Erectile Physiology/Pathophysiology, and Evaluation/Management of Erectile Disorders

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- American Urological Association: Course Faculty (Annual Review Course, Oral Board Review Course), Guidelines Panelist (Priapism)

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Learning Objectives

- Understand physiologic mechanisms of penile erection
- Identify etiologic factors contributing to erectile dysfunction (ED)
- Differentiate between mechanisms of organic and psychogenic ED
- Evaluate evidence-based management options for ED
- Recognize presentation, etiology, and acute management of priapism
- Describe the pathophysiology and management of Peyronie's disease

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Outline

- Erectile function (normal state)
  - Anatomy
  - Physiology
- Erectile disorders
  - Erectile dysfunction
    - Pathophysiology
    - Evaluation and Management
  - Priapism
    - Pathophysiology
    - Evaluation and Management
  - Peyronie's disease
    - Pathophysiology
    - Evaluation and Management

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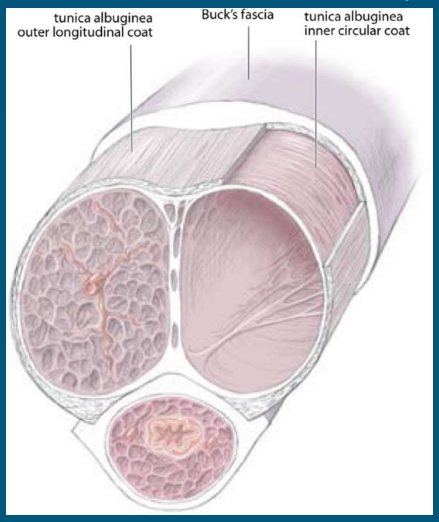
Relevant Anatomy

- Tunica albuginea bilayer
  - Inner circular
  - Outer longitudinal (not at 5-7 o'clock)
- Intracavernosal struts/pillars
- Incomplete septum (weakest portion*)
- Sinusoids composed of endothelium and smooth muscle cells

*Most common site of corporal perforation at implant placement



Hadidi, AT (2022). Surgical Anatomy of the Penis and Urethra

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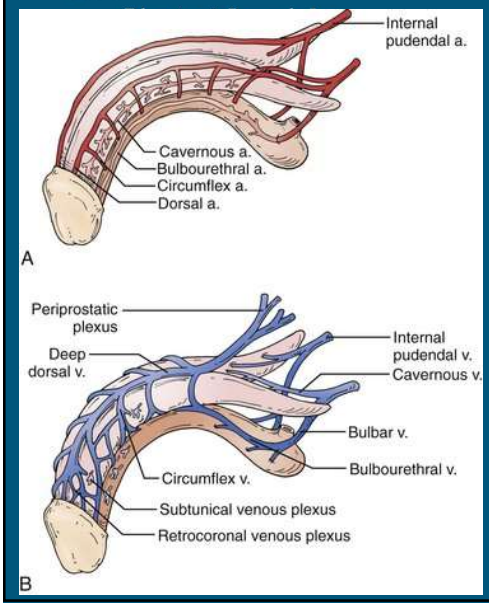
Blood Flow



- Arterial: Via internal iliac to internal pudendal
  - Common penile artery
  - Paired cavernosal and dorsal penile arteries
  - Bulbar artery (continues as bulbourethral artery)
  - Circumflex arteries (collateral branches)
- Venous: Mirrors arterial inflow
  - Deep dorsal vein drains distal 2/3 of corpora
  - Proximal 1/3 via cavernosal veins
  - Connects to periprostatic (Santorini's) plexus
  - Skin/subcutaneous tissue via superficial dorsal vein

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Innervation

- Parasympathetic: Sacral (S2, S3, S4; Onuf's nucleus)
  - Pelvic splanchnics to pelvic plexus to cavernous nerves
  - Facilitates erection
- Sympathetic: Thoracic/Lumbar (T11-L2)
  - Also pass through pelvic plexus to join cavernous nerve
  - Facilitates detumescence and emission of semen prior to ejaculation
- Somatic: Sacral (S2, S3, S4; Pudendal nerve)
  - Sensation via dorsal nerve of penis
  - Control of external sphincter/pelvic floor; role in expulsion
  - Root of penis has sensory from branches of ilioinguinal nerve

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Neural Injuries

- Level of spinal cord lesion dictates scenario
- Sacral cord injuries will lose reflex erections; psychogenic preserved
  - Pudendal nerve from dorsal nerve roots of S2-S4; controls external sphincter (ES)
  - Transection causes weakness of ES and decreased penile sensation
  - Relevant to patients subjected to dorsal rhizotomy
- Psychogenic erections unlikely with SCI above T11
- Cord injuries between T11-L2 disrupt emission and ejaculation*
- Reflex erections (sacral) generally preserved with injury above L2

*Ejaculation may be facilitated by penile vibratory stimulation and electroejaculation.

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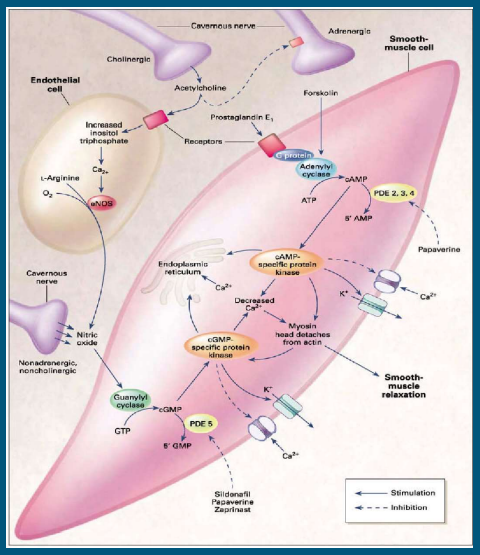
Pathway to Erection

- Nonadreneric, noncholinergic (NANC) cavernous nerve releases nitric oxide (NO)
- Increased cGMP/cAMP decreases Ca^{2+} in cell
- Smooth muscle relaxation (flow)

cGMP: cyclic guanosine monophosphate
cAMP: cyclic adenosine monophosphate



Dean and Lue. Urologic Clinics Nov 2005

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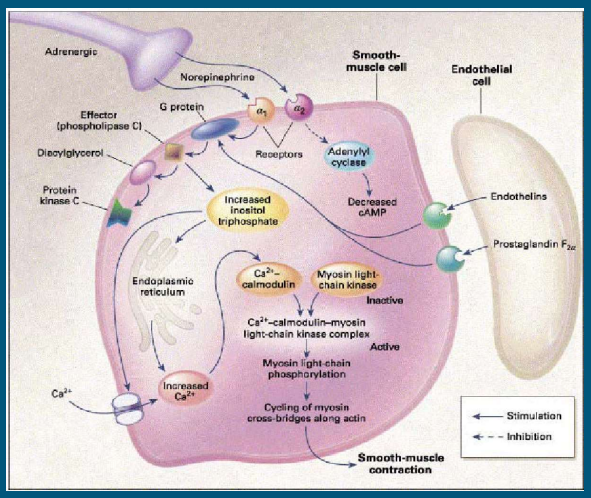
Detumescence

- Adrenergic nerves release norepinephrine
- Decreased cAMP increases Ca^{2+} in cell
- Smooth muscle contraction (initially causes transient rise in intracavernosal pressure)



Dean and Lue. Urologic Clinics Nov 2005

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Erectile Dysfunction (ED)

- Definition: Inability to achieve and maintain for sexual satisfaction
- May be multifactorial
- Etiologies can involve any element related to cascade (head to tail)
- Some degree of ED noted in over 50% of men past age of 40y*
- Association with cardiovascular disease, benign prostatic hyperplasia
- Important to distinguish from premature ejaculation

*Massachusetts Male Aging Study (MMAS)

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Categorization

- Psychogenic (situational?, AM/PM erections? Masturbation/porn?)
  - Component can be present in men with organic causes
  - High placebo response rate in medication trials offers insight to prevalence
  - Couples cognitive-behavioral therapy improves response to medication
- Vasculogenic (arterial or venous)
- Neurogenic (central or peripheral pathologies)
- Medication-related (antihypertensives, antidepressants)

Banner LL and Anderson RU: J Sex Med 2007; **4:** 1117.
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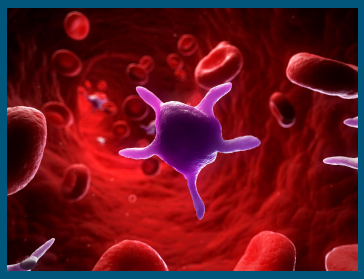
ED and Cardiovascular Disease



- Shared phenomenon of endothelial dysfunction
- Shared independent risk factors
  - Age
  - Smoking
  - Diabetes, hypertension, dyslipidemia, depression
  - Obesity
  - Sedentary lifestyle
- ED symptomatology may precede cardiovascular event by 5 years

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Implicated Medications

- Antihypertensives
  - Thiazides
  - Beta blockers
  - Calcium channel blockers
  - NOT ACE inhibitors
- Antidepressants (e.g., SSRIs, TCAs, MAOIs, Lithium)
- Hormonal agents (e.g., 5ARIs, LHRH agonists, estrogen)
- Substance abuse (e.g., alcohol, cocaine)

SSRI: Selective serotonin reuptake inhibitor
TCA: Tricyclic Antidepressant
MAOI: Monoamine oxidase inhibitor
5ARI: 5 alpha reductase inhibitor
LHRH: Luteinizing hormone-releasing hormone

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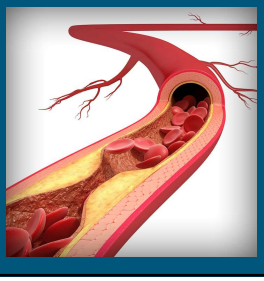
Pathophysiology

- Atherosclerosis, endothelial damage/dysfunction
- Venous leak possible due to changes in smooth muscle
- Neural insults result in lack of signaling, consequent drop in flow
- Less flow = less oxygen = apoptosis/fibrosis
- Psychogenic component can be secondary (additive)



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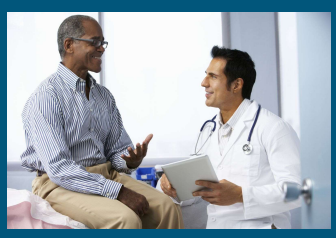
Clinical Evaluation

- History (medical/sexual/psychosocial; symptom score)
- Physical examination (including vitals, waist circumference)
- Goals assessment/shared decision making
- Selective laboratory testing (testosterone, glucose/A1c, lipids)
- Assessment of cardiovascular risk, mental health
- Specialized testing (e.g., penile duplex ultrasound)



Burnett AL, Nehra A, Breau RH et al. J Urol 2018; 200:633

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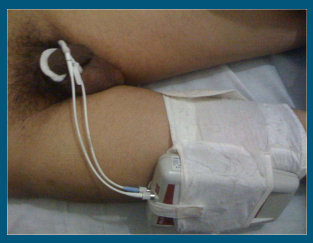
Specialized Testing



- Should only be used if findings will affect management
- Nocturnal tumescence: No longer considered useful
- In-office injection: Self-injection at home provides same information
- Penile duplex ultrasound: Unclear how it changes management
  - History-taking tells provider if oral meds have failed
  - Patient experience will tell if injections effective and no cure for venous leak
- Biosthesiometry, Cavernosometry/Cavernosography: Irrelevant
- Selective Internal Pudendal Angiography: Rare utility

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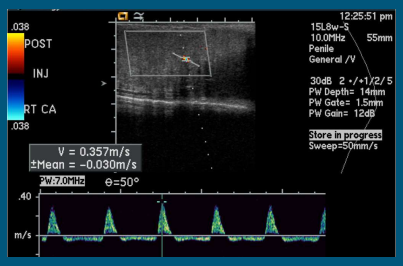
Penile Duplex Ultrasound

- Performed in office with pharmacologic erection (user-dependent)
- PSV <30 cm/s considered arterial insufficiency
- EDV >5 cm/s consistent with veno-occlusive dysfunction (VOD)
- Resistive Index (PSV-EDV/PSV): Value >0.80 considered normal
- Men with very low PSV (<25 cm/s) have 3x risk of major cardiac events



PSV: Peak systolic velocity
EDV: End diastolic velocity

Ioakeimidis N, Vlachopoulos C, Rokkas K et al. J Hypertens 2016; **34:** 860.

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Management

- Lifestyle modifications (diet, activity, substances, overall health, therapy)
- Vacuum erection device (VED)
- Oral phosphodiesterase type 5 inhibitors (PDE5i)
- Topicals (intraurethral alprostadil, evaporative gel)
- Intracavernosal injection (ICI)
- Penile implant (prosthesis)

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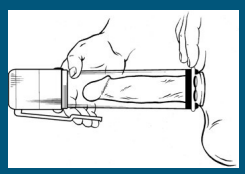
Vacuum Erection Device (VED)

- Mechanism of negative pressure to create inflow
- Risks involve pain, bruising, difficulty w/ejaculation, decreased sensitivity
- Studies reporting high satisfaction largely pre-dated IIEF, PDE5i
- Only VEDs with vacuum limiter should be used
- Can be used in combination with PDE5i
- Use with caution in men on anticoagulation or history of priapism



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PDE5i

- Enzyme inhibition increases cavernosal cGMP (smooth mm relaxation)
- Adverse effects (Flushing, headache, dyspepsia, myalgia, visual)
- Contraindications (e.g., regular nitrate use) vs Cautions*
- Evidence lacking for penile rehab after radical prostatectomy
- Drug response may be improved by correction of low testosterone
- Controversies (skin cancer, prostate cancer recurrence, NAION)

PDE5i: Phosphodiesterase type 5 inhibitor
cGMP: cyclic guanasine monophosphate
NAION: Nonarteritic anterior ischemic optic neuropathy

*Recent MI (<6 months), Retinitis Pigmentosa

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PDE5i: Dosing

- If men carry NTG, avoid use w/in 24 hrs (sildenafil) to 48 hrs (tadalafil)
- Start with lower doses in mild/moderate liver/renal disease, SCI
- Avoid use in men with severe renal or liver disease
- For tadalafil, max dose is 5 mg if CrCl < 30 mL/min
- Efficacy appears similar across different PDE5Is
- AEs appear dose dependent (less headache with daily tadalafil vs OD)

NTG: Nitroglycerin
SCI: Spinal Cord Injury
CrCl: Creatinine Clearance
AE: Adverse Event
OD: On Demand

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PDE5i: Parameters

Agent	Time to peak bioavailability (min)	Dietary limitation	Duration of effect (hr)	Efficacy diminished by alcohol intake
Sildenafil	30-60	Yes	Up to 12*	Yes
Tadalafil	60-120	No	Up to 36	Yes
Vardenafil	30-60	Yes	Up to 10	Yes
Avanafil	15-30	No	Up to 6	Yes

*Most literature encourages pursuing sexual stimulation within 4 hours

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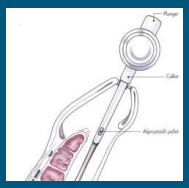
Topical

- Intraurethral alprostadil (prostaglandin E1; 100-1000 mcg)
  - Smooth muscle relaxant; effective in less than 50% of initial users
  - Perform in-office test per Guideline (but not predictive of home success)
  - Urinate before use
  - AEs include pain, burning



- External gel
  - FDA approved, over the counter
  - Cooling effect from evaporation leads to warming effect/tumescence

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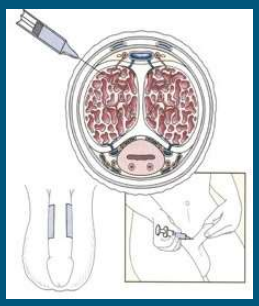
Intracavernosal Injection (ICI)

- Mechanism by agent
  - *Alprostadil (PGE1): smooth mm relaxation via increased cAMP
  - Papaverine: Opium alkaloid; PDEi, smooth mm relaxation
  - Phentolamine: Alpha blocker (vasodilation)
  - Atropine: Anticholinergic, smooth mm relaxation (rarely used)
- In-office testing recommended by Guideline
- Risks
  - Priapism
  - Fibrosis/curvature/retained broken needle fragments
  - Pain, hematoma



*Only alprostadil is FDA approved. This medication warrants refrigeration when used alone or in combination.

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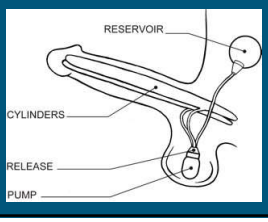
Penile implant

- Set expectations properly (rigidity on demand, not lengthening)*
- Avoid in setting of active infection (systemic, skin, urinary)
- Types include malleable and inflatable (2 vs 3-piece)
- AEs: Pain, infection, injury, hematoma, swelling; future erosion/failure
- Reported satisfaction rates are high (over 85%)
- Salvage replacement should be avoided in sepsis/severe local infection



*Stretched flaccid penile length often used to set preoperative expectation.

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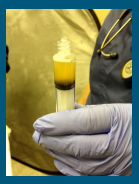
Other options

- Penile arterial reconstruction only in young men with focal occlusion*
- Penile venous surgery is not recommended
- Low-intensity extracorporeal shock wave therapy is investigational
- Intracavernosal stem cell therapy is investigational
- Platelet-rich plasma therapy is experimental
- Guideline does not recommend l-arginine, alone or in combination



*Low success and patient selection is critical.

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Priapism

- Persistent erection (>4 hours) unrelated to sexual stimulation
- Ischemic and nonischemic varieties
- Hematologic (e.g., SCD), pharmacologic, malignancy, trauma, idiopathic
- Homozygous SCD (most common): 23-89% incidence of priapism by 18y
- Hematologic disorders do not change acute management

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Ischemic Priapism

- More common than non-ischemic
- Patient presents with pain
- Cavernosal blood gas shows hypoxia, hypercarbia, acidosis
- If due to ICI and <4h, try intracavernosal phenylephrine w/o aspiration

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Implicated Drugs/Medications

- Erectile dysfunction agents (e.g., injection of alprostadil)
- Antidepressants (e.g., trazodone)
- Antipsychotics (e.g., risperidone)
- Antihypertensives
- Cocaine

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Conservative Therapies

- Do not delay treatment of acute ischemic priapism
- No evidence to support exercise, cool/warm compresses, masturbation
- Oral pharmacotherapy is NOT recommended
  - Pseudoephedrine (PO) not superior to placebo after intracavernosal alprostadil
  - Terbutaline not superior to placebo

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Ischemic Priapism: Management

- History, Physical Exam, Corporal blood gas (+/- ultrasound/labs)*
- Explain chance of ED and low likelihood of recovery if >36 hours
- 1st line[♯]: Aspiration + intracavernosal phenylephrine (+/- irrigation)
- 2nd line: Distal corporoglanular shunt +/- tunneling
- Inadequate evidence for proximal shunts (Quackel, Grayhack, Barry)
- If shunt fails, repeat corporal blood gas or duplex Doppler ultrasound

*Penile duplex Doppler only if type of priapism indeterminate; labs may offer insight to cause but should not delay treatment.

[♯]If duration of priapism >36 hours, provider discretion may allow for primary implant

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Ischemic Priapism: Management

- Ischemia and acidosis impair response to sympathomimetics
- If ischemic priapism >36h or failed shunt, can consider penile implant
  - Unlikely to have meaningful spontaneous erections after shunt
  - Higher duration of ischemia associated with higher rates of post-shunt ED
- Explain risks/benefits of early vs delayed implant
  - Delayed: associated with higher infection and more shortening
  - Early: associated with detumescence, pain relief, length preservation

Zacharakis E, Raheem AA, Freeman A et al. J Urol 2014; **191:** 164.
Ortac M, Cevik G, Akdere H et al: priapism. J Sex Med 2019; **16:** 1290.
Pal DK, Biswal DK and Ghosh B. Urol Ann 2016; **8:** 46.

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Interpretation: Corporal Blood Gas

Blood Gas Values			
Condition	Po_2 (mm Hg)	Pco_2 (mm Hg)	pH
Mixed venous blood	40	50	7.35
Ischemic priapism	< 30	> 60	< 7.25
Nonischemic priapism	> 90	< 40	7.40

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Phenylephrine

- Alpha-1 adrenergic with rapid onset and short duration of action
- Agent of choice, off-label, may cause hypertension and bradycardia
- Patient should be placed on monitor, stop injection if rise in BP
- 100-500 mcg* in 1mL of normal saline, doses 5 min or more apart
- Intracavernosal injection near base of shaft for up to 1 hour
- Consider penile block beforehand and use small needles (e.g., 27G)

*Use of doses up to 2000 mcg in healthy patients without adverse effects have been reported.

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Sickle Cell Disease Patients

- Only provide IVF if NPO or dehydrated
- Only provide oxygenation if hypoxic
- Never use ice packs or cold compresses in SCD patients
- Transfusion not indicated if hemoglobin near baseline
  - Over-transfusion associated with neurologic events
  - Acute exchange transfusion is not indicated
  - Consider PRBC to achieve Hgb of 9-10 g/dL before operative shunting

IVF: Intravenous fluids
NPO: nil per os in Latin; 'nothing by mouth'
SCD: Sickle cell disease
PRBC: Packed red blood cells
Hgb: Hemoglobin

Expert panel report, 2014, available at: http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines.

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Distal Shunting

- Scalpel-based (Al Ghorab, Ebbehoj, T-Shunt) show higher success than needle-based (Winter's)
- Tunneling aids resolution, but may worsen functional outcomes
- Persistent erection after shunting may be non-ischemic (check CBG)
- Induration is not equivalent to persistent ischemia

CBG = Corporal Blood Gas

Zacharakis E, Raheem AA, Freeman A et al. J Urol 2014; **191:** 164.
Ortac M, Cevik G, Akdere H et al. J Sex Med 2019; **16:** 1290.
Pal DK, Biswal DK and Ghosh B. Urol Ann 2016; **8:** 46.
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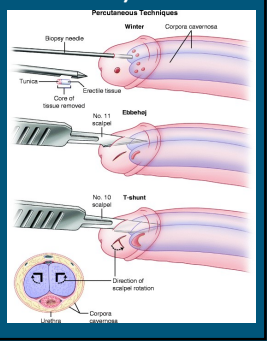

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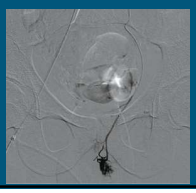
Non-ischemic Priapism

- Non-painful and cavernosal blood gas c/w arterial blood; +/- trauma
- Not emergent and patients should be offered observation (~4 weeks)
- Consider duplex ultrasound for fistula location/size
- For persistent cases desiring treatment, embolization is first line
- Embolization carries risks of failure and ED
- Failed embolization warrants repeat attempt over surgical ligation



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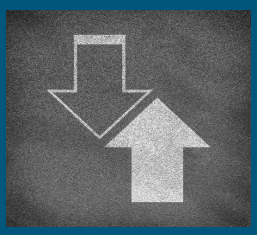
Stuttering Priapism

- Recurrent ischemic priapism with painful unwanted erections
- Intervening periods of detumescence
- Optimal strategies for prevention are unknown
- Hormonal regulators may impair fertility and sexual function
- Erections have been maintained in some men on oral antiandrogens*



*e.g., bicalutamide

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Strategies

- Ketoconazole + Prednisone w/highest reported success, but w/risks
  - Potential liver toxicity (check LFTs)
  - Potential fatigue, hot flashes, breast tenderness, mood alteration, ED
  - May negatively impact sperm parameters
- Conflicting efficacy data for PDE5Is
- SCD patients may be considered for some additional options
  - Etilefrine
  - Hydroxyurea
  - Automated exchange transfusion

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Peyronie's Disease

- Acquired penile deformity characterized by tunical fibrosis
- Active vs Stable disease
  - Active: pain/inflammation, dynamic changes in appearance/experience
  - Stable: Deformity not progressive at least 3 months; pain uncommon
  - Pain typically resolves, but curvature improves spontaneously in only 7-12%
- Epidemiology: Prevalence reported ranges from 0.5 to 20.3%
- Association with Dupuytren's contracture
- Presumed due to buckling trauma during sexual activity

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Peyronie's: Presentation

- Injury leads to change in tunical collagen from type 1 to type 3
- Collagen plaque restricts tunical stretch
- Typical patient mid-50s and unable to recall event
- Most stable patients have mid-shaft dorsal plaque
- Curvature usually dorsal or dorsolateral
- Differential DDx: congenital curvature*, cancer (rare)**

*Young men may confuse this for Peyronie's, but management similar.
**Consider biopsy in men with known metastatic prostate cancer.

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Peyronie's: Evaluation/Management

- H/P, in-office intracavernosal injection before invasive intervention*
- May offer NSAIDs in active phase if men have pain
- Should NOT offer P.O. vitamin E, tamoxifene, etc
- Manage concomitant ED as per established algorithm
- Intralesional clostridial collagenase**, interferon alpha-2b, verapamil
  - Stable disease
  - For collagenase, between 30-90 degrees with intact erectile function
  - Improvement from collagenase over placebo is modest (less than 10 degrees)

*Expert opinion. Some will use patient-provide photography and assess curvature further at time of procedure(s).
**Risk of penile fracture. Avoid sex for 2 weeks after injections.

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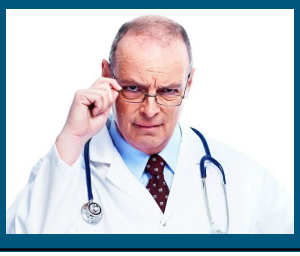
Therapies with Insufficient Evidence

- Oral: Colchicine, pentoxifylline, potassium aminobenzoate, Co-Q10
- Topical: Verapamil, magnesium, liposomal human superoxide dismutase
- Electromotive therapies (e.g., verapamil + dexamethasone)
- Traction therapy
- Do not use shock wave (except for pain) or electromotive therapies



Co-Q10: Co-enzyme Q10

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Peyronie's: Surgical Management

- No agreed-upon minimum curvature necessary to intervene
- Plication acceptable if stable* and adequate rigidity +/- treatment
- Same criteria for plaque incision or excision +/- grafting
- Inflatable penile prosthesis if severe deformity or refractory ED
- Ancillary procedures can be performed with implant placement

*Most lesions stable within 12-18 months from symptom onset.

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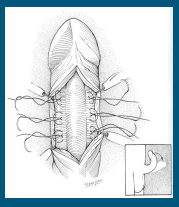
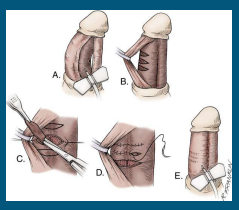
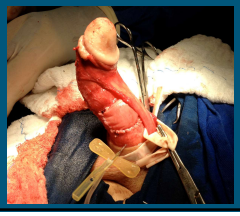
Curvature Correction





- Plication involves shortening of convex side
  - Preserves potency in most patients
  - Common goal is less than 30 deg residual
- Grafting is higher risk procedure
  - Often used for those w/curvature > 60 deg, inadequate length, heavily calcified
  - Erections compromised in 10-54% (20% is a conservative estimate preop)
  - Off-the-shelf grafts often preferred to autologous



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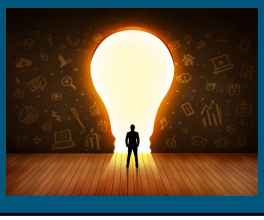
Conclusions

- Sexual health management related to understanding physiology
- ED warrants consideration of overall health and social situation
- Specialized testing rarely warranted in men with ED
- PDE5Is should be used with caution in some scenarios
- Initial management of ischemic priapism >4h unaltered by etiology
- Management of Peyronie's disease is predominantly surgical



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ED: Question 1:

A 22-year-old male suffers a complete T11 injury after a motorcycle accident one year ago. He presents for discussion of sexual health. The scenario that most likely defines his situation is:

A. Normal erection, normal emission, absent ejaculation
B. No erectile function, no emission, and no ejaculation
C. Reflexogenic erections only, no emission, and no ejaculation
D. Normal erection, no emission, absent ejaculation
E. Reflexogenic erections only, normal emission, and retrograde ejaculation

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ED: Question 2:

A 55-year-old male is on hemodialysis for anuric end stage renal disease and presents for 2 years of progressive erectile dysfunction. Testosterone is normal. The following option that would be inappropriate to offer him is:

A. Tadalafil 20 mg on demand
B. Tadalafil 5 mg on demand
C. Sildenafil 100 mg on demand
D. Sildenafil 50 mg on demand
E. Intracavernosal alprostadil

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ED: Question 3:

A 65-year-old diabetic male presents to the office for notching of erections at midshaft, noticed for the past 2 months. He can still achieve an erection, but rigidity has declined such that he cannot maintain it for satisfactory intercourse. The most appropriate option for treatment is:

A. Traction therapy
B. Ibuprofen
C. Intralesional clostridial collagenase
D. Tadalafil
E. Plaque incision and grafting

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ED: Question 4:

A 21-year-old African American male with sickle cell disease presents with a painful erection for the past 8 hours. He has been treated multiple times in the past. Hemoglobin at baseline. Corporal blood gas shows P_{O2} of 20 mm Hg, P_{CO2} of 70 mm Hg, and pH of 7.15. The next step is:

A. Admit to a monitored bed for intravenous hydration
B. Type and cross in preparation for exchange transfusion
C. Distal shunt (e.g., T-shunt)
D. Placement of penile prosthesis
E. Aspiration and intracavernosal phenylephrine

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ED: Question 5:

A 44-year-old male with cocaine addiction presents to the hospital with a painful erection for six hours. He undergoes a T-shunt with tunneling and is admitted for postoperative monitoring. One hour later, his penis still feels indurated and engorged. The next step is:

A. MRI to evaluate corpora
B. Bedside irrigation with phenylephrine
C. Proximal shunt (e.g., Grayhack)
D. Penile implant placement
E. Wait for a repeat corporal blood gas