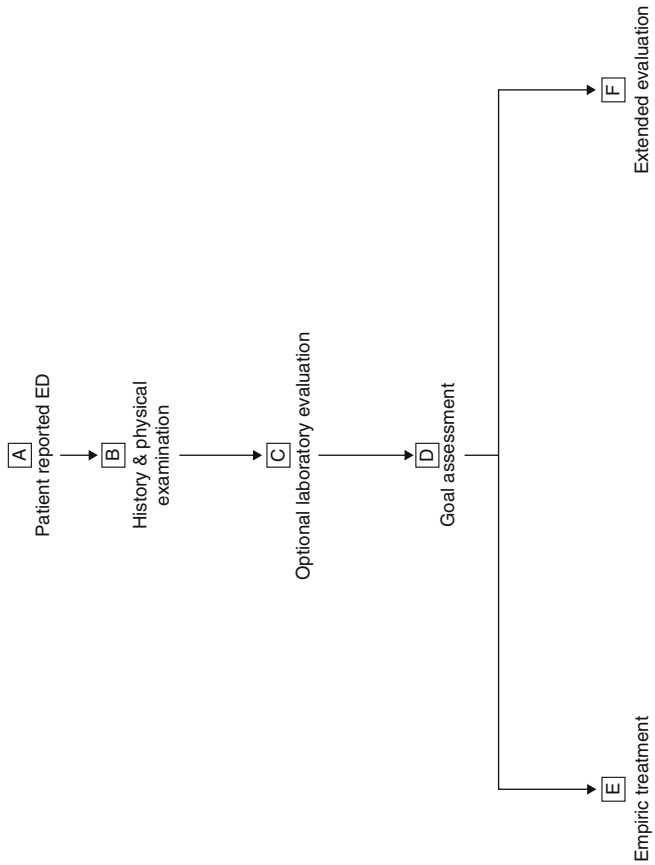
Althof SE. Psychological interventions for delayed ejaculation/orgasm. Int J Impot Res. 2012;24(4):131–6.

Nelson CJ, Ahmed A, Valenzuela R, Parker M, Mulhall JP. Assessment of penile vibratory stimulation as a management strategy in men with retarded orgasm. Urology. 2007;69(3):552–5.

Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol. 1999;19(1):67–85.

Rowland D, McMahon CG, Abdo C, Chen J, Jannini E, Waldinger MD, et al. Disorders of orgasm and ejaculation in men. J Sex Med. 2010;7(4 Pt 2):1668–86.

# Chapter 7
# Erectile Dysfunction: Initial Evaluation

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Erectile dysfunction (ED) is defined as the consistent inability to obtain and/or maintain an erection sufficient for satisfactory relations. It is estimated to affect 50 % of men over 40 years of age. This translates into more than 20 million men in the USA and over 100 million men worldwide suffering from this problem. It is associated with significant decrease in self-confidence, self-esteem, and quality of life. In its organic form it is most commonly associated with vascular risk factors such as hypertension, dyslipidemia, diabetes, obesity, cigarette smoking, and coronary artery disease. Other conditions associated with the development of ED include radical pelvic surgery or radiation, sleep apnea syndrome, neurological conditions (lumbosacral disk disease, Parkinson's disease, stroke), medications including some antidepressants and antihypertensives (Table 7.1) and endocrine conditions including hypogonadism, hyperprolactinemia, and thyroid dysfunction.

## (A)

The diagnosis of ED is made primarily upon history, although if etiology is sought physical examination and adjuvant testing are required. Men may experience the inability to generate an erection, difficulty sustaining an erection, or both. Thus, a man capable of penetrating his partner consistently but who loses erection hardness during intercourse has, by definition, ED. In general, a period of 3 months defines a consistent problem, but any man who has had at least two distinct episodes of erectile failure may be considered for treatment.

## (B)

The key factors in the history (Table 7.2) include duration of the problem and its rapidity of onset. Sudden onset tends to favor a diagnosis of psychogenic ED unless it is paired with a specific event, such as radical prostatectomy or commencing an offending medication. It is also important to establish whether the problem is intermittent or occurs consistently. For men with intermittent ED, the clinician should ask whether ED varies based on location, type of sexual activity, partner, or other factors. Better erectile rigidity with masturbation than with partner-based relations suggests the presence of a large psychological component. Defining the patient's erectile rigidity is useful. Many clinicians use a 10-point hardness scale with 0 representing no erection whatsoever, 6 the first hardness capable of vaginal penetration (7 for anal penetration), and 10 fully rigid. A validated instrument called the erection hardness score (EHS) has recently been developed. The EHS uses a 4-point system: 1—some tumescence but not firm, 2—firm but not hard enough for penetration, 3—hard enough for penetration but not fully hard, and 4—fully rigid. The EHS has been shown to relate well to the International Index of Erectile Function (IIEF), which is considered the gold standard instrument for erectile function assessment. Asking patients about their nocturnal erections, including presence and rigidity is also very useful. Indeed, the best assessment of erectile machinery is nocturnal erectile rigidity, since it circumvents the bedroom pressure and expectation that many men with ED experience. For men with poor erectile rigidity with their partner but excellent nocturnal erectile hardness, one can appreciate that a large psychological component is likely to be at play. Exploring the patient's or couple's sexual dynamic is also important, as is defining goals for treatment. Patients should be asked how often they are sexually active, and whether the activity is typically planned or unpredictable. For example, the dynamics and expectations for a 65-year-old man married to a 65-year-old woman for 35 years will likely be different than for a 65-year-old man who has a new 45-year-old partner. This is also helpful to know in an effort to strategize regarding the optimal first-line PDE5 inhibitor. A review of the patient's comorbidities,

particularly medications (Table 7.1), operative history, and vascular risk factors, is an important step in history taking. Besides erectile function, assessment of the patient's libido, ejaculatory and orgasmic function should also be conducted.

Physical examination is focused on key features that may help define conditions that contribute to the development of ED or may impact upon the clinician's desire to conduct further testing (Table 7.3). Since obesity, in particular, the metabolic syndrome, is a risk factor for ED, a general assessment of body habitus is important. This is preferably combined with an assessment of body mass index (BMI) or, even better, waist circumference. Chest examination should assess for the presence of gynecomastia, the presence of which suggests an imbalance in the testosterone:estradiol ratio. The presence of arterial peripheral vascular disease is an important cause of ED and thus abdominal exam should focus on assessment for an abdominal aortic aneurysm. An assessment of the femoral pulses in the inguinal area is also worthwhile. Although many authorities recommended testing for bulbocavernous reflex, it is absent so frequently (even in men without ED) that it provides useful information only when present. The crux of the examination is the genital examination, which should focus on testicular volume and consistency and the penis itself. The penis should be examined for circumcision status and any preputial pathology. The penis should also be evaluated for its stretch, which becomes impaired by tunical changes (with Peyronie's disease) and corporal fibrosis (with diabetes and after radical prostatectomy). The penis should also be examined in the stretched flaccid state, with careful palpation of the shaft, from pubic bone to coronal sulcus, to elucidate any firmness or induration. The patient may have a Peyronie's disease plaque present. Palpation, applying side-to-side *and* dorso-ventral pressure is the optimal means of outlining plaque and septal anatomy. Side-to-side compression beginning at the 3 and 9 o'clock position on the shaft and rolling firmly upwards (for dorsal plaque) and downwards (for ventral plaque) should be conducted meticulously along the entire shaft.

## (C)

Although no single laboratory test is considered mandatory in the evaluation of ED, several have been cited as optional by the NIH consensus conference. Most authorities advise obtaining an early morning total testosterone level, and some will perform obtain free testosterone, luteinizing hormone, and estradiol levels. If these are low, then a prolactin level is indicated. Evidence suggests that men with ED who have not yet been screened for dyslipidemia have a very high rate (70 %) of lipid abnormalities. ED may be the presenting sign for diabetes and therefore a screening $Hb_{A1C}$ level is worth considering. Patients with overt symptoms of thyroid dysfunction should have thyroid function tests performed. Some patients may benefit from an extended evaluation (see *ED*: *Extended Evaluation* algorithm).

## (D)

The first step in the management of patients with ED is a thorough goal assessment. Some patients present for information only and want to know whether ED is a sign of other, more serious underlying medical conditions. Most men who complain of ED, however, have the more straightforward ambition of simply resuming sexual intercourse and are seeking treatment that will allow them to achieve penetration-hardness erections. Defining the sexual dynamics of the patient or the couple, as previously noted, may help guide the clinician in this regard. Involving sexual partners in the discussion, when possible, can be a very useful for defining goals.

## (E)

Many men will pursue empiric treatment and, indeed, there is not necessarily a benefit to pursuing an extended evaluation for the majority of ED patients. Therapy should follow the process of care model as outlined in the *Treatment of ED* algorithm.

## (F)

Some patients may benefit from a more comprehensive investigation as outlined in the *ED*: *Extended Evaluation* algorithm.

**Table 7.1** Medications most commonly associated with ED

| **SSRI** |
|---|
| Anti-psychotics |
| Thiazide diuretics |
| Beta blockers |
| Digoxin |
| Anti-androgens |
| 5-Alpha reductase inhibitors |

**Table 7.2** Essential aspects of history taking in the ED patient

| **Duration** |
|---|
| Onset |
| Consistency |
| Rigidity |
| Sustainability |
| Nocturnal erectile function |
| Sexual dynamics |
| Comorbidities |
| Medications |
| Libido |
| Ejaculation |
| Orgasm |

**Table 7.3** Essential aspects of physical examination in the ED patient

| **General habitus** |
|---|
| Body mass index |
| Waist circumference |
| Gynecomastia |
| Pulse evaluation |
| Bulbocavernous reflex |
| Testicular volume and consistency |
| Penile stretch |
| Peyronie's disease plaque evaluation |

## Suggested Reading

DeBusk R, Drory Y, Goldstein I, Jackson G, Kaul S, Kimmel SE, et al. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton Consensus Panel. Am J Cardiol. 2000;86:175–81.

Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol. 1994;151:54–61.

Montorsi P, Ravagnani PM, Galli S, Rotatori F, Veglia F, Briganti A, et al. Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial. Eur Heart J. 2006;27:2632–9.

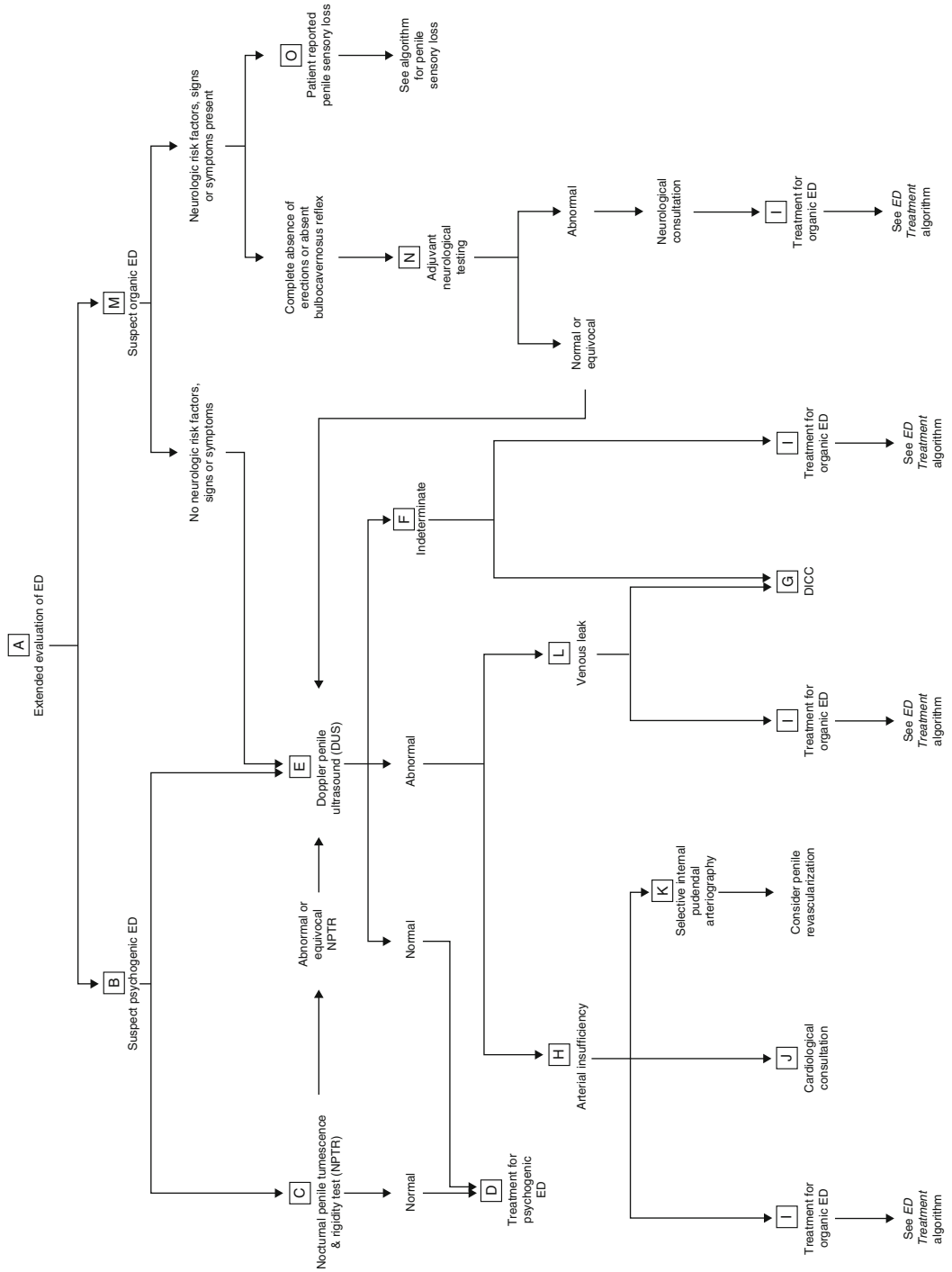
NIH Consensus Development Panel on Impotence. NIH Consensus Conference. Impotence. JAMA. 1993; 270:83–90.

Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49:822–30.

Solomon H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. Heart. 2003;89:251.

Thompson IM, Tangen CM, Goodman PJ, et al. Erectile dysfunction and subsequent cardiovascular disease. JAMA. 2005;294:2996–3002.

# Chapter 8
# Erectile Dysfunction: Extended Evaluation

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## (A)

In the *ED*: *Initial Evaluation* algorithm the patient had a thorough history, physical examination, and laboratory testing performed. At this stage the patient is ready to be treated (see *ED Treatment* algorithm). The purpose of the extended evaluation is twofold: (1) to define if the patient has underlying pathology that will impact upon the clinician's management and (2) to attempt to give the patient a prognosis for his ED (i.e., to determine if the patient is curable or not.) The classic example of the former is a patient diagnosed with venous leak who has used PDE5i without much success. In this scenario, we would move this patient directly to penile injections and not reeducate him about PDE5i use or attempt any other PDE5i. Another example of this concept, based on the recent finding that ED is a harbinger of occult or future coronary artery disease, is the middle-aged healthy man who presents without overt vascular risk factors but has underlying arteriogenic ED revealed on testing. We would suggest to this patient that he seek cardiologic consultation. There is evidence that such men are at greater risk for having an abnormal cardiac stress test. From a prognostic standpoint, the classic example is someone who the clinician believes may have psychogenic ED, as all of such patients are potentially curable. From a causation standpoint, the vast majority of patients with ED have primarily organic ED and this is usually vasculogenic in nature. It is estimated that about 70 % of all men with primarily organic ED have underlying vascular risk factors such as diabetes, hypertension, dyslipidemia, cigarette smoking, or the metabolic syndrome. Such patients sometimes, although not always, have a prior history of vascular disease (myocardial infraction, peripheral vascular disease, or stroke). Other major causes of organic ED include (with approximate estimates) medications (10 %), pelvic surgery (10 %), endocrine problems (3 %), neurological problems (2 %), and other conditions (5 %, lower urinary tract symptoms related to BPH, sleep apnea syndrome, collagen vascular diseases). Thus, a good history and physical examination, combined with judicious use of laboratory testing, will help make most of the nonvascular diagnoses.

There are also patients who "need to know" their diagnosis and in whom adjuvant testing may be reassuring and aid in their treatment and recovery. Thus, when faced with a patient with ED, the clinician should ask themselves the simple question (as with any other medical condition), "will the results of the testing impact upon the management of this patient?" If the answer to that question is yes, then adjuvant testing should be considered. The two groups of patients where we believe such testing is indicated are men at high risk of psychogenic ED (as they are potentially curable) and men without overt vascular risk factors who are at an age where they may have arteriogenic ED which might indicate the need for cardiologic evaluation.

## (B)

While some authorities have encouraged clinicians and researchers to drop the diagnosis of psychogenic ED, we persist in utilizing this categorization. This condition exists in men in whom there is no overt organic etiology. As with all psychogenic sexual dysfunctions, this is a diagnosis of exclusion, so it is inappropriate to assign such a diagnosis without having performed adjuvant testing. We avoid saying to patients, "it is all in your head," as there is a sound physiological basis for psychogenic ED. Specifically, there is either suppression of neural signaling from the central nervous system (medial pre-optic area and paraventricular nucleus) or persistently high levels of adrenaline in the corpus cavernosum. It is worth remembering that the penis remains in the flaccid state due to tonic contraction of the cavernosal smooth muscle (CSM) mediated by adrenaline. This adrenergic tone is turned off upon arousal through the nitric oxide (NO) pathway. In states of anxiety, stress, and frustration, intracavernosal adrenaline levels may stay excessively high and interfere with the NO pathway. This causes

the CSM to stay contracted and venous channels to remain open, thus negating the ability to generate a rigid erection. Since the "erection machinery" is normal in men with psychogenic ED, these patients are potentially curable if the effects of the excess adrenaline can be controlled. We tell men that, "a man is only as good as his last erection," in an effort to communicate the supreme importance of confidence in one's erection. A single failure in the bedroom may be enough to send some men into a spiral where confidence is low and continually being eroded with each passing unsatisfactory sexual encounter.

## (C)

Nocturnal penile tumescence and rigidity (NPTR) testing determines whether a man is having normal erections during sleep. Most men have three to six erections nightly during deep (rapid eye movement, or REM) sleep. Men who have psychogenic ED often have excellent erections during deep sleep. The reported absence of nighttime or early morning erections by history does not mean that a man is not having nocturnal erectile activity. He may just not be waking up during REM sleep. Furthermore, the presence of a firm or rigid nocturnal erection does not necessarily indicate a diagnosis of psychogenic ED. Such a scenario only means the likelihood of the patient having venous leak is extremely low, but he may have mild arteriogenic ED. This test can be done at home (Rigiscan™) or in a sleep laboratory setting. The latter is rarely used anymore by sexual medicine clinicians although, for a patient with a sleep disorder who is undergoing sleep lab testing, some labs still assess nocturnal erectile activity. The Rigiscan™ consists of a box that is strapped to the thigh. Attached to this are two simple bands that sit around the penis (one at the base and the other just distal to mid-shaft). These bands contract continuously and assess for the presence of an erection, its rigidity and duration. In healthy young men, 3–6 erections occur per night, each of about 60–70 % rigidity and each lasting at least 10–15 min. Rigiscan™ is usually done for at least two nights in a row. If good erections occur during sleep, the cause of the erection problems probably is not physical. This test is helpful only in two scenarios (1) if the test is completely normal per the above criteria (Fig. 8.1) or (2) if the tracings are completely flat demonstrating zero nocturnal erectile activity (Fig. 8.2). However, the majority of studies are equivocal (as many factors impact upon REM sleep and thus the presence of nocturnal erections). In functional terms, this test is done with rarity in contemporary medicine (possibly with the exception of patients complaining of painful or long-lasting nocturnal erections or in medico-legal scenarios). However, if the test is performed and completely normal results are obtained, then a diagnosis of psychogenic ED may be assigned to the patient.

## (D)

Historically, patients with psychogenic ED were referred for psychosexual counseling as monotherapy. While counseling remains a valuable tool in the treatment of the psychogenic ED patient, it cannot address in a rapid fashion the primary source of the problem, which by the time the patient has presented to a sexual medicine clinician is lack of sexual self-confidence. No amount of therapy can lead to a rapid turnaround in confidence. The trigger to the problem is sometimes obvious, for example, a single episode in which a patient was inebriated and his erection failed, and thereafter confidence shrank and high levels of adrenaline existed in the bedroom. Sometimes, however the trigger is not evident and a psychosexual counselor will be needed to get to the bottom of this problem. When overt interpersonal conflict, difficulty in commencing dialogue with a partner, absence of attraction, gender dysphoria, prior sexual abuse or sexual orientation conflict are suspected, we readily utilize our mental

health colleagues. The most direct route to curing the man with psychogenic ED is to rapidly restore erectile function to a satisfactory level (as defined by the patient). Thus, we treat them like any patient with organic ED (see *ED Treatment* algorithm). However, in contradistinction to men with organic ED, we discuss with the patient the plan of eventually weaning him off all medications. Unfortunately, about 15 % of men with psychogenic ED in our practice fail to respond to PDE5i in a consistent fashion and are then faced with a decision about pursuing second-line treatment (see *ED Treatment* algorithm).

## (E)

Duplex Doppler ultrasound (DUS) is now the standard testing modality for the diagnosis of vasculogenic ED. Its purpose is to define arterial inflow using peak systolic velocity (PSV) and to define outflow (and the presence of venous leak) using end diastolic velocity (EDV). The accuracy of DUS is related to the level of CSM relaxation. The greater the degree of CSM relaxation, the more accurate the DUS will be. To achieve CSM relaxation, intracavernosal injection of vasoactive agents is used. We use a trimix, in a redosing schedule, although the agent itself is less important than the level of erection. Complete smooth muscle relaxation can only be inferred during DUS. Our practice is to have the patient achieve rigidity consistent with his "bedroom quality erection" or BQE (equivalent to the best erection obtainable at home without erectogenic medication) as a crude surrogate of adequate CSM relaxation. In our DUS clinic, 70 % of men need a second injection and 30 % need three injections to promote CSM relaxation. It should be remembered that, during the DUS, the patient is usually in an environment not conducive to generation of an excellent erection. If he confirms that he feels comfortable with erection assistive materials, then visual (adult magazines) or audiovisual aids (adult DVDs) should be made available to him. The criteria for normalcy on DUS depends entirely upon what sensitivity and specificity one is seeking, but generally accepted criteria are: PSV >30 cm/s and an EDV <5 cm/s. Arteriogenic ED is deemed to be present when PSV is abnormal with a normal EDV; venous leak is diagnosed when the EDV is abnormal with a normal PSV and mixed vascular insufficiency is diagnosed when both PSV and EDV values are abnormal. It is worth repeating that any patient can look like they have venous leak if they have a poor enough erection. It is our experience that men diagnosed with venous leak on a DUS at an outside center who present to us for a second opinion have a significant chance (about 50 %) of not having venous leak on a repeat DUS by us. The main reason for this is the failure to obtain a good erection during their first DUS, likely related to inadequate vasoactive agent administration. This is also true for men diagnosed with arteriogenic ED at an outside center. The false diagnosis of arteriogenic ED is about 30 %. The more intracavernosal injection medication the patient receives, of course, the more likely they are to need intracavernosal injection of phenylephrine after the completion of the study. Our policy is to keep the patient in clinic until we are certain the erection has detumesced below penetration hardness. If the patient is still rigid at the 1-h time-point, the patient is given intracavernosal phenylephrine to ensure that timely detumescence occurs. If the study is normal and all other testing (laboratory etc.) is normal, then the patient is assigned a diagnosis of psychogenic ED and is treated as per (D) above.

## (F)

Even in the setting of complete corporal smooth muscle relaxation, DUS can give a false diagnosis of arteriogenic ED or venous leak. We tell patients that a DUS is never falsely normal but occasionally (probably less than 10 % of the time in our hands) is unable to accurately define the erectile

hemodynamics. Thus, the figures obtained during the study must be put into the context of the medical and sexual history of the individual patient. The classic scenario in this regard is a young male with all of the features of psychogenic ED, who despite three doses of intracavernosal vasoactive agent, has figures consistent with venous leak. In such cases, where an accurate hemodynamic diagnosis is important, consideration should be given to performing (or referring the patients elsewhere for) cavernosometry.

## (G)

While DUS has become the primary mode of erectile hemodynamics assessment, cavernosometry, more formally known as dynamic infusion cavernosometry (DIC) continues to have some advantages in select cases. It is more invasive and requires specialized training and equipment. It has the advantage, however, of providing more accuracy than DUS at diagnosing venous leak. Cavernosography refers to the imaging of the venous outflow systems using intracavernosal contrast agent injection. Cavernosography was historically utilized in the same setting as DIC (which would then be described with the acronym DICC). In select cases (generally young men at risk for isolated crural venous leak) with abnormal venocclusive parameters, the use of cavernosography permits localization of the site(s) of the venous leak. In the era of venous ligation surgery, localization of the patent venous channels was essential for planning the surgical approach. More recently, however, the indication for venous ligation surgery has diminished. The role of cavernosography has therefore been questioned and we rarely perform this form of imaging anymore. When performed, cavernosography is performed using nonionic contrast agent. Despite the use of nonallergenic contrast agent, the procedure is associated with a small but well-defined risk of allergic reaction. On review of the records of the last 400 cavernosographies, an allergic reaction has occurred in only a single case. The primary criterion in DIC that is used for the diagnosis of venous leak is flow-to-maintain (FTM), which is defined as the speed of saline infusion of saline (mL/min) required to keep the intracavernosal pressure at a steady preset level. FTM >3 mL/min is a rigorous criterion for venous leak. Another parameter used to define venous leak is pressure decay (PD). PD is the decrease in intracavernosal pressure (mmHg) over a 30 s period of time from a starting intracavernosal pressure of 150 mmHg. PD values are considered normal if they are <45 mmHg/30 s. Finally, any venous channel visualized on cavernosography is considered abnormal. As with DUS, all DIC studies are conducted using a vasoactive agent-redosing schedule, up to a maximum of three doses being administered to optimize corporal smooth relaxation. A second dose is administered when FTM values are abnormal following the first dose. Likewise, a third dose is administered if the FTM values are abnormal following the second dose of vasoactive agent. Cavernosography is conducted only following a third dose of vasoactive agent and is performed with infusion of nonionic contrast at an intracorporal pressure of 90 mmHg under fluoroscopic control.

## (H)

Men diagnosed with arteriogenic ED fall into two broad categories: those meeting the criteria for penile revascularization surgery and those who do not meet these criteria. The vast majority of men with arteriogenic ED diagnosed on DUS are not candidates for penile revascularization and should be treated for organic ED.

## (I)

See *ED Treatment* algorithm.

## (J)

In men diagnosed with arteriogenic ED, especially in those of middle-age with minimal vascular risk factors and no prior cardiologic evaluation, consideration should be given to a referral for cardiologic consultation. Recognizing ED as a harbinger of occlusive coronary artery disease may permit clinicians to intervene in a more timely fashion with the potential for improved outcomes and quality of life for the patient. Evidence supports the concept that vasculogenic ED and CAD result from endothelial dysfunction or atherosclerosis. There is evidence that ED in some patients may predate the onset of angina symptoms by an interval of 2–5 years. Accepting that atherosclerosis is a systemic process that equally affects all vascular beds, the "artery size" hypothesis postulates that the smaller size of the penile arteries, in comparison with the relatively large coronary arteries, makes them more prone to symptoms from early formation of plaques of a given size. Supporting this hypothesis is the finding that in patients with angiography-confirmed CAD and ED, the duration of ED correlates with the number of vessels involved. Moreover, analysis of the placebo group of the prostate cancer prevention trial (PCPT) showed that the initial report of ED during the study was an independent risk factor for cardiovascular events, even after adjustment for other risk factors. The percentage of patients experiencing a cardiovascular event increased steadily after the initial report of ED, approximately 2 %, 11 %, and 15 % after 1, 5, and 7 years, respectively.

## (K)

While very uncommon, men meeting all the criteria who undergo revascularization (penile artery bypass) surgery are potentially curable. The strict history-based criteria for candidacy for such surgery include: age <40 years old (some centers use 50 years old as a cut-off), pure arteriogenic ED without any venous leak, and no vascular comorbidities. Patients who are interested in this surgery need to undergo a selective internal pudendal arteriogram to define the anatomy. The angiographic criteria for this operation include: occlusion of one or both common penile/cavernosal arteries, presence of an inferior epigastric artery of sufficient size and length to act as a donor artery, presence of at least one dorsal artery of sufficient size to act as a recipient artery and preferably communicating arteries passing from the dorsal artery(ies) into the corpus cavernosum (corpora cavernosa). Discrepancies between the DUS/DIC data and the arteriographic findings should raise concerns about the candidacy of the patient for revascularization.

## (L)

Venous leak refers to the state whereby the valve mechanism within the corporal bodies is defective and blood flow into the corporal cavernosa leaks out of the penis into the systemic circulation. The clinical features of leak are: failure to obtain a rigid erection, short-lived erection, and improved

erection rigidity while standing than while supine. The veno-occlusive mechanism depends on the elasticity of the CSM and its ability to expand in a three-dimensional fashion under nitric oxide (NO) control. As the CSM expands it compresses small venous channels (sub-tunical venules) against the tunica albuginea. Failure of the CSM to expand fully (due to high levels of adrenaline or CSM fibrosis) leaves these aforementioned venous channels open and blood cannot be trapped effectively. Venous leak is believed to be irreversible and portends a poor prognosis for response to PDE5i and limits the ability of intracavernosal injections (ICI) to work well.

## (M)

For many patients presenting at high risk for organic ED, particularly those with known vascular risk factors, there is relatively little benefit from vascular testing. The exceptions are patients in whom the clinician has significant concerns regarding neurogenic ED. The risk factors for neurogenic ED include spinal surgery, lumbar disk disease, Parkinson's disease, and multiple sclerosis. Just as arteriogenic ED can represent a harbinger to occult coronary artery disease, ED may also be an early signal of occult neurological disease. In the latter case, where suspicion is high for isolated neurogenic ED, adjuvant neurological testing may be considered. It is worth noting that it is unlikely for a patient to have isolated neurogenic ED without having dysfunction of some other pelvic organ (i.e., bladder, bowel) given the shared origin of innervation (S2-4). The classic features of complete bilateral neurological interruption are the absence of any erectile activity (sexual or nocturnal) whatsoever along with an absent bulbocavernosus reflex. Lesser degrees of neurological impairment translate into greater degrees of erectile function.

## (N)

Neurological testing is best ordered and conducted by a neurologist. When abnormal, testing is supportive of a neurogenic ED diagnosis. Given the limited treatment options for neuropathies in general and specifically for neurogenic ED (other than the standard process of care model treatment approach), neurological testing is rarely performed. Assessment can be divided into sensory nerve testing (biothesiometry, somatosensory evoked potential testing), motor nerve testing (pudendal electromyography), and autonomic nerve testing (corpus cavernosum electromyography). No single neurological test can evaluate the entire reflex arc. Often a neurologist will also assess spinal and central areas using MRI.

## (O)

For patients whose primary neurological complaint is that of loss of penile sensation, penile sensation testing may be indicated (see *Penile Sensory Loss* algorithm). Of note, in men with ED whose penile sensation changes postdate the onset of ED, the vast majority has a normal penile sensation testing.

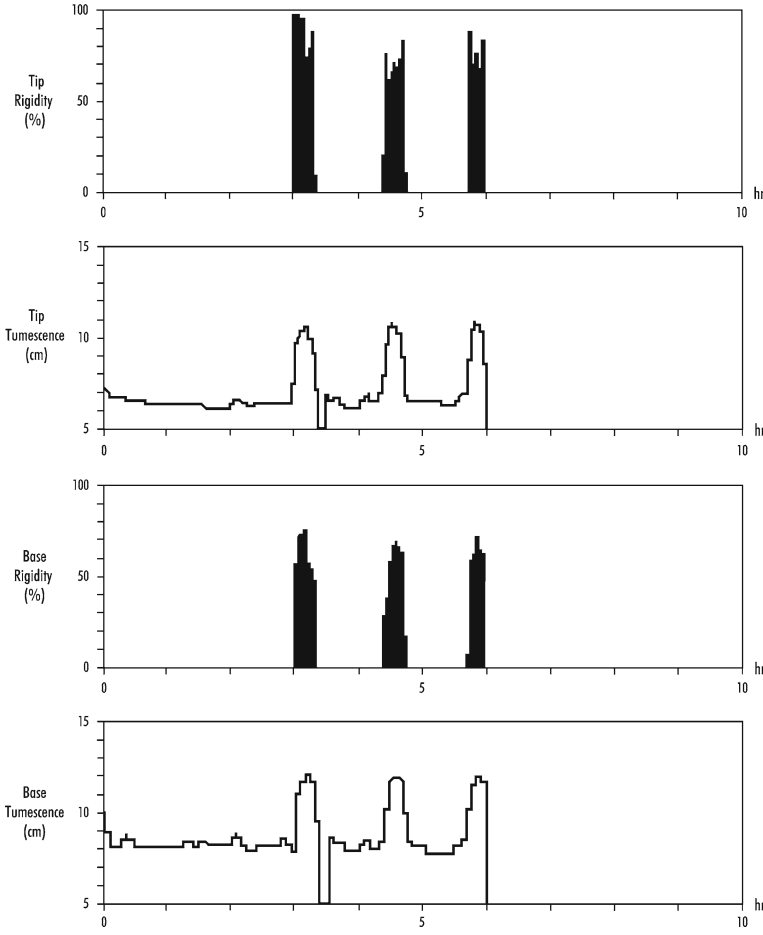



**Fig. 8.1** Normal Rigiscan™ test

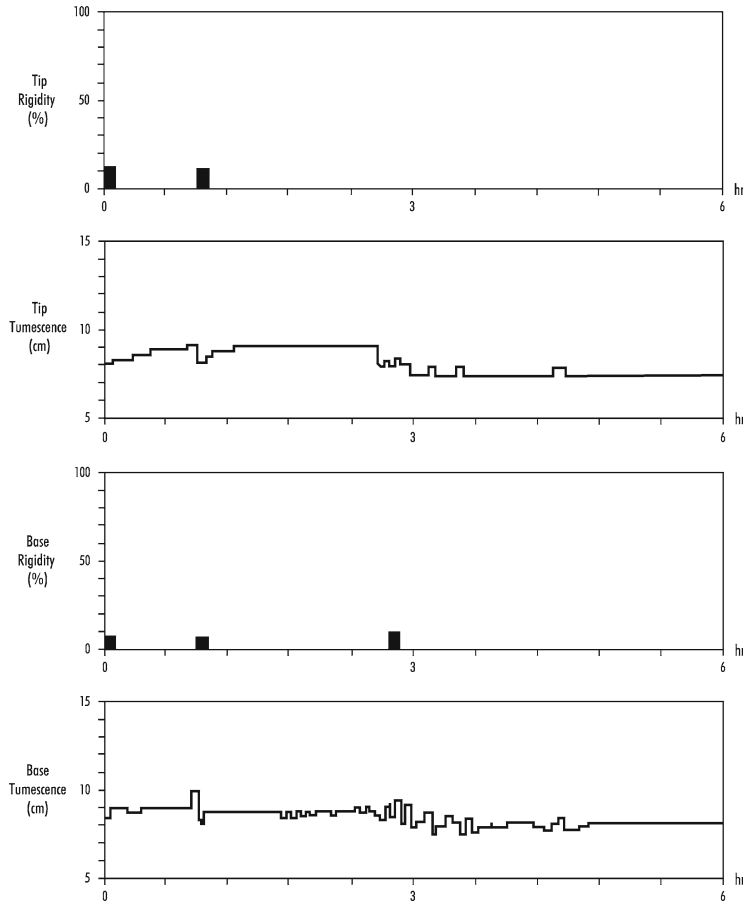
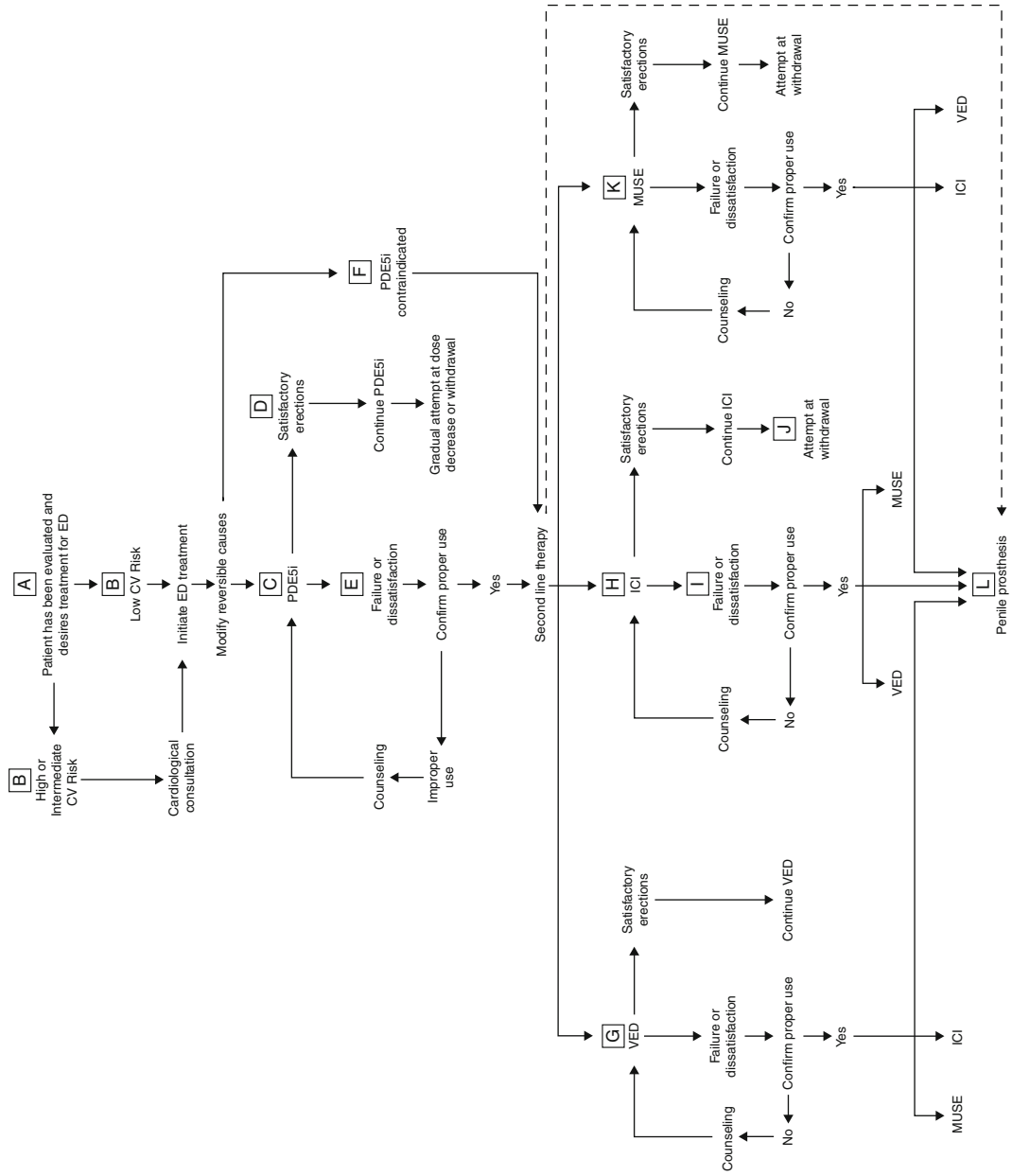



**Fig. 8.2** Rigiscan™ tracings that are completely flat demonstrating zero nocturnal erectile activity

## Suggested Reading

Althof SE. What's new in sex therapy (CME). J Sex Med. 2010;7(1 Pt 1):5–13.
Bookstein JJ, Valji K, Parsons L, Kessler W. Pharmacoarteriography in the evaluation of impotence. J Urol. 1987;137(2):333–7.
LeRoy TJ, Broderick GA. Doppler blood flow analysis of erectile function: who, when, and how. Urol Clin North Am. 2011;38(2):147–54.
Levine LA, Lenting EL. Use of nocturnal penile tumescence and rigidity in the evaluation of male erectile dysfunction. Urol Clin North Am. 1995;22(4):775–88.
McCabe M, Althof SE, Assalian P, Chevret-Measson M, Leiblum SR, Simonelli C, et al. Psychological and interpersonal dimensions of sexual function and dysfunction. J Sex Med. 2010;7(1 Pt 2):327–36.
Mulhall JP. Cavernosometry: is it a dinosaur? J Sex Med. 2008;5(4):760–4.
Mulhall JP, Anderson M, Parker M. Congruence between venocclusive parameters during dynamic infusion cavernosometry: assessing the need for cavernosography. Int J Impot Res. 2004;16(2):146–9.
Mulhall JP, Teloken P, Barnas J. Vasculogenic erectile dysfunction is a predictor of abnormal stress echocardiography. J Sex Med. 2009;6(3):820–5.
Rosen RC, Althof SE, Giuliano F. Research instruments for the diagnosis and treatment of patients with erectile dysfunction. Urology. 2006;68(3 Suppl):6–16.
Shabsigh R, Fishman IJ, Shotland Y, Karacan I, Dunn JK. Comparison of penile duplex ultrasonography with nocturnal penile tumescence monitoring for the evaluation of erectile impotence. J Urol. 1990;143(5):924–7.
Teloken PE, Park K, Parker M, Guhring P, Narus J, Mulhall JP. The false diagnosis of venous leak: prevalence and predictors. J Sex Med. 2011;8(8):2314–9.
Whang SY, Sung DJ, Lee SA, Park BJ, Kim MJ, Cho SB, et al. Preoperative detection and localization of accessory pudendal artery with contrast-enhanced MR angiography. Radiology. 2012;262(3):903–11.

# Chapter 9
# Erectile Dysfunction: Treatment

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## (A)

The willingness to pursue treatment for erectile dysfunction (ED) is dependent on many factors but associated patient bother and distress is a key factor. Other relevant factors to consider include the presence of contraindications to therapy, the absence of partner, lack of willingness of partner to participate in sexual relations, and cost of treatment. As outlined in the other ED algorithms, some patients will have undergone extended evaluation and others will have forgone further assessment. While 50 % of men over 40 years of age have some degree of ED, less than 10 % ever seek treatment, presumably because many of them are not bothered by the ED and are capable of having satisfactory sexual relations despite their ED.

## (B)

The process of care model (Table 9.1) represents a good mechanism of prioritizing therapeutic strategies. The first steps in non-pharmacotherapy-based treatment of the ED patient include adjustment of offending medication, correction of modifiable risk factors, and addressing overt psychosocial issues. There are very few medications that are ever implicated as the sole cause of ED. At the top of the list are antihypertensives (especially thiazide diuretics and beta-blockers), psychotropic medications (antidepressants in particular), digoxin, and 5 alpha reductase inhibitors. However, hypertension and depression in of themselves are potent causes of ED and thus it is often difficult to define the role the medication has played in ED development. The temporal relationship between the use of the medication and the onset of ED may be critical in defining such a role and deciding if the medication is worth stopping. Strict management of hypertension, dyslipidemia, diabetes, and obesity is of benefit for many reasons. There is only a paucity of evidence suggesting that such maneuvers will result in improved erectile function, although we tell patients we believe that these steps may prevent further deterioration of erectile function. We use the services of our mental health colleagues liberally for ED patients with overt relationship issues and those with problems with communication with their partner concerning sexual function issues. However, there are no robust data supporting the concept that psychological counseling as monotherapy translates into improvement in erectile function. The next step is to determine their cardiac reserve or, more specifically, their ability to tolerate exertional activity. While the average sexual encounter generates only two to four Mets of energy, it is recommended that a simple algorithm be followed in defining a patient's cardiac reserve.

The Princeton consensus conference has developed guidelines for the cardiac evaluation of the ED patient (Fig. 9.1). These guidelines divide patients into three groups: low, intermediate, and high risk for a myocardial event during or after sexual activity. The class features are listed in Table 9.2. In our practice all low-risk patients are considered candidates for treatment without further evaluation, but all high-risk patients are sent to a cardiologist for further assessment. It is the intermediate-risk group that requires the greatest level of thought. In our practice all patients get asked two simple questions to define their cardiac reserve and candidacy for ED treatment. Firstly we ensure that patients are not using or even in possession of nitrate containing medications. Even those possessing but not using the nitrates do not get a PDE5i prescription from us. In this case, we write to the nitrate prescribing clinicians to inquire whether the nitrates can be safely stopped. Since initiating this policy we have been impressed by how often (about 40 % of the time) the clinician says that the patient may stop the nitrate medication. Such an affirmative response in men is most likely in men who have not used their nitrate agent in more than 1 year and when the prescribing physician is a cardiologist. The second question is, "can you walk up and down two flights of stairs briskly without chest pain?" The ability to perform

this task is equivalent to successfully completing Level 2 on a modified Bruce protocol for cardiac stress testing. If a patient does not use or possess nitrate medication, and can walk up and down two flights of stairs without chest pain, then he is a candidate for pharmacotherapy. All other patients are referred for cardiological consultation.

## (C)

First-line pharmacotherapy is the use of phosphodiesterase 5 inhibitor (PDE5i) medications. These medications function through blockade of the PDE5 enzyme. This enzyme degrades cyclic guanosine monophosphate (cGMP) into a deactivated from of this second messenger. Nitric oxide (NO) activates guanylate cyclase, which in turn transforms guanosine triphosphate (GTP) into cGMP. Therefore PDE5i work only in the presence of NO. This explains why certain patient populations, in whom NO production is limited, fare so poorly with PDE5i (e.g., diabetics, patients after radical prostatectomy). There are four Food and Drug Administration (FDA) approved PDE5i available in the United States. The characteristics of each agent are listed in Table 9.3. In our practice, the choice of which PDE5i is used first depends on the sexual dynamics of the patient/couple's sex life including frequency of sexual activity requiring a medication and predictability of sexual activity. Sildenafil and vardenafil have windows of opportunity of about eight-12 h while tadalafil has a much longer window of opportunity. Thus, for the patient who has frequent sexual activity (≥3 times per week), or has no predictability, tadalafil is an excellent first-line choice. For the patient with less frequent relations or who has greater predictability, then sildenafil or vardenafil are excellent choices. At the time of writing, avanafil has just been approved and we do not yet have experience with this agent. Its most significant attribute is its rapid speed of onset (20 min) and in trials it appears to be active for at least 6 h. Tadalafil can be used with no regard for food ingestion although its peak effect is no sooner than 2 h after ingestion. During the trial phase, we advise patients to use tadalafil 4 h before relations and that it is active for at least 24 h. Sildenafil and vardenafil are affected to a significant degree by food ingestion (30 % drop in maximum concentration and doubling of the time for absorption) and therefore we advise patients, during the trial phase, to take them 2 h before a meal and that the medications are active for 8 h at least. For such patients we use the phrase, "pill at 5 PM, dinner at 7 PM, active until at least midnight." For all three agents, we start at maximum dose, even in those patient groups for whom caution is suggested (patients >65 years of age and renal failure). We then down-titrate for side effects or if the patient is getting an excellent response at maximum dose. This approach maximizes the change of a patient obtaining an excellent erection with the first dose and thus a significant boost in sexual self-confidence.

Recently, there has been a significant interest in daily tadalafil (2.5 or 5 mg). Ingesting 5 mg of tadalafil daily after 5 days gives a serum level equivalent to a single 8 mg dose. It is common for us to see men who have previously failed maximum dose tadalafil (20 mg) and are then prescribed 5 mg daily. We believe that there is little physiological rationale for this approach, since patients are unlikely to respond to a 40 % maximum dose if they have already failed maximum dose. All PDE5i generally have the same side effects although significant inter-agent variability exists for the individual patient. Headache, facial flushing, nasal congestion, heartburn, and visual disturbances (blurred, double vision, or change in color perception) are the most common adverse effects. Tadalafil is only rarely associated with visual disturbances, although it is associated with myalgia (particularly in the back, legs, and buttocks). Visual disturbances are related to cross-reactivity to PDE6 (retinal phototransduction enzyme) and are usually very transient. We forewarn all patients about this, lest they become distressed when it occurs. There is no robust evidence that PDE5i are causative factors in permanent loss of vision or hearing. The myalgia associated with tadalafil is believed to result from venous pooling of blood in large muscles in response to the long duration of PDE5 inhibition.

## (D)

We recommend our patients call our office to give an initial assessment of their response. Patients with good response and high satisfaction are given an appointment for a follow-up discussion 3–6 months later. It is estimated that one third of patients stop PDE5i after one prescription and 50 % by 6 months after starting therapy. Given that every man with ED has some psychological component to the problem, it is possible that some men can be weaned from the use of PDE5i. This is definitely true for men who have primary psychogenic ED. This is worth discussing at the follow-up visit. While there is no tachyphylaxis to PDE5i, there are some men who become psychologically dependent on these drugs. If an attempt is to be made at withdrawing PDE5i, we recommend that it not be done abruptly, but rather have the patient move from consistent use of PDE5i to intermittent use of the medication, choosing carefully to occasions on which he will forgo the PDE5i.

## (E)

It is estimated that 30–40 % of all patients will fail to respond satisfactorily or consistently to PDE5i. When patients inform the clinician that the "pills are not working," it is essential that this be properly defined. Firstly, the success of erectogenic therapy should be judged off the best response a patient has, irrespective of the agent used. Thus, it is important to define from the patient whether he had, on even one occasion, an excellent response. If even a single good response was obtained, then the patient should be told that he CAN respond to the medication. Reasons for failure include erectile tissue damage, failure to generate a NO response, high adrenaline (stress, anxiety), and failure to use the medication properly. Erectile tissue damage and NO generation problems will require moving to second-line therapy. High adrenaline levels will inhibit the positive effects of PDE5i on the NO pathway. This is the reason that, in our practice, about 15 % of men with proven psychogenic ED fail to respond consistently to PDE5i agents. It is remarkable how often patients have not heard the instructions given to them about how to use these agents properly. Unfortunately, the absence of instructions or incomplete instructions are more likely to be given by non-urologists. Even among urologists, better instructions are given by those with high volume sexual medicine practices. It has been well documented that reeducating a patient will salvage 30–50 % of the so-called PDE5i failures. Making sure patients pay attention to dosing, timing with regard to food and the need for sexual stimulation are key messages to communicate to the patient.

## (F)

Patients who have contraindications to the use of PDE5i will need to move directly to second-line therapies. The most common contraindications are the use/possession of nitrate containing medications and lack of cardiac reserve good enough for exertional activity (this is true for all ED therapies). The mean drop in systolic blood pressure when maximum dose PDE5i is taken within an hour of a nitrate containing medication is about 35 mmHg (this compares to the typically observed 5–8 mmHg drop with ingestion of maximum dose PDE5i without nitrates). Other contraindications (conditions that should be inquired about) include retinitis pigmentosa, macular degeneration, and a history of sudden vision or hearing loss.

## (G)

Vacuum erection devices (VED) have been around for more than a century. The vacuum system comprises a plastic tube attached to a head that is battery driven or a head with plastic tubing attached to a hand pump. The pump generates a vacuum within, which is limited in its maximum pressure through the presence of a pop-off valve, which usually limits the pressure within the tube to 200 mmHg. All FDA approved vacuum devices have such a valve. Devices purchased in sex stores or on the Internet, however, often do not have this safety mechanism. Generation of the vacuum depends upon the presence of a seal at the open end of the cylinder, which is placed over the base of the penis against the pubic bone. This is best accomplished with trimming off some of the pubic hair and the liberal use of a gel preventing air leakage. When used properly, except in the presence of significant venous leak (see *ED*: *Extended Evaluation* algorithm), this device should result in a penetration hardness erection. Patients have best results with the VED if formal in-office training is performed. While routinely successful, the penis does not appear normal since subcutaneous venocongestion changes the appearance (especially in Caucasian men). Patients also sometimes complain that the penis feels cool to the touch. Furthermore, the constriction band worn at the base of the penis is, for some men, uncomfortable and interferes with interest in using the device and sexual satisfaction. In our experience, the minority of men/couples use this device for longer than 6 months.

Two complaints we often hear from our patients are firstly, that the penis hinges at the site of the constriction ring, so this must be placed as far proximally as possible and secondly, that the scrotum often gets sucked into the vacuum tube, which can be uncomfortable. Both of these problems can reduce sexual satisfaction. VEDs range significantly in cost ($100–500) but often there is good insurance coverage for these devices. Complications are uncommon but may be potentially problematic and include: (1) hematoma development; vacuum device use is therefore contraindicated in men using anticoagulant medications, and (2) dorsal nerve neuropraxia if the constriction ring is left in place too long (we limit our patients to 30 min); patients with penile sensory deficits (spinal cord injured men) should not use these devices. While some information suggests that the use of vacuum devices may cause Peyronie's disease, there is no reliable evidence that this is a valid concern. For those patients not responding to a VED, it is worthwhile discussing the correct use with them and perhaps even set up an in-office refresher tutorial. For true failures, intraurethral PGE1 prostaglandin, intracavernosal injection therapy or penile implant surgery are the next steps in treatment.

## (H)

Intracavernosal injection therapy (ICI) has been available for the treatment of ED since 1982. Discovered fortuitously almost contemporaneously by Ronald Virag (France) and Giles Brindley (England) it took hold in the USA in 1985. There are only two FDA approved products, both PGE1 (alprostadil) monotherapy (Caverject and Edex). However, most high volume ICI centers use combination agents such as trimix (papaverine, phentolamine, PGE1) or bimix (papaverine, phentolamine) (Table 9.4). Some centers use a quadmix where atropine is added to trimix, although there is no evidence that this makes any significant difference to efficacy. Papaverine is a nonspecific PDE inhibitor, phentolamine an alpha-adrenergic blocker, and PGE1 a direct cyclic adenosine monophosphate (cAMP) stimulator. PGE1 monotherapy has about a 60 % efficacy rate for all-comers whereas the efficacy of trimix approaches 90 % for the same population. The ability to respond to ICI is independent of nerve function and the NO pathway but is heavily dependent upon the integrity of the cavernosal smooth muscle (CSM). Patients who truly fail ICI have significant CSM damage. CSM damage, in particular collagenization, leads to the development of venous leak. ICI (using trimix in our practice) works in over 90 % of men with arteriogenic ED and 50–70 % of men with venous leak, depending on the grade of leak.

The advantages of ICI are its high level of efficacy, low cost and low rate of adverse events. Compounded trimix or bimix are inexpensive ($60–80 for a 500 unit vial) although there are centers where men are charged $500–1,000 for the same product. On the disadvantage side, it does require self-injection although most men describe the needle prick no worse than a mosquito bite. The only significant adverse event is the risk of priapism, which when the patient is properly educated and monitored is very unusual (0.2 % rate in our practice). With regard to prolonged erections, patients are instructed to take 120 mg of plain pseudoephedrine by mouth if they have a penetration hardness erection that has lasted 2 h, call the on-call staff at 3 h and be in the emergency department at 4 h. See *Priapism* algorithm for further details on management of priapism. Much is written about the link between ICI and the development of penile "fibrosis." Fibrosis is a general term and in writings may be referring to tunical changes (Peyronie's disease) or corporal fibrosis. After a comprehensive review of the world's literature (in vitro, animal, human), there is no robust evidence that ICI causes penile fibrosis of any kind. In our practice, patients are trained over two in-office visits. Each session takes about 1 h and the patient is given the injection by our nursing staff on first visit and give themselves the injection under our supervision on the second visit. The patient is then instructed to keep in close contact over the first four injections at home (which is the usual time frame for men to get to a dose that gives them a satisfactory erection) to permit dose titration to occur (Table 9.5). There is no substitute for experience in understanding the nuances of injection agent titration. However, the attached titration schedule is utilized by nursing staff at our institution only as a guide. When in doubt, nursing personnel should check with the supervising ED specialist.

Finally, men are instructed that they are not permitted to adjust the dose upwards themselves and are not to inject more than once in a 24-h period. Patients are followed up every 6 months in first year, annually for 2 years and then every 2 years if they are happy injecting and responding well. There is a 30–50 % drop-out rate 5 years after commencing ICI. These rates can be limited through setting realistic expectations for patient and partner. The main reasons for drop-out are (in no particular order), medication cost, lack of efficacy, needle-phobia, adverse effects, change in patient or partner goals. As previously stated, true failure to respond to ICI indicates the presence of venous leak. Indeed, patients on doses of trimix 50 units (0.5 mL) or higher have venous leak by definition. Occasionally we see men who have previously responded well to ICI and present complaining that ICI no longer gives them a good erection.

There are several reasons for such a change. If men are using trimix, the first possible reason is the medication has become deactivated. The PGE1 component is an inherently unstable agent and loses some of its activity over the course of 4–6 months. This deactivation is accelerated by failure to refrigerate the medication properly. Changing the medication with a fresh vial will resolve this problem. Another reason for a change in response to ICI is technique-related. This is seen in three particular situations: (1) men who are injecting infrequently can struggle to become proficient in the injection technique, (2) men may perform well when they inject on the side of their dominant hand but struggle when they have to inject on the nondominant side with their nondominant hand, and (3) men who have Peyronie's disease, hit the plaque with needle, and therefore fail to deliver the medication into the correct location to optimize results. Another cause of a change in response is seen in men under high levels of stress who generate a large adrenaline response. High levels of adrenaline can impair ICI working effectively, although ICI is more resistant to this than PDE5i. Finally, if the change has occurred over an extended period of time, erectile tissue damage may be the cause of the reduced ICI response. We see this in diabetic men (especially those with poor glycemic control) and men who have had radiation therapy for prostate cancer or other cause of CSM degeneration. Men with venous leak who have truly failed ICI will notice that, as their dose is increased, little change in erectile response occurs. For these men, the VED and intraurethral suppositories remain options but will inevitably have very limited efficacy. It has been our experience that these men will need to consider penile implant surgery.

## (J)

Ten to thirty percent of men using ICI cease needing ICI and there has been much debate about the mechanism of this. While some authorities cite alterations in CSM in response to ICI, we believe that most men who are weaned off ICI onto oral therapy had a significant psychogenic component to their ED at the outset. In men with documented psychogenic ED who have failed PDE5i therapy, and then moved onto ICI, we can nearly always wean them from ICI back to PDE5i.

## (K)

We reserve the use of intraurethral suppositories for men who are severely needle-phobic and cannot overcome the phobia. MUSE (medicated urethral system for erection) was approved for treatment of ED by the FDA in 1997 and involves the instillation of a gelatinous suppository (about the size of a grain of rice) into the anterior urethra. The patient stands and voids urine first, then instills the suppository with the specially designed applicator. He then needs to stay standing and massage or manipulate the penis for 10–20 min. About 40 % of men presenting with ED respond to this agent. The advantages of MUSE are that it is easy to use and does not involve the need for a needle. On the down side, it is very expensive if not covered by insurance, is not universally effective, and has problems with inconsistency. In certain populations, PGE1 (suppository or injection) is associated with penile pain. The men who experience this most commonly are those with cavernous nerve trauma (radical pelvic surgery) or autonomic neuropathy (diabetes). This pain can be debilitating, although usually it simply represents a nuisance and some men choose to tolerate it if they achieve good erections. If they have not already tried them, MUSE failures are candidates for the vacuum device and ICI.

## (L)

While the process of care model lists penile implant surgery as third-line therapy, if patients have received a comprehensive discussion about second-line therapy and do not wish to pursue any of these strategies, penile implant surgery can be moved up in the algorithm. We do not perform penile implant surgery unless a patient has had a penile injection discussion. While the operative considerations of implant surgery are beyond the scope of this textbook, it is worth noting that most of our penile implants are performed as ambulatory surgery. There are several types of implants, but we only place inflatable devices (for further information on implant types see the reading list below). The advantages of implant surgery are that the penile shaft has the capacity to become 100 % rigid and the erection takes only about 10 s to get to maximum hardness. It is this rigidity and spontaneity that leads to the very high satisfaction rates associated with this procedure. The disadvantages of implant surgery include the need for anesthesia and an operation, the risk of infection (less than 2 %), and mechanical malfunction (approximately 10 % over the first 10 years after implantation). In our practice, patients are given extensive reading material, are asked to view the implants video material, and are encouraged to have a telephone discussion with one of our patients who has already undergone implant surgery.

**Table 9.1** Process of care model

| | |
|---|---|
| First-line therapy | Lifestyle modification |
| | Medication adjustment |
| | Psychology input |
| | Oral agents |
| Second-line therapy | Vacuum devices |
| | Intracavernosal injections |
| | Intraurethral alprostadil |
| Third-line therapy | Penile implant surgery |
| | Penile revascularization |
| | Venous ligation surgery |

**Table 9.2** Princeton consensus conference risk stratification

| Risk Level | Comorbidity |
|---|---|
| Low risk | Asymptomatic patient (<3 CAD[a] risk factors) |
| | Controlled hypertension |
| | Mild, stable angina |
| | Post-successful coronary revascularization |
| | Uncomplicated MI[b] (>6 weeks ago) |
| | Mild valvular disease |
| | CHF[c] (NYHA class I) |
| Intermediate risk | ≥3 major CAD risk factors (excluding gender) |
| | Moderate, stable angina |
| | Recent MI (>2 weeks, <6 weeks) |
| | CHF (NYHA class II) |
| | History of stroke |
| | Peripheral vascular disease |
| High risk | Unstable or refractory angina |
| | Uncontrolled hypertension |
| | CHF (NYHA class III/IV) |
| | Recent MI (<2 weeks ago) |
| | High-risk arrhythmias |
| | HOCM |
| | Moderate/severe valvular disease |

*HOCM* hypertrophic obstructive cardiomyopathy
[a]*CAD* coronary artery disease
[b]*MI* myocardial infarction
[c]*CHF* congestive heart failure

**Table 9.3** Characteristics of the currently available PDE5 inhibitor agents

| Agent | Doses available | Speed of onset (h) | Half-life (h) | Duration of action (h) | Food effect |
|---|---|---|---|---|---|
| Sildenafil (Viagra) | 25, 50, 100 | 0.8 | 3–5 | 8–10 | Yes |
| Vardenafil (Levitra) | 5, 10, 20 | 0.7–0.9 | 4–5 | 8–12 | Yes |
| Tadalafil (Cialis) | 2.5, 5, 10, 20 | 2.0 | 17.5 | 36–48 | No |
| Avanafil (Stendra) | 20, 50, 100 | 0.5–1.5 | 1.5 | >6 | Minimal |

**Table 9.4** Intracavernosal drug mixtures (used in our practice)

| | PGE1 (μg/mL) | Papaverine (mg/mL) | Phentolamine (mg/mL) | Other |
|---|---|---|---|---|
| $PGE_1$ | 5–40 | – | – | – |
| Papaverine | 30–45 | – | – | – |
| Bimix | – | 30 | 1 | – |
| Trimix | 10 | 30 | 1 | – |
| Super-trimix | 20 | 45 | 2.5 | – |
| Quadmix | 20 | 45 | 2.5 | Atropine |

**Table 9.5** Titration schedule (trimix)

| Dose (units) | Response (%) | Duration | Suggested adjustment |
|---|---|---|---|
| 1–5 | ≤20 | Irrelevant | Increase by 10 Units |
| 1–5 | 30–50 | Irrelevant | Increase by 5 Units |
| 1–5 | 60–70 | ≤15 min | Increase by 2 Units |
| 1–5 | 60–70 | 15–60 min | No change |
| 1–5 | 60–70 | >90 min | Decrease by 1 Unit |
| 1–5 | >70 | ≤90 min | No change |
| 1–5 | >70 | >90 min | Decrease by 2 Units |
| 6–10 | ≤20 | Irrelevant | Increase by 10 Units |
| 6–10 | 30–50 | Irrelevant | Increase by 5 Units |
| 6–10 | 60–70 | ≤15 min | Increase by 2 Units |
| 6–10 | 60–70 | 15–60 min | No change |
| 6–10 | 60–70 | >90 min | Decrease by 2 Units |
| 6–10 | >70 | ≤90 min | No change |
| 6–10 | >70 | >90 min | Decrease by 2 Units |
| 11–30 | ≤20 | Irrelevant | Increase by 5 Units |
| 11–30 | 30–50 | Irrelevant | Increase by 5 Units |
| 11–30 | 60–70 | ≤15 min | Increase by 2 Units |
| 11–30 | 60–70 | 15–60 min | No change |
| 11–30 | 60–70 | >90 min | Decrease by 2 Units |
| 11–30 | >70 | ≤90 min | No change |
| 11–30 | >70 | >90 min | Decrease by 2 Units |
| 31–50 | ≤20 | Irrelevant | Increase by 10 Units |
| 31–50 | 30–50 | Irrelevant | Increase by 10 Units |
| 31–50 | 60–70 | ≤15 min | Increase by 5 Units |
| 31–50 | 60–70 | 15–60 min | No change |
| 31–50 | 60–70 | >90 min | Decrease by 2 Units |
| 31–50 | >70 | ≤90 min | No change |
| 31–50 | >70 | >90 min | Decrease by 5 Units |
| 51–75 | ≤20 | Irrelevant | Increase by 25 Units |
| 51–75 | 30–50 | Irrelevant | Increase by 10 Units |
| 51–75 | 60–70 | ≤15 min | Increase by 10 Units |
| 51–75 | 60–70 | 15–60 min | No change |
| 51–75 | 60–70 | >90 min | No change |
| 51–75 | >70 | ≤90 min | No change |
| 51–75 | >70 | >90 min | Decrease by 5 Units |
| 76–100 | ≤20 | Irrelevant | Change to Supertrimix |
| 76–100 | 30–50 | Irrelevant | Change to Supertrimix |
| 76–100 | 60–70 | ≤15 min | Change to Supertrimix |
| 76–100 | 60–70 | 15–60 min | No change |
| 76–100 | 60–70 | >90 min | Check with physician |
| 76–100 | >70 | ≤90 min | No change |
| 76–100 | >70 | >90 min | Check with physician |

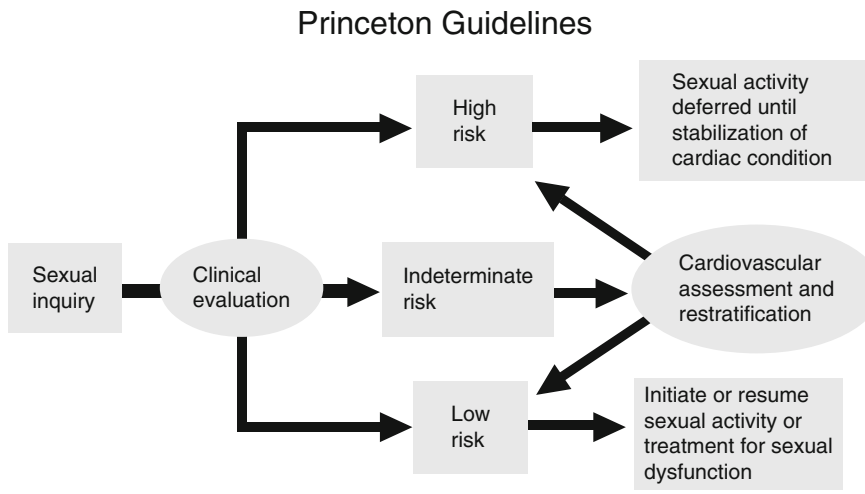



**Fig. 9.1** The Princeton consensus conference guidelines for the cardiac evaluation of the ED patient

## Suggested Reading

Corona G, Mondaini N, Ungar A, Razzoli E, Rossi A, Fusco F. Phosphodiesterase type 5 (PDE5) inhibitors in erectile dysfunction: the proper drug for the proper patient. J Sex Med. 2011;8(12):3418–32.

Garcia JA, Sanchez PE, Fraile C, Escovar P. Testosterone undecanoate improves erectile dysfunction in hypogonadal men with the metabolic syndrome refractory to treatment with phosphodiesterase type 5 inhibitors alone. Andrologia. 2011;43(5):293–6.

Leungwattanakij S, Flynn Jr V, Hellstrom WJ. Intracavernosal injection and intraurethral therapy for erectile dysfunction. Urol Clin North Am. 2001;28(2):343–54.

Melnik T, Soares BG, Nasello AG. The effectiveness of psychological interventions for the treatment of erectile dysfunction: systematic review and meta-analysis, including comparisons to sildenafil treatment, intracavernosal injection, and vacuum devices. J Sex Med. 2008;5(11):2562–74.

Montague DK, Barada JH, Belker AM, et al. Clinical guidelines panel on erectile dysfunction: summary report on the treatment of organic erectile dysfunction. The American Urological Association. J Urol. 1996;156(6):2007–11.

Montorsi F, Adaikan G, Becher E, Giuliano F, Khoury S, Lue TF, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med. 2010;7(11):3572–88.

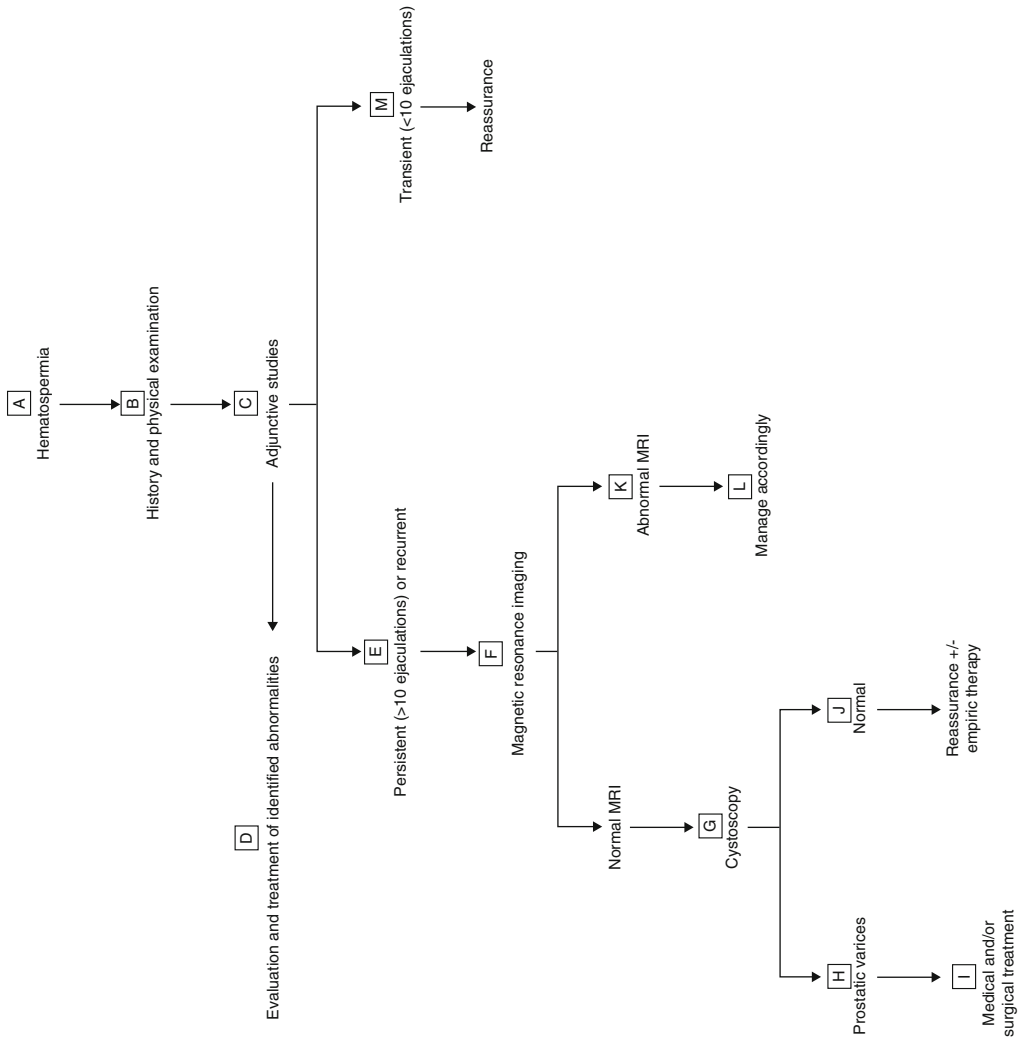
Mulhall JP, Montorsi F. Evaluating preference trials of oral phosphodiesterase 5 inhibitors for erectile dysfunction. Eur Urol. 2006;49(1):30–7.

Mulhall JP, Althof SE, Brock GB, Goldstein I, Junemann KP, Kirby M. Erectile dysfunction: monitoring response to treatment in clinical practice–recommendations of an international study panel. J Sex Med. 2007;4(2):448–64.

Qaseem A, Snow V, Denberg TD, et al. Hormonal testing and pharmacologic treatment of erectile dysfunction: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2009;151(9):639–49.

Tsertsvadze A, Fink HA, Yazdi F, et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. Ann Intern Med. 2009;151(9):650–61.

# Chapter 10
# Hematospermia




J.P. Mulhall et al., *Clinical Care Pathways in Andrology*, DOI 10.1007/978-1-4614-6693-2_10,

## (A)

Hematospermia is defined as the presence of grossly visible blood in the semen. Although the vast majority of cases are the result of a benign condition and are self-resolving, the condition can be very distressing to the patient. While initially the blood is bright red, with time the usual degradation of blood products will result in changes in color to rust and brown in nature. In cases where it is unclear if the discoloration is blood, especially when very dark and a malignant melanoma is considered, early evaluation is warranted. As apparent blood in semen may actually result from contamination of semen with blood from the patient's sexual partner, this also needs to be ruled out. In general, the goal of evaluation is to identify underlying treatable or serious pathologic conditions.

## (B)

The initial evaluation is composed of a history (Table 10.1), physical examination (Table 10.2), and urine testing. In order to distinguish between transient and persistent hematospermia, the physician should elicit the number of episodes. Although some clinicians use duration of time with hematospermia in order to determine which patients need further evaluation, varying frequency of ejaculations between men may render this approach less reliable, and thus we rely on the actual number of ejaculations in which blood has been present. As mentioned above, black discoloration of semen suggests the possibility of melanospermia, which may result from the very rare malignant melanoma of the prostate or seminal vesicles. History of sexually transmitted infection (STI) may indicate causes of hematospermia such as urethritis, prostatitis, or epididymitis. Less likely is tuberculosis (TB), human immunodeficiency virus (HIV), cytomegalovirus, hydatid disease, and bilharziasis. History of genitourinary region trauma or instrumentation (especially transrectal prostate biopsy and brachytherapy for prostate cancer) is associated with transient hematospermia.

A history of hypertension or bleeding disorders and use of anticoagulant medications should also be defined. Common iatrogenic causes of hematospermia include prostate needle biopsy, brachytherapy, vasectomy, orchiectomy, or high intensity focused ultrasound of the prostate. Hematospermia due to these causes is inevitably self-limiting and the patient should be reassured.

Physical exam is important for localizing or identifying systemic sources of hematospermia. Blood pressure should always be measured since severe hypertension has been associated with hematospermia. Abdominal palpation should be performed to rule out hepatosplenomegaly as an indicator of potential hematological disorder. Genital exam should focus on the urethral meatus, testes (since testis tumors may rarely present with hematospermia), epididymes, and spermatic cords including the vasa deferentia. Each vas should be carefully palpated along its entire course to identify nodularity or induration (suggesting tuberculosis). The penis should be examined for bleeding sources such as shaft lesions or a torn frenulum. Digital rectal exam (DRE) is performed to evaluate for prostate tenderness, masses, nodularity, midline cystic structures, or seminal vesicle pathology (although the seminal vesicles are often difficult to palpate). The urethral meatus should be reexamined after DRE to check for bloody discharge.

## (C)

The need for adjuvant diagnostic studies (Table 10.3) in individual patients is based on the findings gleaned from the history and physical examination. Patients who report hematuria in conjunction with hematospermia should be referred to a urologist for appropriate evaluation that may include

urine cytology, upper urinary tract imaging, and cystourethroscopy. Urinalysis and urine culture will confirm the presence of infection and demonstrate or rule out hematuria. A complete blood count and coagulation profile can further define bleeding diatheses or chronic illnesses. Urethral swabs may be obtained to rule out chlamydia, gonococcal, and nonspecific urethritis, particularly in younger men with an STI history. Serum prostate-specific antigen (PSA) testing should be obtained in men greater than 40 years old or in younger men at high risk for prostate cancer. If history suggests exposure to tuberculosis or sterile pyuria was noted on urine culture, tuberculin skin test and acid-fast bacilli test is required for urine and semen. If schistosomiasis is suspected, a semen analysis (SA) can be performed to check for eggs. Some men are uncertain whether they have hematospermia. Uncertainty can be resolved with a condom test, in which ejaculate collected from a condom is assessed for blood, or with standard semen analysis. SA with chromatography can be used to distinguish erythrocytes from melanin. In certain circumstances, semen culture may also shed some light on the underlying etiology.

## (D)

Infection should be treated with appropriate antibiotics or antiviral agents. Patients with bleeding abnormalities, systemic hypertension, melanoma, or hepatosplenomegaly should be referred to specialists that are equipped to manage these conditions.

## (E)

Men with persistent or recurrent hematospermia are considered to be at higher risk for an underlying cause of bleeding that will not spontaneously resolve. Though there are no established definitions, in our practice we consider hematospermia that has not resolved within ten ejaculations to be persistent. Hematospermia that resolves for greater than 1 month (or more than one ejaculation) but then returns is considered recurrent. Patients with persistent or recurrent hematospermia should be evaluated for the underlying etiology of hematospermia.

## (F)

Further evaluation for malignancy or anatomic etiology of hematospermia is appropriate for high-risk patients. Specific testing will depend on patient characteristics and clinical judgment based on history, physical exam, and initial testing. Some authorities advocate utilization of transrectal ultrasonography, which can easily demonstrate calculi in the prostate, ejaculatory ducts, and seminal vesicles, as well as soft tissue masses and cysts. Magnetic resonance imaging (MRI), however, is now considered the gold standard for imaging the prostate, vasal ampulla, and seminal vesicles. We perform this using a transrectal probe (endorectal coil MRI) and have this conducted with and without gadolinium. MRI can demonstrate inflammatory, infective, and neoplastic changes as well as cyst formation. MRI, unlike TRUS, can identify hemorrhage within the prostate or seminal vesicles. When performed with angiography, MRI can also localize sites of active bleeding.

**(G)**

The presence of persistent hematospermia in the context of normal MRI is an indication for cystourethroscopy (Table 10.4). Cystourethroscopy allows for direct visualization of urethral or prostatic lesions, including, stones, foreign bodies, and vascular abnormalities. Midline cysts can be addressed via transurethral incision and drainage. Often, a normal MRI in the presence of persistent or recurrent hematospermia results from prostatic "varices," which are large mucosal veins in the prostatic urethra that tear during orgasm when the intra-prostatic urethra is a high-pressure zone (bladder neck and external sphincter are closed at this time).

**(H)**

In rare cases, these prostatic varices may only be apparent in the setting of a pharmacologically induced erection. In this setting, cystourethroscopy may still be performed with a flexible endoscope.

**(I)**

Fulguration can be used to treat urethral or prostatic urethral varicosities that cause persistent hematospermia. The use of 5-alpha-reductase inhibitors, such as finasteride, has been utilized (without definitive evidence supporting its use) by some clinicians to treat this condition, very much in the same fashion that these agents are used for chronic hematuria believed to result from prostatic varices.

**(J)**

If MRI and cystourethroscopy do not demonstrate any abnormalities, the patient can be reassured that there is no serious etiology underlying the hematospermia. Empiric therapy may include 5-alpha-reductase inhibitors or antibiotic therapy. Fluoroquinolones are often used for 2 weeks in younger men to cover enterobacteria and Chlamydia, while coverage for enterobacteria is usually sufficient in older men. Non-steroidal anti-inflammatory (NSAID) medications can also be empirically used to reduce inflammation that may be contributing to hematospermia.

**(K)**

Most abnormalities identified on MRI are benign. These commonly include midline prostatic cysts that cause obstruction and potentially irritation of the ejaculatory ducts and seminal vesicles.

**(L)**

Any overt prostate or seminal vesicle pathology will need further evaluation by a urologist. Primary seminal vesicle tumors are exceedingly rare and are treated on a case-by-case basis with a combination of surgery, chemotherapy, and radiation therapy. Extension of prostate cancer into the seminal

vesicles is much more common but rarely presents with hematospermia. MRI can demonstrate blood within the seminal vesicles without any overt mass lesion. Investigational treatments including aspiration and/or injection of sclerosing agents into the seminal vesicles may be considered in such cases.

## (M)

Patients who are less than 40 years old and present with hematospermia in fewer than 10 episodes are at very low risk for the presence of any significant underlying pathology. Empiric therapy with antimicrobials or anti-inflammatory agents may be considered but is not supported by robust clinical evidence. These men should be reassured about the extremely low likelihood of significant pathology including cancer and counseled that further testing is only necessary if the hematospermia persists or recurs.

**Table 10.1** Key history points in patients with hematospermia

| |
|---|
| Duration of hematospermia |
| Number of ejaculations with bloody semen |
| History of hypertension |
| History of bleeding diathesis |
| Genital trauma history |
| STI history |
| Urogenital procedures |
| Exotic travel |
| Family history of prostate cancer |
| Anticoagulant medication use |

**Table 10.2** Key physical examination points in patients with hematospermia

| |
|---|
| Blood pressure |
| Hepatosplenomegaly |
| Urethral meatus |
| Preputial pathology |
| Vasal abnormalities |
| Epididymal induration |
| Testicular pathology |
| Digital rectal examination |

**Table 10.3** Adjuvant testing in patients with hematospermia

| |
|---|
| CBC |
| Coagulation profile |
| Urinalysis |
| PSA |
| Urethral swab |
| Semen culture |
| Prostate MRI |
| Cystoscopy |

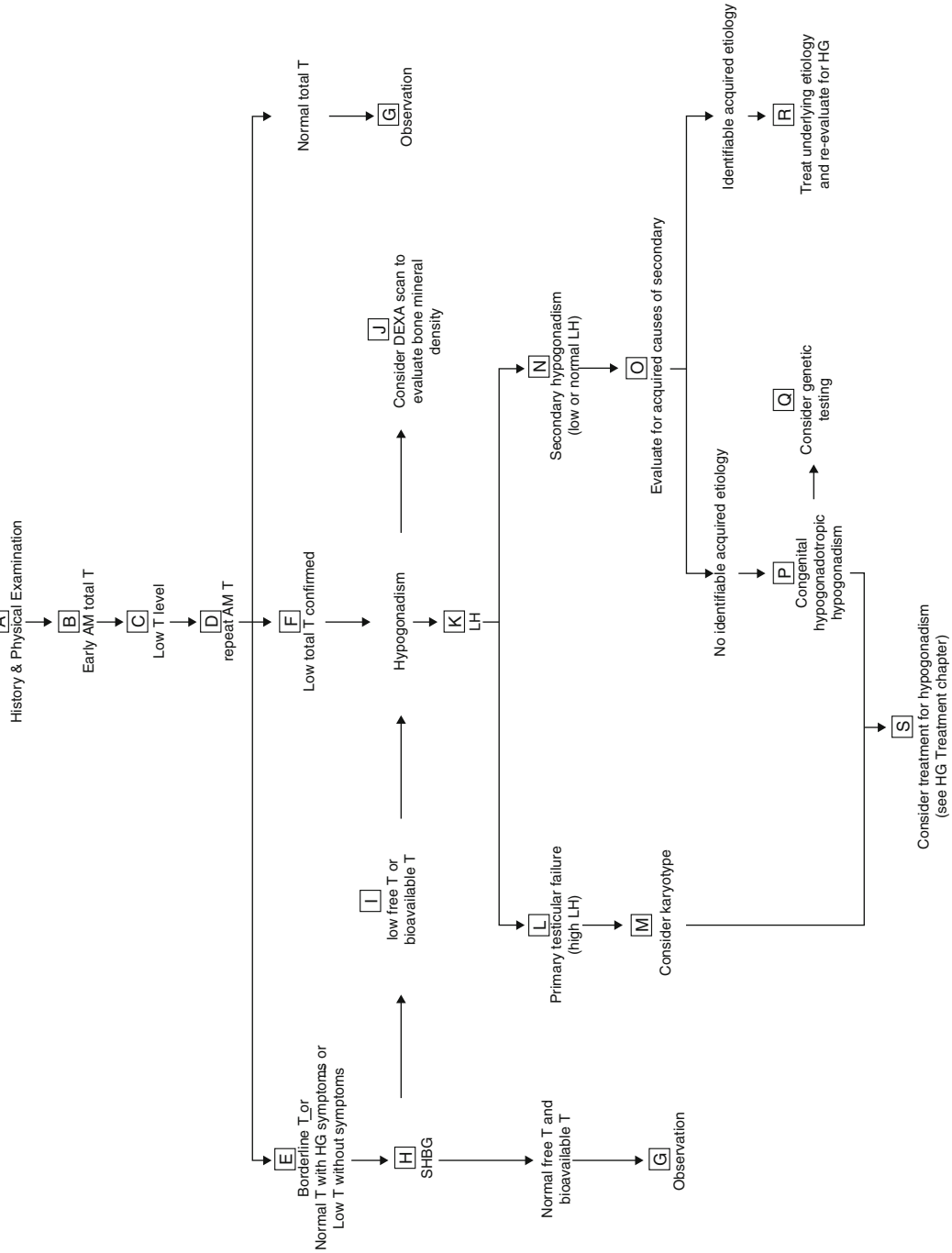
**Table 10.4** Management strategies in patients with hematospermia

| Condition | Evaluation | Treatment |
|---|---|---|
| Prostate biopsy | History | Self-limiting |
| Prostatitis | History<br>Urinalysis<br>Urine culture | Treat underlying cause |
| Prostatic telangiectasia | Cystourethroscopy | Fulguration<br>5-alpha-reductase inhibitors |
| Prostatic varices | Cystourethroscopy | Fulguration<br>5-alpha-reductase inhibitors |
| Prostatic calculi | Cystourethroscopy TRUS | Observation<br>Alkalinization of urine<br>Transurethral stone procedures |
| Prostatic utricle dilation | MRI, Cytourethroscopy | Observation<br>Transurethral unroofing |
| Transurethral resection of prostate | History | Self-limited |
| Prostate brachytherapy | History | Self-limited |
| Prostate cancer | Prostate biopsy | Active surveillance<br>Radical prostatectomy<br>Radiation therapy<br>High-intensity focused ultrasound<br>Androgen deprivation therapy<br>Chemotherapy |
| Urethral cysts | Cystourethroscopy | Observation<br>Transurethral fulguration |
| Urethral polyps | Cystourethroscopy | Observation<br>Transurethral fulguration |
| Urethral condylomata | Cystourethroscopy | Transurethral fulguration |
| Urethral strictures | Cystourethroscopy | Observation<br>Direct visual internal urethrotomy |
| Urethral stones | Cystourethroscopy | Transurethral extraction |
| Seminal vesicle cysts | MRI | Observation |
| Idiopathic seminal vesicle hemorrhage | MRI | Observation |
| Seminal vesicle primary malignancy | MRI | Treat case-by-case |
| Tuberculosis | Acid-fast bacilli stain | Treat underlying condition |
| HIV | HIV test | Treat underlying condition |
| Cytomegalovirus | Viral culture | Antivirals |
| Herpes simplex virus | Serum titers | Antivirals (acyclovir, valacyclovir) |
| *Chlamydia trachomatis* | Serum titers | Azithromycin and doxycycline |
| *Enterococcus faecalis* | Semen culture | Ampicillin or other antibiotics |
| *Ureaplasma urealyticum* | Semen analysis | Doxycylcine or other antibiotics |
| Testicular trauma | History<br>Scrotal ultrasound | Observation<br>Surgical therapy if indicated |
| Perineal trauma | History | Self-limiting |
| Transrectal prostate needle biopsy | History | Self-limiting |
| Hypertension | Blood pressure measurement | Anti-hypertensive medication<br>Lifestyle modification |
| Chronic liver disease | Liver function tests | Treat underlying condition |
| Lymphoma | Serum tests | Treat underlying condition |
| Bleeding diatheses | Serum tests | Treat underlying condition |

## Suggested Reading

Ahmad I, Krishna NS. Hemospermia. J Urol. 2007;177(5):1613–8.
Aslam MI, Cheetham P, Miller MA. A management algorithm for hematospermia. Nat Rev Urol. 2009;6(7):398–402.
Kumar P, Kapoor S, Nargund V. Haematospermia—a systematic review. Ann R Coll Surg Engl. 2006;88(4):339–42.
Mulhall JP, Albertsen PC. Hemospermia: diagnosis and management. Urol. 1995;46(4):463–7.
Munkelwitz R, Krasnokutsky S, Lie J, Shah SM, Bayshtok J, Khan SA. Current perspectives on hematospermia: a review. J Androl. 1997;18(1):6–14.
Papp GK, Kopa Z, Szabo F, Erdei E. Aetiology of haemospermia. Andrologia. 2003;35:317.

# Chapter 11
# Hypogonadism: Evaluation




J.P. Mulhall et al., *Clinical Care Pathways in Andrology*, DOI 10.1007/978-1-4614-6693-2_11,

Hypogonadism (HG), also referred to as testosterone (T) deficiency, refers to a clinical syndrome that results from insufficient serum levels of T to effect adequate action in androgen-sensitive tissues. A constellation of signs and symptoms are associated with HG (Table 11.1). The term HG implies that one or more of these signs and symptoms are present in addition to low serum levels of T. The main difficulty in diagnosing patients with HG is that many of the signs and symptoms of HG are non-specific. The goals of diagnostic evaluation are to identify underlying etiologies (Table 11.2), define which patients are appropriate candidates for treatment, and determine which patients are at risk for medical conditions that are known to result from long-term uncorrected HG (glycemic intolerance, osteoporosis). Diagnosis and treatment of HG may also be relevant in select cases of male factor subfertility, although the most commonly used methods of T replacement therapy (TRT) actually impair spermatogenesis and are contraindicated in this context.

## (A)

The diagnosis of HG begins with clinical suspicion for the condition based on history and physical examination. The presence of signs or symptoms of HG (Table 11.1) should prompt measurement of the serum testosterone level. Several validated questionnaires are available which assess for symptoms consistent with HG (Appendices 1 and 2). Serum testosterone measurement is also recommended in certain clinical conditions that are associated with a high risk of androgen deficiency (Table 11.3), even in the absence of typical symptoms of HG. It is also particularly important to note whether a patient has a history of prostate or breast cancer, since all testosterone products have explicitly defined in their label that testosterone replacement therapy (TRT) is contraindicated in these conditions. The contraindication is largely historical in nature, and it should be noted that an increasing number of men's health authorities consider TRT in select with prostate cancer patients. As part of the evaluation for HG, transient causes for low T must be considered and ruled out. These include acute or sub-acute illness, chronic use of opiates or steroids, excessive exercise, and eating disorders such as bulimia and anorexia. It is recommended that serum T levels not be obtained during an illness because they may be falsely low. Treatment directed towards the underlying cause will usually restore normal T levels. Thus, the history should focus on defining symptoms consistent with HG and also searching for conditions that may be associated with low T. Physical examination should focus on body habitus, in particular three aspects of this: (1) look at adipose tissue distribution as low T is associated with central obesity, (2) a general assessment of muscle development is also important given the link between low T and sarcopenia (muscle loss), and (3) assess body hair distribution, as low T is associated with loss of pubic, axillary, and body hair. Men sometimes complain that they no longer need to shave as often. Examination for gynecomastia should be performed as changes in testosterone:estradiol ratio can cause breast development. It is important on exam to differentiate between chest fat pads and true gynecomastia. Genital examination should assess penile size as men with low T from pre-pubertal age may have microphallus. The most important aspect of the examination is assessment of testicular volume and consistency. Small and/or soft testes are often associated with a low serum T level. Furthermore, an assessment for the presence of a varicocele or varicoceles is important given the link between the latter and low T.

## (B)

When signs and/or symptoms are consistent with the diagnosis of HG, a morning serum total testosterone level should be obtained. The importance of obtaining a level in the morning is based on the observation that peak T levels occur early in the day and decline thereafter. This diurnal variation is especially pronounced in younger men. In middle-aged and older men the effect persists but may be

blunted. Fasting before the blood draw is not necessary. We recommend that patients do the blood draw before 10 AM. In the infertile male measuring serum follicle stimulating hormone (FSH) level is also advisable. While measurement of total T level is a minimum requirement, some authorities measure a serum-free T level also, although it is acceptable to withhold this until the total T level is known. Other tests that are done routinely as an initial screen by some authorities include serum luteinizing hormone (LH) and estradiol (E2) level. It is perfectly acceptable to commence with a total T level alone initially (and an FSH level in infertile or young men).

## (C)

HG is a clinical diagnosis and there is no specific value for serum T that defines the diagnosis. However, many clinicians consider morning T levels of <350 ng/dL to be suggestive of low T and levels <300 ng/dL to be definitive for low T. Different laboratories use their own ranges for normal serum T levels. The lower end of each laboratory's range may also be used as a threshold for the diagnosis of HG.

## (D)

Given the significant intra and inter-individual variability in serum T levels, it is prudent to repeat a morning serum level prior to embarking on treatment or further work-up for HG. Approximately one third of men with a morning total T in the mildly hypogonadal range will have normal serum T upon repeat testing.

## (E)

In some patients the repeat total T level is borderline and the diagnosis of HG remains unclear. Other patients may have significant signs or symptoms of HG but normal levels of T, or low serum T without typical signs or symptoms of HG. In these patients adjunctive serum hormonal tests may be obtained to help clarify or define the HG status.

## (F)

The diagnosis of HG is made when the repeated serum morning total T level is low. It is important to confirm the initial level since a significant number of men may have a normal T level on repeat analysis.

## (G)

If the repeat serum total T level or the free and bioavailable T levels are normal then no further testing is warranted. In these cases, we reassure the patient and recommend serum T level assessment in 6–12 months, presuming he continues to manifest the signs or symptoms that prompted the suspicion for HG. If the levels are considered borderline, however, repeat serum testing for HG may be obtained in a shorter time frame.

## (H)

Several adjunctive blood tests are available to help further characterize androgen status when the total serum T level is borderline or discrepant with the patient's clinical presentation. Specifically, these tests can reveal how much of the total T is available for use, or "bioavailable." Circulating T exists in the bloodstream in three states: tightly bound to sex hormone binding globulin (SHBG) and therefore physiologically unavailable, loosely bound to albumin and potentially physiologically available, or unbound (free) and physiologically available. The serum total T assay measures the sum of T in all three states and is usually well correlated with the amount of bioavailable T (defined as albumin-bound T plus free T). Alterations in SHBG levels do not affect the serum total T level but do affect the free T and bioavailable T levels. In patients with altered SHBG, therefore, the serum total T may not be reflective of the patient's true androgenic status. Medical conditions associated with *increased* SHBG values include aging, liver disease, hyperthyroidism, HIV, and use of anticonvulsant medications. These patients may have decreased free or bioavailable T despite normal total T levels and are at risk for signs, symptoms and sequelae of HG. Conditions associated with *decreased* SHBG values include obesity, hypothyroidism, steroid use, diabetes mellitus, and the nephrotic syndrome. These patients may have low total T levels but normal amounts of free and bioavailable T.

## (I)

Assays for direct measurement of free and bioavailable T are highly variable in technique and accuracy and must be cautiously interpreted. These assays are best performed by a reference laboratory and should be interpreted using each laboratory's reference range. Another approach is calculation of free and bioavailable T from measured serum values of total T, SHBG, and albumin, which has a decent correlation with direct measurement in serum. Several equations are available for these calculations and many laboratories will report results of calculated free and bioavailable T. Alternatively, free online calculators are available (http://www.issam.ch/freetesto.htm). Although consensus threshold values do not exist to define low free and bioavailable T, most investigators consider free T < 9 ng/dL or bioavailable T < 150 ng/dL to be diagnostic of HG when clinical signs or symptoms are present.

## (J)

Long-term HG has been identified as a risk factor for decreased bone density. Men with low T have approximately double the fracture rate compared to men with normal T concentrations. Treatment of men with HG and bone density loss (osteopenia or osteoporosis) has been shown to improve bone density. Dual Energy X-ray Absorptiometry (DEXA) scans are considered non-invasive, inexpensive imaging tests with low radiation exposure that can be used to predict risk of fracture. Therefore we recommend a low threshold for obtaining DEXA scans in men with moderate to severe HG. DEXA scans typically evaluate the bone mineral density of the lumbar spine, femoral neck, and hip (axial scans) and forearm (appendicular scan) since they are the points considered most likely to fracture with osteoporosis. DEXA scan results are reported in two forms: a *T* score and a *Z* score. The *T* score is used to compare bone density of a given patient with that of young, healthy men. A *T* score above −1.0 standard deviations below the young adult male is considered normal, −1.0 to −2.5 is considered osteopenia, and below −2.5 standard deviations below the young adult male is considered osteoporosis. The *Z* score is used to compare bone density of a given patient with that of age and race-matched men. *Z* scores are assigned as follows: above −1.0 standard deviations below

the age/race-matched male is considered equivalent bone density, −1.0 to −2.5 is considered lower than average for matched peers (bottom 1–14 %), and below −2.5 is considered much lower than matched peers (bottom 1 %). Favorable *Z* scores are helpful as comparisons but do not necessarily mean that a patient is not at risk for fracture, since the matched group may overall be at risk for osteoporosis.

## (K)

The complete evaluation of men with HG includes a serum luteinizing hormone (LH) concentration. LH is produced by the anterior pituitary and stimulates testicular Leydig cells to produce T. LH production is regulated by the hypothalamus via pulsatile secretion of gonadotropin releasing hormone (GnRH) that reaches the anterior pituitary through the hypophyseal portal system and is subject to negative feedback mediated by the serum T and estradiol levels. The serum LH level is the best indicator of whether the HG is primary (testicular) or secondary (central). In reality, we measure free T, SHBG, LH, and estradiol levels when the initial total T level is low or borderline.

## (L)

The diagnosis is primary (testicular failure) when low T is accompanied by a high serum LH level. High LH occurs in such cases due to absent feedback inhibition of the pituitary. Primary testicular failure is the most common cause of HG and may result from many clinical conditions including gonadotoxin exposure, prior testicular injury, and Klinefelter syndrome (KS). However, in most cases an etiology is not identifiable and the HG is classified as idiopathic primary testicular failure.

## (M)

Non-mosaic Klinefelter syndrome (KS) (47, XXY) is the most common chromosomal anomaly in men, occurring in 1/500 males within the general population. Although easily diagnosed by serum karyotyping, KS is an often-overlooked cause of primary testicular failure. Some patients exhibit the classically described features of under-virilization, tall stature, long limbs, and pubertal delay; but other patients have many phenotypic qualities that overlap with those of normal men within the general population. Affected men invariably have low testicular volumes. Cytogenetic evaluation for KS should therefore be performed in any man with unexplained primary testicular failure and small volume testes (<5 mL per testis). A simple blood test or buccal swab can assess for this.

## (N)

The diagnosis is secondary hypogonadism when low T is accompanied by low or normal serum LH. HG results in such cases from insufficient hypothalamic or pituitary drive of testicular T production. Secondary HG may be congenital or acquired. Congenital causes are rare and include Kallman's syndrome and idiopathic hypogonadotropic hypogonadism (IHH). Acquired causes include anabolic steroid abuse, pituitary infarction, pituitary irradiation, pituitary tumors (especially prolactinomas), and hemochromatosis.

## (O)

All patients with secondary hypogonadism should be evaluated for acquired causes, which may be amenable to treatment and may also be medically important to identify. In particular, tumors of the sella turcica and pituitary should be ruled out with magnetic resonance imaging (MRI) in all patients with the following conditions: (1) serum T < 150 ng/dL and pan-hypopituitarism, (2) serum prolactin > 150 ng/dL, and (3) HG associated with headaches or visual disturbances (in particular bitemporal hemianopsia). It is also important to directly ask the patient about anabolic steroid abuse. Some androgenic compounds are not detectable by serum testosterone assays. These patients are typically very muscular but may have small, soft testes and usually have highly suppressed serum LH levels. Endogenous T production is also suppressed, leading to very low serum total T levels despite abuse of exogenous androgens (when the exogenous androgen is not detectable by standard serum T assays).

## (P)

Congenital hypogonadotropic hypogonadism (CHH) is characterized by lifelong hypogonadism that results from inadequate central gonadotropin production. These disorders either result from defects in the gonadotropin production pathway or failed migration of GnRH neurons from the olfactory placode to the hypothalamus during embryonic development. The latter case may be associated with complete (anosmia) or partial loss of olfaction (hyposmia) and is referred to as Kallman's syndrome. When olfaction is normal, the condition is referred to as isolated CHH. Affected patients are typically tall with small testes and underdeveloped penises. Most patients are diagnosed as adolescents but some escape diagnosis during childhood and present with infertility.

## (Q)

Patients with CHH may benefit from genetic testing, though such tests are not yet widely available. Genetic anomalies are detectable in one third of patients. Diagnosis provides insights into the patient's underlying pathophysiology and can be informative about the risks of CHH in siblings and offspring.

## (R)

Some acquired etiologies of HG are amenable to treatment, which often reverses the HG and ameliorates the need for TRT. Most patients recover testicular function after cessation of anabolic steroid abuse, in particular if the exposure has been short, though recovery may take up to 1–2 years and may require use of agents such as clomiphene citrate or human chorionic gonadotropin (hCG). Pituitary tumors may be treated medically (bromocriptine or cabergoline treatment for prolactinoma) or by surgical excision. Pituitary insufficiency may be treated with gonadotropin replacement therapy.

## (S)

Many men with confirmed HG may benefit from TRT in multiple ways: improved overall sense of wellbeing, libido, energy, stamina, muscle strength, alertness, and bone mineral density, to name a few. HG treatment if effective (good serum levels associated with symptom/sign improvement) may be lifelong, however, and side effects and limitations of various TRT options must be carefully considered and discussed with patients.

## Appendix 1. Androgen Deficiency In The Aging Male (ADAM) Questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased 'enjoyment of life'?
6. Are you sad or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

A positive questionnaire result is defined as a 'yes' answer to questions 1 or 7 and any 3 other questions

## Appendix 2. Aging Male Symptoms (AMS) Questionnaire

| | None (1) | Mild (2) | Moderate (3) | Severe (4) | Extremely Severe (5) |
|---|---|---|---|---|---|
| Decline if general feeling of well-being | | | | | |
| Joint pain and muscular ache | | | | | |
| Excessive sweating | | | | | |
| Sleep problems | | | | | |
| Increased need for sleep, often feeling tired | | | | | |
| Irritability | | | | | |
| Nervousness | | | | | |
| Anxiety | | | | | |
| Physical exhaustion, lacking vitality | | | | | |
| Decrease in muscular strength | | | | | |
| Depressive mood | | | | | |
| Feeling that you have your peak | | | | | |
| Feeling burnt out, hitting rock-bottom | | | | | |
| Decrease in beard growth | | | | | |
| Decrease in ability/frequency to perform sexually | | | | | |
| Decrease in number of morning erections | | | | | |
| Decrease in sexual desire/libido | | | | | |

## Appendix 3. Quantitative Androgen Deficiency In The Aging Male (QADAM) Questionnaire

How would you rate your libido (sex drive)?
1 (terrible) 2 (poor) 3 (average) 4 (good) 5 (excellent)

How would you rate your energy level?
1 (terrible) 2 (poor) 3 (average) 4 (good) 5 (excellent)

How would you rate your strength and/or endurance?
1 (terrible) 2 (poor) 3 (average) 4 (good) 5 (excellent)

How would you rate your 'enjoyment of life'?
1 (terrible) 2 (poor) 3 (average) 4 (good) 5 (excellent)

How would you rate your happiness level?
1 (terrible) 2 (poor) 3 (average) 4 (good) 5 (excellent)

How strong are your erections?
1 (extremely weak) 2 (weak) 3 (average) 4 (strong) 5 (extremely strong)

How would you rate your ability to play sports?
1 (terrible) 2 (poor) 3 (average) 4 (good) 5 (excellent)

How often do you fall asleep after dinner?
1 (never) 2 (1-2/week) 3 (3-4/week) 4 (5-6/week) 5 (every night)

How would you rate your work performance?
1 (terrible) 2 (poor) 3 (average) 4 (good) 5 (excellent)

How much height have you lost?
1 (2" or more) 2 (1.5-1.9") 3 (1-1.4") 4 (0.5-0.9") 5 (none-0.4")

**Table 11.1** Symptoms and signs of hypogonadism

| |
|---|
| *Symptoms* |
| Incomplete or delayed sexual development |
| Loss or decrease of spontaneous or nocturnal erections |
| Decreased libido |
| Breast tenderness |
| Sub-fertility |
| Hot flashes |
| Decreased energy |
| Depressed or irritable mood |
| Impairment in concentration |
| Muscle weakness or reduced endurance |
| Reduced energy, fatigue |
| Reduced ejaculate volume |
| Decreased penile sensitivity |
| Delayed/difficulty achieving orgasm |
| Sleeping difficulty |
| *Signs* |
| Decreased body or facial hair |
| Gynecomastia |
| Small testes |
| Loss of bone density |
| Loss of muscle mass (sarcopenia) |
| Anemia |
| Increased body fat |
| Decreased nocturnal erections |

**Table 11.2** Causes of hypogonadism

| |
|---|
| Hypogonadotropic HG (Kallman's syndrome, idiopathic) |
| Adrenal hypoplasia |
| Systemic malignancies |
| 5-alpha-reductase deficiency |
| Androgen insensitivity syndromes |
| Hypopituitarism |
| Hypothyroidism |
| Malnutrition |
| Idiopathic testicular failure |
| Prior testicular vascular or traumatic insults |
| Medication effects |
| Gonadotoxin exposure (chemotherapy, radiation, medications) |
| Clinical depression |
| Pituitary macro-adenoma |
| Prolactinoma |

**Table 11.3** Conditions associated with hypogonadism

| |
|---|
| Human immunodeficiency virus (especially when associated with cachexia) |
| End-stage renal disease |
| Osteoporosis and/or osteopenia |
| Diabetes mellitus |
| Male factor infertility/subfertility |
| Presence of a varicocele |
| Chronic obstructive pulmonary disease |
| Chronic glucocorticoid use |
| Chronic opioid use |
| Current or prior malignancy |
| Rheumatoid arthritis |
| Alcoholism |
| Chronic liver disease |

## Suggested Reading

Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab. 2007;92:4241–7.

Arver S, Lehtihet M. Current guidelines for the diagnosis of testosterone deficiency. Front Horm Res. 2009;37:5–20.

Cohen PG. Pitfalls in the diagnosis of testosterone deficiency. Aging Male. 2008;11(2):49–50.

Ghanem HM, Salonia A, Martin-Morales A. Physical examination and laboratory testing for men with ED. J Sex Med. 2012.

Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endo Metab. 2001;86:724–31.

Morales A, Lunenfeld B. International Society for the Study of the Aging Male: investigation, treatment and monitoring of late-onset hypogonadism in males. Aging Male. 2002;5(2):74–86.

Morales A, Collier CP, Clark AF. A critical appraisal of accuracy and cost of laboratory methodologies for the diagnosis of hypogonadism: the role of free testosterone assays. Can J Urol. 2012;19(3):6314–8.

Morley JE, Charlton E, Patrick P, Kaiser FE. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism. 2000;49:1239–42.

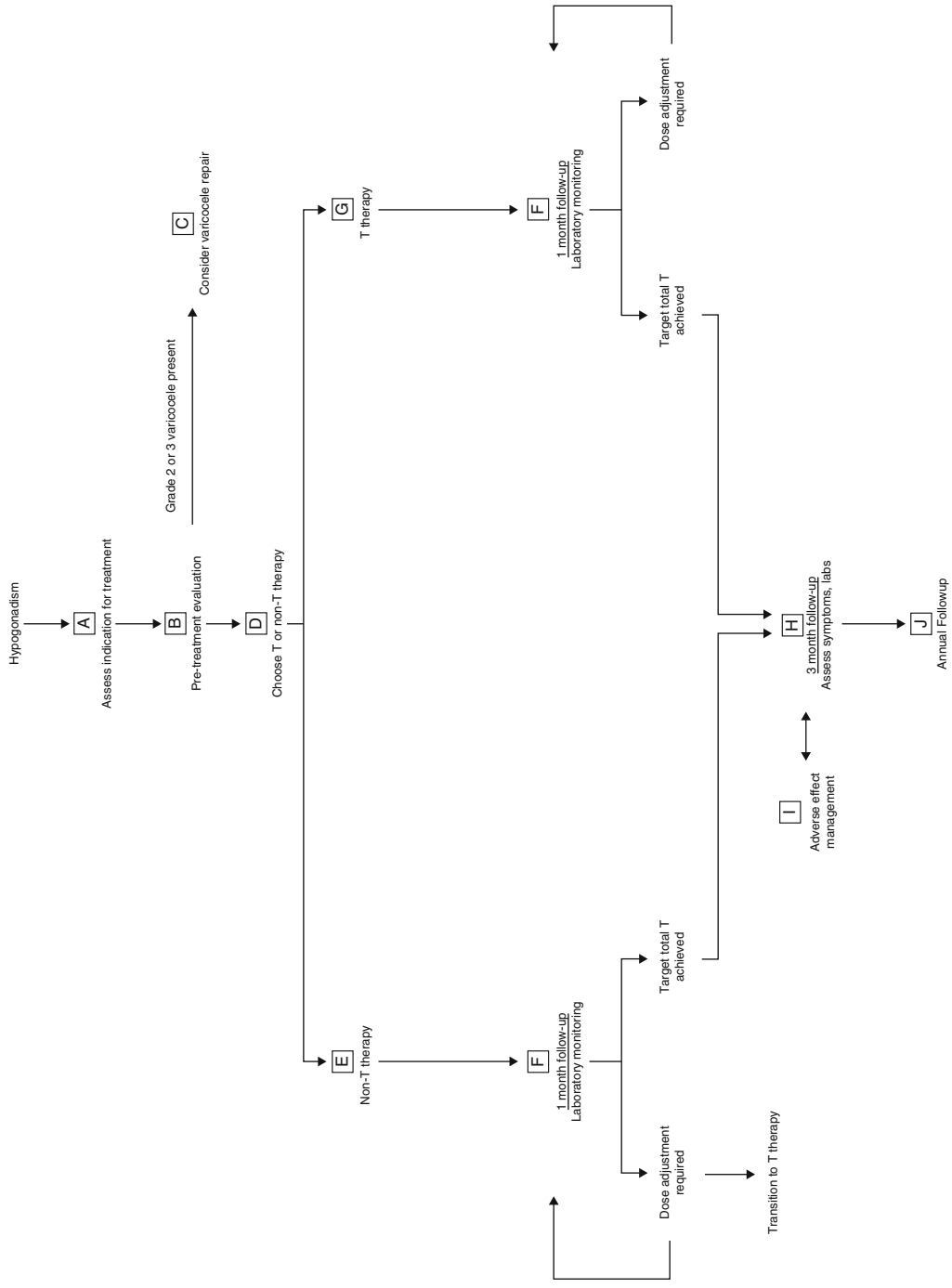
Petak SM, Nankin HR, Spark RF, Swerdloff RS, Rodriguez-Rigau LJ. American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients. Endocr Pract. 2002;8(6): 440–56.

Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. Arch Intern Med. 2006;166:1660–5.

Sokol RZ. Endocrinology of male infertility: evaluation and treatment. Semin Reprod Med. 2009;27(2): 149–58.

Young J. Approach to the male patient with congenital hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2012;97(3):707–18.

# Chapter 12
# Hypogonadism: Treatment




J.P. Mulhall et al., *Clinical Care Pathways in Andrology*, DOI 10.1007/978-1-4614-6693-2_12,

## (A)

Treatment for hypogonadism (HG) is indicated in men with laboratory evidence of testosterone (T) deficiency who have clinically significant signs or symptoms, and in whom contraindications to treatment (Table 12.1) are not present. Treatment may also be warranted to preserve bone density in asymptomatic hypogonadal men on high-dose chronic steroids and to promote short-term weight gain in asymptomatic hypogonadal men with HIV. Treatment to increase T levels in eugonadal men is medically ineffective and inappropriate. The primary goal of treatment varies between individuals depending upon the clinical presentation. In most men, treatment for HG is directed at reversing loss of bone density, improvement in endurance or work performance, improving libido, or improvement in quality of life. Non-testosterone-based therapies for low T may be utilized in the treatment of male subfertility.

## (B)

Candidates for HG treatment should be evaluated for the most common contraindications to therapy. All such patients should be evaluated for benign and malignant prostate diseases of the prostate. Risk assessment for prostate cancer should include a digital rectal examination and a serum PSA. Patients with abnormal digital rectal examinations or elevated serum PSA level should undergo full evaluation for prostate cancer (including prostate biopsy) prior to treatment for HG. Although the association between prostate cancer progression and T therapy in patients with mild to moderate HG is largely historical and unsubstantiated by rigorous studies, HG therapy in such cases should only be offered by experts in the highly monitored setting. Assessment of urinary symptoms that may result from benign prostatic hyperplasia (BPH) is best performed by utilization of the American Urologic Association Symptom Score (AUASS) questionnaire (Appendix 1), which is a validated instrument to assess severity of lower urinary tract symptoms. Patients with severe symptoms (AUASS >19) may be at risk for urinary retention or worsening of their symptoms with treatment and should be evaluated and potentially treated for BPH prior to initiation T therapy. Candidates for HG treatment should also be assessed for the risk of therapy-induced polycythemia by checking a serum complete blood count (CBC). Polycythemia may increase the risk of thromboembolic events, particularly in patients with cardiovascular disease, though thromboembolic complications of T therapy have rarely been reported in the literature. Most experts consider HG treatment to be contraindicated when the baseline hematocrit >50 %.

Physical exam should include testis measurement (with an orchidometer for the inexperienced clinician) and palpation of each spermatic cord for varicoceles. Varicoceles should be evaluated as the patient performs the Valsalva maneuver in the standing position. Finally, fertility planning status should be clearly ascertained in all men prior to starting TRT, since exogenous T severely diminishes spermatogenesis, while alternative strategies for increasing T levels may improve spermatogenesis parameters. Assumptions regarding individuals' fertility planning should never be made by the physician without specifically addressing the issue, irrespective of patient age. Regardless of the patient's fertility planning status, the expected effects of exogenous T supplementation (Table 12.2) should be discussed, especially its effects on sperm production and the potential induction of testicular atrophy should be clearly explained.

## (C)

There is substantial evidence that varicoceles are associated with HG. Surgical repair of clinically significant varicoceles (that is, grade 2 or 3 varicoceles) has, furthermore, been shown to increase T levels regardless of patient age or varicocele laterality. Although varicoceles have long been associ-

ated with decreased spermatogenesis, the concept linking varicoceles to HG is relatively new. Large, likely randomized, controlled studies will need to be conducted to define the exact role of varicocele ligation surgery in the management of hypogonadism.

## (D)

As previously stated, testosterone therapy suppresses spermatogenesis and should not be used in a man actively trying to conceive. Use of testosterone therapy in a man who desires future biological paternity is controversial. The most robust available data indicate that full recovery of sperm production occurs in 90 % and 100 % of patients within 1 and 2 years, respectively. Nonetheless, cases of permanent infertility resulting from T therapy have been reported. Many experts advocate delaying T therapy or using alternative non-T therapies for treatment of HG until a man no longer desires conception. If man has been unresponsive to non-T-based strategies and desires to move forward with exogenous T supplementation despite desiring to father children, we recommend that he bank sperm before starting T therapy.

## (E)

For men seeking fertility, or who may seek fertility in the future, most experts advocate alternative therapies to administration of exogenous T. Exogenous TRT, in any form, will increase circulating serum T levels but exert negative feedback signaling to the hypothalamus and anterior pituitary, thereby resulting in decreased luteinizing hormone (LH) elaboration. LH stimulates testicular Leydig cells to produce T, and decreased LH results in decreased testicular production of T. Testicular T concentration is normally hundreds of times greater than serum levels, and this high-T environment is essential for spermatogenesis. Inhibition of LH secondary to TRT may result in long-lasting impairment of sperm production. Several cases of permanent infertility after TRT have been reported. Since testicular T cannot be measured in the clinical setting, the aforementioned mechanism of infertility is often unappreciated by physicians who prescribe TRT. For patients who have HG in the setting of infertility, or have HG and are interested in future fertility, pharmacologic strategies for increasing T include estrogen receptor modulation, human chorionic gonadotropin (hCG) administration, and aromatase inhibition. Selection of an appropriate non-T therapy is based upon the clinical scenario and the preferences of the prescribing physician (Table 12.3).

*Clomiphene Citrate*

Estrogen receptor modulation raises T indirectly by blocking the coupling of estradiol, a T metabolite, with receptors. The lack of negative feedback from receptors stimulates increased endogenous production of LH and T if the testis is responsive. Clomiphene citrate (CC) 25 mg tablets taken orally every other day is an excellent starting dose. Increased testicular production of T has the benefit of improving, or at least not deleteriously impacting, the local environment for seminiferous tubules while simultaneously raising serum T levels. Since CC depends on raising LH levels that subsequently raise T levels, it is considered less effective in men who have relatively high baseline LH levels compared with those with low LH levels. Some evidence suggests that LH levels >6 IU/mL portend a poor prognosis for CC response. It should also be noted that some patients seem to respond less well symptomatically to CC compared with TRT, even with similar serum T levels. The reason for this is not well understood, but switching to TRT should be considered and discussed with men who have persistent HG symptoms on CC despite a eugonadal state.

*Human Chorionic Gonadotropin* (*hCG*)
This agent is a natural LH analog that stimulates testicular production of T. This medication is particularly useful in men with hypogonadotropic HG in whom pituitary gonadotropin production is insufficient, and in patients who have not responded adequately to estrogen receptor modulation or aromatase inhibition. hCG is typically administered 1,000–2,000 units intramuscularly or subcutaneously 2 or 3 times weekly. Dosing is then titrated to achieve nadir T levels (in the mid-normal range) 48 h after injection.

*Aromatase Inhibitors*
T is normally converted to estradiol (E2) by the enzyme aromatase in peripheral tissues. Serum T to E2 ratio (T:E2) should normally be ≥ 10. Men with HG and a T:E2 ratio < 10 can be treated with aromatase inhibitors. This class of medication increases T levels while simultaneously decreasing E2 levels, thereby having the effect of normalizing both serum T and the T:E2 ratio. Treatment is usually with anastrozole 1 mg PO daily. Men with Klinefelter syndrome have been shown to have a better response to testolactone 100–200 mg PO daily, although this medication in not available in the United States.

## (F)

For the reasons elucidated in the description of the pre-treatment evaluation, monitoring of patients on HG medications should include serum concentrations of T, E2, PSA, and CBC. Although no consensus exists on the optimal laboratory schedule, a reasonable regimen includes obtaining these levels at 1 month after starting non-T-based therapies and 2 weeks after exogenous T (except IM T when we check peak and trough levels) and again at 6 months following initiation of treatment. Laboratory assessment every 6–12 months thereafter is advised. We check an annual PSA and CBC with T levels. Based on symptomatic response and serum T concentrations, doses should be titrated so that total T levels fall between 400 and 700 ng/dL. We aim for 500–650 ng/dL as this represent the middle tertile of the range for most laboratories. Patients who decide they are no longer interested in fertility have the option of transitioning to the traditional T therapies.

## (G)

Men who are not interested in future fertility have many therapeutic options for replacing T.

*Androderm Patch*
The Androderm transdermal patch (5 g) or patches (10 g) is/are applied to a flat area of the body with minimal hair. Usually a spot on the stomach, back, thighs, or upper arms is chosen. Every 24 hours the patch is removed and a new one is applied in a different place. The patches have largely been supplanted by gel treatments since they are more efficacious, but some patients prefer them to injections or gel application. They are associated with about 2 % incidence of skin reactions, which vary from mild (itchiness) to severe (raised red wheals). The use of steroid creams can alleviate these symptoms but do not represent a long-term management strategy.

*Transdermal Gels*
Transdermal gels are currently the most commonly used first line T delivery modality. There are four FDA-approved products: AndroGel (Abbott), Testim (Auxilium), Fortesta (Endo), and Axiron (Lilly). The gels are applied daily since T serum levels start to decrease after 24 hours. AndroGel and Testim

need to be applied to areas of the body with minimal hair for maximal absorption. Axiron, on the other hand, is meant to be applied to the armpits in the same manner as deodorant. Fortesta is designed to be applied to the inner thighs.

*Buccal Tablets*
Buccal administration of T is an alternative therapy that involves placing an adhesive pellet between the gums and upper lip. This product, call Striant, is replaced every 12 hours and should be used continuously.

*Intramuscular Injectable Agents*
Short-acting intramuscular (IM) injections come in three forms: propionate, cypionate, and enanthate. T propionate requires daily injection and is therefore seldom used. T cypionate and enanthate are interchangeable. Injections are typically administered into the buttocks or anterior thigh. It is our preference to teach patients how to inject themselves. There are two major advantages to T injections over the other treatments. T injections can achieve higher blood concentrations than the other treatments, and this often translate into greater symptomatic improvement. T injections are generic and treatment is typically less expensive than with other methods. We commence patients at a dose of 200 mg IM which they receive the day they are getting trained. We recommend drawing blood the following day to assess the peak total T level. We then suggest that patients have a repeat blood test the day before or of the second IM injection (first at-home injection) to assess the nadir total T level. We routinely check an estradiol level at the same time as the "peak" blood draw to ensure the patient does not experience hyperestrogenism due to the likely high T level. Based on the peak and trough total T levels, we adjust dose and injection interval. For example, if the peak level were > 1,200 ng/dL the dose should be decreased. If the peak level were < 800 (which would be extremely unlikely if a correct injection technique has been used) the dose should be increased. If, on the other hand, the "trough" level were < 400 ng/dL then the interval between injections should be decreased. If the trough level were > 600 then the interval between injections should be increased. These injections cause a rapid rise in T serum concentrations over several days, which is followed by a gradual decline until the next injection. By reducing the discrepancy between peak and trough levels, we can minimize the likelihood of a T "crash," where men at the end of their injection cycle have symptoms of HG despite having normal serum total T levels. Some authorities use an alternative strategy of obtaining blood draws but, for the aforementioned reasons, we prefer the peak and trough approach.

*Oral Tablets*
Oral T undecanoate is not available in the United States because of the risk of liver toxicity.

*Testopel*
Subcutaneous T pellet administration involves insertion of extended-release T pellets (75 mg) under the skin (usually in the buttock or flank). The major benefit of this product, called Testopel, is that patients can avoid daily gel, patch administration, and avoid the need for self-administered injections. In our experience, Testopel pellets maintain normal T levels for 3–5 months and therefore need to be inserted only 3–4 times per year. The insertion procedure takes approximately 5 min. A 3 mm puncture incision is made, under local anesthesia, with an 11 blade over the upper buttock or flank (love-handle) areas. A specially designed disposable trochar is used to make channels within the subcutaneous fat. We usually commence by inserting ten pellets in V-shaped fashion (5 per channel). The pellets are passed through the sheath of the trochar once the stylet is removed. The puncture wound is sutured closed with a 5–0 plain catgut suture. A dry, sterile dressing is applied over the incision and a five pound sandbag is placed over the insertion area for 15 min after the procedure with the patient lying on the non-insertion side. We draw blood for total T levels at 1 and 3 months. The latter level dictates when the patient returns for the next insertion.

## (H)

Three months after starting therapy, the patient returns to the office for a thorough evaluation of T levels, symptom improvement, and adverse events. Most symptoms that are going to improve on therapy (T or non-T-based) should have done so by the third month. At this visit, a discussion is held about the patient's interest in continuing the therapy. For the patient on non-T-based therapy a discussion is held about the need or desire to transition to TRT. At this time, patients on TRT will be forewarned about the risk of testicular atrophy which we typically see occurring somewhere between 6 and 18 months of therapy. Again, this is not a concern with clomiphene, hCG, or aromatase inhibitors.

## (I)

Adverse effects can be managed by decreasing dosage, increasing intervals between treatments (for IM T), or switching to another treatment option. Adverse effects are specific to the modality of the agent used to treat HG. Common treatment-specific adverse effects are detailed in Table 12.2. Lack of serum T level response (seen in up to 20 % of patients using transdermal T agents) can also be considered an adverse response, and doses should be titrated or medications should be switched. Sudden large increases in PSA should prompt discontinuation of treatment and prostate biopsy if indicated. The mean change in PSA over the 12 months after commencing TRT is less than 0.5 ng/dL. Subjective failure of response in terms of HG symptoms is also a relative indication for changing medication or medication dose. Hematocrit (Hct) levels above 50 % need close monitoring and, in our practice, Hct levels > 55 % prompt referral to a hematologist for evaluation and discussion regarding phlebotomy.

## (J)

Annual follow-up should consist of DRE (for the patients who still has a prostate), assessment of urinary symptoms, and serum T levels, PSA, and CBC. Bone mineral density should be re-assessed by dual-energy X-ray absorptiometry (DEXA) in men with a history of osteopenia or osteoporosis. The use of one of the validated questionnaires allows a more objective comparison of symptomatic response (see Appendices at end of the *Hypogonadism Evaluation* chapter).

# AUA SYMPTOM SCORE

| Last Name | First Name | Date |
|---|---|---|
| | | |

**Highlight or bold or change font color of the response correct for you and type in your score in the far right box for all SEVEN questions**

1. **Incomplete emptying:** Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

| 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 |
|---|---|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | |

2. **Frequency:** Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?

| 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 |
|---|---|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | |

3. **Intermittency:** Over the past month, how often have you found that you stopped and started again several times when you urinated?

| 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 |
|---|---|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | |

4. **Urgency:** Over the past month, how often have you found it difficult to postpone urination?

| 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 |
|---|---|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | |

5. **Weak-stream:** Over the past month, how often have you had a weak stream?

| 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 |
|---|---|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | |

6. **Straining:** Over the past month, how often have you had to push or strain to begin urination?

| 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 |
|---|---|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | |

7. **Nocturia:** Over the past month or so, how many times did you get up to urinate from the time you went to bed until the time you got up in the morning?

| 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 |
|---|---|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | |

**Add up your scores for total AUA score =** _____

**Quality of Life Due to Urinary Symptoms:** 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? (Bold, Highlight, or Underline)

| Delighted | Pleased | Mostly satisfied | Mixed | Mostly dissatisfied | Unhappy | Terrible |
|---|---|---|---|---|---|---|

**Table 12.1** Proposed contraindications to testosterone replacement therapy

| |
|---|
| History of prostate cancer[a] |
| History of breast cancer[a] |
| Palpable prostate nodule |
| Elevated prostate-specific antigen serum level that has not been evaluated with prostate biopsy |
| Hematocrit >50 %[a] |
| Untreated severe obstructive sleep apnea[a] |
| Severe lower urinary tract symptoms secondary to benign prostatic hyperplasia[a] |
| Uncontrolled or poorly controlled heart failure |
| Desired future fertility potential[a] |

[a]Some authorities identify these conditions as precautions and not contraindications

**Table 12.2** Expected effects of increasing serum testosterone levels

| |
|---|
| Improved libido |
| Improved erections and/or response to PDE-5 inhibitors |
| Improved overall sense of well-being |
| Improved energy |
| Improved mood |
| Improved mental alertness |
| Decreased spermatogenesis (except in response to estrogen receptor blockers or aromatase inhibitors) |
| Decreased testicular volume (except in response to estrogen receptor blockers or aromatase inhibitors) |
| Possible acne |
| Possible gynecomastia |

**Table 12.3** Hypogonadism therapies

| Category | Formulation | T 1/2 | Standard dosage | Advantages | Disadvantages | Monitoring guidelines |
|---|---|---|---|---|---|---|
| Transdermal agents | Gel 1 %<br>Gel 1.62 % (Androgel) | 6 h | 2.5–10 g daily<br>2–8 g daily | Flexible dose titration<br>Easily stopped<br>Mimics circadian rhythm | Daily administration<br>Risk of transfer<br>Best applied to skin areas with minimal hair<br>Risk of transfer<br>Best applied to skin areas with minimal hair | T levels 2 weeks after initiation treatment<br>T levels every 6 months thereafter<br>Blood draw 2–4 h after applying patch, adjust dose accordingly<br>T levels 2 weeks after initiation treatment |
| | Cream 1 % (Testim) | 6 h | 2.5–10 g daily | | Musky odor<br>Daily administration<br>Risk of transfer<br>Best applied to skin areas with minimal hair | |
| | Underarm T solution 2 % (Axiron) | 6 h | 60–120 mg daily | Flexible dose titration<br>Easily stopped<br>Mimics circadian rhythm<br>No need for administration to hairless skin areas | Musky odor<br>Daily administration<br>Risk of transfer<br>Solution can "run" down from armpit and soil clothing | |
| | Gel (Fortesta) | 6 h | 40 mg daily | Low volume of gel needed | Must be applied to thighs | |
| | T patch (Androderm) | 10 h | 5–10 mg daily | Flexible dose titration<br>Easily stopped<br>Mimics circadian rhythm | Daily administration<br>Skin irritation<br>Visible patch<br>Patch slippage when seating heavily | T levels 2 weeks after initiation treatment<br>T levels every 6 months thereafter<br>Blood draw 2–4 h after applying patch, adjust dose accordingly |
| Subcutaneous Pellet | T pellets (Testopel) | – | 8–12 75 mg pellets implanted every 3–4 months | Administration only 2–4 times annually<br>100 % compliance for period following implantation | Mild pain during and/or following implantation<br>Risk of infection<br>Risk of extrusion | T levels 1 and 3 months after initiation treatment<br>T levels every 6 months thereafter<br>Use trough T level to define need for dose adjustment. Adjust number of pellets or interval between implantations if T > 700 ng/dL or <400 ng/dL |

(continued)

**Table 12.3** (continued)

| Category | Formulation | T 1/2 | Standard dosage | Advantages | Disadvantages | Monitoring guidelines |
|---|---|---|---|---|---|---|
| Intramuscular agents | T enanthate<br>T cypionate (DepoTestosterone)<br>T propionate | 4–5 days<br>8 days<br>20 h | 100–300 mg every 1–3 weeks<br>100–300 mg every 1–3 weeks<br>50–100 mg every 2 days | Low cost<br>No need for daily use | Need for injections<br>Fluctuating T levels<br>Burden of coordinating timing peak and trough serum T levels | Measure T level midway between injections. If T > 700 ng/dL or <400 ng/dL, adjust dose or frequency<br>Alternatively, measure day after injection (peak level) and also immediately before next injection (trough value). If peak T>1200 ng/dL or trough level <400 ng/dL adjust dose or interval between injections |
| | T undecanoate in castor oil (Nebido) | 34 days | 1,000 mg every 10–14 weeks | Long-lasting with less frequent administration | Need for injections<br>Currently unavailable in U.S.A. | T levels 1 and 3 months after initiation treatment<br>T levels every 6 months thereafter<br>Use trough T level to define need for dose adjustment. Adjust number of pellets or interval between implantations if T>700 ng/dL or <400 ng/dL |
| Buccal agent | Buccal T | 12 h | 30 mg twice daily | | Oral irritation; twice-daily dosing, unpleasant taste | T levels 3–6 months after initiation treatment<br>Annually thereafter<br>T level immediately before or after application |
| Oral agents | T undecanoate | 4 h | 120–420 mg 2–3 times daily | Oral convenience | Widely varying T and clinical responses; Must be taken with meals | T levels 3–6 months after initiation treatment<br>Annually thereafter<br>Measure T level 3–5 h after ingestion |
| | Methyltestosterone | 3.5 h | 20–50 mg 2–3 times daily | Oral convenience | Potential hepatotoxicity; treatment considered obsolete | T levels 3–6 months after initiation treatment<br>Annually thereafter<br>Measure T level 3–5 h after ingestion |
| | Mesterolone | 8 h | 100–150 mg 2–3 times daily | Oral convenience | Non-aromatizable to estrogen | T levels 3–6 months after initiation treatment<br>Annually thereafter<br>Measure T level 6–8 h after ingestion |

| | | | | | | |
|---|---|---|---|---|---|---|
| Selective estrogen receptor modulator | Clomiphene citrate | 5–7 days | 25 mg qd, 25–50 mg qod | Oral convenience, does not suppress endogenous testicular function or sperm production | Caution in hepatic disease. Common side effects breast tenderness, visual disturbances, headache | T, E, LH levels at 1 month and 1 month after adjustment |
| Aromatase Inhibitors | Anastrozole | 50 h | 1 mg qd | Oral convenience, does not suppress endogenous testicular function or sperm production | Caution in ischemic heart disease. Common side effects arthralgia, asthenia, nausea/vomiting, back pain, headache, hypertension | |
| | Testolactone | 2 days | 100–200 mg qd | Oral convenience, does not suppress endogenous testicular function or sperm production | Hypertension, paresthesia, malaise, edema, nausea/vomiting | |

## Suggested Reading

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2539–59.

Corona G, Rastrelli G, Forti G, Maggi M. Update in testosterone therapy for men. J Sex Med. 2011;8(3):639–54.

Cunningham GR, Toma SM. Clinical review: why is androgen replacement in males controversial? J Clin Endocrinol Metab. 2011;96(1):38–52.

Hsiao W, Tenover JS, Ritenour C. The role of Testosterone Replacement Therapy in Contemporary Urological Practice. American Urological Association Update Series. 2008.

Katz DJ, Nabulsi O, Tal O, Mulhall JP. Outcomes of clomiphene citrate treatment in young hypogonadal men. BJU Int. 2012;110(4):573–8. doi:10.1111/j.1464-410X.2011.10702.x.

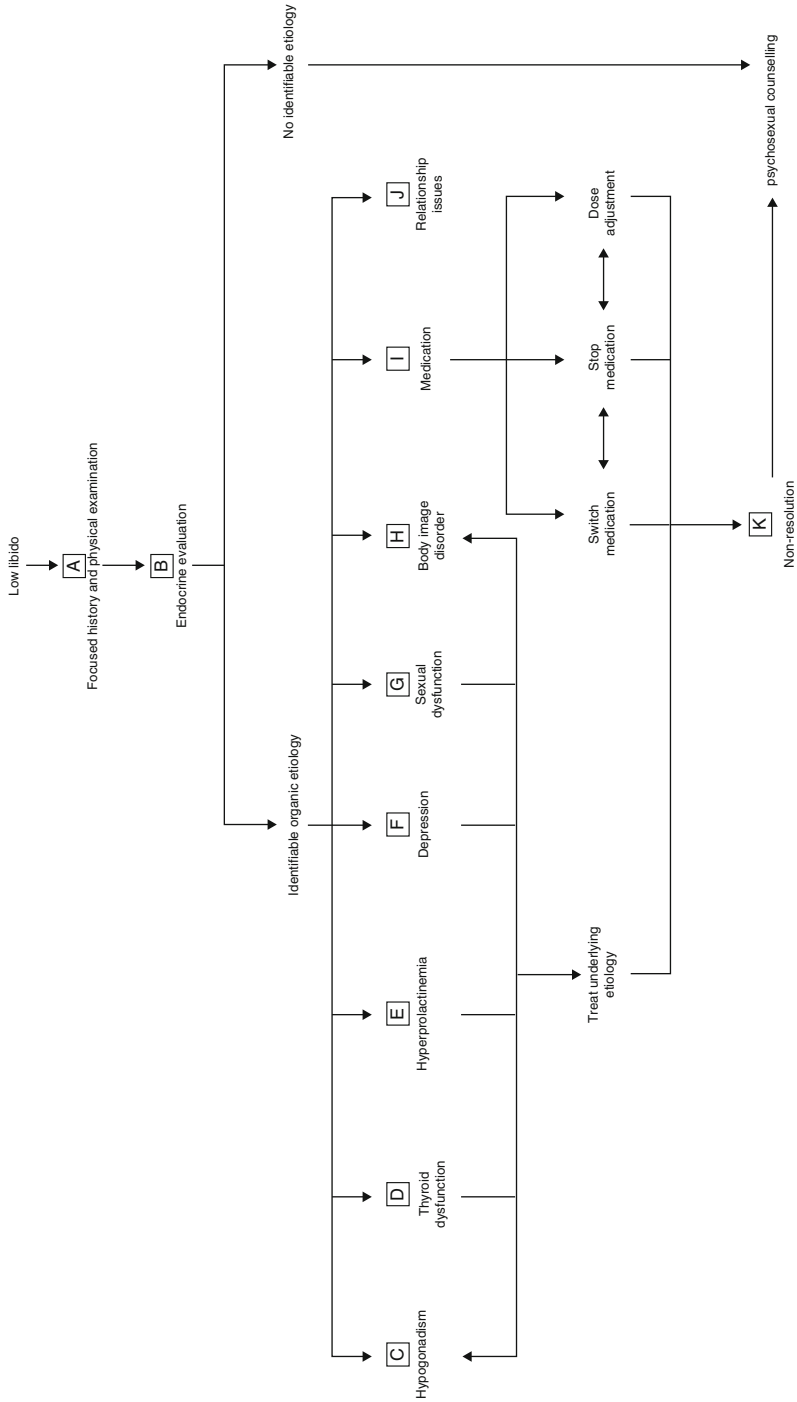
Moskovic DJ, Katz DJ, Akhavan A, Park K, Mulhall JP. Clomiphene citrate is safe and effective for long-term management of hypogonadism. BJU Int. 2012;110(10):1524–8. doi:10.1111/j.1464-410X.2012.10968.x.

Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Male Reproduction and Urology. Androgen deficiency in the aging male. Fertil Steril. 2008;90(5 Suppl):S83–7.

Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Eng J Med. 2004;350:482–92.

Sokol RZ. Endocrinology of male infertility: evaluation and treatment. Semin Reprod Med. 2009;27(2):149–58.

# Chapter 13
# Low Libido




J.P. Mulhall et al., *Clinical Care Pathways in Andrology*, DOI 10.1007/978-1-4614-6693-2_13,

Hypoactive sexual desire disorder (HSDD), or low libido, is defined as the persistent or recurrent absence or deficiency of sexual fantasies and a desire for sexual activity that causes marked distress or interpersonal difficulty. There is a subtle difference between intellectual and visceral libido. Some men may report intellectually desiring a sex life, but this should not be confused by the practitioner for true libido or "sexual hunger."

## (A)

History should include pubertal development, gonadotoxin exposure, sources of stress, history of depression or anxiety disorder, prior libido, sexual history, and relationship history. Symptoms of hypogonadism (HG) should be established (including low energy, afternoon fatigue, loss of muscle, increased body fat, loss of body hair, decreased strength and endurance). Medications, especially those that were recently initiated, should be recorded. Focused physical examination of the genitals is performed, with particular attention to the size and consistency of the testes. We use a 10-point libido rating scale (as no validated instrument exists), where "10" = libido level of the patient when he was 18 years old and "0" = complete absence of libido. Defining whether the libido change was sudden or gradual in onset may be helpful in elucidating a cause.

## (B)

Endocrinopathies commonly cause low libido. All men with low libido should have morning serum total testosterone (T) levels drawn and, if these levels are abnormally low, they should be repeated for confirmation. Along with repeat T we recommend a more extensive panel that may include free testosterone (fT), luteinizing hormone (LH), estradiol (E2), and sex hormone binding globulin (SHBG). If the LH level is low a prolactin (PRL) level is worth checking. For patients with significant symptoms of thyroid dysfunction, obtaining thyroid function tests (TFTs) is reasonable.

## (C)

HG, or abnormally low testosterone levels, is a particularly well-known and common cause of low libido. Besides low libido, hypogonadism is also associated with decreased nocturnal erections, decreased ease of arousal, orgasm delay and, in men with profoundly low levels, poor erectile function. Treatment results in normal serum T levels and increased libido. Evaluation and treatment of hypogonadism are discussed in detail in Chap. 12.

## (D)

More than half of men with hypothyroidism have been shown to have HSDD, and nearly a quarter of men with hyperthyroidism have HSDD. Hypothyroidism is most commonly caused by Hashimoto's thyroiditis, an autoimmune inflammatory condition. The so-called secondary hypothyroidism is caused by under-production of thyroid stimulating hormone (TSH) or thyroid releasing hormone

(TRH) by the pituitary. Secondary hypothyroidism is usually caused by a hypothalmic or pituitary tumor. Nearly all patients with hypothyroidism from any cause will respond to the oral medication levothyroxine. Men with a pituitary tumor may also need directed medical treatment or surgery for that condition.

## (E)

Severe hyperprolactinemia (>35 ng/mL or 735 mIU/L) impairs libido, T level, and erectile function. PRL levels at this level are often secondary to pituitary tumors, which exert deleterious effects both via mass effect and PRL-induced suppression of gonadotropin secretion. Heavy opiate use also may also cause significantly elevated PRL levels. Selective serotonin reuptake inhibitors (SSRI) use can also produce significantly elevated PRL levels. Magnetic resonance imaging (MRI) of the brain is the most sensitive modality for detecting pituitary tumors. Medical treatment includes dopamine agonists such as cabergoline or bromocriptine. Surgical and radiation treatment is reserved for rare severe cases that do not respond to medication.

## (F)

Low libido occurs in up to 40 % of men with depression. Antidepressant medications independently impair libido as well (see J), so the actual incidence of depressed men with low libido is quite high. Other psychological factors lowering libido include anxiety disorder, chronic stress, or fatigue.

## (G)

Any chronic sexual dysfunction (e.g., ED, delayed orgasm, and Peyronie's disease) may cause great patient and partner distress and lead to avoidance behavior (secondary to low sexual self-confidence) of the man experiencing the problem. This may be perceived by him and his partner as low sex drive. The practitioner should be able to distinguish, with further questioning, whether they have truly low libido or whether they are merely sexually frustrated.

## (H)

Body dysmorphic disorder (BDD) is a psychiatric condition that is strongly associated with low libido. BDD is defined as a somatoform disorder in which the patient perseverates on a perceived defect of his body. The condition is historically considered more common in women but recent evidence shows that men are affected at nearly equal rates. The excessive focus on body image is associated with depression, obsessive-compulsive disorder, and social phobia. BDD is treated with psychotherapy, cognitive-behavioral therapy, psychiatric medications, and SSRI.

## (I)

Medications can cause low libido (Table 13.1). Three strategies exist for addressing medications implicated in causing low libido: discontinuing the medication, switching medication to another in its class (or using a similar drug), and adjusting the dose.

## (J)

Relationship issues including conflict, resentment, and loss of attraction for his partner can lead to low libido in a man. Sometimes this is simply a function of the familiarity factor, the fact that a man has been with the same partner for 30 years and has lost visceral sexual attraction for his partner.

## (K)

If no clear issue or factor is identifiable or no resolution is achieved satisfactorily, then the patient should be referred for psychosexual counseling. Psychosexual therapists are trained to help patients and their partners explore underlying issues that may be manifesting in low libido, along with other sexual problems, and teach strategies and exercises to manage specific issues.

**Table 13.1** Classes of medications associated with low libido

| **SSRI/SNRI** |
|---|
| 5-Alpha reductase inhibitors |
| Spironolactone |
| Benzodiazepines |
| Tricyclic antidepressants |
| Clonidine |
| Phenytoin |
| Anti-androgens |
| Estrogenic agents |
| Narcotics |
| Chemotherapy |
| H2 antagonists |
| Anti-psychotics |

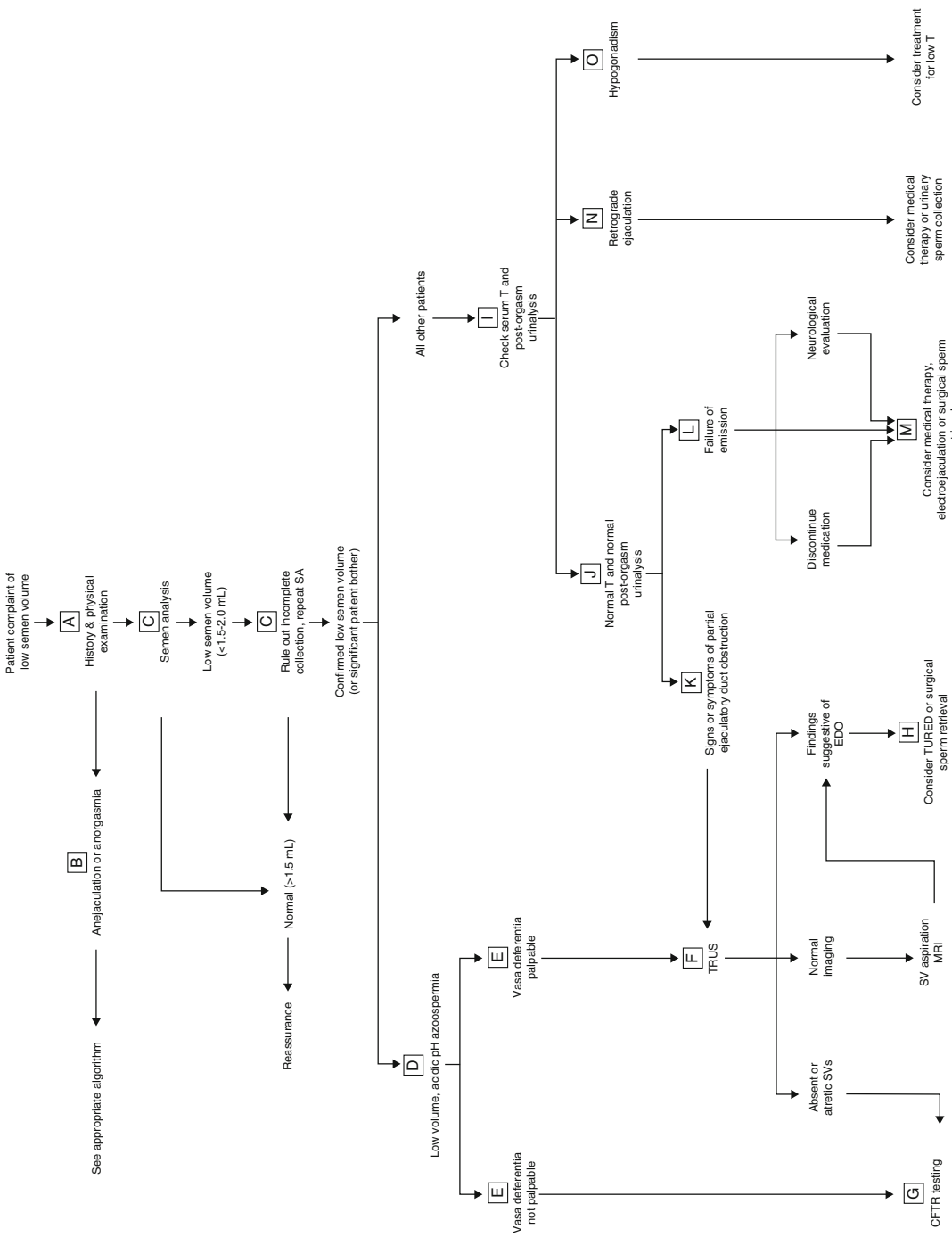
## Suggested Reading

Bianchi-Demicheli F, Ortigue S, Meyer P. Hypoactive sexual desire disorder in men: clinical approach in sexual medicine. Rev Med Suisse. 2010;6(241):614–6, 618–9.

Brotto LA. The DSM, diagnostic criteria for hypoactive sexual desire disorder in men. J Sex Med. 2010;7(6):2015–30.

Montorsi F, Adaikan G, Becher E, Giuliano F, Khoury S, Lue TF, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med. 2010;7(11):3572–88.

# Chapter 14
# Low Semen Volume

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Low semen volume refers to the consistent finding of low volume of ejaculated fluid on semen analysis. This is usually defined as a semen volume consistently less than 1.5 mL. It is important to remember that this semen parameter is highly variable and depends critically upon an appropriate abstinence period of at least 2 days prior to sample collection. Low semen volume (or perceived low semen volume) may be a bothersome symptom for which a man seeks clinical evaluation and treatment, or may be discovered during evaluation for subfertility. The goals of the diagnostic evaluation are to identify or exclude contributory underlying conditions and to guide the selection of medical or surgical therapy when treatment is indicated. The differential diagnosis of low semen volume is presented in Table 14.1. Understanding ejaculatory physiology is essential when formulating the differential diagnosis for men with low semen volume. Ejaculatory volume depends on several processes including adequate production of fluid by the seminal vesicles and prostate, successful emission of seminal and prostatic fluid into the posterior urethra, and forceful expulsion of the fluids deposited in the posterior urethra out the urethral meatus of the penis. The testicular contribution (sperm) to the ejaculate comprises less than 5% of semen volume and therefore semen volume does not provide any information about testicular function or spermatogenesis. Fluid production by the seminal vesicles and prostate are androgen-dependent processes that may be impaired when the serum testosterone level is low or when the seminal vesicles are incompletely developed or dysfunctional. Emission is a complicated neurobiological event that may be impaired by diseases or surgeries that disturb function of the sympathetic nervous system, drugs that block alpha-adrenergic activity or anatomic obstructions of the ejaculatory ducts through which sperm and seminal fluid (but not prostatic fluid) are deposited into the posterior urethra. Expulsion is a similarly complex reflex mediated by sacral autonomic and somatic nerves during which coordinated contraction of peri-urethral and pelvic floor muscles propels semen in an antegrade direction while the bladder neck is closed (preventing retrograde ejaculation). Inadequate expulsion may therefore result from neuropathies or inadequate bladder neck closure. The latter case manifests clinically as retrograde ejaculation.

## (A)

The initial evaluation of low semen volume should include a detailed medical history and a directed physical examination. Important points in the medical history and physical examination are listed and explained in Tables 14.2 and 14.3. The history should also define why the patient is bothered by this symptom. For a man concerned about fertility this is an important problem to correct. However, for a man who is not interested in fertility, defining the root source of their bother is worthwhile. For example, many men incorrectly believe that the intensity of orgasm is related to the volume of semen produced. Furthermore, especially in men with psychogenic sexual dysfunction, the patient can become "semenocentric," focusing on semen volume, color, and consistency, while often there is no semen pathology, and the changes discovered by the patient are simply a manifestation of the normal variation in macroscopic semen parameters.

## (B)

In some cases the detailed sexual history of a patient reporting low semen volume will reveal anorgasmia or anejaculation. Sometimes patients may be confused by pre-orgasmic peri-urethral gland secretions (from the urethral glands of Littré) that may be mistaken for very low volume ejaculation. Patients found to have anorgasmia or anejaculation do not have low semen volume and should be evaluated specifically for these conditions (see *Delayed Orgasm* and *Anejaculation* algorithms).

## (C)

Semen analysis enables standardized, objective assessment of ejaculate volume and is an integral component of the evaluation of low semen volume. An abstinence period of at least 2 days is critical, as semen volume increases approximately 10% per day during the first 4 days of abstinence. The World Health Organization (WHO) previously defined low semen volume as <2.0 mL, but recently changed their reference range to <1.5 mL in 2010. It is important to remember that the WHO reference range for semen volume is derived from statistical analysis of a cohort of healthy, fertile men and does not have a validated relationship with ejaculatory dysfunction or infertility. The finding of low semen volume in an infertile or bothered patient should always prompt repeat semen analysis and specific questioning about the method of semen collection and whether or not there was any difficulty with specimen collection. Specimen collection issues, when discovered, should prompt repeat semen analysis. If the repeat semen analysis reveals normal semen volume, the patient should be reassured and no further evaluation is required. When the repeat semen analysis confirms low semen volume, the other semen parameters may provide clues about the cause of low semen volume. Azoospermia (complete absence of sperm) is associated with complete bilateral ejaculatory duct obstruction (EDO), seminal vesicle atresia, or failure of emission (FOE). Decreased sperm concentration, motility, or morphology in the context of low semen volume suggests partial EDO. Normal semen parameters suggest incomplete semen specimen collection or partial retrograde ejaculation. Some authorities advocate the assessment of semen fructose in such cases. Fructose is produced only by the seminal vesicles. Thus, its presence is supportive of at least one seminal vesicle being present and functional as well as at least one ejaculatory duct being patent. The absence of any fructose in semen arises from either bilateral seminal vesicle absence or atresia or complete bilateral ejaculatory obstruction. It can also result from technical problems with the chemical reaction used to assess for fructose in semen. Fructose is measured using the chemical reagent resorcinol. Due to the light sensitivity of this agent, if it is not properly stored, the agent can degrade and give a false negative reaction on testing.

## (D)

Low volume, low pH azoospermia always indicates the absence of both the testicular (sperm) and seminal vesicle (alkaline seminal fluid that typically comprises 70% of ejaculatory volume) contributions to semen. In such cases the ejaculate predominantly comprises prostatic fluid that is deposited in the posterior urethra via prostatic ducts that do not communicate with the ejaculatory ducts. The acidic pH of prostatic secretions invariably yields semen pH values <7.0. Complete absence of seminal vesicle fluid from the ejaculate occurs in only two clinical scenarios: (1) absent or atretic seminal vesicles, or (2) complete bilateral EDO.

## (E)

Physical examination of the scrotal vasa deferentia may enable distinguishing between seminal vesicle malformations and EDO as the cause of low volume, acidic azoospermia, which together account for most cases. Bilateral seminal vesicle absence or atresia is almost always associated with congenital bilateral (CBAVD) or unilateral absence of the vasa deferentia (CUAVD) because these structures share a common embryological origin from the mesonephric (Wolffian) duct. The diagnosis of CBAVD can be made on physical examination (see *Azoospermia* algorithm). When the scrotal vasa

deferentia can be palpated in men with low volume, acidic azoospermia, EDO is the most common diagnosis. However, in rare atypical variants of congenital vasal absence one or both scrotal vasa deferentia may be palpable while the pelvic vasa are absent and/or seminal vesicles are still atretic or absent bilaterally.

## (F)

Imaging of the seminal vesicles and prostate is indicated when complete or partial obstruction (often manifesting in profound oligozoospermia associated with complete asthenozoospermia) of the ejaculatory ducts is suspected. Transrectal ultrasonography (TRUS) enables detailed evaluation of the seminal vesicles and prostate and is relatively inexpensive. Seminal vesicle absence or atresia is easily diagnosed and, if identified, should be considered consistent with congenital vasal absence and evaluated accordingly. The diagnosis of EDO is supported by dilation of the seminal vesicles to >1.5 cm in greatest anteroposterior dimension, dilation of the ejaculatory ducts to >2 mm, or by identification of midline prostatic cysts or calcifications of the ejaculatory ducts. However, TRUS is neither sensitive nor specific for the diagnosis of EDO. Adjuvant diagnostic tests such as seminal vesicle aspiration (sperm being found in the seminal vesicle is pathological) and magnetic resonance imaging (MRI) may therefore be considered when TRUS is unrevealing but clinical suspicion for EDO remains high.

## (G)

The cystic fibrosis transmembrane conductance regulator (CFTR) gene encodes a chloride channel that regulates the fluidity of epithelial cell secretions in exocrine tissues and plays an important role in embryological development of the mesonephric (Wolffian) duct structures, including the vasa deferentia and seminal vesicles. Between 50 and 82% of healthy men with CBAVD harbor detectable mutations in one or both alleles of the CFTR gene (it is believed that all men with CBAVD have some genetic mutation but some it is not currently detectable). Patients with palpable vasa but atretic or absent seminal vesicles are also at risk. Testing for CBAVD mutations is critically important for all patients interested in reproduction because their offspring are at risk for both infertility due to CBAVD and overt clinical cystic fibrosis (CF). Testing is also informative about the risks of infertility and CF in siblings, and even may explain gastrointestinal or pulmonary dysfunction in the affected patient. Identification of a CFTR gene abnormality should prompt testing of the patient's female partner and immediate referral to a genetic counselor prior to any attempts at reproduction.

## (H)

Selection of treatment for EDO depends upon the indication for treatment. Patients can generally be categorized into two groups: patients who desire fertility, and patients with symptoms of EDO including low semen volume or orgasmic pain. Fertility patients are candidates for transurethral resection of the ejaculatory ducts (TURED) or surgical sperm retrieval combined with assisted reproduction, whereas TURED is the only established treatment option available to the other patients.

Prior to TURED a close review of the TRUS images is critical in planning the operation. If there is a midline prostatic cyst causing compression of the ejaculatory ducts, aspiration or unroofing of this cyst should be the first option. If there is no prostatic cyst, close attention should be paid to the distance between the urethral mucosal edge and the point at which the ejaculatory dilation commences. If the EDO starts some distance from the urethra, TURED may be considered a poor option because of concerns for rectal injury. Natural pregnancy rates are 20–30% after TURED performed for infertility, and improvements in semen parameters after TURED have been described in patients with suspected partial EDO. For symptomatic patients, limited evidence suggests that relief of pain associated with sexual activity can be expected in 60% of cases. Improvements in semen volume are expected in most cases, but TURED for the specific indication of improving semen volume should be approached cautiously. Complications from TURED are reported in 10–20% of cases and include persistent watery ejaculate, secondary azoospermia, hematuria, and rarely rectal injury or urinary incontinence.

## (I)

Evaluations for hypogonadism and retrograde ejaculation are indicated in all patients with low semen volume except for those with low pH azoospermia, in whom such testing is usually unnecessary. Testing for hypogonadism should be performed by assessment of an early morning serum total testosterone level. Testing for retrograde ejaculation is done by post-orgasm urinalysis (sometimes termed retrograde semen analysis). This test is best performed in conjunction with a semen analysis. The patient empties his bladder prior to semen collection, provides a semen sample through masturbation, and voids 10–15 min later into a specimen container. The patient should not make special efforts to over-hydrate himself as high volumes of urine may impair the ability to identify semen and sperm. The urine sample is centrifuged at 300 g for 15 min, after which the supernatant is discarded and the pellet is resuspended in 1 mL. The sample is then evaluated for the presence and quantity of sperm, which may be compared to the quantity of sperm present in the antegrade semen sample. Interpretation of a post-orgasm urinalysis is difficult. Standard criteria to define retrograde ejaculation do not exist and small numbers of sperm are present in the urine of the majority of men with normal fertility and ejaculatory function. Results of this test must therefore be interpreted on an individual basis with consideration of the clinical presentation of each patient.

## (J)

Patients with low semen volume in whom the serum testosterone level is normal and significant retrograde ejaculation is absent have either partial EDO or FOE.

## (K)

Partial EDO should be considered when low semen volume is associated with poor semen quality (low sperm concentration and low percent or absent motility), when there is orgasmic pain associated with ejaculation, or when hematospermia is present. The diagnosis of partial EDO may be supported by TRUS, and this condition may be amenable to surgical treatment by TURED.

## (L)

FOE may be neurogenic, medication-induced, or idiopathic and may manifest clinically as low semen volume. Alpha-adrenergic blockers (for hypertension or benign prostatic hyperplasia) are the most commonly encountered offending medications and may be associated with either retrograde ejaculation in addition to FOE.

Semen volume often improves once the agent is stopped. Neurogenic FOE should be considered when risk factors such as prior retroperitoneal pelvic surgery or spinal cord injury are present, or when signs and symptoms of neurological dysfunction are elicited during the patient evaluation. Low semen volume may in fact be the presenting symptoms of neurological diseases such as multiple sclerosis or diabetic peripheral neuropathy. Formal neurological evaluation should be considered. In some cases the etiology of low semen volume is not readily apparent and the patients are classified as having idiopathic low semen volume.

## (M)

Selection of treatment for low semen volume associated with neurogenic or idiopathic FOE depends upon the patient's goals. Empiric sympathomimetic or anticholinergic therapy may improve emission and thereby increase ejaculatory volume. This strategy may benefit patients with infertility or distress related to low semen volume, though evidence supporting this approach is mostly anecdotal and the described regimens have only been reported for short-term use in infertile men. Regimens that have been described include ephedrine sulfate 25 mg twice daily, imipramine hydrochloride 25 mg 3 times daily, midodrin hydrochloride 7.5 mg on demand 2 h prior to anticipated ejaculation, and pseudoephedrine hydrochloride 120 mg twice daily. Electroejaculation and surgical sperm retrieval combined with assisted reproductive techniques are alternative options for patients rendered infertile by their ejaculatory dysfunction.

## (N)

Retrograde ejaculation (RE) is a diagnosis made based on results of the patient's semen analysis, post-orgasm urinalysis, and clinical presentation. Failure of bladder neck closure during the expulsion phase of ejaculation results in retrograde flow of seminal fluid into the bladder. The diagnosis is clear when there is no antegrade ejaculate but semen is present in urine. However, partial RE is difficult to diagnose due to absence of standardized diagnostic criteria and the consistent finding of sperm in the urine of men with normal fertility and normal ejaculatory function. Medical treatment in the form of short-term sympathomimetic therapy restores antegrade ejaculation in 22–39% of cases. Regimens that have been described are the same as those used to treat FOE: ephedrine sulfate 25 mg twice daily, imipramine hydrochloride 25 mg 3 times daily, midodrin hydrochloride 7.5 mg on demand 2 h prior to anticipated ejaculation, and pseudoephedrine hydrochloride 120 mg twice daily. Medical therapy for RE enables natural reproduction in some previously infertile men and may reduce bother associated with low semen volume. Urinary sperm collection for assisted reproduction is another option for men with RE who pursue fertility. The urine is typically alkalinized prior to sperm harvest with sodium bicarbonate (500 mg of baking soda 12 and 2 h prior to sperm collection) or 5–10 cc potassium citrate syrup with each dose of sympathomimetic (for a total of about 30 cc) to reduce the adverse effects of acidic urine on sperm survival and function.

## (O)

Hypogonadism is a correctable cause of low semen volume. Development and secretory function of the seminal vesicles and prostate are androgen-dependent processes that may be impaired when levels of testosterone and its metabolite dihydrotestosterone are deficient. Patients with low semen volume found to have hypogonadism should undergo complete evaluation to investigate the etiology of their testosterone deficiency. In rare cases low semen volume may be the presenting symptom of underlying medical disorders such as Klinefelter syndrome or congenital or acquired hypogonadotropic hypogonadism. Restoration of serum testosterone to normal levels may improve semen volume. This may be accomplished in patients who are not interested in fertility by testosterone replacement therapy. However, exogenous testosterone can suppress spermatogenesis and should be avoided in men interested in fertility. In such patients clomiphene citrate or hCG may be used to stimulate endogenous testosterone production.

**Table 14.1** Differential diagnosis of low semen volume

| | |
|---|---|
| Semen collection issues | Incomplete semen sample collection<br>Inappropriately short abstinence period prior to semen analysis |
| Prostate pathology | BPH<br>Ejaculatory duct obstruction (EDO) |
| Ejaculatory dysfunction | Retrograde ejaculation<br>Failure of emission or expulsion |
| Testosterone | Hypogonadism |
| Seminal vesicle pathology | Seminal vesicle atresia or agenesis<br>Seminal vesicle infections<br>Cystic disease of the seminal vesicles<br>Seminal vesicle stones |

**Table 14.2** Important points to elicit in the medical history

| Medical history | Interpretation |
|---|---|
| Details of specimen collection | May reveal obvious, non-pathological causes of low semen volume including incomplete semen sample collection or inappropriately short abstinence prior to semen analysis |
| Onset and consistency of low semen volume | Lifelong low semen volume suggests congenital conditions such as seminal vesicle atresia, EDO, or congenital hypogonadal states such as Klinefelter syndrome or hypogonadotropic hypogonadism<br>New onset low semen volume suggests acquired etiologies such as surgery, developing neuropathy, new medication<br>Intermittently low semen volume is usually behavioral or psychogenic in origin |
| Symptoms of hypogonadism (see *Hypogonadism Evaluation* algorithm) | Suggests the possibility of low T, which is a treatable cause of low semen volume |
| Neurological symptoms (bowel or bladder dysfunction) | May suggest underlying neurological disease that may affect ejaculation |
| Cloudy urine after ejaculation | Suggests retrograde ejaculation |
| History of hematospermia or painful ejaculation | Suggest infection, stones, or obstruction of the seminal vesicles or ejaculatory ducts |
| Gastrointestinal or pulmonary dysfunction | May be associated with mutations in the CFTR gene-associated seminal vesicle atresia |

(continued)

**Table 14.2** (continued)

| Medical history | Interpretation |
|---|---|
| Fertility history | Assessment of the patient's reproductive goals is important for determining eventual treatment of low semen volume<br>Prior biological paternity eliminates the possibilities of seminal vesicle atresia or congenital EDO |
| Orgasm history (see *Delayed Orgasm* and *Anejaculation* algorithms) | Anorgasmia and anejaculation are separate clinical entities from low semen volume that may masquerade as low semen volume. Careful, specific questioning is often required |
| Medical history | Systemic diseases with neurologic sequelae (diabetes) may cause ejaculatory dysfunction<br>Neurological diseases or trauma may cause ejaculatory dysfunction |
| Surgical/trauma/radiation history | Prostate surgery for benign prostatic hyperplasia is a common cause of low semen volume<br>History of pelvic or retroperitoneal surgery or trauma suggests the possibility of injury to the autonomic pelvic nerves<br>History of pelvic irradiation may predispose to fibrosis of the seminal vesicles and/or ejaculatory ducts |
| Family history | Family history of clinical cystic fibrosis or infertility suggests the possibility of seminal vesicle atresia associated with CFTR gene abnormalities |
| Medication history | Alpha-adrenergic antagonists are a common cause of low semen volume<br>5 alpha reductase inhibitors months at high dose may be associated with this problem<br>Other drugs are rarely associated with low semen volume (thiazide diuretics, neuroleptics) |

**Table 14.3** Important points to elicit when performing physical examination

| Physical examination | Interpretation |
|---|---|
| Signs of hypogonadism (see *Hypogonadism Evaluation* algorithm) | Suggests the possibility of low T, which is a treatable cause of low semen volume |
| Vasal absence | CBAVD is associated with seminal vesicle atresia, and always results in low semen volume |
| Digital rectal examination | Palpation of the prostate may suggest prostate pathology that can contribute to low semen volume<br>Prostatic tenderness suggests the possibility of prostatitis and/or seminal vesiculitis |
| Neurological signs | Postural hypotension suggestive of autonomic neuropathy<br>Extremity sensory neuropathy suggestive of diabetes |
| Surgical scars | Abdominal scars suggest the possibility of iatrogenic ejaculatory dysfunction due to disruption of retroperitoneal nerves<br>Scrotal or inguinal scars alert the clinician to prior surgeries that may have affected testicular function |

## Suggested Reading

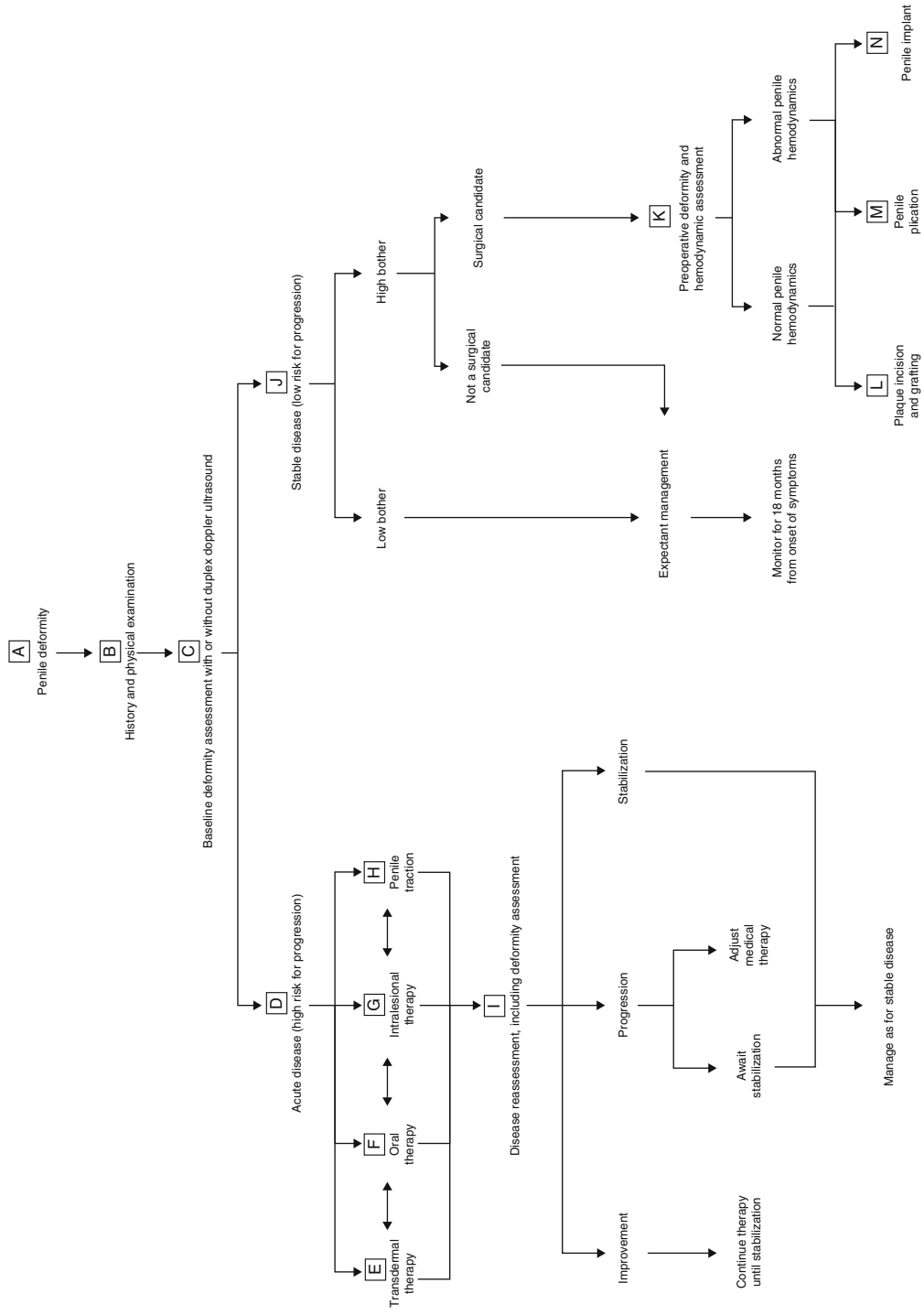
Kamischke A, Nieschlag E. Treatment of retrograde ejaculation and anejaculation. Hum Reprod Update. 1999;5(5):448–74.

Ohl DA, Quallich SA, Sonksen J, Brackett NL, Lynne CM. Anejaculation: an electrifying approach. Semin Reprod Med. 2009;27(2):179–85.

Roberts M, Jarvi K. Steps in the investigation and management of low semen volume in the infertile man. Can Urol Assoc J. 2009;3(6):479–85.

Rowland D, McMahon CG, Abdo C, Chen J, Jannini E, Waldinger MD, et al. Disorders of orgasm and ejaculation in men. J Sex Med. 2010;7(4 Pt 2):1668–86.

# Chapter 15
# Penile Deformity: Peyronie's Disease




J.P. Mulhall et al., *Clinical Care Pathways in Andrology*, DOI 10.1007/978-1-4614-6693-2_15,

Peyronie's disease (PD) is an acquired localized connective tissue disorder of the penile tunica albuginea. PD is characterized by changes in the collagen composition and the formation of fibrous plaques in the surrounding vascular tissue of the corpora cavernosum. Epidemiological studies available in the literature have estimated the prevalence of PD to range from 0.4 to 9 %, depending upon the population studied. Clinically, PD occurs predominantly in middle-aged males with the majority presenting over the age of 40 years. The presenting symptoms can include curvature or deformity of the erect penis, pain that occurs in the flaccid or erect state, presence of a palpable lump or plaque, and erectile dysfunction (ED). This disorder is thought to have distinct phases. The initial acute phase occurs early over 9–12 months and is characterized by changing deformity and, occasionally, plaque tenderness. The stable phase follows in which the plaque is fully organized, the degree of deformity stabilizes, and pain resolves. Many theories have been proposed for the cause of this enigmatic disorder, including microvascular trauma in the penis, fibrin deposition with failure of degradation, and aberrant wound healing. It is likely that minor repetitive trauma to the erect or semierect penis in the PD-susceptible patient initiates a cascade of events resulting in excessive collagen deposition. The natural history of PD has not been clearly elucidated although there are reports in the literature citing the predisposition towards spontaneous resolution on the order of 13–39 %. Medical therapy for Peyronie's disease includes oral agents, topical therapies, and intralesional agents, in addition to a number of other therapies. Many authorities believe that medical therapy is best commenced at the earlier stages of this disorder, during or as close to the inflammatory acute phase as possible, but no robust data exist to confirm this concept. The aims of medical therapy are to provide symptomatic pain relief, stabilize and prevent progression of the plaque, resolve the penile deformity by dissolving the plaque, and produce correction of the penile curvature.

## (A)

Penile deformity is either acquired (as in PD) or congenital (congenital penile curvature, CPC). Differentiating between the two is not particularly challenging. Lifelong curvature is supportive of CPC. Furthermore, any kind of deformity other than a uniplanar curvature (i.e., hourglass deformity, indentation, or tapering) is suggestive of PD. On examination, CPC is not associated with any tunical plaque. Furthermore, with erection, CPC generally manifests as a gentle bowing deformity as opposed to the angulation that is classic for PD.

## (B)

All men undergoing a work-up for PD warrant a detailed past medical, surgical, and sexual history, as well as a thorough history of disease presentation, progression, and prior therapy. Particular attention should be paid to the nature and magnitude of the deformity, duration of symptoms, presence of pain with and without erection, change in deformity over time, and presence of ED. Degree of rigidity, ability to sustain an erection, presence of nocturnal erections, and the timing of onset (specifically, before or after onset of PD) will aid in assigning an etiology to the ED. Men often report good overall erectile rigidity but complain of loss of rigidity only distal to the plaque or point of maximum curvature and/or indentation. It is critical to establish the degree of bother for patient and partner since this will also aid the clinician in the long-term management. Clinicians should determine if the patient's bother is related to functional and/or psychological impairment. At initial presentation, defining the duration of the condition is paramount for defining a treatment plan, as the approach to the acute phase patient (who is at risk of further progression) will differ in its urgency and treatments offered

compared to the patient with stable disease. In addition to a complete physical and genitourinary exam, the patient's hands are examined for evidence of Dupuytren's contracture (DC), since men with PD have an elevated risk for this condition. The penis should be examined in the stretched flaccid state, with careful palpation of the shaft from pubic bone to coronal sulcus, in order to elucidate any firmness or induration. The patient may have more than one plaque present and may have counterbalancing plaques on the dorsum and ventrum. The latter group of patients will often have no significant deformity, as the plaques counteract each other, but typically complain of significant penile length loss. Palpation, applying side-to-side *and* dorsoventral pressure, is the optimal means of outlining plaque and septal anatomy. Side-to-side compression beginning at the 3 and 9 o'clock position on the shaft and rolling firmly upwards (for dorsal plaque) and downwards (for ventral) plaque should be conducted meticulously along the entire shaft. The plaque location, morphology, and size should be documented and measurement of the stretched flaccid length is advisable (pubic bone to coronal sulcus). Plaque morphology is highly variable and, as previously stated, there is a poor correlation between plaque volume and deformity nature and degree.

## (C)

An accurate appraisal of the deformity is a critical step in the management of the PD patient. The goal of this evaluation is threefold: to identify the type(s) of deformity, to assess the magnitude or severity, and to evaluate penile stability. The initial focus is to assess the nature of the deformity. It is imperative to document characteristics such as direction of the curvature and whether the curvature is simple or multiplanar. The point of maximum deformity on the shaft should be identified. Associated deformities such as indentation, hourglass deformity, or penile rotation should be recorded. The second part of the assessment is focused on the magnitude of the deformity. Curvature with erection is recorded in number of degrees, preferably using a goniometer. The Peyronie's Disease Assessment Device, or P.D.A.D. (http://www.urosciences.com) (Fig. 15.1), is a commercially available disposable goniometer that is specifically designed for this purpose. In patients with biplanar curvature, each respective magnitude should be separately recorded. Two subjective factors (pain and ability to penetrate) and five objective parameters (induration, number of plaques, size, deviation, and location of curvature) are appraised. Indentation assessment is more complicated and less standardized. It is our recommendation that an indentation depth be measured with an excursion ruler such as that found on the P.D.A.D. (Fig. 15.1). Width and position on the shaft should also be recorded, ideally with a photograph or a drawing placed in the medical record. The third and final part of the deformity assessment is the recording of the presence and severity of penile instability. Many patients have degrees of curvature that do not preclude them from having penetrative sexual relations. Associated indentation(s) or the position of the curvature (particularly when positioned in the retrocoronal position immediately behind the coronal sulcus), however, can render the penis unstable as it buckles at the time of axial loading during attempted penetration. As with indentation measurement, there is no standardized means of recording instability, but documenting its presence and the degree of force (low, moderate, high) required to cause buckling is worthwhile. While there are commercially available rigidometers, their application to the evaluation of penile stability in the man with PD has not been adequately evaluated to date. Options for deformity measurement include patient self-assessment, at-home photography (AHP), application of in-office VED, and intracavernosal injection (ICI)-assisted erection. A truism in urology is that the degree of penile deformity is greatest at maximum erectile rigidity and therefore, when in order to accurately identify the magnitude of deformity, maximal erectile rigidity is required. AHP and VED are notorious for inaccurately defining the nature and degree of deformity. Photographs are often presented to clinicians but are unreliable since they are often taken at odd angles, in bad lighting, and (most importantly) with less than full rigidity, thereby underestimating the

degree of curvature. The most reliable means of assessing deformity and accomplishing all three goals of assessment is by formal physician measurement utilizing office-based intracavernosal injections. Inducing an erection of sufficient rigidity to accurately define the nature and magnitude of deformity will sometimes require more than one injection in an effort to overcome the sympathetic discharge that occurs during an in-office penile injection. It is recommended to monitor such patients in the office for up to an hour after the injection to ensure that the patient does not develop a prolonged erection. The ultimate purpose of the assessment is, again, threefold. Naturally, the first goal is to diagnose PD. Some young men present with the belief that they have PD, but on exam have no palpable plaque and actually have CPC. The second purpose is to precisely document a pre-treatment baseline so that pre- and posttreatment deformity can be accurately compared. When comparing pre- and post-therapy deformity, it is essential that the erectile rigidity for both assessments be comparable since there is a correlation between rigidity and degree of deformity. No imaging study is mandatory for a complete PD workup, but under select circumstances additional evaluation with imaging may be useful. Penile Doppler duplex ultrasound (DUS) may be helpful in carefully selected men. DUS has the potential to locate and document plaques that are not easily palpated, identify calcification within a plaque, and define erectile hemodynamics in men with concomitant ED and/or prior to undergoing penile reconstruction for PD. On DUS, plaques can be appreciated as hyperechoic areas with shadowing when calcified or ossified. Ultrasound is also very useful in identifying an intraseptal hematoma or plaque as these are often not amenable to palpation.

## (D)

The majority of patients with PD have deformity stabilization by 12 months and nearly all patients are stable by 18 months. Some patients, however, are stable within the first 6 months. Acute PD by definition puts the patient at risk of progression with worsening of the condition. It has become accepted that about 50 % of men presenting within 6 months are at risk of deformity worsening, while 10 % experience improvement and 40 % stay the same. The first step in planning treatment is deciding if the patient is at risk of progression. The features of the acute plaque are listed above. The literature has focused (incorrectly in our opinion) on the ability of medical therapy to reverse deformity when in fact halting progression of deformity is, in itself, for many men a success. Many centers use a combination of the following therapies.

## (E)

Transdermal therapy using agents such as steroids, lidocaine, and verapamil have been used alone or in combination. It has been established that transdermal agents do not penetrate into the tunical plaque, unless iontophoresis (also known as electromotive drug administration (EMDA)) is used. Despite its attractiveness due to its noninvasive nature, there does not yet exist robust data supporting transdermal agents in the management of acute PD.

## (F)

Oral agents such as vitamin E, colchicine, tamoxifen, potassium para aminobenzoate, and carnitine have been used for many years and yet there is no randomized, placebo-controlled data to support their utility reversing or preventing worsening of the PD deformity. More recently, there has been

great interest in the use of L-arginine, pentoxifylline, and PDE5 inhibitors in PD. To date, there are no data supporting or refuting a role for these agents (Table 15.1).

## (G)

In high volume PD centers, intralesional injection therapy is the backbone of medical therapy. Despite its introduction in 1994 there are only two randomized, controlled trials (including an extremely small study using verapamil and a larger study assessing interferon). The former study did not demonstrate significant improvement in deformity in the treatment arm. The interferon study showed a benefit with treatment compared to placebo, although patients injected with intralesional saline also experienced a higher rate of deformity improvement that would be expected based on natural history studies. Several single-institution noncontrolled studies have demonstrated benefit from both agents when using both reversal of deformity and prevention of progression as endpoints. Most authorities use a bi-weekly course of 6–12 injections administered with penile local anesthetic blocks. The only significant adverse event, penile ecchymosis and swelling, is usually mild and always self-limiting. At this time, the phase III randomized controlled data on intralesional clostridial collagenase are awaited and its Federal Drug Administration (FDA) approval is expected in 2013.

## (H)

The use of a penile extender device, termed traction therapy, is based on years of experience with this concept in orthopedics. At this time there is a dearth of randomized, controlled trials and data are limited to small series with mixed results. Anecdotally patients have frequently gained benefit from the use of traction, but predictors of response to traction therapy have not yet been identified. The device is applied for 2–8 h per day, in 2-h segments for a period of 6 months. Every 2–4 weeks the patient is instructed to apply new extending segments to the device to continuously keep the plaque under tension. Although many patients find this regimen difficult to comply with for logistical reasons, no significant adverse events are known to occur with this device.

## (I)

After a course of treatment, we recommend that all patients have a repeat deformity assessment, as described above, with or without a penile ultrasound. We encourage all clinicians to record center-specific data so that patients can be given realistic expectations prior to treatment. If patients improve or stabilize, they should be monitored until they are at least 12 and preferably 18 months after PD onset. If patients worsen while on medical therapy, adjustment of medical therapies can be tried but it is our experience that second line medical therapy will be no more effective.

## (J)

After a period of 12–18 months, irrespective of whether medical therapy has been effective in improving or stabilizing deformity, all patients will become stable. If patients have significant deformity after medical therapy and are physically or psychologically impaired, those with high bother become

candidates for a penile reconstructive surgery discussion. Patients with low bother are managed expectantly. Patients with minimal residual deformity and high bother are a complicated group of patients, in that they are often obsessed with obtaining a perfectly shaped penis. Great care must be taken in counseling these men and giving them realistic expectations. Men with curvature magnitudes below 30° are not ideal candidates for surgery.

## (K)

For those wishing to pursue a surgical approach, it is recommended that preoperative erectile hemodynamic assessment be performed, most often using duplex Doppler penile ultrasound, although some centers still perform cavernosometry. The technical considerations of this test have been discussed above. The four factors taken into account when deciding on the optimal surgical management of the PD patients are: nature of the deformity, magnitude of the deformity, erectile hemodynamics, and penile dimensions. The first step is defining the erectile hemodynamics status. If this is abnormal then options are limited to penile implant surgery or plication surgery (if the patient responds to erectogenic pharmacotherapy). Options for men with normal erectile hemodynamics include plication and plaque incision and grafting. The nature of the deformity refers to whether the curvature (if present) is uniplanar or multiplanar and is associated with indentations, hourglass deformity, tapering, and instability. Plication is best utilized in men with mild to moderate, uniplanar curvature without any instability. Plaque incision and grafting is useful for deformity of all kinds, including men with hourglass deformity. It is our experience that men with significant penile instability are best served by having penile implant surgery.

## (L)

Plaque incision and grafting addresses the plaque directly and is best utilized for patients with: complex deformities, with hourglass deformity, short penile length, any degree of curvature and, of critical importance, normal erectile function. The advantages of this approach are that it generally preserves penile length (although there is approximately a 10–30 % risk of penile shortening) and is useful in patients with complex deformities. The disadvantages include worsening erectile function (25 % chance in men with normal preoperative erectile function/hemodynamics) and dorsal nerve neuropraxia (if the neurovascular bundles require elevation) that can lead to prolonged sensory disturbances such as anesthesia or dysesthesia.

## (M)

Plication procedures address the side of the penile shaft opposite to the location of the plaque. The best candidates for plication have the following characteristics: minimal concern about length loss (typically when generous preoperative length is present), uniplanar curvature, mild-moderate magnitude of curvature, and combined PD/ED that is responsive to erectogenic pharmacotherapy. This group of procedures may be further subdivided into tunical incising and imbrication (non-incising) procedures. The advantages of these approaches include short surgical time, no significant negative effect on erectile hemodynamics, and good cosmetic outcomes. These procedures are considered relatively simple, safe, and effective in providing straightening. The major disadvantages are shortening

of the "long side" of the penis. Furthermore, these procedures do not adequately address the issues of hourglass deformity or lateral indentations, and the presence of multiplanar curvature is difficult to adequately correct. Tunical incising procedures involve making incisions in the tunica and excising a wedge or ellipse (Nesbit procedure), leaving an intervening segment of tunica intact and covering it over with a suture line that connects the two tunical incisions (modified corporoplasty), or fashioning a longitudinal incision and closing it in a Heineke-Mikulicz fashion transversely (Yacchia procedure). Although these repairs have the advantage of healing by primary intention, they require incising the tunica and therefore theoretically put erectile tissue at risk. Imbrication procedures do not involve making a tunical incision and instead fold the tunica, so that the integrity of the curvature correction is dependent upon the strength of the suture used to imbricate the tunica (Essed-Schroeder, 16-dot procedures).

## (N)

Penile implant surgery for PD is best reserved for patients with combined PD and ED, particularly with ED that is nonresponsive to pharmacotherapy. Some authorities have suggested that patients with hourglass deformity should be considered for penile implant surgery because of anecdotally based reports of poorer outcomes for patients undergoing lateral plaque incision and grafting procedures. The advantages of penile implant surgery in PD patients include excellent rigidity and, in patients with mild-moderate curvature, excellent deformity correction without the need for intraoperative adjuvant maneuvers. The disadvantages of this approach are the complications of penile prosthesis surgery including infection and device malfunction. Success with penile reconstructive surgical procedures is defined as end-of-operation residual curvature ≤15°. For patients with residual curvature greater than 15° immediately after penile implant insertion, intraoperative consideration should be given to performance of maneuvers aimed at straightening the residual curvature. Such maneuvers include manual modeling (molding) and plaque incision with or without grafting.

**Table 15.1** Oral therapies for PD

| Treatment | Proposed mechanism of action | Dosing | Adverse effects |
|---|---|---|---|
| Vitamin E | Antioxidant reversing or stabilizing tunical plaque | 400–800 IU daily | None (at doses suggested) |
| Colchicine | Inhibits fibrosis and collagen deposition | 0.6–1.8 mg daily | Diarrhea, agranulocytosis (rare) |
| Potassium aminobenzoate | Reduces fibrogenesis | 6 g four times daily | Nausea, GI upset |
| Tamoxifen | Reduces TGF-beta release from fibroblasts | 20 mg daily | Bone pain; constipation; coughing; hot flashes; muscle pain; nausea; tiredness; alopecia |
| Carnitine | Believed to inhibit acetyl coenzyme-A. | 1 g twice daily | Efficacy not proven, and more investigation is needed. |
| L-Arginine | Promotes nitric oxide release—anti-fibrotic properties | 2–3 g daily | Facial flushing |
| Pentoxifylline | Reduces collagen levels in PD plaques. | 400 mg three times daily | Occasional GI upset |


**Fig. 15.1** The Peyronie's Disease Assessment Device, or P.D.A.D. (http://www.urosciences.com), a commercially available disposable goniometer

## Suggested Reading

Chiles K, Mulhall JP. Medical management of Peyronie's disease. Parts I and II. AUA Update Series (2013).

Hellstrom WJ. Medical management of Peyronie's disease. J Androl. 2009;30(4):397–405.

Larsen SM, Levine LA. Peyronie's disease: review of nonsurgical treatment options. Urol Clin North Am. 2011;38(2):195–205.

Mulhall JP. Expanding the paradigm for plaque development in Peyronie's disease. Int J Impot Res. 2003;15 Suppl 5Suppl 5:S93–102.

Mulhall JP, Creech SD, Boorjian SA, Ghaly SA, Kim E, Moty A, et al. Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. J Urol. 2004;171(6):2350–3.

Mulhall JP, Parker M, Anderson M. A surgical algorithm for men with combined Peyronie's disease and erectile dysfunction: functional and satisfaction outcomes. J Sex Med. 2005;2(1):132–8.

Mulhall JP, Schiff J, Guhring P. An analysis of the natural history of Peyronie's disease. J Urol. 2006;175(6):2115–8.

Müller A, Mulhall JP. Peyronie's disease intervention trials: methodological challenges and issues. J Sex Med. 2009;6(3):848–61.

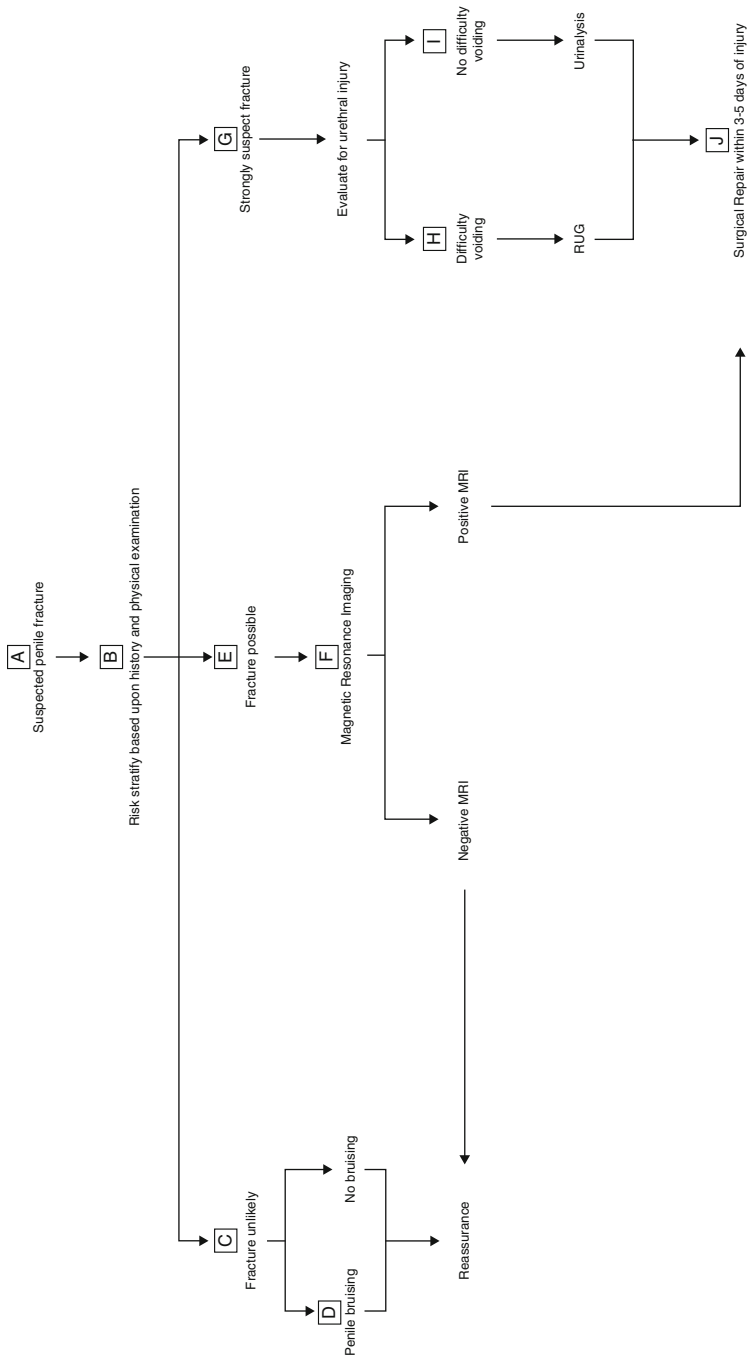
Nelson CJ, Diblasio C, Kendirci M, Hellstrom W, Guhring P, Mulhall JP. The chronology of depression and distress in men with Peyronie's disease. J Sex Med. 2008;5(6):1985–90.

Ohebshalom M, Guhring P, Parker M, Mulhall JP. Measurement of penile curvature in Peyronie's disease patients: comparison of three methods. J Sex Med. 2007;4(1):199–203.

Ralph D, Gonzalez-Cadavid N, Mirone V, Perovic S, Sohn M, Usta M, et al. The management of Peyronie's disease: evidence-based 2010 guidelines. J Sex Med. 2010;7(7):2359–74.

Tal R, Heck M, Teloken P, Siegrist T, Nelson CJ, Mulhall JP. Peyronie's disease following radical prostatectomy: incidence and predictors. J Sex Med. 2010;7(3):1254–61.

# Chapter 16
# Penile Fracture

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## (A)

Penile fracture is defined as traumatic rupture of the tunica albuginea of the corpus cavernosum. Fracture is typically caused by sudden axial overloading of the erect penis. The erect penis is prone to fracture because during erection, in contrast to the flaccid state, the tunica albuginea is thin and under extreme tension. Penile fracture is best managed by surgical repair as surgical treatment is associated with improved outcomes compared with conservative treatment.

## (B)

When a man presents with possible penile fracture, careful history and physical examination are critical for risk stratification and determining whether the patient needs to be brought to the operating room or can be managed conservatively (Table 16.1). There are several common scenarios in which fracture commonly occurs, but the most common is when the penis slips out of the vagina and strikes the perineum or pubis. Penile fracture often occurs with the woman in the "straddling" position. It has been observed that about half of penile fracture cases occur during an extra-marital affair, during which sexual activity is likely to be rushed and/or occur in unusual locations. Clinical experience shows that most fractures occur with the man or couple inebriated. With true penile fracture, patients typically hear or feel a "pop" in their penis. The presence or absence of immediate detumescense following the injury is the most important fact to ascertain, since penile fracture invariably results in instantaneous loss of erection. Continuation of sexual activity following a penile injury rules out, by definition, the diagnosis of penile fracture. Blood at the urethral meatus or, in rare cases, inability to urinate signifies a urethral injury.

On physical exam, men with penile fracture will have penile hematoma and tenderness. In rare cases a defect in the tunica albuginea may be palpated under the hematoma, although many patients present in such a delayed fashion that this is usually not possible given the amount of blood accumulation on the penile shaft. When corporal bleeding is contained by Buck's fascia (as is most often the case), ecchymosis and swelling will be limited to the shaft of the penis, resulting in the classic "eggplant" appearance of the penile shaft. In more severe cases of fracture, when bleeding occurs through Buck's fascia, ecchymosis is limited by Colles' fascia and may result in the classic "butterfly" perineal ecchymosis appearance. The location of the injury is important for diagnosis, since penile fracture invariably occurs near the base of the penis. Patient description, or physical exam findings, consistent with injury on the more distal aspect of the penis are less consistent with fracture. The diagnosis of penile fracture is made clinically. Based on the history and physical examination, the physician should be able to ascertain the likelihood of penile fracture. Patients presenting with penile trauma and ecchymosis/hematoma formation can be categorized as unlikely, possible, and high risk of fracture based on the presence or absence of classic features of the condition.

## (C)

Patients who give a history that is inconsistent with penile fracture, especially if they deny immediate detumescense, are at exceedingly low risk for having had penile fracture. However, they should still undergo focused penile examination to evaluate for ecchymosis or other injuries. Men who are considered low risk for penile fracture, and have no visible ecchymosis, can be reassured that they do not have penile fracture or other significant injuries. No further evaluation is needed.

## (D)

If ecchymosis is present on the shaft, despite a history inconsistent with penile fracture, the bleeding is usually attributed to superficial venous trauma or suspensory ligament tear. Sensory ligament disruption may be confirmed by tenderness where the corporal bodies are attached to the pubic bone or the palpation of a gap between the pubic symphysis and the base of the penis. No further immediate evaluation is needed and the patient can be reassured. There are some men who suffer a partial tear of the tunica albuginea, which is not transmural and therefore the penis is not fractured. Such trauma may lead to penile ecchymosis and may go on in the future to develop into Peyronie's disease. In this population, scheduling a follow-up appointment is reasonable to define if plaque development occurs.

## (E)

Some men will have certain aspects of their histories or physical examination history that suggest penile fracture, but others that are inconsistent. An indeterminate level of risk of fracture can also occur when the patient is unable or unwilling to provide a clear history. If fracture is possible, but not strongly suspected, a magnetic resonance imaging (MRI) evaluation of the penis should be performed.

## (F)

MRI of the pelvis is the diagnostic imaging modality of choice because it can precisely demonstrate the presence, location, and extent of penile tunical disruptions, which appear as discontinuities of the tunica albuginea. Typically there are heterogeneous adjacent areas of increased signal intensity representing associated hematomas. MRI also provides information related to cavernosal or urethral injury. Men with fracture ruled out by MRI can be reassured and treated with supportive measures such as pain medications, if necessary. Men with tunical rupture best confirmed on T2-weighted MRI with gadolinium should proceed to surgical repair within a short period of time. Urethral injuries are usually apparent on MRI and can be addressed during surgery.

## (G)

When the diagnosis of penile fracture can be made with certainty, based on the history and physical examination, the first question is whether concomitant urethral injury is present. Urethral injury has been reported to occur in 15–30 % of penile fracture cases.

## (H)

If a man presents with a recent penile fracture, has difficulty voiding, and has suprapubic distension and/or pain, then a retrograde urethrogram (RUG) should be performed. Confirmation of urethral injury will require placement of a suprapubic catheter for bladder drainage, either percutaneously or

via open incision, in order to divert the urine without risking converting a partial disruption into a complete one. Formal repair of the urethra can then be performed at the time of surgical intervention along with repair of the tunical defect.

## (I)

Men who are able to void without difficulty are unlikely to have a serious urethral injury. It is still advisable, however, to obtain a urine sample. The presence of >3 red blood cells per high power field (or any degree of gross hematuria) suggests urethral injury, and RUG should be strongly considered in order to rule out this condition prior to, or during, surgical repair of the tunica albuginea. If the urinalysis is negative, then urethral injury is not present. The key consideration at hand is preparation for repairing a urethral tear during surgery.

## (J)

Although penile fractures have historically been treated conservatively, studies have shown that clinical outcomes are improved with early surgical intervention. Rates of erectile dysfunction and Peyronie's disease are increased with conservative treatment compared with surgery. When presentation is delayed, the value of surgical intervention is less clear. Treatment should be individualized depending on the duration of delay. Although authors disagree with regard to the optimal timeline for repair, we believe that most patients should go to the operating room within 3–5 days of injury. Surgery is performed under general anesthesia. A common surgical approach involves a subcoronal circumferential incision and degloving of the penile skin. We prefer to use a transverse scrotal incision since it provides excellent exposure of the tunica at the base of the penis where fractures are most likely to have occurred. Hematoma is evacuated by lavage and the tunical defect is identified and repaired with interrupted 2-0 PDS sutures in a horizontal mattress fashion. Occasionally, debridement of the tunical edges is required. If a urethral injury has been diagnosed by MRI or RUG, it is repaired with absorbable suture, such as 5-0 monocryl, in a watertight fashion. An indwelling catheter is left in place for approximately 2 weeks.

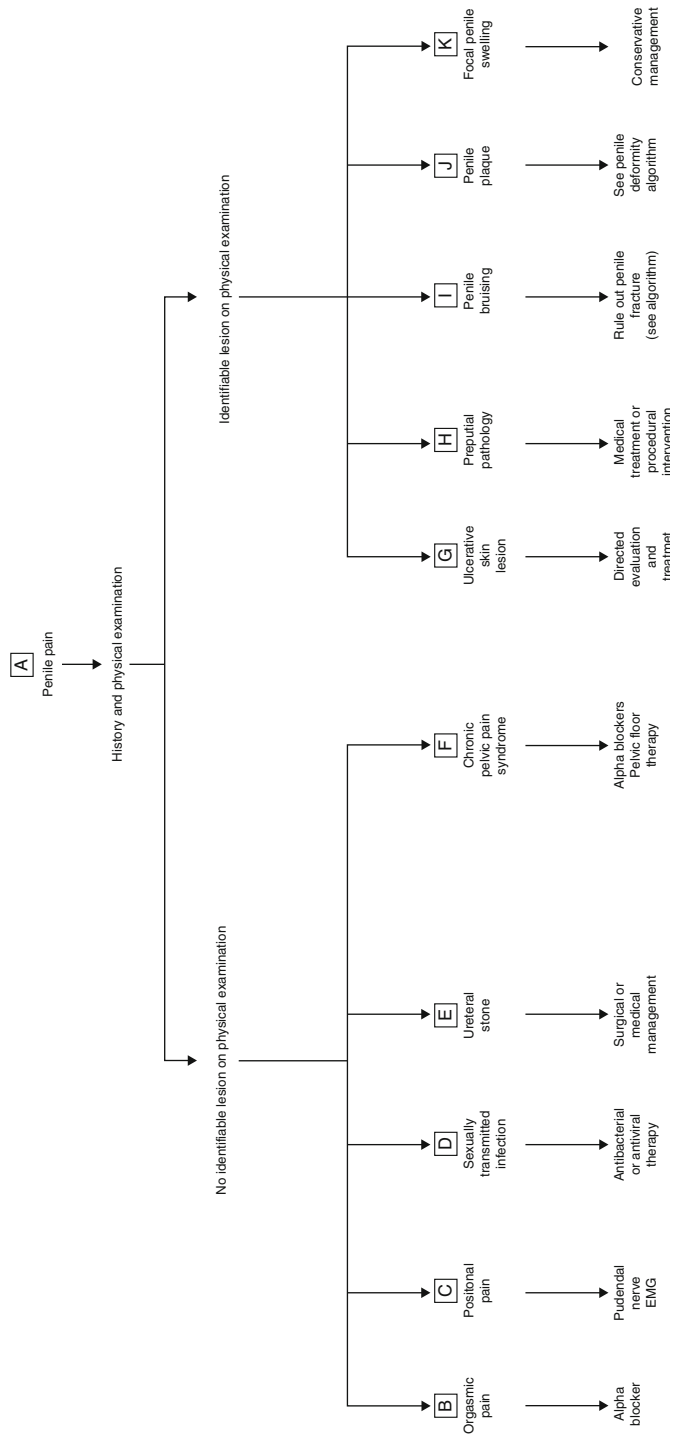
**Table 16.1** Key findings consistent with penile fracture

| |
|---|
| *History* |
| "Popping" noise or sensation occurring during sexual activity |
| Immediate detumescence followed by swelling, ecchymosis, hematoma formation, and pain |
| Difficulty voiding or hematuria indicating concomitant urethral injury |
| *Physical examination* |
| Penile hematoma or ecchymosis usually confined to penile shaft |
| "Butterfly" perineal ecchymosis suggests tear in Buck's fascia but contained with Colles' fascia |
| Blood at urethral meatus indicates concomitant urethral injury |

## Suggested Reading

Al-Shaiji TF, Amann J, Brock GB. Fractured penis: diagnosis and management. J Sex Med. 2009;6(12):3231–40.
Gamal WM, Osman MM, Hammady A, Aldahshoury MZ, Hussein MM, Saleem M. Penile fracture: long-term results of surgical and conservative management. J Trauma. 2011;71(2):491–3.
Garaffa G, Raheem AA, Ralph DJ. Penile fracture and penile reconstruction. Curr Urol Rep. 2011;12(6):427–31.
Myers JB, McAninch JW. Management of posterior urethral disruption injuries. Nat Clin Pract Urol. 2009;6(3):154–63.

# Chapter 17
# Penile Pain

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## (A)

Penile pain is a broad term with many different possible underlying etiologic factors, most of which can be readily identified by careful history and physical examination. On history, medical co-morbidities such as diabetes mellitus, psychiatric disorder, and chronic pain disorders are established. Patients should be queried regarding location, onset, quality, duration, and intensity of pain. Alleviating and exacerbating factors, including shifting positions and the relationship of the pain to orgasm, should be determined. The presence or absence of associated pelvic, abdominal, or perineal pain should be documented. Sexual history should be taken with attention to erectile rigidity, curvature and/or length loss with erection, and risk factors and symptoms related to sexually transmitted infections (STIs). Other important history points include urethral discharge, nephrolithiasis, genital trauma, and lower urinary symptoms. Physical examination of the penis includes visual examination for lesions on the shaft, glans, and prepuce. The urethral meatus is gently opened and examined for lesions and discharge. The stretched, flaccid penis should be palpated carefully for plaques. In uncircumcised men, the prepuce should be retracted to fully expose the glans and then returned to its normal anatomic position. If no lesions are identified on physical examination, then adjuvant testing is performed as directed by the history (Table 17.1).

## (B)

Pain that occurs with orgasm, or dysorgasmia, is a poorly understood condition that is associated with radical surgery or radiation therapy for prostate cancer. It is also a feature of chronic pelvic pain syndrome (CPPS). Dysorgasmia after radical prostatectomy has been shown to significantly decrease in severity for almost all patients by 2 years after surgery. Treatment with oral alpha-adrenergic blockers, such as tamsulosin or alfuzosin, is effective at decreasing the intensity of pain with orgasm in most men, suggesting that dysorgasmia may be related to spasm of the bladder neck and/or pelvic floor muscles. In men with refractory dysorgasmia, pelvic floor trigger point massage therapy may be indicated.

## (C)

Pudendal nerve entrapment is a rare cause of neuropathic pelvic and penile pain and numbness that results from compression of the pudendal nerve within Alcock's canal. The pain is characterized by varying with position and is typically worsened with sitting and alleviated by standing. The condition should be distinguished from CPPS, which is much more common and has similar symptoms (except for the positional component). Evaluation is performed with pudendal nerve electromyography (EMG), magnetic resonance imaging (MRI), or diagnostic nerve blocks. Treatment options include pelvic floor physical therapy, pudendal nerve blocks, pain medications, neurostimulation, and pudendal nerve decompression surgery.

## (D)

Pain of the penile urethra, or urethritis, can be experienced during STI. STIs are categorized as chlamydia or gonorrhea, depending on the causative organism, and are associated with urethral discharge, dysuria, and urinary frequency. Both conditions can be diagnosed with urine tests or urethral swab and

culture. Treatment should be directed at both conditions since they commonly co-exist, and sexual partners should be treated as well. Treat with Cefixime 400 mg orally in one dose plus Azithromycin 1 mg orally in a single dose. An alternative to Azithromycin is doxycycline 100 mg orally twice daily for 7 days.

## (E)

Urolithiasis can cause referred pain in the penis, typically at the tip, when the calculus becomes lodged at the ureterovesical junction. Penile pain usually follows after the onset of flank pain and lower abdomen pain as the calculus travels distally down the ureter. Patients often have a known history of urolithiasis. The diagnosis is confirmed with abdominal X-ray or CT scan without contrast of the abdomen and pelvis. Treatment consists of alpha-adrenergic blockers, which relax the ureter and help the stone to pass into the bladder, hydration, and pain medications. In refractory cases, endoscopy is performed to retrieve the stone, pulverize the stone, or pass a ureteral stent to relieve the obstruction and divert urine from the kidney to the bladder.

## (F)

Chronic prostatitis/CPPS is a poorly understood cause of pain in the lower pelvic region, including the penis, scrotum, and perineum. Urinary symptoms are common and include urinary frequency, urgency, and dysuria. Urine samples are taken to rule out infection, which is not present in CPPS. Treating the condition is difficult and often unsatisfying. A useful resource for the clinician is the UPoint website (www.UPointMD.com). This schema uses six domains of symptoms: urinary symptoms, psychosocial consequences, orgasm specific (prostate tenderness), infection (urine culture, urethral swabs), neurologic, and tenderness of pelvic floor.

## (G)

Chancroid is a painful ulcerative skin lesion that is associated with lymphadenopathy in approximately 50 % of patients. The lesions are sharply defined, have irregular borders, and bleed easily if scraped. Ulcers are biopsied and microscopically evaluated for the presence of *Haemophilus ducreyi*, the causative bacterial agent of chancroid. No laboratory testing is available for chancroid. Antimicrobials should be initiated when the diagnosis is suspected, even in the absence of a definitive diagnosis. Treatment is a single dose of oral Azithromycin 1 g or intramuscular ceftriaxone 250 mg. Herpetic lesions may be located on the penis, scrotum, or inner thighs, and typically begin as clusters of small bumps. These develop over several days into blisters and then into open ulcers. Herpes lesions are very painful and may be preceded by prodromal syndromes such as tingling and itching. The diagnosis is confirmed by viral culture from material collected from the sores. Oral acicylovir is used to treat outbreaks and can also be used prophylactically to limit the frequency and duration of recurrences, as well as reduce the likelihood of transmission. Since men with chancroid or genital herpes are considered at high risk for other STIs, additional testing for gonorrhea, chlamydia, human immunodeficiency virus (HIV), and syphilis is recommended.

## (H)

Preputial pathology can be categorized into three groups: phimosis, paraphimosis, and balanoposthitis. *Phimosis*, or preputial stenosis, is the inability to retract the foreskin. The condition is strongly associated with poorly controlled diabetes mellitus (DM). Chronic irritation caused by poor hygiene leads to cracking and tenderness of the prepuce. Erection can cause increased pain as the swollen glans put pressure on the sclerotic prepuce. In severe phimosis that obstructs the urethral meatus, urine can become trapped within the prepuce and cause severe pain and irritation. Topical steroids can allow for retraction in some patients. Circumcision is a definitive treatment. Be aware of the link between balanitis xerotica obliterans (BXO) and phimosis. This condition is worth diagnosing early lest it progresses to meatal stenosis and urethral involvement.

*Paraphimosis*, or retraction of the foreskin that cannot be reduced (protracted) to the normal anatomic position, is severely painful and considered a urological emergency. As edema of the glans and distal penis progresses, it becomes increasingly more difficult to reduce the prepuce, ultimately leading to vascular compromise and glanular necrosis. The condition commonly occurs after indwelling urethral catheter placement. Urgent manual reduction should be attempted. Oral pain medications and local anesthetics are usually required. Robust manual compression of the glans for a prolonged period may be required to squeeze out edematous fluid prior to reduction. A two-handed approach is used, so that the thumbs put pressure on the glans while the second and third fingers pull the foreskin in the opposite direction. If manual reduction is not possible, then a dorsal slit is performed to release the constricting band. Formal completion of the circumcision should be performed at later date. *Balanophosthitis* refers to inflammation of the glans and prepuce. The condition is usually caused by *Candida* fungal infection and is associated with phimosis, poor hygiene, DM, and immunocompromised states such as HIV. It is characterized by pain, erythema, and edema of the foreskin and glans. Balanitis is a similar condition that describes inflammation of the glans only. Good hygiene with soap, water, and frequent exposure of the glans to air is the most effective treatment. The glans and foreskin should be kept clean and dry. Underlying conditions such as DM should be controlled. Oral fluconazole for severe symptoms, or topical Clotrimazole 1 % cream applied twice daily, is an immediate treatment that should be continued until the condition resolves. Topical hydrocortisone is sometimes added for severe inflammation. Circumcision is an effective strategy to treat and prevent recurrence of balanoposthitis.

## (I)

Penile pain associated with visible bruising is usually associated with penile trauma. Ecchymosis usually is the result of a tear in one of the superficial veins or suspensory ligament disruption. Frank penile fracture is associated with hematoma formation on the penile shaft (see *Penile Fracture* algorithm).

## (J)

Peyronie's disease (PD) is a connective tissue disorder involving fibrosis of the tunica albuginea of the penis. Patients with PD may report penile deformity or shortening with erection, but the initial complaint is sometimes penile pain. PD can be associated with pain in the erect and often in the early stages, flaccid states. Evaluation and management of PD is covered in Chap. 15.

## (K)

Focal penile swelling can occur with penile sclerosing lymphangitis (SL) and penile superficial venous thrombosis (SVT). SL usually presents as a mildly to moderately tender indurated cord lying subcutaneously on the penile shaft. It most commonly occurs after vigorous sexual activity. In all cases, resolution is spontaneous and the patient should be reassured. SVT of the penis, also known as Mondor's disease, presents with a thickened and possibly erythematous cord on the dorsal aspect of the penis. The cord is actually the thrombosed dorsal vein, which can result from vigorous or traumatic sexual activity, pelvic neoplasms, and abuse of intravenous drugs. The condition is painful but resolves spontaneously within 2 months without long-term consequences. Some authorities advocate the use of aspirin to accelerate resolution of the thrombosed vein.

**Table 17.1** Important history and physical examination points

| |
|---|
| History |
| Medical co-morbidities |
| Onset, duration, location, quality, and severity of pain |
| Associated pelvic, abdominal, or perineal pain |
| Exacerbating factors |
| Association with orgasm |
| Concomitant erectile dysfunction |
| Penile deformity or length loss with erection |
| Penile trauma |
| Lower urinary tract symptoms |
| Urethral discharge |
| Physical examination |
| Penile plaque |
| Genital ulcers |
| Preputial inflammation or irritation |
| Penile ecchymosis |
| Penile deformity |
| Palpable dorsal cordlike structure |
| Urethral discharge |

## Suggested Reading

Hayashi Y, Kojima Y, Mizuno K, Kohri K. Prepuce: phimosis, paraphimosis, and circumcision. Scientific World J. 2011;11:289–301.

Konkle KS, Clemens JQ. New paradigms in understanding chronic pelvic pain syndrome. Curr Urol Rep. 2011;2(4):278–83.

Matsushita K, Tal R, Mulhall JP. The evolution of orgasmic pain (dysorgasmia) following radical prostatectomy. J Sex Med. 2012. doi:10.1111/j.1743-6109.2012.02699.x.

Popeney C, Ansell V, Renney K. Pudendal entrapment as an etiology of chronic perineal pain: diagnosis and treatment. Neurourol Urodyn. 2007;26(6):820–7.

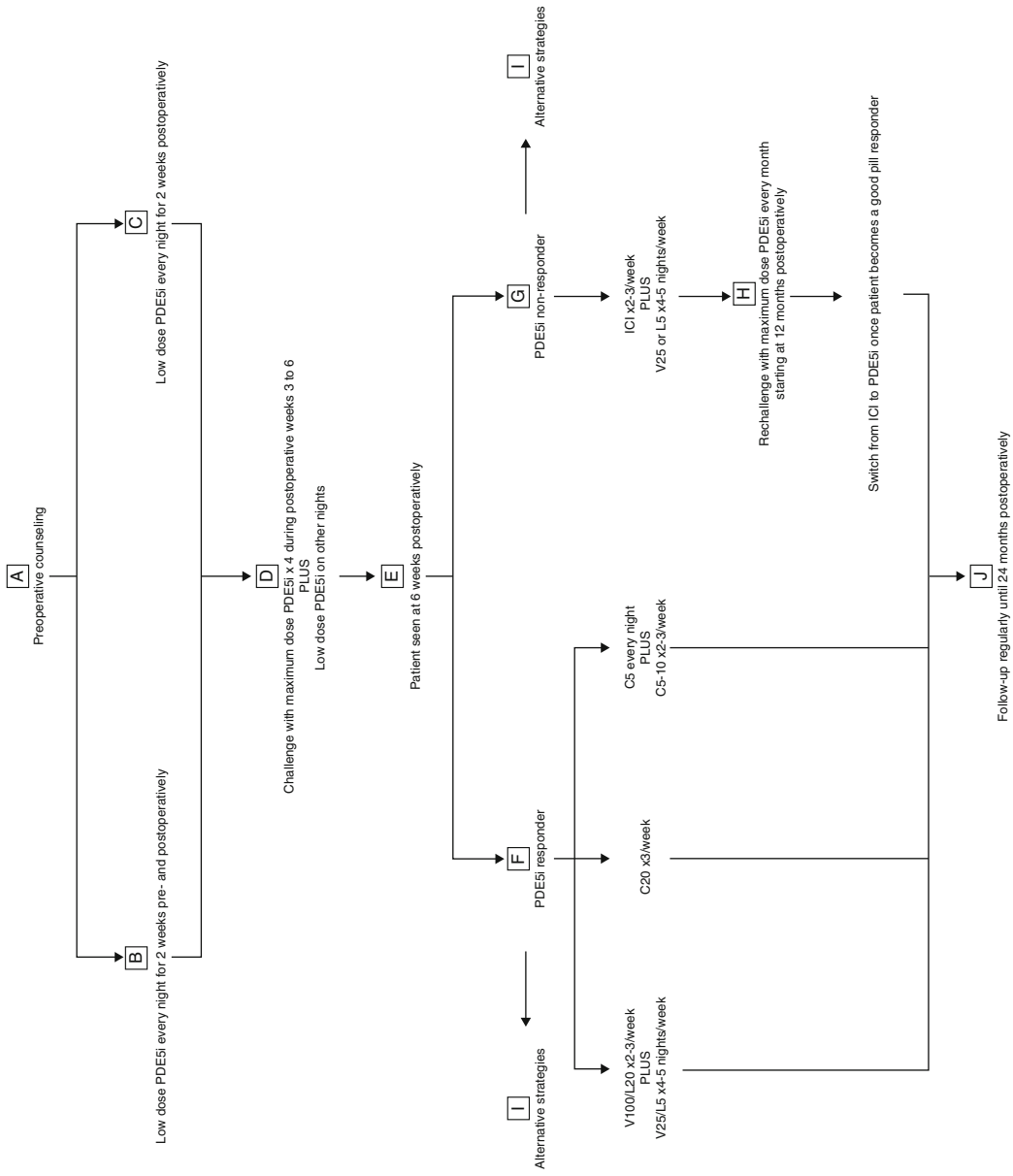
Ralph D, Gonzalez-Cadavid N, Mirone V, Perovic S, Sohn M, Usta M, et al. The management of Peyronie's disease: evidence-based 2010 guidelines. J Sex Med. 2010;7(7):2359–74.

Rosen T, Hwong H. Sclerosing lymphangitis of the penis. J Am Acad Dermatol. 2003;49(5):916–8.

Schade GR, Faerber GJ. Urinary tract stones. Prim Care. 2010;37(3):565–81.

Workowski KA, Berman SM. Centers for disease control and prevention of sexually transmitted disease treatment guidelines. Clin Infect Dis. 2011;53 Suppl 3Suppl 3:S59–63.

# Chapter 18
# Penile Rehabilitation

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The concept of penile rehabilitation revolves around protection of erectile tissue (i.e., cavernosal smooth muscle and endothelium) during the phase when the cavernous nerves are non-functioning or functioning poorly, such as often occurs as a result of radical prostatectomy (RP). Cavernous nerve damage, and subsequent impairment of erectile tissue, results in natural erections that are of poor quality or non-existent. The aim of rehabilitation is to preserve erectile tissue such that, if and when the nerves regenerate, the patient has the best chance of returning close to his baseline erectile function. The purpose of penile rehabilitation is not only to allow a man have sexual intercourse during the rehabilitation period but also, more specifically, to maximize his long-term erectile function recovery. This concept is called "back-to-baseline recovery."

It is worth noting that many men are capable of intercourse with a 60 % rigid erection (surgeons will declare this patient as being "potent" postoperatively), but if they were 100 % rigid preoperatively, they will have experienced a 40 % reduction in erectile rigidity after RP. These men are not happy and end up using some erectogenic medication for sexual relations.

While it is not clear how rehabilitation exerts a positive effect, it is likely that it is a multifactorial process involving tissue stretch, oxygenation, activation of endothelial factors, and possibly, smooth muscle preservation and mild neurotrophic effects.

There are robust data that erectile tissue degeneration (collagenization) occurs as early as 2 months (and possibly earlier) after RP. There are also data supporting the fact that end-organ failure (venous leak) occurs in a time-dependent fashion after RP. Indeed, significant rates of venous leak are evident as early as 4 months after RP. This rate is dependent upon a number of factors including baseline erectile function, patient age, and nerve-sparing status during RP. Finally, there are some data indicating that earlier institution of rehabilitation results in better long-term recovery compared to delayed commencement of rehabilitation.

The penile rehabilitation committee of the International Consultation of Sexual Medicine (ICSM) reported that all men should be spoken to about rehabilitation after RP and that the patient, rather than the surgeon or clinicians, should decide whether the effort and cost are appropriate for him. Unfortunately, there do not exist data to define the optimal agents of rehabilitation (i.e., oral tablets, injections, vacuum device therapy, or a combination) and the optimal start time or duration of treatment. We believe that radical cystectomy and radical rectal surgery patients, in addition to men undergoing RP, are also excellent candidates for penile rehabilitation.

## (A)

Under ideal circumstances, patients should be seen before RP and counseled regarding erectile function recovery. Particular attention should be paid to factors including early loss of erectile function, the time-course to recovery of erectile function, and realistic figures for recovery (based on individual characteristics such as preoperative function, age, nerve-sparing status, comorbidity status, and commitment to rehabilitation). This encounter also permits the clinician to discuss other sexual dysfunctions associated with RP such as anejaculation, orgasmic intensity changes, orgasmic pain, sexual incontinence, penile length loss, and penile morphology changes.

## (B)

We consider it ideal to have the patient seen pre-RP for a comprehensive discussion regarding sexual function impact of RP, in an effort to transmit realistic expectations prior to surgery and minimize postoperative regret. If the patients are seen prior to their operation, we consider it ideal

to commence patients on a PDE5 inhibitor before surgery. This is based on the concept of "endothelial preconditioning."

Experimental data show that, in response to neuropraxia, the endothelium in the penis undergoes degenerative changes. In an effort to up-regulate endothelial function, to protect against this effect, preoperative PDE5i use is employed. The endothelial protective effect of PDE5i in humans is well established, with improved flow-mediated dilation in at-risk populations as well as generation of endothelial progenitor cells. However, the only data supporting such an approach pre-RP to date are based on the rat cavernous nerve injury model.

There are no head-to-head trials evaluating the efficacy of sildenafil, vardenafil, tadalafil, or the recently approved avanafil in endothelial protection or endothelial preconditioning, so the specific choice of agent is left to the practitioner. Patients are prescribed low-dose (quarter maximum dose) PDE5i to be used every night for 2 weeks before their operation and for the first 2 weeks after RP. For example, if the patient is using sildenafil, he would take 25 mg (a quarter of a 100 mg pill) every night, seven nights per week.

## (C)

While we think it is best that the patient undergoes pre-RP counseling, the majority of patients are more focused on their cancer care prior to surgery and many present for a discussion of sexual function after their operations. We recommend that patients start low-dose PDE5i as early as possible after their RP, preferably the night they return home after hospital discharge. We recommend that they use low-dose (quarter maximum dose) PDE5i every night for the first 2 weeks after RP. Thus, as in (A), if the patient is using sildenafil, he would take 25 mg (a quarter of a 100 mg pill) every night, seven nights per week.

## (D)

Patients are advised to see a sexual medicine clinician or their surgeon if such a clinician does not exist at approximately 6 weeks after RP. During weeks 3–6, patients are instructed to change their PDE5i regimen to low-dose six nights per week and, on 1 day (or night) per week, to use maximum dose PDE5i with sexual stimulation. In this way, patients will have tried maximum dose PDE5i before they present for discussion at 6 weeks postoperatively.

## (E)

During the 6-week visit, the clinician can define whether the patient is a PDE5i responder. We suggest that the definition of "PDE5i responder" revolves around the ability to generate a penetration-hardness erection (60 % rigidity) when using maximum dose PDE5i. Some patients at this time frame, either with or without PDE5i, experience excellent rigidity. It is important to note that the nadir in erectile hardness occurs between 3 and 4 months after RP. It is important to discuss and forewarn patients of this phenomenon, as it is important for them to avoid going long periods of time without erections of penetration-hardness rigidity.

The literature would suggest that, for the patients experiencing good rigidity at 6 weeks, there is approximately a 25 % chance that they will drop their rigidity below penetration-hardness by 12–16

weeks post-RP. Even when this occurs, the vast majority will return to their early postoperative rigidity by 12 months, in contrast to the 18–24 months that most men have to wait to experience optimization of their erectile rigidity.

## (F)

For the patient who at 6 weeks is a PDE5i responder, there are now a number of options for PDE5i-based rehabilitation. The patients can use the maximum dose of a short-acting PDE5i (sildenafil, vardenafil, avanafil) 2–3 times per week, with stimulation, to generate a penetration-hardness erection. This should be alternated with a low-dose (quarter maximum dose) on the other nights. The patient using sildenafil, for example, would use 100 mg twice per week to generate rigidity and 25 mg five nights per week as an endothelial protectant.

Alternatively, if the patient prefers to use tadalafil, he may use 20 mg 3 days per week (alternating, e.g., Tuesday, Thursday, Saturday). This permits him to generate two to three penetration-hardness erections per week and covers him for the entire week (from an endothelial protection standpoint).

The introduction of daily tadalafil 5 mg facilitates patients using this strategy. It is important to remember that after 5 consecutive days of tadalafil 5 mg use, the patient has a serum level equivalent to that of a single dose of 8 mg (and it plateaus at this level). It is not common that post-RP patients are capable of responding with a penetration-hardness erection when using 40 % maximum dose PDE5i. Therefore, it is likely that men using tadalafil 5 mg daily will need to add a boost (5 or 10 mg) to this regimen on the day that penetration-hardness erections are planned.

We encourage patients to use their low-dose PDE5i at night because it may generate nocturnal erections and further improve cavernosal oxygenation and stretch.

## (G)

For the majority of patients after RP, even when nerve-sparing is employed, PDE5i are ineffective for generating erectile rigidity in the first postoperative year. Most men will optimize their erectile function recovery between 18 and 24 months post-RP. For patients who do experience erectile function recovery, the nerves typically “wake up” between 10 and 14 months after surgery (initially manifested by nocturnal erections and gradual improvement in their PDE5i response).

Given the importance of erections, we encourage all PDE5i non-responders at 6 weeks after RP to do intracavernosal injections. Once men are trained to perform at-home ICI, we urge them to use injections 2–3 times per week and low-dose short-acting PDE5i (sildenafil, vardenafil, avanafil) on the other nights. The typical patient injects two nights per week and would use low-dose (quarter pill) on the other five nights of the week. We do not permit patients to use PDE5i and injection within 18 h of each other. Patients who alternate injections with pills do not use tadalafil since it can remain active for several days and thus interact with injections. While many will consider this extremely conservative, our priapism rate in our injection program is 0.2 %.

The delivery of initial information given regarding injections is critical for compliance. We present penile injections as a rehabilitation strategy and tell all patients that our ultimate goal is to have patients cease injections and shift back to using PDE5i for sexual relations. We discourage men making a decision about penile injections based on mental imagery (which all men instinctively do when first they hear about injections). Finally, men should attempt an initial injection in the office setting, after which an informed decision regarding their interest in pursuing injections can be made.

## (H)

As previously mentioned, neural recovery appears to commence for most men approximately between 10 and 14 months after RP. Thus, we encourage all men to re-challenge themselves with a maximum dose PDE5i starting early in the second year postoperatively. We suggest that a once-per-month trial is adequate until the patient is capable of generating a penetration-hardness erection with a PDE5i.

Once the patient can achieve an erection of ≥60 % rigidity with a PDE5i, he is instructed that he may abandon injections. Perhaps surprisingly, many patients continue to use injections despite good PDE5i response because of the excellent speed of onset, rigidity, and duration of response achievable with intracavernosal injections.

## (I)

While we do not employ either vacuum device therapy or intraurethral suppositories in our program, there is increasing interest in these alternative strategies. There do not exist randomized, controlled trials that have addressed these approaches as rehabilitation strategies. Intraurethral PGE1 suppository use is notoriously associated with aching penile pain, particularly in men who have had cavernous nerve resection performed. It is conceivable that there may be some intrinsic protective benefit of PGE1 delivery in the corpus cavernosum. Until clinical research addressing PGE1 suppositories as a rehabilitation strategy has been conducted, however, this agent is unlikely to assume a significant role in rehabilitation programs.

Vacuum devices have historically been touted as failing to oxygenate the corpora cavernosa because the blood drawn into the penis is of mixed venous oxygenation level. This dogma has recently been challenged with work using novel animal models. Regardless, there are no trials addressing vacuum device therapy as a rehabilitation strategy (although the FDA has surprisingly granted permission to include rehabilitation as an indication in vacuum device labels). There are good data supporting the concept that regular vacuum device use is associated with penile length preservation. We therefore contend that the best way to preserve penile length is to generate regular erections (with a PDE5i or injection therapy) and thus confine the use of vacuum devices to men who refuse to perform intracavernosal injections.

## (J)

We continue to follow all of our RP patients until at least 24 months postoperatively. This is the time point by which most men who are going to recover functional erections have done so (i.e., via natural or PDE5i response). It is important for the clinician to conduct a thorough assessment of the erectile function "mechanism" at this time-point. The most reliable and simple way to do this is by assessing the patient's nocturnal erections. During sexual activity with a partner, especially after a prolonged period of time when erections have not been good enough for intercourse, stress and anxiety generate high levels of adrenaline.

Adrenaline is an extremely potent anti-erection chemical. Thus, it is common for men at this point to report that their bedroom erections are poor with their partner but that their nocturnal erections are excellent. These men have a good prognosis for further recovery of erectile rigidity beyond 24 months. Patients with absent or poor nocturnal erectile rigidity are challenged with a full dose of a PDE5i just before bedtime, in an effort to see if they experience improved nocturnal erections. If they are able to generate good erectile rigidity in this scenario then the prognosis for recovery to point of being able to respond to a PDE5i is good.

## Suggested Reading

Mulhall JP, Bella AJ, Briganti A, McCullough A, Brock G. Erectile function rehabilitation in the radical prostatectomy patient. J Sex Med. 2010;7(4):1687–98.

Müller A, Parker M, Waters WB, Flanigan RC, Mulhall JP. Penile rehabilitation following radical prostatectomy: predicting success. J Sex Med. 2009;6(10):2806–12.

Mulhall JP, Parker M, Waters WB, Flanigan RC. The timing of penile rehabilitation after bilateral nerve sparing radical prostatectomy impacts upon erectile function recovery. BJU Int. 2009;105(1):37–41.

Tal R, Valenzuela R, Aviv N, Parker M, Waters WB, Flanigan RC, et al. Persistent erectile dysfunction following radical prostatectomy: the association between nerve sparing status and the incidence and chronology of venous leak. J Sex Med. 2009;6(10):2813–9.

Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: a meta-analysis. J Sex Med. 2011;6(9):2538–46.

Mulhall JP. The role and structure of a post-radical prostatectomy penile rehabilitation program. Curr Urol Rep. 2009a;10(3):219–25.

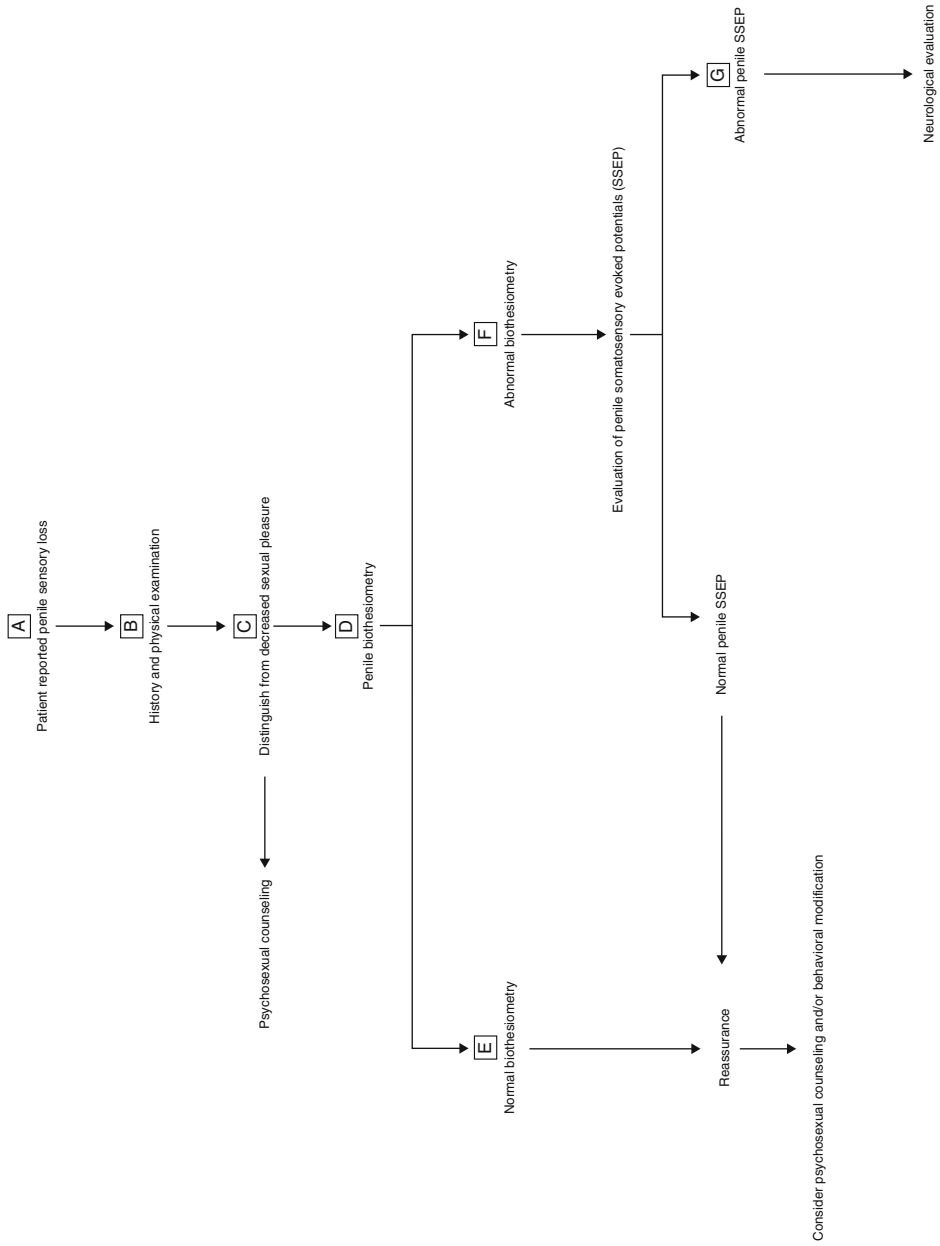
Mulhall JP. Defining and reporting erectile function outcomes after radical prostatectomy. J Urol. 2009b;181(2): 462–71.

Montorsi F, Brock G, Lee J, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol. 2008;54:924–31.

Padma-Nathan H, McCullough AR, Levine LA, et al. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res. 2008;20:479–86.

Mulhall JP, Morgentaler A. Penile rehabilitation should become the norm for radical prostatectomy patients. J Sex Med. 2007;4:538–43.

# Chapter 19
# Penile Sensory Loss

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## (A)

While written about infrequently, it is not uncommon for an andrologist to have a patient complaining of loss of penile sensation. This perplexing symptom may be organically based (penile sensory neuropathy) or psychogenic (perceptual). Any cause of neuropathy can cause penile sensation loss, but most common is diabetes mellitus. Of note, it is not uncommon for patients after radical prostatectomy to believe that the nerve injury associated with that operation leads to penile sensation loss. Of course, the nerves injured at the time of this procedure are autonomic in nature and thus are not implicated in penile sensory loss. Reduced penile sensation may be a secondary psychological sexual dysfunction. In men, particularly young men with sexual problems, the typically encountered penocentricity (that is, obsessive focus on the penis) associated with the latter can lead to the complaint of penile sensation loss.

## (B)

The medical history should focus on conditions and medications (particularly chemotherapy) that are associated with neuropathy, especially sensory neuropathy. The time course of a neuropathy varies and may shed light on the underlying etiology (Table 19.1). Psychogenic sensation loss is often sudden in onset. The presence of pain associated with the sensation loss is more suggestive of an organic etiology, in particular ischemic neuropathy and small-fiber neuropathies. The pain may be burning, lightning-like, or aching and may be associated with dysesthesia. Patients may sometimes complain of pain with innocuous stimuli such as sheets rubbing over their penis (allodynia). The clinical assessment should include a careful past medical history to evaluate for systemic diseases associated with neuropathy, such as diabetes or hypothyroidism. Many medications can cause a peripheral sensorimotor neuropathy (Table 19.2). The review of systems should focus on symptoms implicating other organ involvement and the possible presence of a paraneoplastic syndrome. A detailed sexual history is essential. Not only is organic penile sensory loss associated with orgasm delay, but the sexual dysfunction may predate the sensory loss. It is important to define the temporal relationship between sensation loss and the start of the sexual problems. A routine genital examination should be performed. Specific attention should be made to signs of S2-4 root pathology, including the bulbocavernosus reflex. In a patient with a sensorimotor neuropathy, the sensory examination shows reduced sensitivity to light touch, pin-prick, temperature, and vibration.

## (C)

It is worth defining if the patient actually has loss of sensation or decreased pleasure. Sometime patients complain of decreased sensation when in fact they have reduced orgasmic intensity or absence of pleasure associated with sexual activity (sexual anhedonia). Before launching into a complex evaluation, it is important to differentiate between these entities.

## (D)

The biothesiometer (Fig. 19.1) is an instrument designed to measure simply and accurately the threshold of appreciation of vibration in human subjects (http://www.biothesiometer.com). The instrument is used as a tool in the assessment of the patient with neuropathy or at risk for neuropathy. It is essentially an "electrical tuning fork" with adjustable amplitude that may be gradually increased until the threshold of vibratory sensation is reached. Conversely, the amplitude may be lowered until the vibration is no longer discernible. In all cases the amplitude may be determined at any given level with a high degree of accuracy. There is a nomogram available (Appendix 1) to define normalcy of vibration thresholds that has been shown to be superior to the use of a tuning fork in accuracy. We typically commence by applying the tip of the handheld probe to the pulp of each index finger. This helps the patient get used to the process and may aid in the diagnosis of a systemic neuropathy. We then apply the probe to each side of the midshaft of the penis, each side of the glans and the frenular area. All of the figures obtained are recorded and compared to the nomogram. It is our experience that when a neuropathy is present, the figures obtained are at least double the upper limit of normal for the patient's age.

## (E)

When the biothesiometry is normal, the patient can be reassured.

## (F)

When biothesiometry is abnormal we recommend that a more sophisticated test be performed, such as somatosensory-evoked potentials (SSEP). Penile SSEPs consist of a series of waves that reflect sequential activation of nerves and is usually conducted using electrical stimulation of dorsal nerve of the penis along with the peroneal nerve as a control. Recording electrodes are placed over the scalp, spine, and peripheral nerves proximal to the stimulation site. SSEPs allow definition of the level at which the nerve injury or pathology exits (peripheral nerve, plexus, spinal root, spinal cord, brain stem, or cortex). While an abnormal SSEP result demonstrates that there is pathology within the somatosensory pathways (subjects cannot fake an abnormal SSEPs, unlike with biothesiometry), a normal SSEP study can occur in patients with sensory deficits (due to the multiple sensory pathways between organ and the central nervous system). The tracings are complicated and are best interpreted by a trained neurophysiologist.

## (G)

All patients with an abnormal SSEP study are sent to a neurologist for evaluation. We acquiesce all further testing (laboratory and imaging) to the neurological consultant. In situations where there is no access to SSEP testing, we recommend neurological consultation referral for patients bothered by their sensation loss. When the SSEP is normal, even in the setting of an abnormal biothesiometry, we tend to reassure patients unless there is significant bother and other signs are consistent with the presence of a neuropathy. Of note, while SSEP testing of most peripheral nerves is readily available, finding an expert who is comfortable doing dorsal penile nerve SSEP can be difficult.

**Appendix 1**

## B I O T H E S I O M E T R Y

**Patient:** _____

**History Number:** _____

**Date:** _____

| | Right | Left |
|---|---|---|
| **Index Finger** | | |
| **Shaft** | | |
| **Glans** | | |
| **Frenulum** | | |

## N O M O G R A M F O R P E N I L E B I O T H E S I O M E T R Y

| AGE | Pulp | Shaft | Glans |
|---|---|---|---|
| **18-29** | **3** | **3** | **3** |
| **30-39** | **4** | **4** | **4** |
| **40-49** | **4** | **5** | **5** |
| **50-59** | **5** | **6** | **7** |
| **60-69** | **5** | **7** | **7** |

**DIAGNOSIS**

- ❑ **Consistent with neuropathy**
- ❑ **Normal**

**TREATMENT**

- ❑ **Neurology consult**
- ❑ **SSEP**
- ❑ **Monitor**

**Comments** _____

**Table 19.1** Differential diagnosis of penile sensation loss

| |
|---|
| Pudendal nerve entrapment |
| Myxedema |
| Amyloidosis |
| Trauma |
| Diabetes |
| Vasculitis |
| Sarcoidosis |
| Leprosy |
| HIV/AIDS |
| Alcoholism |
| Vitamin B12 deficiency |
| Toxin exposure |
| Heavy metal exposure |
| Paraneoplastic syndrome |
| Porphyria |
| Medications |
| Psychogenic |

**Table 19.2** Medications associated with neuropathy

| |
|---|
| Vincristine |
| Paclitaxel |
| Cisplatin |
| Thalidomide |
| Colchicine |
| Isoniazid |
| Hydralazine |
| Metronidazole |
| Pyridoxine |
| Lithium |
| Alpha-interferon |
| Dapsone |
| Phenytoin |
| Cimetidine |
| Disulfiram |
| Chloroquine |
| Ethambutol |
| Amitriptyline |
| Amiodarone |


**Fig. 19.1** The biothesiometer is an instrument designed to measure simply and accurately the threshold of appreciation of vibration in human subjects (http://www.biothesiometer.com)

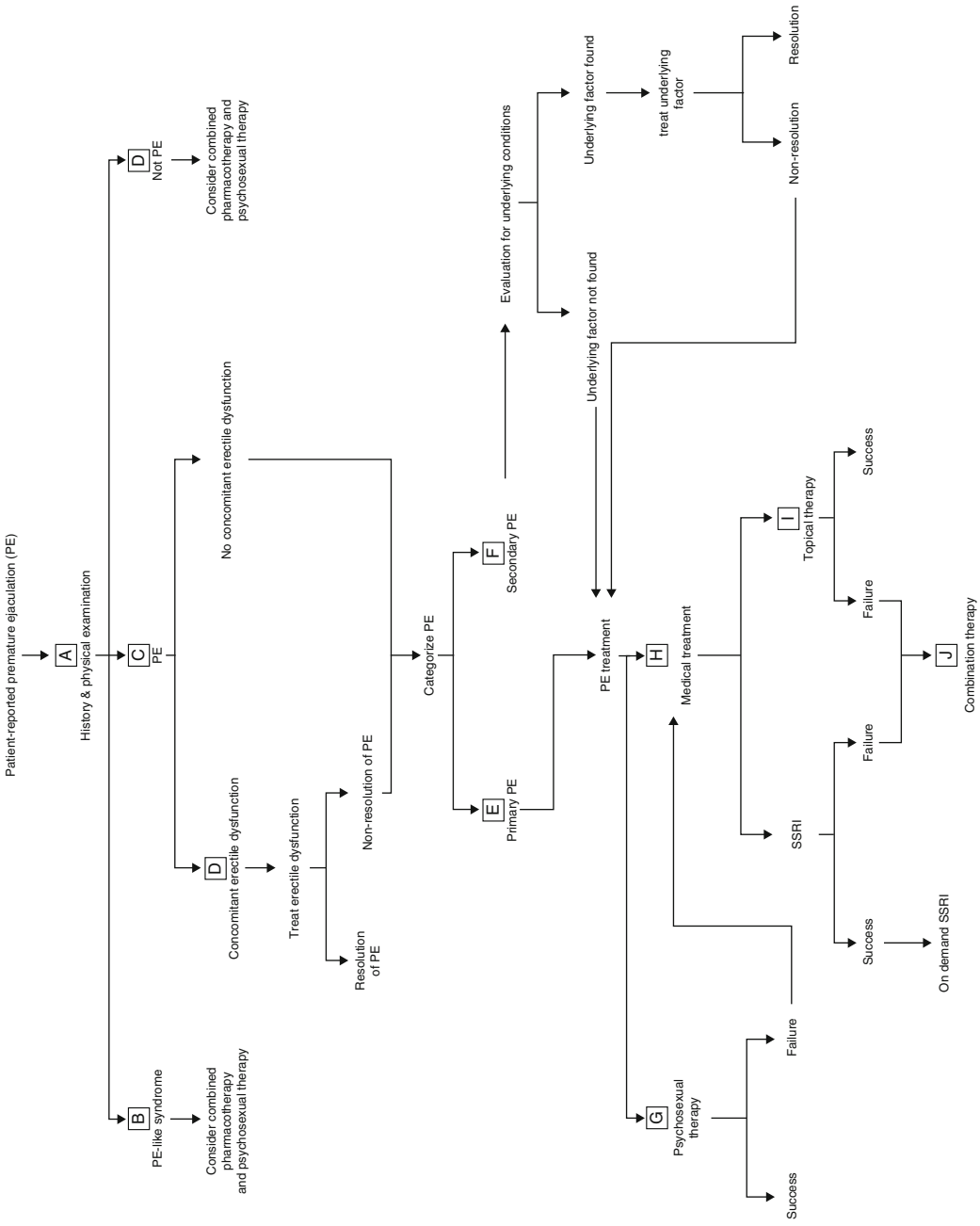
## Suggested Reading

Azhary H, Farooq MU, Bhanushali M, Majid A, Kassab MY. Peripheral neuropathy: differential diagnosis and management. Am Fam Physician. 2010;81(7):887–92.

Legatt AD, Benbadis SR. General principles of somatosensory evoked potentials. Medline. http://emedicine.medscape.com/article/1139906-overview#a30. Accessed July 2012.

Poncelet A. An algorithm for the evaluation of peripheral neuropathy. Am Fam Physician. 1998;57(4):755–64.

# Chapter 20
# Premature Ejaculation

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A new definition was recently developed by a consensus panel of the International Society for Sexual Medicine (ISSM). It is likely that no single dimension defines premature ejaculation (PE) and that the definition should involve multiple dimensions, such as time, perceived control over ejaculation, personal and partner distress, reduced sexual satisfaction, and relationship difficulty. Time is measured by the intravaginal ejaculatory latency time (IELT), the duration in seconds or minutes that pass from the first moment of vaginal penetration to ejaculation/orgasm. The ISSM panel defined PE as having three components: (1) ejaculation which always or nearly always occurs within about 1 min of vaginal penetration, (2) the inability to delay ejaculation on all or nearly all vaginal penetrations, and (3) negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy. Waldinger has attempted to categorize PE into four subtypes with significant clinical utility: lifelong, acquired, natural variable PE, and premature-like ejaculatory dysfunction (Table 20.1). PE has been estimated to affect approximately one quarter of all men, although not all men with the condition are bothered by it (Table 20.2).

## (A)

The American Urological Association (AUA) guidelines on PE management state that clinicians should "explicitly communicate the circumstances of the condition" as it is the "fundamental basis of assessment with time to ejaculation (IELT) as the most important feature." In addition to evaluation of IELT, the AUA recommends the following be taken into consideration: (1) the duration and frequency of PE, (2) the rate of occurrence of PE with some or all sexual encounters and partners, (3) the degree to which sexual stimuli cause PE, and (4) the nature and frequency of sexual activity including foreplay, masturbation, and intercourse. IELT, however, should not be taken into account alone and other key factors including perceived control over ejaculation, bother experienced by the patient because of the rapidity of ejaculation, and the impact upon the patient's sexual relationship should be considered. A simple PE history should therefore be taken, firstly, asking how long the patient has experienced PE (that is, whether it is lifelong or acquired). As lifelong PE is believed to be a potential neuroendocrine problem, with alterations in serotonin levels or serotonin receptor sensitivity, most of these men are not considered curable although they are eminently treatable. On the other hand, many men with PE related to the presence of ED or some underlying medical comorbidity (such as ED, hyperthyroidism, chronic prostatitis, or opiate withdrawal) or related to a major life stressor are potentially curable. Defining the IELT from a patient is useful but it must be appreciated that some men overestimate their IELT. Seeking corroboration of the IELT from the partner, if present at the visit, is helpful. Some men ejaculate quickly routinely because of partner issues (including rapid orgasm on behalf of the partner). Bother from PE and the impact it has had upon his relationship should be assessed as mild, moderate, or severe. Low bother and minimal impact on the relationship usually translate into no need for treatment, while high bother and/or high negative impact upon the relationship (irrespective of IELT) may warrant treatment. While it is recommended that a physical examination be conducted, more often than not it yields very little information pertaining to the patient's PE complaint. Such examination should include an assessment of signs and symptoms of conditions believed to be associated with PE, such as thyroid dysfunction and chronic prostatitis. A urologic genital exam is routinely conducted and some recommend assessment of the sacral reflexes and lower limb neuromuscular evaluation. It must be stated, however, that it is rare to find anything on physical exam that would help define the etiology of the patient's PE or would change the management plan. There are no specific investigations designed for the patient with PE and any adjuvant testing should be aimed at confirming findings uncovered by the history and physical examination. A number of instruments have been developed to assess the impact of treatment on men with PE (Appendices 1, 2, and 3) and, although they have not been adopted into routine clinical practice, they are useful for research purposes. These inventories

include the Premature Ejaculation Profile (PEP), the Index of Premature Ejaculation (IPE), the Male Sexual Health Questionnaire-Ejaculation (MSHQ-EjD), and the Premature Ejaculation Diagnostic Tool (PEDT). All of the aforementioned questionnaires have been validated and have demonstrated robust psychometrics.

## (B)

Premature-like ejaculatory dysfunction is also a common presentation where men have a subjective perception of rapid ejaculation despite having IELT values well within the normal range. These men may also have a preoccupation with imagined rapid ejaculation and poor control over ejaculation. Men with IELT values of 5 min or more who express poor control over ejaculation present a challenge and are often best managed by combined short-term treatment of PE and mental health evaluation and treatment. Many of these men have acquired "PE" and for much of their lives were able to keep IELT values of 10 min plus and have more recently had shortening of their IELT.

## (C)

The most useful definition is that of the ISSM.

## (D)

From a history standpoint it is critically important to be able to differentiate PE from ED. Both are common conditions and may coexist in the same patient. However, there are many patients who have ED, specifically with loss of sustaining capability, who are erroneously diagnosed with PE and vice versa. The critical point in the history is defining the onset of the patient's problem. For example, there are many patients who have ED who develop secondary PE. This is commonly seen in men who have loss of sustaining capability, whether organically or psychologically based. These men condition themselves to ejaculate more rapidly so that they can achieve orgasm prior to loss of erectile rigidity. This patient clearly has primary erectile problems with secondary ejaculatory problems and treatment should be directed towards his erectile dysfunction first. Treatment of ED, in this context, often translates into improvement of acquired PE as well as ED. On the other hand, there are patients who have lifelong PE and develop ED as they age. While treatment of this type of patient may commence with erectogenic pharmacotherapy, it is likely that his eventual management will require pharmacological therapy for PE as well.

## (E)

In cases where there is no concomitant ED or where PE associated with concomitant ED has failed to resolve with treatment for ED, medical therapy of PE is warranted if the patient and/or partner are bothered. For the patient without ED, categorizing the PE is useful for two reasons. Primary PE patients are not curable, but are treatable, and will need to consider remaining on lifelong treatment. On the other hand, men with acquired PE may have an underlying etiology or contributor that can be

addressed before pharmacotherapy is undertaken. Accumulating evidence suggest that primary PE may be a genetic condition. As early as the 1940s, it was suggested that a familial predisposition existed for PE. Recently research has been conducted into serotonin transporter (5-HTT) promoter region polymorphisms. 5-HTT is a specific protein transporter that permits serotonin re-uptake from the synapse and is the target of selective serotonin re-uptake inhibitor (SSRI) medications. Having a high affinity for serotonin, 5-HTT controls the duration, availability, and signaling capacity of 5-HT in the synapse. The 5-HTT functioning is moderated by a polymorphism in the 5-HT key promoter region of the SERT gene (5-HTTLPR). 5-HTTLPR has a short and a long allele, with genotypes of L/L, S/L, and SS. The S allele has been associated with a nearly 50 % reduction in the expression of the 5-HTTLPR protein, vulnerability for mood disorders, inadequate response to SSRI medications and their side effects, and most recently primary PE.

## (F)

Historically, a number of potential psychological explanations for PE have been proposed, including high stress and anxiety, the latter confirmed in recent studies. It has also been suggested that young men with PE have higher testosterone levels than men without PE. A recent study suggested that the majority of men with hyperthyroidism have PE and that changing patients to a euthyroid state drops the PE rate. With regard to penile sensitivity and circumcision status, there is no evidence supporting a link between either and PE. Finally, there are number of studies that suggest that chronic prostatitis is more prevalent among men with a diagnosis of PE. The possibility of chronic prostatitis is worth exploring and can be discerned easily on history. Treatment of underlying conditions associated with PE can ameliorate PE but, when ineffective, usual PE therapy is indicated.

## (G)

Psychosexual therapies are a well-recognized treatment for PE and their use predates the use of pharmacological agents by decades. The first maneuver described for PE involved the partner stimulating the man's penis until he has the sensation of almost climaxing (inevitable orgasm), at which time stimulation is abruptly stopped until this feeling disappeared. This technique became known as the "stop–start" technique. In 1970, Masters and Johnson reported a similar maneuver where the partner is advised to squeeze the penile frenulum or glans, just upon cessation of penile stimulation at the time of inevitable orgasm, thereby which can partially restrain erection. The female partner then restarts the stimulation at least 30 s later. This is known as the "squeeze" technique. Both methods focus on distraction and a reduction of excitement or stimulation, which may also detract from overall sexual satisfaction. These strategies are based on the theory PE occurs because the patient fails to pay sufficient attention to pre-orgasmic levels of sexual tension. The primary goals of traditional psychosexual treatment for PE are to boost male self-confidence in sexual activity, reduce anxiety, resolve any interpersonal difficulties, and increase couple communication. Although behavioral therapy has been shown to have a 45–65 % success rate, the benefits are generally short-lived and the condition generally recurs. Currently, combined pharmacotherapy and psychotherapy is suggested as the modern approach to PE treatment. The severe PE patient often requires greater levels of intervention than drugs alone. A great challenge in sexual medicine, however, is to convince a man to have a consultation with a mental health professional. For this reason we reserve psychosexual therapy for men who have overt interpersonal conflict or partner communication issues. When psychosexual therapy fails as first-line therapy, routine pharmacotherapeutic approaches are indicated.

## (H)

Given the mechanism of ejaculatory control (serotonin), the use of centrally acting agents, especially those with a serotonergic mechanism of action, has a sound scientific rationale. The agents with proven efficacy in the treatment of PE include clomipramine and the older SSRI agents, paroxetine, fluoxetine, sertraline, and citalopram. Newer agents fluvoxamine and venlafaxine have not demonstrated any significant effectiveness in the treatment of PE. At this time, in the USA no pharmacological therapy has been approved by the FDA. In Europe a novel SSRI (Dapoxetine) has recently been approved but has performed poorly for treating PE. In the USA all SSRI use is considered off-label. The features of the most commonly used oral agents for PE are listed in Table 20.2. Overall, SSRI agents improve IELT in about 70 % of men with PE. Those with lifelong PE must realize that this may be a lifelong therapy, although the compliance with these agents in this population is poor, with 75 % stopping therapy by the sixth month. Men with acquired PE are potentially curable. For these patients, we routinely suggest daily SSRI use for at least 6 months before ceasing the medication. There are only a small number of studies addressing on-demand use of SSRI and, based on current data, it is difficult to compare the efficacy of on-demand use and daily use of SSRI. The issue of daily vs. on-demand SSRI use remains unanswered. Future well-designed studies are required to address this issue definitively. It is our experience, however, that on-demand use is not as effective as daily therapy. Another oral therapy that has been introduced for PE treatment is Tramadol. This is a synthetic opioid analgesic that acts in the central nervous system. Tramadol has been used for many years for pain control and its safety is widely accepted. The action mode of Tramadol is not fully understood. Recent data support improvement in IELT with this agent. A potential adverse effect of this agent is addiction. Finally, another group of agents explored for PE are PDE5 inhibitors. At least 30 % of men with PE have co-existing erectile dysfunction (ED). It is generally believed that PE secondary to ED is a psychogenic issue. In men with PE predated by ED, PDE5i monotherapy is indicated. However, in men with PE without ED, a recent systematic review of published reports of PDE5i in PE treatment has concluded that there is limited evidence to support the role of PDE5i in PE treatment. However, in difficult-to-treat cases the addition of a PDE5i to an SSRI may offer select patients some benefit.

## (I)

While large, randomized, controlled trials on transdermal agents have not been conducted, there is some trial and much anecdotal evidence that some men with PE benefit from this strategy. There are many creams available in a variety of forms. The topical eutectic mixture for PE (TEMPE, also known as PSD-502, Plethora) is a metered-dose spray of lidocaine and prilocaine recently developed and currently in trials. Another agent that is available over-the-counter is a benzocaine–lidocaine mixture called Promescent (Absorption Pharmaceuticals). For patients who are reticent to use daily SSRI agents, topical therapy offers a reasonable and safe alternative. A concern with anesthetic sprays, however, is that it may inadvertently reduce genital sensation of the patient's partner.

## (J)

In patients refractory to either oral or topical therapies, we use combination therapy (concomitant oral and topical agents). While there are no large studies assessing combination therapy we have anecdotally had some success with difficult-to-treat patients.

# Appendix 1. Premature Ejaculation Diagnostic Tool (PEDT)

| | Not Difficult (0) | Somewhat Difficult (1) | Moderately Difficult (2) | Very Difficult (3) | Extremely Difficult (4) |
|---|---|---|---|---|---|
| 1.How difficult is it for you to delay ejaculation? | | | | | |

| | Never/almost never (0) | Less than half the time (1) | About half the time (2) | More than half the time (3) | Always/almost always |
|---|---|---|---|---|---|
| 2. Do you ejaculate before you want to? | | | | | |
| 3. Do you ejaculate with very little stimulation? | | | | | |

| | Not at all | Slightly | Moderately | Very | Extremely |
|---|---|---|---|---|---|
| 4. Do you feel frustrated because you ejaculate before you want to? | | | | | |
| 5. How concerned are you that your time to ejaculation leaves your partner sexually unfulfilled? | | | | | |

# Appendix 2. Premature Ejaculation Profile (PEP)

| Concept | Question | Very Poor (0) | Poor (1) | Fair (2) | Good (3) | Very Good (4) |
|---|---|---|---|---|---|---|
| Perceived control | How was your control over ejaculation? | | | | | |
| Satisfaction | How was your satisfaction with sexual intercourse? | | | | | |
| Personal distress | How distressed are you by how quickly you ejaculate? | | | | | |
| Interpersonal difficulty | To what extent does how quickly you ejaculate cause difficulty in your relationship? | | | | | |

# Appendix 3. Index Of Premature Ejaculation (IPE)

Preface all questions by "Over the past 4 weeks during sexual intercourse …"

| | No sexual intercourse (0) | Never/ almost never (1) | Less than half the time (2) | About half the time (3) | More than half the time (4) | Always/ almost always (5) |
|---|---|---|---|---|---|---|
| How often did you have control over when you ejaculated? | | | | | | |
| How much confidence did you have over when u ejaculated? | | | | | | |
| How often was it satisfactory for you? | | | | | | |
| How satisfied were you with your sense of control over when you ejaculated? | | | | | | |
| How satisfied were you with the length of intercourse before you ejaculated? | | | | | | |
| How satisfied have you been with your sex life overall? | | | | | | |
| How satisfied have you been with your sex relationship with your partner? | | | | | | |
| How much pleasure has sexual intercourse given you? | | | | | | |
| How distressed have you been by how long you lasted before you ejaculated? | | | | | | |
| How distressed have you been about your control over ejaculation? | | | | | | |

**Table 20.1** Variations of premature ejaculation

| Type | Features |
|---|---|
| Lifelong | PE at all or nearly all intercourse attempts |
| | With all or nearly all women |
| | In majority of cases within 1 min |
| | Consistent during life |
| Acquired | Rapid ejaculation occurring at some point in life |
| | Normal ejaculation prior to onset of PE |
| | Often source of problem identifiable (organic, psychological) |
| Natural variable | Rapid ejaculation inconsistent and irregular |
| | Inability to control ejaculation may be absent |
| Premature-like ejaculatory dysfunction | Subjective perception of rapid ejaculation |
| | IELT in normal range |
| | Preoccupation with imagined rapid ejaculation |
| | Preoccupation with poor control of ejaculation |
| | Preoccupation not accounted for by another mental disorder |
| | Inability to control ejaculation may be absent |

**Table 20.2** Characteristics of oral agents for PE treatment

| Agent | Trade name | Standard daily dose | *T½* (h) | Adverse effects | Contraindication | DDI |
|---|---|---|---|---|---|---|
| Clomipramine | Anafranil | 25–50 mg/day | 19–37 | Dry mouth, constipation | MAOI | Anti-cholinergics, Anti-psychotics, Barbiturates, Charcoal, Cimetidine, Clonidine; Oral contraceptives |
| Flouxetine | Prozac Sarafem | 5–20 mg/day | 36 | Nausea, anxiety, insomnia, anhidrosis, libido loss, ED | MAOI | 5-HT1 agonists, Benzodiazepines, Beta blockers, Buspirone, Carbamazepine, Clozapine, Cyclosporine, Cyproheptadine; Haloperidol, Hydantoins, Lithium, Sympathomimetics TCA |
| Paroxetine | Paxil, Seroxat, Pexeva | 10–40 mg/day | 21 | Nausea, anxiety, insomnia, anhidrosis, libido loss, ED | MAOI | Alcohol, Anti-coagulants, Cimetidine, Cyclosporine, Cyproheptadine, Drugs metabolized by CYP2D6, Digoxin, Phenobarbital, Phenytoin, Procyclidine, St. John's Wort, Sympathomimetics, Theophylline, Thioridazine, TCA, Tryptophan; Zolpidem |
| Sertraline | Zoloft | 25–200 mg/day | 26 | Nausea, anxiety, insomnia, anhidrosis, libido loss, ED | MAOI | Alcohol, Cimetidine, Clozapine, Disulfiram, Hydantoins, Pimozide, St. John's Wort, Sympathomimetics, Tolbutamide, TCA, Antiarrhythmics (1C), Zolpidem |
| Dapoxetine* | Priligy | 15–60 mg[a] | 1.5 | Nausea, diarrhea, headache, dizziness, somnolence | MAOI | Ketoconazole, Lithium, Linezolid, Nefazadone, Protease inhibitors, Tryptophan; St. John's Wort, Thioridazine, Tramadol, Sumitriptan |
| Tramadol | Ultram | 25–50 mg[a] | 5–7 | Nausea, dizziness, insomnia, dyspepsia, seizures | MAOI, SSRI, TCA | Digoxin, Erythromycin, Ketoconazole; Quinidine, Rifampin, St. John's Wort, Tegretol; Warfarin |

*T½*: half-life

*SSRI* selective serotonin re-uptake inhibitor; *MAOI* monoamine oxidase inhibitor; *TCA* tricyclic antidepressants

*Not currently FDA approved but approved in Europe

[a]For on-demand use

## Suggested Reading

Althof SE, Abdo CH, Dean J, Hackett G, McCabe M, McMahon CG, et al. International Society for Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation. J Sex Med. 2010;7(9):2947–69.

Giuliano F, Patrick DL, Porst H, La Pera G, Kokoszka A, Merchant S, et al. Premature ejaculation: results from a five-country European observational study. Eur Urol. 2008;53:1048–57.

McMahon CG, Abdo C, Incrocci L, Perelman M, Rowland D, Waldinger M, et al. Disorders of orgasm and ejaculation in men. J Sex Med. 2004;1:58–65.

McMahon CG, Althof SE, Waldinger MD, Porst H, Dean J, Sharlip ID, et al. An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. J Sex Med. 2008;5:1590–606.

Montague DK, Jarow J, Broderick GA, Dmochowski RR, Heaton JP, Lue TF, et al. AUA guideline on the pharmacologic management of premature ejaculation. J Urol. 2004;172:290–4.

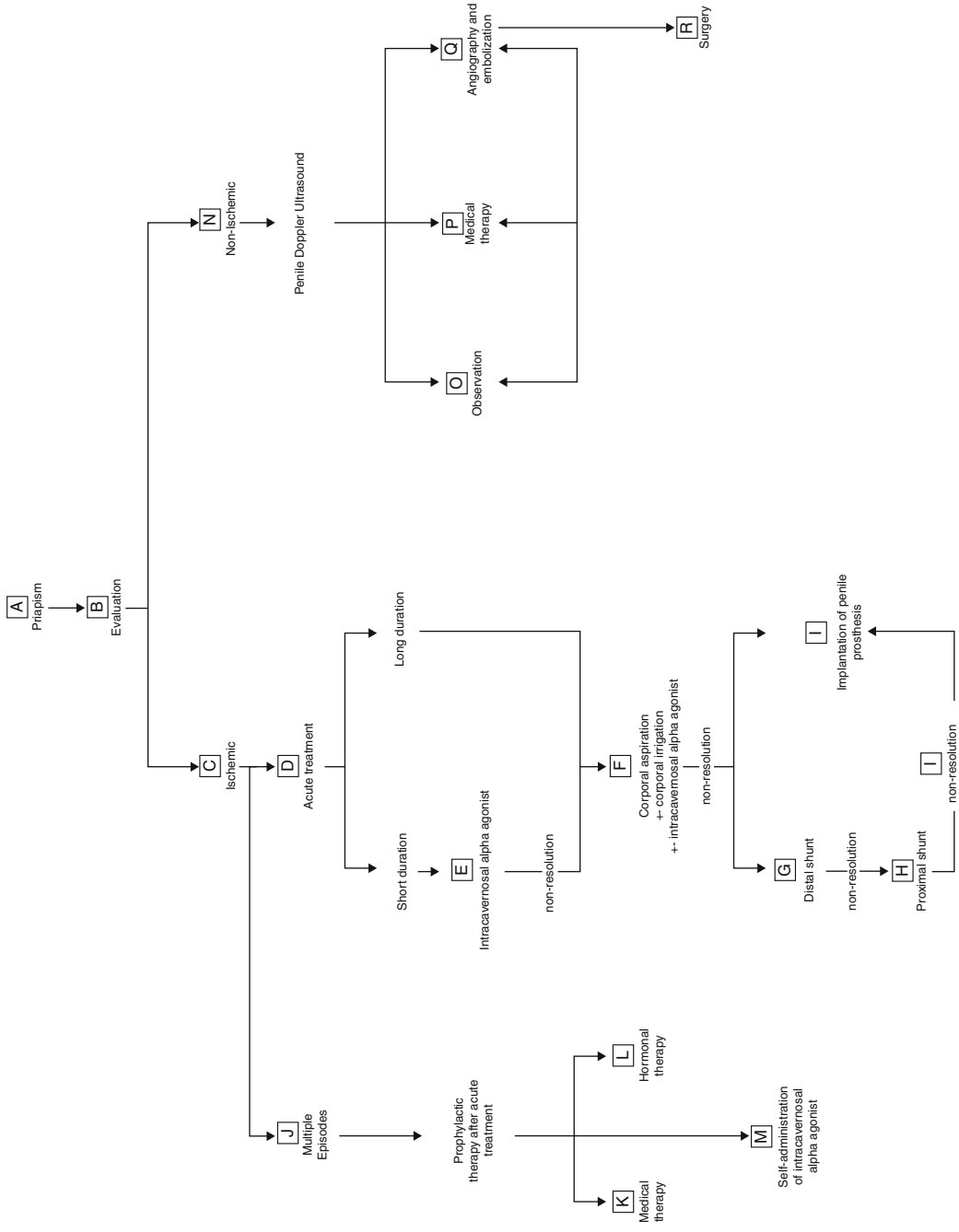
Morales A, Barada J, Wyllie MG. A review of the current status of topical treatments for premature ejaculation. BJU Int. 2007;100:493–501.

Mulhall JP. Premature ejaculation. In: Wein A, Kavoussi L, Peters C, Partin A, editors. Campbell-Walsh urology. 10th ed. Philadelphia: Elsevier; 2011.

Porst H, Montorsi F, Rosen RC, Gaynor L, Grupe S, Alexander J. The Premature Ejaculation Prevalence and Attitudes (PEPA) survey: prevalence, comorbidities, and professional help-seeking. Eur Urol. 2007;51:816–23.

Waldinger MD. Premature ejaculation: state of the art. Urol Clin North Am. 2007;34:591–9.

# Chapter 21
# Priapism




J.P. Mulhall et al., *Clinical Care Pathways in Andrology*, DOI 10.1007/978-1-4614-6693-2_21,

## (A)

Priapism is defined as a penile erection lasting longer than 4 h, unrelated to sexual stimulation, and persistent even after ejaculation/orgasm. It is sub-divided into two major types: ischemic (synonymous with low flow or venocclusive) priapism, which is a medical emergency that requires immediate attention and non-ischemic (synonymous with high flow or arterial) priapism, which is not an emergency. Ischemic priapism results from failure of the venocclusive mechanism to open during erection. This results from paralysis of the cavernosal smooth muscle (CSM) with prolonged occlusion of the sub-tunical venules (veins between the corpus CSM and the tunica albuginea). A triggering event (Table 21.1) induces an erection unassociated with sexual stimulation and not relieved by ejaculation/orgasm. After 2 h, with no exchange in arterial and oxygenated blood, there is a significant drop in oxygen partial pressure ($pO_2$) levels in the corporal bodies which causes the cavernosal muscle to go into a state of paralysis. In contradistinction, non-ischemic priapism results from unregulated inflow of arterial blood into the corporal bodies with no pathology in the venocclusive mechanism. This condition is most likely to result from trauma to the perineum or penis. Blunt perineal trauma, such as a straddle injury or kick, may weaken the cavernosal artery wall and upon the next erection the arterial wall blows out, creating a fistula with the corpus cavernosum. Trauma to the penis may be blunt or penetrating. The former is identical to that occurring in the perineum. Penetrating trauma, such as the placement of a large-bore needle into the corpus cavernosum, can lacerate the cavernosal artery and cause immediate non-ischemic priapism. This is sometimes seen in men who have been treated for ischemic priapism. Stuttering priapism refers to recurrent episodes of prolonged erection (often 1–2 h in duration), which eventually lead to a full-blown event. One final cause of a persistently hard penis is malignant priapism, which is a misnomer, as it results from malignant infiltration of the corpora cavernosa. The underlying malignancy is usually urologic (i.e., prostate, bladder, renal) but can occur due to other cancers (i.e., leukemia, osteosarcoma).

## (B)

History and physical examination are helpful in differentiating between ischemic and non-ischemic priapism but the essential test is a corporal blood gas evaluation using a 19-gauge butterfly needle placed in the mid-shaft. Local anesthesia is administered using either a 0.5 mL subcutaneous weal or a full basal/dorsal penile block. We utilize the latter when we are certain that corporal aspiration will be required. Some authorities advocate that experienced clinicians place the butterfly through the glans directly into the corporal body (as is done during penile reconstructive surgery). The advantage of this approach is that it circumvents the high risk of ecchymosis and hematoma formation associated with the mid-shaft needle placement, as well as decreasing the likelihood of cavernosal artery laceration that can result in non-ischemic priapism. Some centers use duplex Doppler penile ultrasonography to differentiate between ischemic and non-ischemic priapism. Arterial inflow can be easily demonstrated by ultrasound and strongly supports the diagnosis of non-ischemic priapism. Ultrasound can also be used to visualize the cavernous artery-corpus cavernosum fistula that is pathognomonic of non-ischemic priapism.

## (C)

Given the different treatment pathways for ischemic and non-ischemic priapism, making the correct diagnosis is essential (Table 21.2). There may or not be a history supportive of ischemic priapism. A history of intracavernosal injection use, sickle cell disease, hematological malignancy, cocaine ingestion, and use of anti-psychotics or trazadone represent the most common etiologies.

The patient usually complains of a painful, fully rigid erection and corporal blood gas analysis reveals low $pO_2$ and high carbon dioxide partial pressure ($pCO_2$) with low pH (often less than 7.0). Duplex Doppler ultrasound will usually confirm absence of cavernosal arterial inflow, although rarely inflow does occur and thus the test is only helpful if there is no blood flow.

## (D)

Ischemic priapism represents an acute urological emergency and timely detumescence is of the utmost importance. In documenting the management of such a patient, it is important to date and time stamp the notes as the chronology of care may become a medico-legal issue should the patient have a poor outcome. Four hours into an ischemic priapism episode, microscopic smooth muscle damage can already be seen and as time passes the degree of damage increases and likelihood of reversibility decreases. In cases where the penis has been erect for fewer than 6 h, usually a single (sometimes multiple) intracavernosal injection of an alpha agonist (most commonly phenylephrine) will suffice. As time progresses to around 8 or more hours, both aspiration and phenylephrine administration will be required. In regard to the patient with sickle cell disease who presents with priapism, numerous ineffective strategies have historically been initially employed (e.g., hydration, alkalinization, plasmapheresis) while ignoring the critical step which is immediate detumescence of the penis as outlined for the non-sickle cell disease patient. The first step in the management of all these patients is intracavernosal injection of an alpha agonist with corporal aspiration as needed. In any patient with priapism who is going to be treated medically or surgically, consent should be obtained explicitly stating that priapism and any corrective maneuvers are associated with the development of permanent ED.

## (E)

The value of using a pure alpha agonist for detumescence is the avoidance of any significant cardiac effects such as would occur with a combined alpha and beta-adrenergic agent such as epinephrine. If a butterfly has been used for corporal blood gas testing, we leave this in place and use it for intracavernosal drug administration and aspiration. If a butterfly needle has not been used, a 27-gauge needle and insulin syringe will suffice. Neosynephrine in the USA comes in a 1 mL vial containing 10 mg (10,000 μg) of the drug. This should be mixed with 9 mL of injectable saline to give a 1,000 μg/mL solution. We maintain this in a 10 mL syringe to be used as necessary. We place all patients on an automated sphygmomanometer and, if a cardiac history exists, on a cardiac monitor as well. We administer 1,000 μg intracavernosally every 10 min and repeat as long as there is a clear sign that detumescence is occurring. If there is no change in rigidity after three injections, then we perform aspiration. The hemodynamic consequence of intracavernosal phenylephrine is hypertension and reflex bradycardia. Of note, the only significant contraindication to the use of phenylephrine is the use of monoamine oxidase inhibitor medications, which fortunately are not used with great frequency in contemporary medicine.

## (F)

In patients who present with an erection duration of 8 h or longer we would commence by placing a butterfly needle and performing corporal aspiration. We typically do not irrigate with a dilute phenylephrine solution but some centers do so. Irrigation with dilute phenylephrine solution involves

1,000–5,000 μg of phenylephrine injected into 250–500 mL of injectable saline. The corpora are irrigated with 10 mL aliquots of the resultant solution. As described above, the patient should be placed on an automated sphygmomanometer and, if indicated by cardiac history, also a cardiac monitor. After aspirating blood (which is usually very dark in color), we inject phenylephrine in 1,000 μg doses and continue for an hour, aspirating and injecting every 5–10 min. There is no upper dose of phenylephrine as long as the patient is hemodynamically stable. Penile rigidity that persists after an hour likely may not resolve without performance of a surgical shunt. Some authorities suggest that consideration be given to performing a repeat blood gas at the termination of corporal aspiration or a Doppler penile ultrasound (to assess cavernosal artery inflow) prior to moving forward with surgical management. The conduct of the latter maneuvers is left to the discretion of the supervising clinician.

## (G)

There are no data regarding the optimal time point after initiation of medical treatment (corporal aspiration and alpha agonist administration) for performance of a procedure, although many practitioners and the International Society of Sexual Medicine expert panel recommend attempting medical therapy for at least 1 h prior to considering surgical intervention. A thorough discussion should be held with the patient concerning the risks (including permanent ED, urethral injury, failure to resolve priapism) and benefits (detumescence) of shunt surgery and clear documentation of this discussion should appear in the medical record. While generally accepted that the longer priapism lasts, the more likely permanent ED is to occur, the time point at which this becomes a certainty is unclear. Another unanswered question is at what time surgical intervention is no longer warranted. It is generally recommended that shunting be considered for priapism events lasting ≤72 h. However, shunting is probably of no benefit if priapism has lasted >5 days. For priapism events lasting between 3 and 5 days, judgement regarding the value of shunt surgery is left to the discretion of the individual clinician. Some centers perform MRI in such men in an effort to delineate the degree of erectile tissue necrosis, hoping to be able to avoid surgical intervention in those not likely to benefit from it. This approach is not fully validated and we do not currently use MRI in our treatment algorithm. Some authorities also suggest corporal smooth muscle biopsy be considered at the time of shunt surgery to define the degree of smooth muscle damage. If biopsy is planned, this should be delineated on the informed consent form.

The primary purpose of shunt surgery is oxygenation of the CSM. Shunts do not always result in immediate detumescence as the CSM may remain paralyzed for some time and depending upon the duration of the priapism event significant tissue edema may be present, which can appear as penile rigidity. Distal shunt procedures are subdivided into two groups: (1) percutaneous distal shunts (Winter, Ebbehoj, T-shunt with or without tunneling) and (2) open distal shunt (Al-Ghorab, with or without tunneling). It is recommended that a penile local anesthetic block be performed if percutaneous shunts are to be performed without general or spinal anesthesia. The Winter shunt is performed using a Tru-cut (or analogous biopsy needle). Through a single stab incision (made with an 11 scalpel blade) in the glans, two passes are made on each side of the glans. The tip of the biopsy needle must be placed through the tunica albuginea into the CSM. Once the biopsy needle is fired, a piece of tunica albuginea is removed and a communication is made between glans (corpus spongiosum) and corpus cavernosum. The skin puncture usually does not require any suturing. The Ebbehoj shunt uses only an 11 blade is used to penetrate the tunica. The blade is passed in a vertical plane and when withdrawn is simultaneously rotated 90° in an effort to maximize the size of the cavernosal–spongiosal communication. The T-shunt is similar to the Ebbehoj shunt except that, rather than a pass resulting in a single line, a perpendicular second line is made at the mid-point of the original incision. This is aimed at making a bigger more permanent shunt. Even more recently, the “snake maneuver” has been

described. The snake maneuver involves the passage of a small bore dilator (for example, a 9 French Hegar dilator) down the glans/tunical incision to create a passageway within the edematous/fibrotic corporal tissue to permit arterial inflow and corporal oxygenation. Some authorities perform this at the bedside in the emergency department while others prefer to do this in the operating room. Despite decades of such shunts being performed, scant literature exists on the ability of these shunts to achieve permanent detumescence of the penis. Given the absence of good outcome data we tend not to utilize the aforementioned procedures.

It is our preference to commence surgical management with an Al-Ghorab type shunt in an operating room setting under general anesthesia. An incision is made just distal to the coronal sulcus on the glans. The tunica albuginea is identified and a segment of tunica is excised so that a generous communication is created between the corpora spongiosum and cavernosum on each side. One of the clear advantages of this approach is that dark blood and/or clot can be evacuated from corporal bodies through the tunical defect and an assessment of blood color (and therefore gas content) can be accomplished prior to wound closure. If we cannot generate fresh, oxygenated arterial inflow we then use the aforementioned "snake maneuver." The glanular incision is then sutured and the penis is gently wrapped with an absorbent dressing. There are no data comparing percutaneous and open distal shunt outcomes. The factors involved in the success of shunts are shunt patency and degree of CSM damage at presentation/pre-shunt surgery. It is reasonable to assume that if duration of priapism and CSM status are controlled for, then larger shunts are likely to result in higher patency rates. Prior to leaving the operating room, an assessment of shunt patency should be conducted by confirming that fresh blood is flowing into the corporal cavernosa. There are several ways to do this, but the simplest are: (1) seeing bright red blood, (2) obtaining a corporal blood gas level, (3) Doppler ultrasound of the cavernosal artery. Documentation of at least one of these findings must be made in the operation report. The presence of bright red blood signifies that oxygenated blood is circulating through the corpora cavernosa, which is the main purpose of shunt surgery.

## (H)

In cases where a distal shunt fails, a proximal shunt may be considered if the surgeon believes the CSM is viable. "Proximal" indicates that the location of the shunt is behind the glans. This decision may be made in the operating room after the completion of the distal shunt procedure if patency cannot be established or if oxygenated blood is not present within the corporal bodies. Alternatively, a decision to do a proximal shunt can be made within hours of performance of the distal shunt. The most commonly performed proximal shunt (Quackles or, when bilateral, Sacher) involves performing a transverse scrotal or perineal incision. Prior to creation of the cavernosal–spongiosal communication, a urethral catheter is placed. Small ellipses of tunica albuginea of the corpus cavernosum and external lining of the corpus spongiosum are excised on one (Quackles) or both (Sacher) sides. There are no data comparing bilateral and unilateral cavernosal–spongiosal shunts. When performed bilaterally, it is advisable that these communications be staggered so that right side and left side are separated by a distance of at least 1 cm in order to minimize the risk of urethral stricture at the point of fistulization. The edges of the ellipses are sutured in watertight fashion. This technique permits "milking" of old blood and assessment of blood color/gas content prior to wound closure. After wound closure, the penis is gently wrapped with a dressing. In cases where proximal shunt fails, some authorities advocate performing a saphenous vein bypass procedure (Grayhack procedure), where the saphenous vein is interrupted below its junction with the femoral vein and tunneled subcutaneously for an anastomosis to one corporal body by excising an ellipse of tunica albuginea. The literature has a paucity of outcome analyses on the success of any of these procedures, but it is likely that their ability to achieve oxygenation of CSM is related to the size of fistula between spongiosum and cavernosum, and their

ability to lead to preservation of erectile function is related to duration of priapism event and the extent of CSM structural changes at the time of the shunt procedure. For patients who have difficulty voiding or for patients who have undergone proximal shunting a urethral catheter or suprapubic tube should be left in place.

Once the patient has exited the operating room, it is essential that repeated evaluation be conducted to ensure that the shunt remains patent. It is recommended that the patient be re-evaluated prior to leaving the recovery (post-anesthesia care) unit if the procedure was done in the operating room or evaluated serially in the hospital room if done in the emergency room. At each assessment, shunt patency or corporal blood oxygenation gas needs to be defined. Relying on the degree of penile tumescence alone or patient-reported pain is unreliable. Oftentimes, despite good shunt patency, patients continue to have penile pain as a result of the trauma from aspiration attempts and the shunt procedures themselves. Furthermore, residual penile tumescence due to CSM edema is common in men whose ischemic priapism event has lasted longer than 12 h. Thus, patency evaluation should include either corporal blood gas (oxygenated blood = shunt patency) or performing a simple penile compression maneuver. Manual compression of the penile shaft from side-to-side proximal to the shunt (generating suprasystolic pressure), in an effort to occlude the cavernosal arterial inflow, should result in immediate detumescence of the penis if the shunt is patent. It is important to avoid circumferential compression since this will cause complete venocclusion and prevent efflux of blood from the penis. The patient should not be discharged from hospital until a final determination has been made that either permanent detumescence has been achieved or that irreversible erectile tissue damage has occurred.

Following discharge from the hospital, the patient should be followed up within a few weeks for wound assessment. At further follow-up meetings, assessment of residual erectile function should be made. While postulated, the role of strategies for penile fibrosis minimization (oral PDE5i, colchicine) and penile length preservation (vacuum device, penile extender) is unclear in the absence of outcomes data. Any conversation with the patient regarding the use of erectogenic medications (PDE5 inhibitors, intra-urethral agents, intracavernosal injection agents) must include discussing the fact that their use in men with a history of priapism must be accompanied by careful monitoring.

## (I)

Some authorities suggest performing immediate penile prosthesis implantation for late presentation priapism. The most appropriate duration of priapism at which this should be considered is unclear. We do not use immediate penile implant placement in our treatment algorithm. However, it is recommended that any discussion pertaining to early implant insertion be documented and include a comprehensive review of the advantages and disadvantages (infection, mechanical malfunction, urethral injury, device erosion). The most obvious advantage of this approach is preservation of penile length, as post-priapism CSM will result in penile length loss. This process leads to a difficult penile prosthesis insertion when performed in a delayed fashion. Penile implant after a prior distal shunt (particularly, an Al-Ghorab shunt) may be associated with a higher incidence of distal corporal perforation because of the tunical defect at the distal end of the corpora cavernosa. Implant insertion in the setting of a proximal shunt may be associated with a higher incidence of urethral injury (at the point of the shunt).

## (J)

Recurrent episodes of ischemic priapism, also known as stuttering priapism, has many causes but two conditions underlie the vast majority of cases: sickle cell disease and recurrent idiopathic priapism. Recent evidence suggested both of these conditions might result from a dysregulation of PDE5 expres-

sion. In the sickle cell disease patient, priapism events only occur with patients who are poorly controlled and in a sickling phase. In an acute priapism episode, these patients are treated in an identical fashion as all other ischemic priapism patients. However, there are a number of maneuvers used to limit the number of episodes experienced and the need for emergency department visits.

## (K)

Medical preventive therapy involves a number of pharmacotherapeutic strategies for which there is very little good outcome data. Such agents include: digoxin, terbutaline, gabapentin and baclofen. Most recently, the regular use of PDE5 inhibitors has been explored in men with recurrent priapism with mixed results.

## (L)

Hormonal therapy is aimed at suppressing testosterone (T) levels in an effort to limit the number of nocturnal erections. The basis for this is the observation that these priapism episodes commence during a nocturnal erection. There is some evidence to support the use of GnRH agonists, which results in complete T suppression with its obvious sequelae. More recently, we have been using partial androgen suppression using ketoconazole. The protocol involves starting the patients on 200 mg three times a day with 5 mg prednisone daily (to cover adrenal steroid suppression), and then tapering to 200 mg nightly without prednisone once it has been established that there are no breakthrough episodes.

## (M)

The cornerstone of management for patients with stuttering priapism is teaching them to perform home intracavernosal phenylephrine. This maneuver limits the duration of the priapism episode, prevents CSM damage and keeps patients out of the emergency department. Patients are taught to inject just like patients using home intracavernosal vasoactive agents for ED. The patients are forewarned about hemodynamic changes. We instruct patients to administer 250 μg (0.25 mL of the aforementioned phenylephrine solution) if the erection is penetration-hardness for 1 h. If the first injection does not resolve the erection within 15 min we suggest they take a second injection. If the second injection is also unsuccessful they should proceed immediately to the nearest emergency department for formal priapism management.

## (N)

Non-ischemic priapism is not emergent and can be observed indefinitely. There may or not be a history supportive of non-ischemic priapism, such as penile or perineal trauma. The patient usually complains of a painless, less-than-fully-rigid erection and corporal blood gas analysis reveals normal $pO_2$, low $pCO_2$, and pH of approximately 7.4. Duplex Doppler ultrasound may be performed on the penis and transperineally, without the need for intracavernosal vasoactive agent injection. Ultrasound in the setting of non-ischemic priapism will reveal cavernosal arterial inflow and a fistula should be identified.

## (O)

For patients who are not bothered by the presence of a 40–60 % rigid erection, no definitive therapy is needed, although it is estimated that less than half of all fistulae will ever spontaneously close. Definitive treatment can be undertaken at any time in the course of the priapism.

## (P)

There has been a recent suggestion that the use of anti-androgen therapy may work in this population also. The idea revolves around suppression of sexual and nocturnal erections, thus increasing the chances of the fistula closing but, to date, no outcome data exist to support this concept.

## (Q)

It is recommended that angio-embolization be considered the first line treatment in patients opting for intervention for non-ischemic priapism. In cases of long-standing arterial priapism, where the likelihood of a well-developed pseudocapsule around the fistula is greater (to aid localization) surgical ligation has been reported to be successful.

Surgical ligation is reserved for patients who do not wish to pursue expectant management and are either poor candidates for (or have already failed) angioembolization. The optimal clot material remains a matter of debate. There are no robust data that address this question, although autologous clot or gelfoam is usually recommended as first line material. Coils are often reserved for patients who have a recurrence of the priapism after angio-embolization with absorbable materials.

**Table 21.1** Causes of ischemic priapism

| Class of etiologic agent | Categories | Example |
|---|---|---|
| Hematological | Malignancies | Multiple myeloma, leukemia |
| | Hypercoagulation states | Sickle cell disease, Thallasemia, Fabry disease |
| Dialysis | Renal dialysis | |
| Parenteral nutrition | | Lipid supplements |
| Medications | Intracavernosal vasodilatators | Papaverine, phentolamine, PGE1 |
| | Psychopharmacologic agents | Trazadone, anti-psychotics |
| | Alpha-adrenergic blockers | Prazosin, doxazosin, terazosin |
| | Ganglion blockers | Reserpine |
| | Epidural anesthetic agents | Heparin, warfarin |
| | Testosterone | Cocaine |
| | Anti-coagulants | |
| | Recreational drugs | |
| Toxin | Venom | Black widow spider |

**Table 21.2** Differentiating between ischemic and non-ischemic priapism

| Factor | Ischemic priapism | Non-ischemic priapism |
|---|---|---|
| Corpora fully rigid | ✓ | × |
| Penile pain | ✓ | × |
| Abnormal corporal blood gases | ✓ | × |
| History of hematologic abnormality | ± | × |
| Recent ICI[a] | ± | ± |
| Well-tolerated tumescence without full rigidity | × | ✓ |
| Perineal/penile trauma | × | ✓ |
| Cavernosal artery inflow on duplex Doppler US[b] | × | ✓ |

[a]Intracavernosal injection of erectogenic medication (such as papaverine, bimix or trimix)
[b]Ultrasound

## Suggested Reading

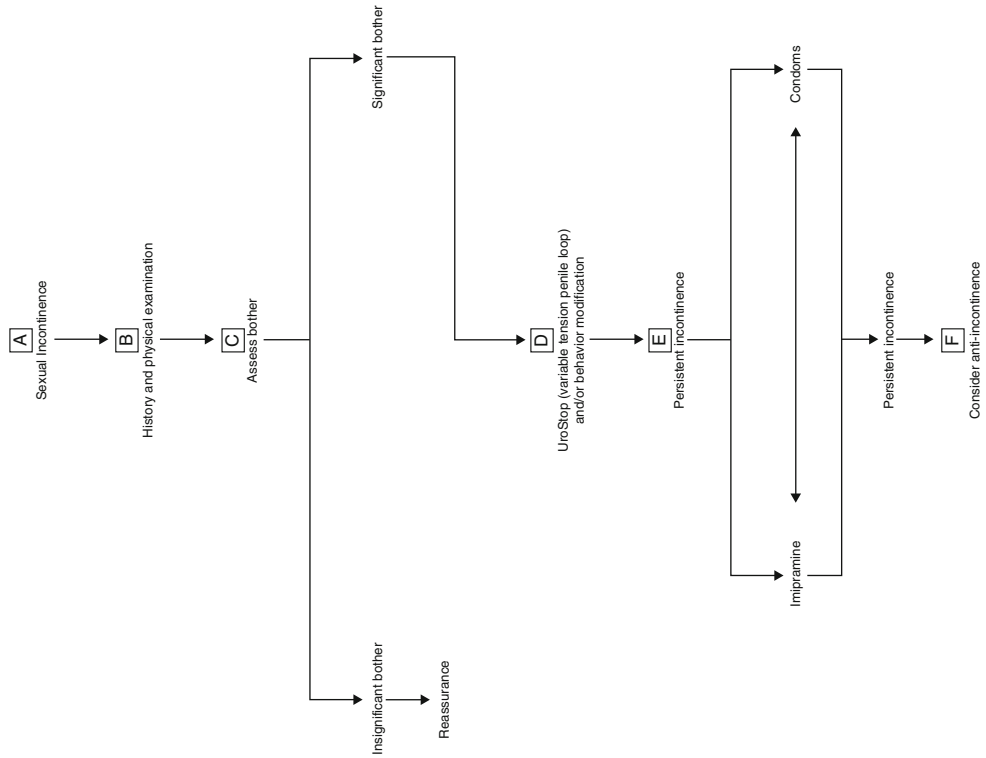
Berger R, Billups K, Brock G, Broderick GA, Dhabuwala CB, Goldstein I, et al. Report of the American Foundation for Urologic Disease (AFUD) Thought Leader Panel for evaluation and treatment of priapism. Int J Impot Res. 2001;13 Suppl 5Suppl 5:S39–43.

Broderick GA, Kadioglu A, Bivalacqua TJ, Ghanem H, Nehra A, Shamloul R. Priapism: pathogenesis, epidemiology, and management. J Sex Med. 2010;7:476–500.

Burnett AL. Surgical management of ischemic priapism. J Sex Med. 2012;9(1):114–20.

Montague DK, Jarow J, Broderick GA, Dmochowski RR, Heaton JP, Lue TF, et al. American Urological Association guideline on the management of priapism. J Urol. 2003;170:1318–24.

# Chapter 22
# Sexual Incontinence




J.P. Mulhall et al., *Clinical Care Pathways in Andrology*, DOI 10.1007/978-1-4614-6693-2_22,

## (A)

Sexual incontinence (SI) is an umbrella term that encompasses two similar but distinct entities: arousal incontinence and climacturia. As the names suggest, *arousal incontinence* refers to inadvertent loss of urine during sexual arousal, while *climacturia* specifically refers to involuntary urine leakage at orgasm (moment of climax, ergo the term climacturia). The term SI implies that the patient does not have significant urinary incontinence in a nonsexual context, but both continuous urinary incontinence and SI present great barriers to intimacy.

## (B)

Incontinence associated with sexual arousal and orgasm is a specific consequence that occurs most commonly following radical prostatectomy (RP) for prostate cancer. Following RP the external urethral sphincter, rather than the bladder neck, predominantly provides urinary continence. A brief review of ejaculatory physiology is appropriate here. At the time of ejaculation/orgasm, the bladder neck closes tightly as does the external sphincter. This creates a high pressure zone in the urethra between these two structures. The bladder neck remains closed throughout but the external sphincter opens and in normal men the ejaculate is expelled in an antegrade fashion. Prior to orgasm, the external sphincter is closed preventing urine leakage. In men after RP, where the integrity of the external sphincter is compromised early after surgery, this may not appose effectively and urine may leak out, as the bladder neck is also usually incompetent early after surgery. This leads to arousal incontinence. This is usually no more than drops but is associated with significant distress for the man and sometimes his partner as it is unpredictable and occurs through the sexual encounter. At the time of orgasm the bladder neck should close and the external sphincter should open. An incompetent bladder neck leads to climacturia. The volume of urine leakage is variable from drops to several ounces, but in contrast to arousal incontinence, it is predictable being timed with orgasm. For this reason the distress level appears to be lower for a man and his partner with the latter compared to the former. Following RP, patients should be queried regarding the degree of overall continence. Even with minimal or no stress urinary incontinence (SUI), the presence of SI should be asked about specifically, as patients may not complain of it otherwise. The duration and frequency of SI should be assessed, if present, and the patient should be asked to estimate the typical amount of urinary loss (small (drops), moderate (<30 mL) or large (>30 mL)). Patients should also be asked to assess their own and their partner's distress from the presence of SI. Focused genitourinary physical examination should include documentation of evidence of incontinence, such as active urinary dribbling, soiled underwear or sanitary pads.

## (C)

Quality of life studies of prostate cancer survivors have shown that nearly half of patients with SI have significant distress. Patients with insignificant bother need no therapy other than reassurance. Patients with significant bother, or have a partner who is significantly bothered, have several treatment options.

## (D)

There are several strategies for minimizing the impact of SI. These include emptying the bladder immediately before sexual contact and avoiding oral-genital contact. Another strategy is to engage in sexual activity in the shower so that the running water obscures urine leakage (and so that bed sheets remain dry). The UroStop (http://www.urosciences.com) penile variable tension loop is a simple, noninvasive device that can significantly reduce or eliminate urinary leakage (Fig. 22.1). After placing the UroStop around the base of the erect penis, tension is adjusted by the patient to the degree that the urethra is compressed but no discomfort is experienced. With use of a variable tension loop, post-RP climacturia has been shown to resolve in approximately 50 % of men with rare or occasional occurrence in the remainder. The use of this type of device has also been associated with a significant reduction in the amount of patient and partner bother.

## (E)

Additional steps for treating men with persistent incontinence despite using the UroStop including adding medication and/or the use of condoms. Imipramine is a tricyclic antidepressant oral medication that can also be used (in lower doses) with beneficial effects in patients with urinary incontinence. The medication has dual effects: contracting the bladder neck while simultaneously relaxing detrusor muscle, thereby increasing bladder capacity. Imipramine has been shown to be effective in men with mixed SUI and urgency incontinence, and several studies have also reported efficacy in men with pure SUI after RP. The benefit in men with sexual incontinence alone has not been studied. Side effects include dry mouth, blurry vision, constipation, and sedation. Condom use is a simple way to prevent urine from directly contacting the patient's partner, but this method has some drawbacks. Firstly, many men with sexual incontinence after RP also have some degree of post-surgical erectile dysfunction. The desensitizing effect of condoms may decrease rigidity to below penetration-hardness. Secondly, condoms are not designed to collect urine and are ineffective for large volumes of urinary leakage. The benefit of condoms is that they are inexpensive and have no side effects. No formal analysis of condom use in the management of sexual incontinence has been conducted.

## (F)

If all the above-mentioned methods and treatments fail, even in combination with each other, then the patient should consider anti-incontinence surgery such as a male sling or artificial urinary sphincter (AUS). We typically do not recommend this approach for the treatment of sexual incontinence until the patient is at least 12–18 months after RP. Men with bothersome sexual incontinence who undergo either procedure for SUI can expect marked improvement in their sexual lives after the procedure.

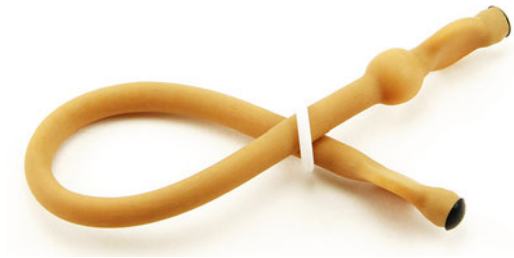


**Fig. 22.1** The UroStop (http://www.urosciences.com) penile variable tension loop is a simple, noninvasive device that can significantly reduce or eliminate urinary leakage

## Suggested Reading

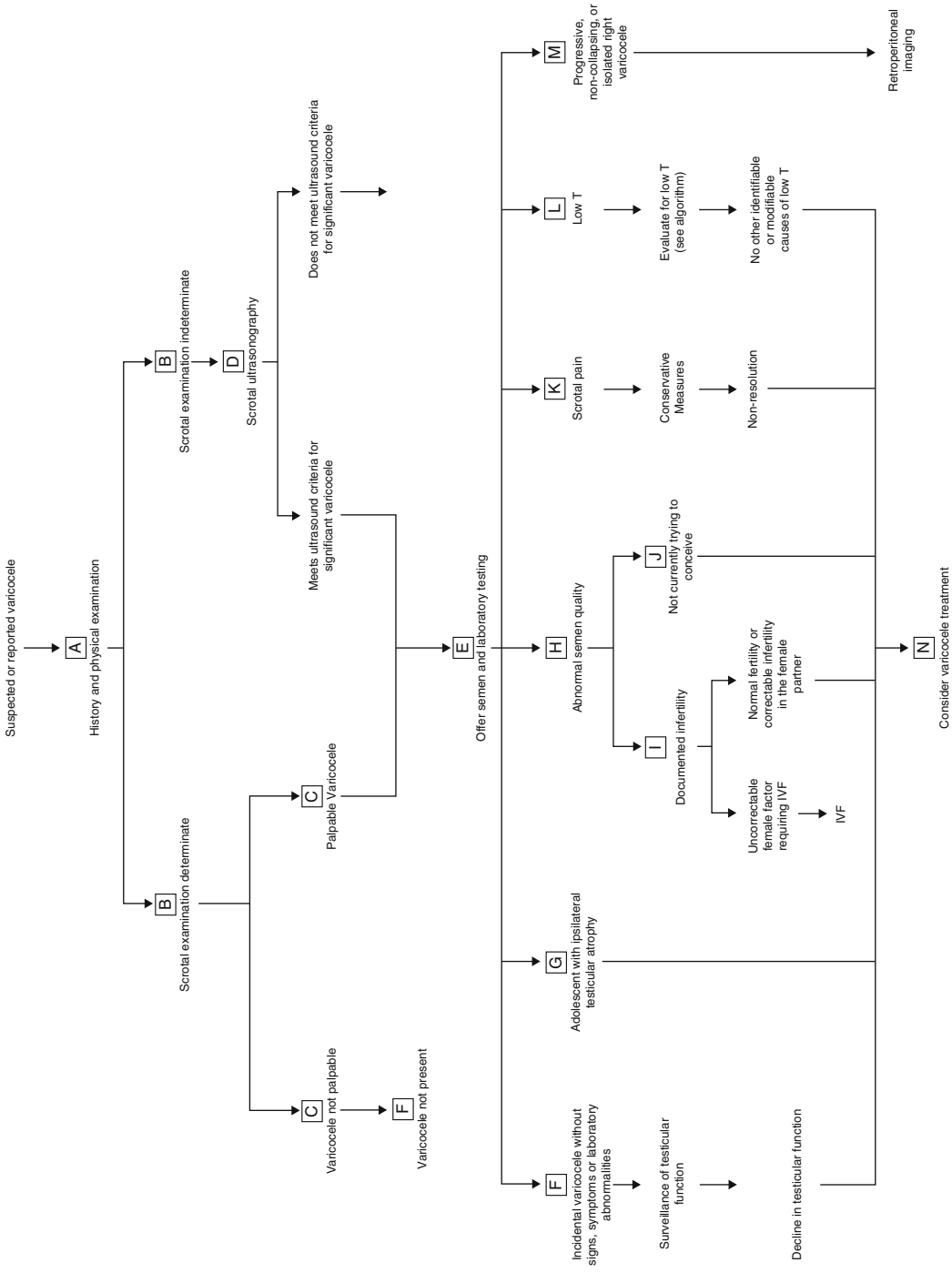
Choi JM, Nelson CJ, Stasi J, Mulhall JP. Orgasm-associated incontinence (climacturia) following radical pelvic surgery: rates of occurrence and predictors. J Urol. 2007;177(6):2233–6.

Mehta A, Deveci S, Mulhall JP. Efficacy of a penile variable tension loop for improving climacturia after radical prostatectomy. BJU Int. 2013;111(3):500–4. doi: 10.1111/j.1464-410X.2012.11269.x. [Epub ahead of print].

Mitchell SA, Jain RK, Laze J, Lepor H. Post-prostatectomy incontinence during sexual activity: a single center prevalence study. J Urol. 2011;186(3):982–5.

Nilsson AE, Carlsson S, Johansson E, Jonsson MN, Adding C, Nyberg T, et al. Orgasm-associated urinary incontinence and sexual life after radical prostatectomy. J Sex Med. 2011;8(9):2632–9.

# Chapter 23
# Varicocele




J.P. Mulhall et al., *Clinical Care Pathways in Andrology*, DOI 10.1007/978-1-4614-6693-2_23,

Varicocele refers to dilatation of the internal spermatic veins within the spermatic cord. Palpable varicoceles are found in approximately 15 % of the general male population and are the most commonly identified abnormality in infertile men, occurring in 35–40 % of cases. Although many men with varicoceles have normal fertility, significant evidence suggests that varicoceles negatively affect semen quality and fertility, and that varicocele repair improves semen quality and natural pregnancy rates. Aside from infertility, varicocele may cause scrotal pain and has been associated with testosterone deficiency. Rarely, varicocele may also be a presenting sign of occult retroperitoneal diseases including malignancy. The goal of the diagnostic evaluation is to determine whether or not the varicocele is clinically significant and to identify signs or symptoms that may be associated with the varicocele (infertility, pain, testicular atrophy, and/or testosterone deficiency). Treatment should be considered for patients with clinically significant varicoceles associated with signs or symptoms.

## (A)

The initial evaluation of varicocele should include a directed history and physical examination. Important points in the history and physical examination are listed and explained in Tables 23.1 and 23.2. Physical examination of the scrotum for varicocele diagnosis is best performed with the scrotum (cremaster and dartos muscles) relaxed. The examination should begin with the patient in the supine position. The spermatic cord is palpated to establish spermatic cord fullness in the supine position, and to assess for the presence of each vas deferens. Testicular consistency and size (preferably measured with an orchidometer) are noted. The examination is then repeated with the patient standing, both prior to and during Valsava maneuver. Dilatation or tortuosity of the pampiniform venous plexus within the spermatic cord that is visible or palpable in the standing position, with or without Valsalva, is diagnostic of varicocele (graded as per Table 23.2). Care must be taken to distinguish cremaster muscular tissue from Grade I varicoceles, which may be difficult for the inexperienced examiner.

## (B)

Adequate physical examination for varicocele is not possible in all cases. Examination is often difficult in patients with prior scrotal surgery, small tight scrotums, or obesity. Scrotal ultrasonography is indicated for varicocele assessment when the physical examination is inadequate or indeterminate. Scrotal ultrasonography is not indicated for varicocele assessment when physical examination can be adequately performed.

## (C)

Physical examination is the cornerstone of varicocele evaluation when barriers to accurate scrotal examination are absent. Varicoceles that are not palpable are not likely to be clinically significant and generally do not warrant treatment. In contrast, palpable varicoceles have a well-established association with impairment of testicular function. Palpable varicoceles should be assigned a clinical grade (as described in Table 23.2). The clinical grade correlates with the degree of impairment from the varicocele and the anticipated magnitude of treatment response. In general, larger varicoceles are associated with greater impairment of testicular function, but also with more robust improvements after varicocele treatment.

## (D)

Assessment for varicocele with color Doppler ultrasound (CDUS) is indicated when physical examination is inadequate. CDUS is more sensitive and specific for varicocele detection than physical examination, but is hampered by the absence of widely accepted consensus criteria for methodology and interpretation. Methodological differences in imaging protocol that have significant impact on study results include patient position (supine, standing, or both), site of imaging along the spermatic cord, use of Valsava maneuver, and whether or not and how to quantify reversal of blood flow.

Until methodological practices are standardized and widely accepted, it is recommended that the maximum venous diameter be determined with and without Valsava maneuver by B-mode grey-scale ultrasonography of the spermatic cord, in the high scrotum, in both the supine and standing positions. CDUS should also be used to qualitatively evaluate for reversal of blood flow during Valsava, which most experts consider a defining characteristic of varicocele. Well-defined and widely accepted threshold values for venous diameter measured on CDUS to determine the presence or absence of varicocele do not exist. Moreover, it is important to remember when interpreting CDUS that maximum venous diameter is affected by the patient's position (standing vs. supine) and state of abdominal muscular contraction (relaxed vs. Valsava). Most experts agree that a significant varicocele is present when the maximum venous diameter >2.5–3 mm and reversal of blood flow during Valsava maneuver is observed.

## (E)

Patients with clinically significant varicoceles should be evaluated for testicular dysfunction. Semen analysis should be offered to those interested in current or future fertility. Some experts advocate adjunctive tests of semen quality that may reveal subtle semen abnormalities that are undetectable on standard semen analysis. Examples of such tests include assessment of sperm DNA integrity with the sperm chromatin structure assay (SCSA), and assessment of oxidative stress in seminal fluid. Assessment of serum total testosterone and follicle stimulating hormone (FSH) should be considered to assess testicular function.

## (F)

Varicoceles that are incidentally detected in men with normal semen quality, normal testicular examinations, normal testosterone, and normal FSH can be safely followed. Consensus protocols for the surveillance of such patients do not exist. Some practitioners recommend annual or biannual assessments of testicular function (semen analysis, serum testosterone testing, and physical examination) in patients with a varicocele. Treatment should be considered if there is evidence of testicular functional decline. Younger men, particularly those with large varicoceles, may theoretically benefit from repair even in the absence of testicular impairment to prevent duration-dependent deleterious effects of varicocele, but this is a controversial concept.

## (G)

The incidence of varicocele in both boys and men (in the general population) is approximately 15 %. Patient selection for treatment is challenging since there is no certain method to determine which boys with varicocele will eventually develop testicular dysfunction. The main indication for varicocele

treatment in adolescents is ipsilateral testicular hypotrophy. In adults, ipsilateral hypotrophy is highly predictive of abnormal semen quality in adult men with varicoceles. Furthermore, up to 80 % of adolescents with varicocele and ipsilateral testis hypotrophy show "catch-up" testis growth following varicocele repair, suggestive of treatment efficacy. Most experts advocate varicocele treatment when the discrepancy in testicular size is greater than 20 %.

## (H)

Presence of varicocele (both unilateral and bilateral) is associated with decreased semen quality. The classical description of semen analysis parameters in men with varicocele is the so-called stress pattern: low sperm count, poor motility, and low percentage of sperm with normal morphology. In practice, however, varicocele may be associated with single or multiple abnormalities in any of the semen analysis parameters. In addition, varicocele may also cause subtle semen quality abnormalities, such as abnormal sperm DNA integrity, that are not apparent on standard semen analysis.

## (I)

Infertility has traditionally been defined as failure to conceive within 12 months of initiating appropriately timed, unprotected sexual intercourse. However, this definition of infertility has evolved to include couples with shorter durations of failure to conceive (or even simply concern regarding fertility), particularly in cases of advanced female age. Men with abnormal semen quality and documented infertility are prime candidates for varicocele treatment. However, the fertility status of the female partner must be considered in decision-making regarding varicocele treatment. In general, varicocele repair is only indicated when the female partner has normal fertility or correctable infertility. Varicocelectomy is of limited benefit in most cases when the couple is committed to use of assisted reproduction.

## (J)

Even if a man is not currently trying to conceive, the presence of a varicocele that is associated with abnormal semen quality should prompt discussion about varicocele treatment. Repair may be beneficial to preserve future fertility potential.

## (K)

Varicocele repair has long been considered an option for the treatment of scrotal pain. Pain associated with varicocele is generally characterized as a dull aching pain or heaviness that progresses throughout the day with prolonged standing or exertional activity, and that is alleviated in the supine position. Conservative measures (scrotal support) and evaluation for other possible etiologies of pain are critical considerations prior to repair. Most published studies have reported high rates of pain resolution and improvement (>70 %), but must be interpreted with caution due to inclusion of limited numbers of patients and retrospective, observational designs. Affected patients should be counseled prior to treatment that pain may persist subsequent to treatment.

## (L)

Over the past few years there has been increased focus on the relationship between varicocele and hypogonadism (HG). Recent studies have shown that microsurgical varicocele repair results in a significant increase in T level in nearly 70 % of men, and the increase is independent of laterality or grade. Although varicocele can cause low T a complete HG evaluation should be considered (see *Hypogonadism Evaluation* algorithm) in order to avoid missing other potential causes. If no other modifiable factors associated with low T are identified, then the patient with symptoms of HG and a varicocele deserves a discussion of risks and benefits of varicocele repair. HG is a relatively new indication for varicocele repair but is gaining acceptance rapidly as the supporting data is accumulating.

## (M)

Whether unilateral or bilateral, virtually all varicoceles involve the left side. When a unilateral right-sided varicocele is encountered, a retroperitoneal mass compressing the right testicular vein must be considered and ruled out. Varicoceles on either side that fail to collapse when the patient goes from a prone to supine position should also raise suspicion of a retroperitoneal mass. Finally, varicoceles on either side that progress rapidly in size should prompt concern for retroperitoneal mass. In such cases masses that may be causing retroperitoneal obstruction of the spermatic vein(s) can be ruled out with abdominal ultrasound, CT scan or MRI. Ultrasound is typically performed first since it is inexpensive, can usually be obtained in a timely fashion, and does not expose the patient to ionizing radiation. Abnormal findings on ultrasound would prompt either a follow-up CT scan or MRI, both of which can provide more detailed information regarding retroperitoneal pathology.

## (N)

The goal of any varicocele treatment is permanent occlusion of the abnormally dilated veins of the pampiniform plexus with simultaneous preservation of the arterial supply and lymphatic drainages of the testis. Several surgical approaches, as well as radiographic embolization, are currently utilized in clinical practice. Surgical options include the classic open (Palamo) retroperitoneal varicocelectomy, laparoscopic varicocelectomy, and sub-inguinal or inguinal varicocelectomy with or without microsurgical magnification. Most comparative studies have demonstrated that the sub-inguinal microsurgical approach has the highest efficacy, lowest risk of recurrence, and lowest risk of complications (particularly hydrocelectomy).

When performed for infertility, varicocele repair improves semen quality in 50–80 % of sub-fertile men, and has been associated with improved spontaneous pregnancy outcomes in both retrospective studies and randomized clinical trials. Repair may also be effective for the treatment of scrotal pain (>70 % resolution or improvement), testosterone deficiency (significant improvement in T in 70 % of men), and testicular hypotrophy in adolescents.

**Table 23.1** Important points to elicit in the medical history

| Medical history | Interpretation |
|---|---|
| History of prior fertility | The duration-dependent adverse affects of varicocele on testicular function often result in secondary infertility |
| Symptoms of hypogonadism | Varicocele is associated with Leydig cell dysfunction and has become increasingly identified as a risk factor for androgen deficiency |
| Scrotal pain or discomfort | Varicocele may cause scrotal pain. The typical pain associated with varicocele is a dull ache that worsens over the course of the day or with exertional activity and improves or resolves when the patient is supine |
| Varicocele onset and progression | Rapidly progressive varicoceles raise suspicion for retroperitoneal pathology, especially when non-collapsing in the supine position, and should prompt retroperitoneal imaging |
| Fertility status of female partner | Varicocele treatment for infertility should only be offered to couples in whom the female partner has normal fertility or correctable infertility |

**Table 23.2** Important points to elicit during physical examination of a patient with suspected varicocele

| Physical examination | Interpretation |
|---|---|
| Varicocele grade | Subclinical: non-palpable; detected on imaging such as ultrasound<br>Grade I: varicocele *palpable* in the spermatic cord *with Valsalva* maneuver<br>Grade II: varicocele *palpable* in the standing position *without Valsalva* maneuver<br>Grade III: varicocele *visible* in the standing position *with or without Valsalva* maneuver |
| Testicular size and consistency | Varicocele may be associated with ipsilateral testicular atrophy, which is a relative indication for varicocele treatment (particularly in the pediatric population) |
| Presence of vasa deferentia | In the absence of pain or androgen deficiency, varicocele treatment is only indicated in cases when male infertility is correctable |

## Suggested Reading

Abdel-Meguid TA, Al-Sayyad A, Tayib A, Farsi HM. Does varicocele repair improve male infertility? an evidence-based perspective from a randomized, controlled trial. Eur Urol. 2011;59(3):455–61.

Cozzolino DJ, Lipshultz LI. Varicocele as a progressive lesion: positive effect of varicocele repair. Hum Reprod Update. 2001;7(1):55–8.

Esteves SC, Oliveira FV, Bertolla RP. Clinical outcome of intracytoplasmic sperm injection in infertile men with treated and untreated clinical varicocele. J Urol. 2010;184(4):1442–6.

Fretz PC, Sandlow JI. Varicocele: current concepts in pathophysiology, diagnosis, and treatment. Urol Clin North Am. 2002;29(4):921–37.

Goldstein M, Tanrikut C. Microsurgical management of male infertility. Nat Clin Pract Urol. 2006;3(7):381–91.

Lee R, Li PS, Goldstein M, Schattman G, Schlegel PN. A decision analysis of treatments for nonobstructive azoospermia associated with varicocele. Fertil Steril. 2009;92(1):188–96.

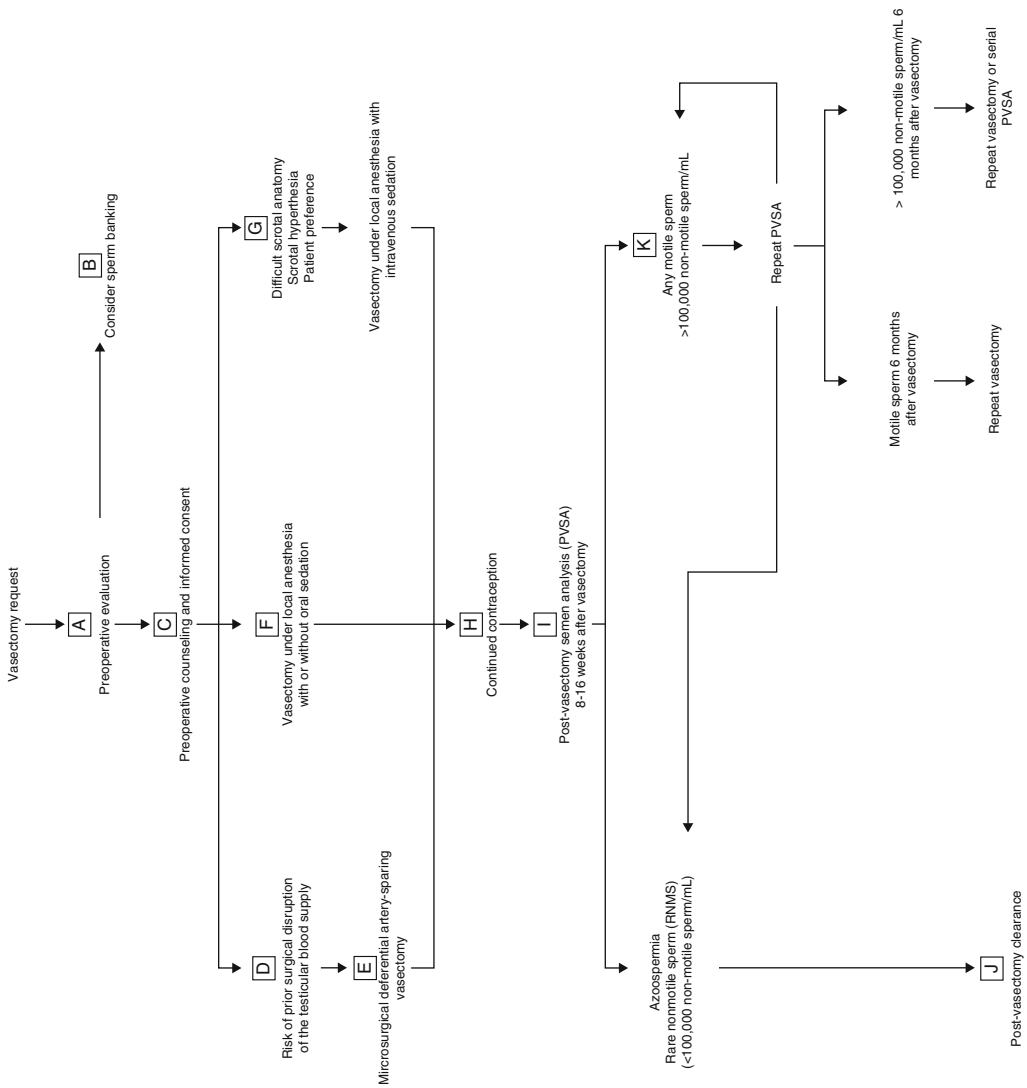
Male Infertility Best Practice Policy Committee of the American Urological Association, Practice Committee of the American Society for Reproductive Medicine. Report on varicocele and infertility. Fertil Steril. 2004;82 Suppl 1:S142–5.

Park HJ, Lee SS, Park NC. Predictors of pain resolution after varicocelectomy for painful varicocele. Asian J Androl. 2011;13(5):754–8.

Stahl P, Schlegel PN. Standardization and documentation of varicocele evaluation. Curr Opin Urol. 2011;21(6):500–5.

Zini A, Boman JM. Varicocele: red flag or red herring? Semin Reprod Med. 2009;27(2):171–8.

# Chapter 24
# Vasectomy




J.P. Mulhall et al., *Clinical Care Pathways in Andrology*, DOI 10.1007/978-1-4614-6693-2_24,

More than 500,000 vasectomies are performed annually in the United States, making vasectomy one of the most common procedures performed by urologists and the fourth most commonly used method of contraception. Any physician providing vasectomy services should be well-versed in all essential components of the male sterilization process including preoperative evaluation, prevasectomy counseling, technique for vasal occlusion, and postvasectomy follow-up.

## (A)

History and physical examination are critical to optimize the safety and efficacy of vasectomy. The history should focus on assessment of the patient's prior fertility, the reasons the patient desires vasectomy, and the presence of medical conditions or prior surgeries that might predispose to complications. Patients should be questioned in particular about bleeding disorders, conditions that may predispose to wound infection or excessive bleeding, and surgical history. The physical examination is important for identification of testicular pathology that might contraindicate routine vasectomy (such as testicular tumor) and to identify patients with scrotal hypersensitivity, difficult scrotal anatomy, or significant anxiety during scrotal examination. Patients who exhibit marked anxiety during examination are candidates for vasectomy under sedation or general anesthesia.

## (B)

Sperm banking is offered prior to vasectomy based upon patient and physician preference. Some physicians believe that patients interested in sperm banking clearly do not desire permanent contraception and are not candidates for vasectomy. However, sperm cryopreservation may be beneficial for patients who are certain about their desire for contraception, but would consider future reproduction if grave unforeseen circumstances arise, such as the death of one of their children. In all cases, the subject should at least be raised so that the patient is aware of the option.

## (C)

Preoperative counseling should be provided to all patients considering vasectomy and should cover several essential points (Table 24.1).

## (D)

The testicular blood supply is derived from three sources. The testicular (internal spermatic) artery is the main blood supply and comes directly from the aorta. Other arterial inflow comes from the deferential artery (artery of the ductus deferens), a branch of the hypogastric or one of the vesicle arteries, and the cremasteric (external spermatic) artery, which is a branch of the inferior epigastric artery. The testicular artery is at risk routinely during several common surgical procedures including nonmicrosurgical varicocelectomy, orchidopexy for intra-abdominal testis, donor nephrectomy, retroperitoneal lymph node dissection, and renal transplantation. In patients who have a history of these procedures vasectomy should be approached cautiously as testicular perfusion may be heavily dependent upon the deferential artery.

**(E)**

Microsurgical deferential artery-sparing vasectomy should be considered in patients at risk for prior surgical disruption of their testicular artery. Optical magnification enables safe separation of the vas deferens from the deferential artery, thus minimizing the risk of testicular hypoperfusion after vasectomy.

**(F)**

Vasectomy is most commonly performed in the office under local anesthesia with or without oral sedation. Occlusion of the divided vas deferens is best performed by mucosal cautery with or without fascial interposition. Clipping or suture ligation of the cut ends of the vas is another option for occlusion that is the option for surgeons with training and experience in such methodology. Some clinicians perform both cautery and clipping, or cautery and suture ligation, in the same setting.

**(G)**

Patients with vasa that are difficult to palpate, high-riding testes, or scrotal hypersensitivity may benefit from intravenous sedation during vasectomy.

**(H)**

Alternative methods of contraception must be continued after vasectomy until the patient is cleared to stop contraception based upon postvasectomy semen analysis (PVSA). This is an essential point that needs to be made absolutely clear to the patient. Sperm present within the vas deferens or seminal vesicles on the abdominal side of the vasectomy may persist within the male excurrent ductal system for weeks to months (depending on the frequency of ejaculation) and could contribute to pregnancy despite vasectomy. In addition, occlusive failure occurs in some cases (<1 %) and must be ruled out prior to cessation of alternative contraception.

**(I)**

PVSA should be performed 8–16 weeks after vasectomy based upon surgeon preference. Patients who ejaculate more frequently after vasectomy may clear their vasa of sperm more quickly, and this may be a factor in determining the timing of the first PVSA. PVSA should be performed by microscopic analysis of fresh, uncentrifuged semen within 2 h of specimen production. The number of many semen analyses that should be performed is a topic of debate. Some authorities recommend only a single semen analysis while others perform two, particularly if sperm are seen on the first sample. The timing of these tests is less important than the number of ejaculations achieved.

## (J)

While azoospermia is the most reassuring finding on PVSA, the finding of rare (defined as <100,000 per mL) nonmotile sperm (RNMS) is also sufficient to permit men to resume intercourse without contraception. However, all patients cleared after vasectomy must understand that the risk for unintended pregnancy after vasectomy is never zero. Pregnancy rates of approximately 1/2,000 are reported in patients with azoospermia or RNMS after vasectomy.

## (K)

The presence of any motile sperm or >100,000 nonmotile sperm per mL on PVSA should prompt continued use of alternative contraceptive methods and repeat PVSA at 1–2 month intervals. Clearance for cessation of contraception may be given if azoospermia or RNMS develops. Persistence of any motile sperm on PVSA 6 months after vasectomy indicates vasectomy failure and should prompt repeat vasectomy. Clinical judgment should be used in the management of men with persistence of >100,000 nonmotile sperm per mL for greater than 6 months. Options include continued contraception with serial PVSAs or repeat vasectomy.

**Table 24.1** Essential concepts to be covered during discussion prior to vasectomy

| Concept | Explanation |
|---|---|
| Permanent intent | Should only be performed when permanent sterility is desired |
| Sperm banking | Offered to increase future reproductive options |
| Future fertility | Vasectomy reversal<br>Sperm retrieval or use of cryopreserved sperm with assisted reproduction<br>Not always possible and potentially expensive |
| Continued contraception | Until vasal occlusion confirmed by semen analysis |
| Risks | Vasal occlusive failure requiring repeat vasectomy (<1 %)<br>Pregnancy after vasal occlusion confirmed (1/2,000)<br>Immediate surgical complications (bleeding or infection) (1–2 %)<br>Chronic scrotal pain (1–2 %) |
| Reassurances | NOT associated with prostate cancer, heart disease, stroke, or testicular cancer |
| Alternative: tubal ligation | Similar efficacy in pregnancy prevention<br>Requires general anesthesia<br>Potential for serious complications (i.e., bowel injury) |
| Postoperative expectations | Ejaculatory abstinence for 1–2 weeks<br>Need for postvasectomy semen analyses |
| Informed consent | Written, informed consent essential<br>Mandatory waiting period in some states |

## Suggested Reading

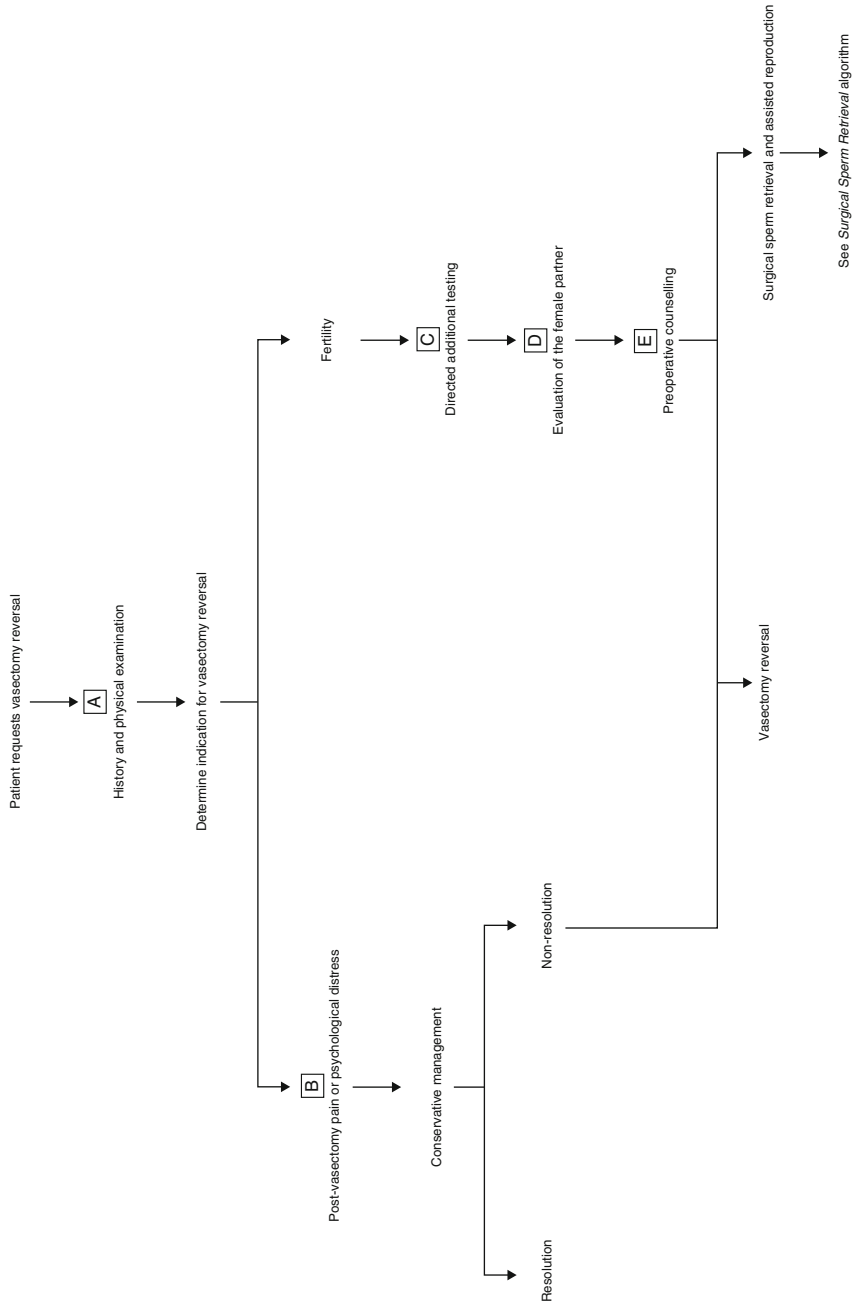
Dohle GR, Diemer T, Kopa Z, et al. European association of urology guidelines on vasectomy. Eur Urol. 2012;61(1):159–63.

Jow WW, Goldstein M. No-scalpel vasectomy: a minimally invasive procedure. Contemp Urol. 1993;5(4):37–44. 50–2.

Senanayake E, Pacey AA, Maddireddy V, Shariff U, Hastie K, Rosario DJ. A novel cost-effective approach to post-vasectomy semen analysis. BJU Int. 2011;107(9):1447–52.

Sharlip ID, Belker AM, Honig S, et al. AUA: vasectomy guideline. http://www.auanet.org/content/clinical-practice-guidelines/clinical-practice-guidelines.cfm. Accessed 16 Jul 2012.

# Chapter 25
# Vasectomy Reversal

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Half a million men undergo vasectomy annually in the United States. Studies suggest that up to 6 % of such men will request vasectomy reversal. Divorce with remarriage is by far the most common reason for vasectomy reversal. Other reasons include a simple change in desire to have more children and death of a child. Unlike surgical sperm retrieval with assisted reproduction (which is the alternative treatment for patients who desire children after vasectomy), vasectomy reversal allows for natural reproduction, does not require hormonal manipulation of the female partner, and allows couples to have multiple children without additional treatment. This is the preferred strategy when the vasectomy is fewer than 15 years old and the female partner has normal fertility. Vasectomy reversal is among the most technically challenging surgical procedures in urology and should be performed using microscopic magnification. Outcomes depend largely upon the type of reconstruction (vasovasostomy (VV) vs. vasoepididymostomy (VE)) required and the technical expertise of the reconstructive microsurgeon. VE may be required in cases of secondary epididymal obstruction, which occurs when increased pressure in the epididymis after vasectomy causes rupture and subsequent scarring of the single epididymal tubule. Sperm return to the ejaculate after 70–99 % of vasectomy reversals, allowing for unassisted pregnancy in 30–80 % of couples. Outcomes of VV are far better than outcomes of VE due to the increased technical difficulty of VE and bypass of part of the epididymis during sperm transit after VE, where sperm gain much of their functional capacity.

## (A)

The history and physical examination should focus first on identifying the indication for vasectomy reversal. Although most patients want to restore their fertility, some seek resolution of postvasectomy pain or psychological distress. For patients interested in fertility restoration, it is critical to assess the patient's reproductive potential so as to avoid reversing a vasectomy in a patient with inadequate sperm production. Important points in the history and physical examination are listed and explained in Tables 25.1 and 25.2.

## (B)

Chronic scrotal pain that negatively impacts quality of life is referred to as postvasectomy pain syndrome and occurs in 1–2 % of men after vasectomy. First-line management includes scrotal support and noninvasive measures. Options include including antibiotics, nonsteroidal anti-inflammatory agents, tricyclic antidepressants, and neuromodulators such as gabapentin. Some authorities advocate the use of spermatic cord blocks with local anesthesia to confirm that the pain is organic and due to intra-scrotal pathology. If medical management fails, some experts advocate infiltration of the spermatic cord with or without steroids, which can be repeated at regular intervals if successful. Vasectomy reversal is another effective option and should be considered in patients who fail conservative management. Pain improves or resolves in 50–90 % of patients after microsurgical reconstruction.

## (C)

Additional testing should be considered in patients prior to vasectomy reversal performed for restoration of fertility. Such testing is particularly important when there is concern about sperm production. Measurement of the serum follicle stimulating hormone (FSH) level is helpful in patients without any

prior history of unassisted biological paternity and those with small or soft testes on physical examination. An elevated FSH (>8 IU/L) is worrisome for impaired spermatogenesis and should prompt consideration of diagnostic testicular biopsy prior to reconstructive microsurgery. Semen analysis may also be helpful and is advocated by some experts for all patients prior to vasectomy reversal. The goals of semen analysis are to confirm the absence of motile sperm from the ejaculate and to identify rare nonmotile sperm (RNMS—present in 10 % of patients postvasectomy). The finding of any motile sperm should prompt consideration of assisted reproduction using ejaculated sperm in lieu of vasectomy reversal. The finding of RNMS is associated with a high likelihood of need for VV (as opposed to VE) and a favorable prognosis.

## (D)

Evaluation of the female partner's reproductive potential is recommended prior to vasectomy reversal. This may easily be performed by eliciting a reproductive history from the female partner and by measuring her ovarian reserve with an appropriate serum biomarker. The two most widely used such tests are the FSH level on day 3 of the menstrual cycle and anti-Mullerian hormone (AMH) level. Formal evaluation by a reproductive endocrinologist should be performed when the female partner has known sub-fertility, is greater than 35 years old, has risk factors for infertility, or has laboratory evidence of diminished ovarian reserve (day 3 FSH > 10 IU/L or AMH < 0.7 ng/mL).

## (E)

All patients considering vasectomy reversal for fertility restoration should be counseled about surgical sperm retrieval with assisted reproduction, which is the alternative treatment. Factors to be considered are the time interval since vasectomy, the number of desired children, the fertility status of the female partner, and the costs of each option, which vary from couple to couple based on insurance coverage and provider-specific charges for vasectomy reversal and assisted reproduction. Vasectomy reversal is generally favored when the interval since vasectomy is less than 15 years and the female partner has normal fertility. Patients electing to proceed with vasectomy reversal should be counseled about the anticipated outcomes and complications of surgery. For VV, patients may be counseled that sperm return to the ejaculate in 75–99 % of cases, allowing for a pregnancy rate of approximately 50 %. For VE, the chance of sperm returning to the ejaculate is 80 % in the hands of an experienced microsurgeon, and pregnancy may be achieved in over 30 % of cases. It is also prudent to discuss simultaneous cryopreservation of vasal or epididymal sperm at the time of reconstruction, which is particularly important if bilateral VE is required. The complications of vasectomy reversal include infection, scrotal hematoma, scrotal edema, chronic scrotal pain, and, rarely, testicular atrophy. Each should be specifically discussed when obtaining informed consent for surgery.

## (F)

Intraoperative decision-making is critical during vasectomy reversal. Each operation should begin with scrotal exploration to identify the vasectomy sites. Intraoperative macroscopic and microscopic assessment of fluid retrieved from the testicular end of the transected vas deferens (on the testicular side of the vasectomy) determines whether VV or VE should be performed. If no fluid is initially

seen upon vasal transection, the testicular end of the vas may be barbotaged with saline by catheterization of the vasal lumen with a 24-gauge angiocatheter. Fluid is collected and placed on a slide for examination with a benchtop light microscopic, which should be present in the operating room. VV is indicated when any sperm or sperm parts are present in the fluid, and also when copious crystal clear watery fluid without sperm is present. VE should be performed when sperm are absent from the intravasal fluid, which is characteristically thick and white but may vary in macroscopic appearance. It is prudent to assess distal vasal patency prior to each anastomosis by injection of saline into the abdominal end of the vas with a 24-gauge angiocatheter, which should inject easily without back pressure.

## (G)

Simultaneous cryopreservation of sperm retrieved from the vas deferens or epididymis should be considered for all patients undergoing vasectomy reversal. This approach provides a safety net for the patient in the event of surgical failure. Sperm cryopreservation is generally not necessary if at least one VV is performed by an experienced microsurgeon because failure is exceedingly rare. Sperm cryopreservation is best discussed preoperatively.

## (H)

Immediate postoperative care should include preventive measures to minimize the likelihood of complications. Ice packs and compression should be applied to the scrotum for 72 h after surgery to decrease scrotal bleeding and edema. Strenuous physical activity should be avoided for several weeks, and the patient should be instructed to abstain from ejaculation for 4 weeks to minimize stress on the anastomoses. The schedule for follow-up semen analyses varies according to surgeon preference. Semen analyses should generally be obtained every 3–6 months until the sperm count plateaus, pregnancy is achieved, or the patient remains persistently azoospermic for 12–18 months. Most patients in whom VV is successful experience return of sperm to the ejaculate within 6 months. Sperm in the ejaculate my take up to 12 months following VE. Some experts advocate elective sperm cryopreservation once sperm return to the ejaculate because there is a risk of secondary azoospermia due to late anastomotic shutdown, which occurs in approximately 10 % of patients overall (and is especially likely after VE).

**Table 25.1** Important points to elicit in the medical history

| Medical history | Interpretation |
|---|---|
| Prior fertility history | Prior unassisted biological paternity suggests normal sperm production |
| Time interval since vasectomy | Short intervals (<5 years) are associated with decreased need for vasoepididymostomy |
| General medical and surgical history, including medications | Important in all pre-surgical patients |

**Table 25.2** Important points to elicit when performing physical examination

| Physical examination | Interpretation |
|---|---|
| Testicular size | Small soft testes are associated with impaired sperm production |
| Epididymal irregularity or induration | May be associated with need for vasoepididymostomy |
| Gap between cut ends of vasa | Predicts need for vasal mobilization during surgery, which affects choice of surgical incision |
| Sperm granuloma | Associated with decreased need for ipsilateral vasoepididymostomy |

## Suggested Reading

Belker AM, Thomas AJ, Fuchs EF, Konnak JW, Sharlip ID. Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. J Urol. 1991;145(3):505–11.

Brannigan RE. Vasectomy reversal: indications and outcomes. J Urol. 2012;187(2):385–6.

Goldstein M, Tanrikut C. Microsurgical management of male infertility. Nat Clin Pract Urol. 2006;3(7):381–91.

Hsiao W, Goldstein M, Rosoff JS, et al. Nomograms to predict patency after microsurgical vasectomy reversal. J Urol. 2012;187(2):607–12.

Jarow JP, Sigman M, Buch JP, Oates RD. Delayed appearance of sperm after end-to-side vasoepididymostomy. J Urol. 1995;153(4):1156–8.

Jarow JP, Oates RD, Buch JP, Shaban SF, Sigman M. Effect of level of anastomosis and quality of intraepididymal sperm on the outcome of end-to-side epididymovasostomy. Urology. 1997;49(4):590–5.

Pierpaoli S, Mulhall JP. Vasectomy reversal in the age of intracytoplasmic sperm injection. Curr Opin Urol. 1998;8(6):531–4.

Practice Committee of American Society for Reproductive Medicine. Vasectomy reversal. Fertil Steril. 2008;90(5 Suppl):S78–82.

Shridharani A, Sandlow JI. Vasectomy reversal versus IVF with sperm retrieval: which is better? Curr Opin Urol. 2010;20(6):503–9.

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