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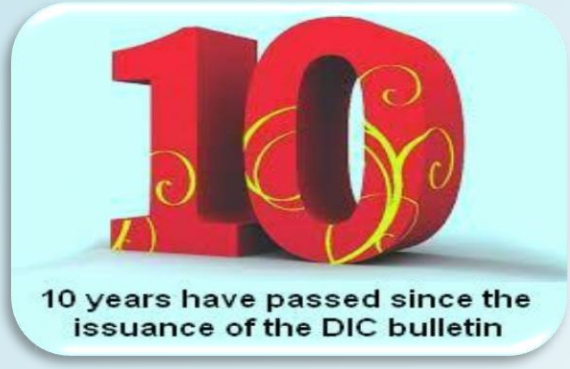

In This Issue…

- Pediatric vesicouretral reflux
- FDA Approves portrazza to Treat advanced squamous non-small cell lung cancer

Editorial Board

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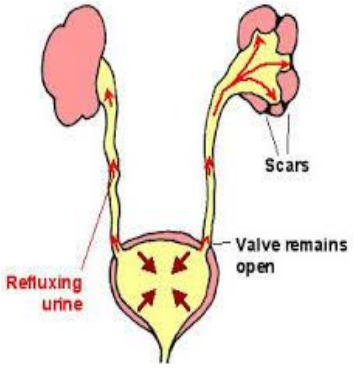
Pediatric Vesicoureteral Reflux

Vesicoureteral reflux (VUR), or the retrograde flow of urine from the bladder into the ureter, is an anatomic and functional disorder that can result in substantial morbidity, both from acute infection and from the sequelae of reflux nephropathy.

Signs and symptoms



The diagnosis of UTI in children can be difficult, for these reasons:

- Children often present with nonspecific signs and symptoms; infection in infants can manifest as failure to thrive, with or without fever; other features include vomiting, diarrhea, anorexia, and lethargy
- Older children may report voiding symptoms or abdominal pain
- Pyelonephritis in young children is more likely to manifest as vague abdominal discomfort rather than as the classic flank pain and tenderness observed in adults
- The presence of fever, while highly suggestive of pyelonephritis, is not reliable enough to lead to the diagnosis
- Children occasionally present with advanced reflux nephropathy manifesting as headaches or congestive heart failure from untreated hypertension or with uremic symptoms from renal failure
- A small group of children without evidence of UTI present with symptoms of sterile reflux, which can include flank or abdominal pain As with the history, few findings on physical examination suggest VUR or UTI. Fever, flank or abdominal tenderness, or an enlarged palpable kidney may be present.

Risk factors for vesicoureteral reflux include:

- **Race.** White children appear to have a higher risk of vesicoureteral reflux.
- **Sex**. Generally, girls have about double the risk of having this condition as boys do. The exception is for vesicoureteral reflux that's present at birth, which is more common in boys.
- **Age.** children up to age 1 are more likely to have vesicoureteral reflux than older children
- **Family history**. Primary vesicoureteral reflux tends to run in families. Children whose parents had the condition are at higher risk of developing it.

Complications

- Kidney damage is the primary concern with vesicoureteral reflux. Complications may include:Kidney (renal) scarring , High blood pressure and renal failure.

Tests and diagnosis

Urinalysis can reveal whether the child has a UTI. Other tests are necessary including :

- **Kidney and bladder ultrasound.** Ultrasound can detect structural abnormalities.This same technology, often used during pregnancy to monitor fetal development, may also reveal swollen kidneys in the baby, an indication of primary vesicoureteral reflux.
- **Voiding cystourethrogram (VCUG).** This test uses X-rays of the bladder when it's full and when it's emptying to detect abnormalities. A (catheter) is inserted through the urethra and into

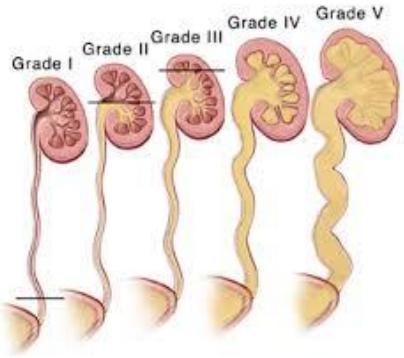
the bladder while the child lies on his or her back on an X-ray table.After contrast dye is injected into the bladder through the catheter, the child's bladder is X-rayed in various positions. Then the catheter is removed so that the child can urinate, and more X-rays are taken of the bladder and urethra during urination to see whether the urinary tract is functioning correctly.

- **radionuclide cystogram:** Nuclear scan.**,** uses a procedure similar to that used for VCUG, except that instead of dye being injected into the child's bladder through the catheter, this test uses a radioactive tracer (radioisotope). The scanner detects the tracer and shows whether the urinary tract is functioning correctly.

Grading the condition

Grade of vesicoureteral reflux according to the degree of reflux.
The International Classification System for VUR is as follows :

Grade I Reflux into nondilated ureter
Grade II Reflux into renal pelvis and calyces without dilation
Grade III Reflux with mild to moderate dilation and minimal blunting of fornices
Grade IV Reflux with moderate ureteral tortuosity and dilation of pelvis and calyces
Grade V Reflux with gross dilation of ureter, pelvis, and calyces, loss of papillary impressions, and ureteral tortuosity



Management

- General principles of management in children with known VUR are as follows:
- Spontaneous resolution of VUR is common in young children but is less common as puberty approaches
- Severe reflux is unlikely to spontaneously resolve
- Sterile reflux, in general, does not result in reflux nephropathy
- Long-term antibiotic prophylaxis in children is safe
- Surgery to correct vesicoureteral reflux is highly successful in experienced hands

Surveillance

- Still frequently used among older children with vesicoureteral reflux, especially boys who have never had a UTI
- Children with low-grade VUR, especially those who have never had a UTI, are sometimes followed on surveillance without antibiotic prophylaxis
- Infrequently used among those with high-grade VUR; antibiotic prophylaxis is usually well tolerated, and there are medicolegal concerns regarding the risk of kidney damage while on surveillance

Antibiotic prophylaxis

- Started once a child has completed treatment of the initial UTI
- Discontinued if no VUR is seen on imaging studies
- If VUR is present, prophylactic antibiotics are continued until the VUR resolves or is surgically corrected, or the child grows old enough that prophylaxis is deemed no longer necessary

Antibiotics are used as follows:

- The typical dose is one fourth of the therapeutic dose
- Antibiotics are usually administered as suspensions once daily, typically in the evening to maximize overnight drug levels in the bladder.
- In neonates with antenatally diagnosed hydronephrosis and in infants younger than 8 weeks who have been treated for UTI, the agent of choice is amoxicillin.

- For older children, the most common antibiotics used are trimethoprim-sulfamethoxazole, nitrofurantoin, and penicillins
- Cephalosporins are used less often.
- The prophylactic regimen also includes regular follow-up care and imaging (eg, renal ultrasonography and VCUG or nuclear cystography every 12-18 months).
- Children with dysfunctional elimination require aggressive bladder and bowel management. In toilet-trained children with recurrent UTI, voiding postponement behaviors, incomplete emptying, and constipation are extremely common and may be much more important etiologic factors than the reflux itself. Anticholinergic medication, in conjunction with timed voiding, may improve symptoms of dysfunctional voiding and reduces the risk of infection

Surgical care : Accepted indications for surgical treatment include the following:

- Breakthrough febrile UTIs despite adequate antibiotic prophylaxis .
- Severe reflux (grade V or bilateral grade IV) that is unlikely to spontaneously resolve, especially if renal scarring is present .
- Mild or moderate reflux in females that persists as the patient approaches puberty, despite several years of observation .
- Poor compliance with medications or surveillance programs.
- Poor renal growth or function or appearance of new scars
- Virtually all open antireflux operations involve reconstruction of the ureterovesical junction to create a lengthened submucosal tunnel for the ureter, which functions as a one-way valve as the bladder fills. Dozens of procedures have been described. Options include open antireflux surgery via an extravesical or an intravesical approach and endoscopic antireflux surgery.

Lifestyle and home remedies

Urinary tract infections, which are so common to vesicoureteral reflux, can be painful. But there are steps to ease the child's discomfort until antibiotics clear the infection. They include:

- Encourage the child to drink fluids**,** particularly water. Drinking water dilutes urine and may help flush out bacteria.
- Avoid juices and drinks containing citrus and caffeine until the child's infection has cleared. They can irritate the bladder and tend to aggravate the frequent or urgent need to urinate.
- Provide a warm blanket or towel, Place a towel or blanket in the dryer for a few minutes to warm it up. Be sure the towel or blanket is just warm, not hot, and then place it over the child's abdomen. The warmth can help minimize feelings of bladder pressure or pain.

Reference: *1*) http://emedicine.medscape.com/article/1016439-overview
2) http://www.mayoclinic.org/diseases-conditions/vesicoureteral-reflux/basics/definition/con-20031544

Terminology
Tapotement

The word, tapotement is derived from the old French term *tapir,* meaning “light blow.”
tapotement is a massage technique involves a series of brisk percussions, in rapid, alternating, and rhythmic fasion. This is done by chopping the area with the sides of the hands or hitting the area being treated with cupped, fisted hands, palm, or fingers. This technique is useful in helping patients with bronchitis to loosen the mucus in the air passages of their lungs, thus helping them to cough it up.

Reference: *1)* *Marcovitch H. 2005. Black's Medical Dictionary. 41th ed. London: A&C Black Publishers Limited. p 693*
2) http://www.massageprocedures.com/techniques-procedures/swedish-massage/tapotement/

WHO Pharmaceuticals Newsletter

Amiodarone and hepatitis C treatments containing sofosbuvir
Serious slowing of the heart rate with co-administration

Egypt, EU and USA. The regulatory authorities have warned of serious symptomatic *bradycardia* when antiarrhythmic drug *amiodarone* is used with hepatitis C treatments containing *sofosbuvir* in combination with other drugs (e.g. *ledipasvir, daclatasvir or simeprevir)*. *Sofosbuvir* containing medicines (Harvoni® and Sovaldi®) are indicated for treatment of chronic hepatitis C virus, The US Food and Drug Administration (FDA) review of post-market reports of adverse events found that patients can develop serious and life-threatening symptomatic bradycardia when a sofosbuvir containing hepatitis C drug in combination with another direct-acting antiviral is taken together with *amiodarone.* The reports included the death of one patient due to cardiac arrest and three patients requiring placement of a pacemaker to regulate their heart rhythms. The other patients recovered after discontinuing either the hepatitis C drugs or *amiodarone*, or both. The FDA recommends heart monitoring in an inpatient hospital setting for the first 48 hours. Subsequently, monitoring in a doctor's office or self-monitoring of the heart rate should be done every day through at least the first 2 weeks of treatment. Patients discontinuing amiodarone just prior to starting sofosbuvir containing hepatitis C drugs in combination with another direct-acting antiviral, should also undergo similar cardiac monitoring as outlined above. The FDA is adding information about serious slowing of the heart rate, known as symptomatic bradycardia, to the labels of *sofosbuvir* containing hepatitis C drugs.

The Egyptian Pharmaceutical Vigilance Center (EPVC) has advised health-care professionals;

- A fixed dose combination with *edipasvir/sofosbuvir* should not be co-administered with *amiodarone.*
- Sofosbuvir combined with another hepatitis C drug, such as investigational drug *daclatasvir* or *simeprevir,* should not be co-administered with *amiodarone*.
- Patients should be advised to seek medical attention immediately if they have signs and symptoms of bradycardia including: fainting (syncope) , dizziness or light headedness , malaise , weakness , shortness of breath , chest pains , confusion or memory problems
- For patients taking *amiodarone* who have no other alternative treatment options and who will be co-administered either a fixed dose combination with *ledipasvir/sofosbuvir* or *sofosbuvir* in combination with another direct acting antiviral:
- Counsel patients about the risk of serious symptomatic bradycardia :
  cardiac monitoring in an in-patient setting for the first 48 hours of co-administration is recommended, after which outpatient or self-monitoring of the heart rate would occur on a daily basis through at least the first 2 weeks of treatment . Patients who are taking either a fixed dose combination with *ledipasvir/sofosbuvir or sofosbuvir* in combination with another direct acting antiviral, who need to start *amiodarone* therapy due to no other alternative treatment options, should undergo similar cardiac monitoring as outlined above.
- Due to the long half-life of amiodarone, patients discontinuing amiodarone just prior to starting a fixed dose combination with ledipasvir/sofosbuvir or sofosbuvir in combination with another direct-acting antiviral should also undergo similar cardiac monitoring as outlined above.

References: Newsletter, Egyptian Pharmaceutical Vigilance Center (EPVC), Volume 6, Issue 5, May 2015

Test your knowledge

- Concern the use of the following drugs during pregnancy

A) co-trimoxazole
B) gliclazide
C) mesalazine
D) lisinopril
E) streptomycin

Select, from A to E, which one of the above:
Q1. may cause skull defects.
Q2. has an increased risk of neonatal haemolysis during the third trimester.
Q3. may cause vestibular or auditory nerve damage.
Q4. should be stopped at least 2 days before delivery.
Q5. consists of a folate antagonist that poses a teratogenic risk.

FDA News

FDA approves Portrazza to treat advanced squamous non-small cell lung cancer

November 24, 2015

The U.S. Food and Drug Administration approved Portrazza (necitumumab) in combination with two forms of chemotherapy to treat patients with advanced (metastatic) squamous non-small cell lung cancer (NSCLC) who have not previously received medication specifically for treating their advanced lung cancer.

Lung cancer is the leading cause of cancer death in the United States, with an estimated 221,200 new diagnoses and 158,040 deaths in 2015. The most common type of lung cancer, non-small cell lung cancer, is further divided into two main types named for the kinds of cells found in the cancer – squamous cell and non-squamous cell (which includes adenocarcinoma).

“Lung cancer tumors can be varied, so treatment options need to be tailored to the specific type of lung cancer in the patient,” said Richard Pazdur, M.D., director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research. “Today’s approval provides certain patients with squamous cell lung cancer a new option that may extend survival.”

Portrazza is a monoclonal antibody that blocks activity of EGFR, a protein commonly found on squamous NSCLC tumors.The safety and efficacy of Portrazza were evaluated in a multicenter, randomized, open-label clinical study of 1,093 participants with advanced squamous NSCLC who received the chemotherapies gemcitabine and cisplatin with or without Portrazza. Those taking Portrazza plus gemcitabine and cisplatin lived longer on average (11.5 months) compared to those only taking gemcitabine and cisplatin (9.9 months). Portrazza was not found to be an effective treatment in patients with non-squamous NSCLC.The most common side effects of Portrazza are skin rash and magnesium deficiency (hypomagnesemia), which can cause muscular weakness, seizure, irregular heartbeats and can be fatal. Portrazza includes a boxed warning to alert health care providers of serious risks of treatment with Portrazza, including cardiac arrest and sudden death, as well as hypomagnesemia.Portrazza is marketed by Eli Lilly and Company, based in Indianapolis, Indiana.

References：http://www.fda.gov/

Real Enquiries

At the "Drug Information Center", we respond to enquiries from the professional health team as well as from others. Here's one of the enquiries received at the center!

Enquiry received from: ph / Alaa Kassem , Womens' Health Hospital- Assiut University

Enquiry: How is ephedrine diluted for IV administration?

***Summary of* Answer:**

The ampoules contain a concentrate for solution for injection containing 30 mg ephedrine hydrochloride in each ml of solution. This medicine should be administered immediately after dilution with sterile isotonic sodium chloride in a ratio of 1:10.

Complementary medicine

Marshmallow

Species (Family): Althaea officinalis L. (Malvaceae)
Part(s) Used: Leaf, root

Constituents:

- Polysaccharides
  Mucilage polysaccharides (5–10%), consisting of galacturono-rhamnans, arabinans, glucans, arabinogalactans.
- Flavonoids
  Hypolaetin 8-glucoside, isoscutellarein 40-methy-lether-8-glucoside-2-sulfate.
- Phenolic acids Caffeic, p-coumaric, ferulic, p-hydroxybenzoic and syringic.
- Other constituents Asparagine 2%, calcium oxalate, coumarins (scopoletin), pectin, starch and tannin.

Food Use

Marshmallow is listed by the Council of Europe as a natural source of food flavouring (category N2). This category indicates that marshmallow can be added to foodstuffs in small quantities,with a possible limitation of an active principle (as yet unspecified) in the final product. Previously in the USA,marshmallow has been approved for use in foods.

Herbal Use

Marshmallow is stated to possess demulcent, expectorant,emollient, diuretic, antilithic and vulnerary properties.Traditionally, it has been used internally for the treatment of respiratory catarrh and cough, peptic ulceration,inflammation of the mouth and pharynx, enteritis, cystitis,urethritis and urinary calculus, and topically for abscesses, boils and varicose and thrombotic ulcers. The German Commission E approved use of root and leaf for irritation of oral and pharyngeal mucosa and associated dry

cough and root for mild inflammation of gastric mucosa. Marshmallow root is used in combination with anise fruit, eucalyptus oil, liquorice and with anise fruit,liquorice and primrose root and with anise fruit and primrose root for catarrh of the upper respiratory tract and resulting dry cough.

Dosage

Dosages for oral administration (adults) for traditional uses recommended in older and contemporary standard herbal and/or pharmaceutical reference texts are given below.

- *Dried leaf:* 2–5 g as an infusion three times daily.
- *Leaf, liquid extract*: 2–5mL (1: 1 in 25% alcohol) three times daily.
- *Ointment*: 5% Powdered althaea leaf in usual ointment base three times daily.
- *Dried root*: 2–5 g by cold extraction three times daily.
- *Root, liquid extract*: 2–5mL (1: 1 in 25% alcohol) three times daily.
- *Syrup of Althaea*: 2–10mL three times daily.

Source: Barnes J, Anderson A, Phillipson D. *Herbal Medicines,* 3rd ed. London: Pharmaceutical Press;2007.

Answers to " Test Your Knowledge":

1. (D)

Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor and ACE inhibitors should be avoided during pregnancy. ACE inhibitors may adversely affect fetal and neonatal blood pressure control and renal function. They may also cause neonatal skull defects

2. (A)

Co-trimoxazole is a folate antagonist and should be avoided in the first and the third trimesters of pregnancy. In the third trimester there is an increased risk of neonatal haemolysis and methaemoglobinaemia, whereas in the first trimester there is a teratogenic risk caused by the trimethoprim (folate antagonist) component

3. (E)

All aminoglycosides are associated with auditory or vestibular nerve damage,especially during the second and third trimesters. The risk is greatest with streptomycin and is lower with gentamicin and tobramycin

4. (B)

Gliclazide is a sulphonylurea. In general, diabetic patients are switched over to insulin during pregnancy. Sulphonylureas should be stopped at least 2 days before delivery (in patients who are still receiving them) because of the risk of neonatal hypoglycaemia

5. (A)

Co-trimoxazole consists of trimethoprim and sulphamethoxazole combined, because of their synergistic antimicrobial effects. Trimethoprim is a folate antagonist that poses a teratogenic risk.