SEPTEMBER 2008 | VOLUME 1 No. 2 | Quarterly Publication

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The Laboratorian SM .com

Intrauterine Growth Restriction

Author: Eli Mordechai, Ph.D.

The definition of Intrauterine Growth Restriction (IUGR) compares birth weight with a standard distribution by gestational age and is most commonly defined as a fetus whose abdominal circumference is below the 2.5th percentile with an estimated weight below the 10th percentile (1). At term, the cutoff birth weight is 2,500 g or 5 lb, 8 oz. (1) (**Figure 1**). Upon delivery, affected newborns generally appear pale with loose, dry skin and a thin dull-looking umbilical cord. They may often present with a characteristic wide-eyed look. Many babies are simply genetically small and considered normal but small-for-gestational-age (SGA). IUGR babies, however are often malnourished or dysmorphic.

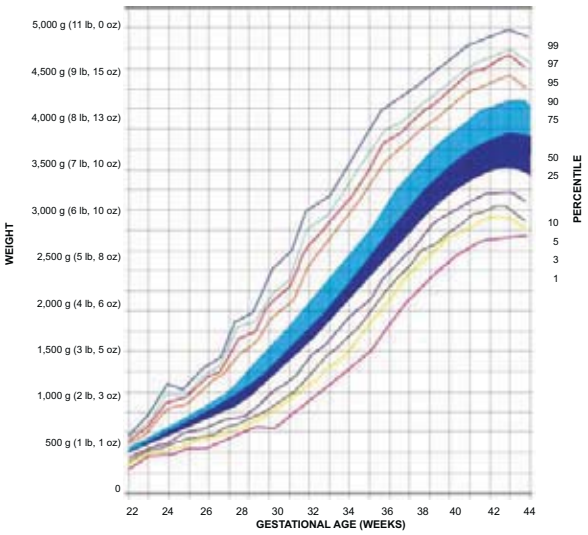

Figure 1. Fetal weight percentiles throughout gestation (1)

Causes of IUGR

IUGR results when an abnormality or problem prevents normal growth of cells or tissues. Factors that may contribute to IUGR are summarized in **Table 1**.

Table 1: Some Causes of IUGR

Maternal Factors
- Medical issues including hypertension, diabetes and immunological disorders, e.g. Systemic Lupus Erythematosus (SLE).
- Socioeconomic and nutritional factors.
- Drug use including alcohol, tobacco, cocaine, and amphetamines.
- Prescription medication use including anticonvulsants, warfarin, and steroids.
- Infectious diseases including CMV, HSV, Rubella and Toxoplasmosis.

Placental Factors
- Abnormalities of placental morphology
- Recurrent abruption
- Placenta praevia
- Placenta accretia
- Placental insufficiency
- Immunological disorders affecting the quality of placentation

Fetal Factors
- Genetic/chromosomal anomalies
- Multiple gestation (1)
- Birth defects

Continued ..... pg 2

WHAT'S INSIDE ➤➤

UPCOMING EVENTS ➤➤

09/10-13 **UMDNJ:** University of Medicine & Dentistry of NJ School of Osteopathic Medicine 12th Annual Board Review **Mt. Laurel, NJ**

09/12-13 **WHCF-C:** Women's Healthcare Forum Chicago Conference & Exhibition **Rosemont, IL**

09/19-20 **WHCF-P:** Women's Healthcare Forum Philadelphia Conference & Exhibition **Philadelphia, PA**

10/2-3 **PSPA:** Pennsylvania Society of Physician's Assistants Annual CME Conference **Valley Forge, PA**

10/11-14 **AAP-NCE:** American Academy of Pediatrics National Conference & Exhibition **Boston, MA**

10/17-19 **ACOG District V:** American College of Obstetrician & Gynecologists **Cincinnati, OH**

10/22-25 **ACOG:** Central Association of Obstetricians & Gynecologists Annual Meeting **New Orleans, LA**

Bladder Cancer Review

Author: Jack H. Mydlo, MD, FACS

The role of the bladder in normal human functions can be put into two simple roles: to store urine, and to empty urine. Yet, as a person gets older, these two simple roles have become problematic and account for most of the problems seen in a typical urological practice. However, treatment of benign bladder conditions such as stress urinary incontinence and bladder stones, for example, while certainly vexing, do not carry the potential seriousness that can develop when one presents with bladder cancer. This disease can be insidious, and its simple treatment, especially when caught in the early stages of disease, makes one realize the importance of early detection and screening in high risk groups.

Incidence and Prevalence:

The urothelium of the bladder, composed of transitional cells, is a continuous lining starting from the urethra and bladder going through the ureters and ending up in the renal pelvis of the kidney. This entire urothelium behaves as a "wall-to-wall carpet" which is susceptible to malignant transformation. Acquired alterations in DNA may lead to the induction of oncogenes or loss of tumor suppressor genes, which can result in neoplasia. Since transitional cell carcinoma, the most prevalent of the bladder cancers, may present in multiple sites, this demonstrates the potential for multiple field changes. Furthermore, after resection of bladder tumors, the transitional cells can still migrate and implant into other sites. This can make it difficult to assess whether recurrence of lesions represent a new tumor, an inadequately resected old tumor, an implant site, or multi-focality.

There are about 60,000 new cases of bladder cancer per year in the United States. For men, bladder cancer represents the fourth most common tumor, and for women, it is the eighth. The disease is almost twice as prevalent in Caucasian men as compared to African American men, and about 1.5 times as common in Caucasian women as compared to African American women. However, this increased risk among Caucasians pertains more to the superficial disease, as there is evidence that African Americans may have an increased incidence of the aggressive form of the disease.

Interestingly, bladder cancer has almost never been reported as an incidental finding at autopsy. This is very different than autopsy findings for prostate cancer and other malignancies. This suggests several possible scenarios: 1) everyone with bladder cancer has the disease already diagnosed, or 2) it implies that the latency of this tumor, from the time it is detected cystoscopically, to the time it is symptomatic, must be very

Continued ..... pg 4

Intrauterine Growth Restriction (IUGR)

Continued from ..... pg 1

Some predisposing factors of IUGR also include women who were themselves growth restricted at birth, previous IUGR pregnancy, and a sister who has had an IUGR pregnancy (2). One study found the recurrence risk to be 29% if one prior pregnancy was affected, and 44% if two prior pregnancies were affected (2). It has also recently been proposed that a genetic predisposition exists, associated with insulin-like growth factor 1 receptor (IGF-1R) gene mutations, leading to impaired IGF-1R function, which may result in restricted intrauterine growth.

Symmetric and Asymmetric IUGR

Cases of IUGR can usually be classified as symmetric or asymmetric. Symmetric growth restriction refers to a proportionally small fetus. Asymmetric growth restriction refers to an undernourished fetus whose resources have been redistributed to maintain the growth of certain vital organs such as the brain and heart at the expense of the liver, muscle, and fat. This presents as a fetus with normal head dimensions, but small abdominal circumference and thinned skin due to the decreased liver size, muscle mass, and fat. Asymmetric growth restriction is usually a result of placental insufficiency.

Table 2: Diagnostic and assessment tools relating to IUGR (2).

Screening
- Biochemical
  - o Alpha-fetoprotein
    If ↑ in absence of fetal anomaly, risk of IUGR later in pregnancy is ↑ 5-10 X
  - o Clinical
    - ♦ Palpation
    - ♦ SFH measurement (customized)
  - o Ultrasound
    - ♦ Head circumference (HC)
    - ♦ Abdominal circumference (AC)
    - ♦ Estimated fetal weight (EFW)

    <10th percentile on customized charts or reduced growth velocity indicate IUGR

Confirmation of Diagnosis
- Ultrasound

  Fetal/placental morphology
  - o Umbilical artery (UA) doppler
  - o ± assess for TORCH infections
  - o ± fetal karyotyping

Monitoring of IUGR affected pregnancy
- Ultrasound
  - o UA doppler
    - ♦ ± Middle cerebral artery (MCA) doppler
    - ♦ ± Fetal venous studies
  - o Amniotic Fluid Index (AFI)
  - o ± Biophysical profile (BPP)
- ± Cordocentesis (rarely)

Genital Flora and IUGR

The effect of common genital microbes on fetal growth has been described in several studies. Most reports have focused on the relationship between birth weight and the genital isolation of *Bacteroides* spp., *Chlamydia trachomatis*, *Neisseria gonorrhoeae,* and *Ureaplasma urealyticum.* In a study by Polak *et al*., a group of predominantly black, high-risk pregnant women, infected with *C. trachomatis* and *Candida albicans* were at higher risk of giving birth to SGA babies, even after adjusting for other factors associated with fetal growth (3). In a large multicenter cohort study (N = 13,914) of pregnant women, Germain *et al*. reported a strong trend for increased risk of IUGR associated with *Bacteroides* spp., Prevotella, *Porphyromonas* spp., *Mycoplasma hominis*, and *Ureaplasma urealyticum*. In this study, Group B streptococci, *N. gonorrhoeae, C. trachomatis,* and *C. albicans* were not significantly associated with IUGR (3). The association between genital flora and IUGR remain ill defined.

Diagnosis of IUGR

Diagnosis of IUGR involves several factors. It is imperative to accurately date a pregnancy when making the diagnosis of IUGR. Ultrasound scanning (USS) in the first trimester generally provides accuracy within 5 days, while second trimester scanning should be accurate to within 10 days (2). In accurately dated pregnancies, only 10% to 15% of fetuses identified as being SGA are "true" IUGR cases. Approximately 80% to 85% are constitutionally small but healthy and the remaining 5% to 10% of fetuses are affected by chromosomal/structural anomalies or chronic intrauterine infection (1). Fetal growth should be monitored throughout the pregnancy and is easily accomplished via measurement of symphysis fundal height (SFH). A consideration of risk factors as well as previous pregnancy history should be taken into consideration as well. Prior history of a SGA infant has been reported to be among the most predictive factors for subsequent IUGR with up to a two- to four-fold increased risk of another similarly affected fetus.

Management

The management of IUGR must be individualized for each patient. In addition to managing any maternal illness, maternal nutrition may be supplemented to increase gestational weight gain and thus fetal growth. Bed rest may be implemented to improve circulation to the fetus. A detailed sonogram should be performed to search for fetal anomalies. Fetal karyotyping may be considered to rule out aneuploidy or an inappropriate number of chromosomes. Due to the fact that symmetric restriction may be due to a fetal chromosomal disorder or infection, the patient may decide to undergo amniocentesis for further studies. Due to the fact that the earlier and more severe the growth restriction, the greater the risks to the fetus, serial ultrasound examinations are important to determine the severity and progression of IUGR.
Some controversy surrounds the decision to expedite delivery. It is widely held that delivery should be expedited if the risks of complications unique to IUGR outweigh the risks associated with preterm delivery such as intrauterine demise due to chronic oxygen deprivation.

References:

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2. Sheridan C. 2005. Intrauterine growth restriction: diagnosis and management. *Aust Fam Physician*. **34(9)**:717-23.
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New Test Announcements

Now available on *OneSwab*®

Infectious Pathogens

581	*Candida albicans* fluconazole resistance by X-Plate Technology™ (#551 Req.)
582	*Candida glabrata* fluconazole resistance by X-Plate Technology™ (#559 Req.)
583	*Candida parapsilosis* fluconazole resistance by X-Plate Technology™ (#558 Req.)
584	*Candida tropicalis* fluconazole resistance by X-Plate Technology™ (#557 Req.)
362	Prevotella Species Group 1 (*P. bivia, P. disiens, P. intermedia, P. melaninogenica)* by Real-Time PCR
363	Prevotella Species Group 2 (*P. corporis*m, *P. albensis*) by Real-Time PCR

Genetic Carrier Screening

1213	Ashkenazi Jewish Carrier Screening Panel by Bio-Plex Analysis (Canavan Disease, Cystic Fibrosis, Familial Dysautonomia, Tay-Sachs Disease)
1214	Ashkenazi Jewish Carrier Screening Expanded Panel by Bio-Plex Analysis (Bloom Syndrome, Canavan Disease, Cystic Fibrosis, Familial Dysautonomia, Fanconi Anemia Type C, Gaucher Disease, Mucolipidosis Type IV, Niemann-Pick Disease Type A, Tay-Sachs Disease)
1207	Bloom Syndrome by Bio-Plex Analysis
1209	Canavan Disease by Bio-Plex Analysis
1210	Familial Dysautonomia by Bio-Plex Analysis
1205	Fanconi Anemia Type C by Bio-Plex Analysis
1211	Gaucher Disease by Bio-Plex Analysis
1212	Mucolipidosis Type IV by Bio-Plex Analysis
1206	Niemann-Pick Disease Type A by Bio-Plex Analysis
1208	Tay-Sachs Disease by Bio-Plex Analysis

Now available on *UroSwab*®

Infectious Pathogens (Males Only)

205	Epstein-Barr virus by Real-Time PCR
318	*Legionella pneumophila* by Real-Time PCR
335	*Mycoplasma penetrans* by Real-Time PCR
362	Prevotella Species Group 1 (*P. bivia, P. disiens, P. intermedia, P. melaninogenica)* by Real-Time PCR
363	Prevotella Species Group 2 (*P. corporis*m, *P. albensis*) by Real-Time PCR
215	Varicella-Zoster virus (VZV) by Real-Time PCR

Female Urinary Tract Infections

141	*Escherichia coli* by Real-Time PCR
148	*Klebsiella pneumoniae* by Real-Time PCR
146	*Proteus mirabilis* by Real-Time PCR
151	*Staphylococcus saprophyticus* by Real-Time *PCR*

Now available on Blood (Yellow Top ACD solution A)

361	*Chlamydophila psittaci* by Real-Time PCR
580	Coccidioides Species (*C. immitis, C. posadasii*) by Real-Time PCR
434	Colorado Tick Fever Virus by Real-Time PCR
362	Prevotella Species Group 1 by Real-Time PCR (*P. bivia, P. disiens, P. intermedia, P. melaninogenica)*
363	Prevotella Species Group 2 by Real-Time PCR (*P. corporis*m, *P. albensis*)

AS OF OCTOBER 1, 2008, THE FOLLOWING TEST REPLACEMENTS WILL TAKE EFFECT:

Discontinued	104	Chlamydia subtype (*C. pneumoniae, C. trachomatis*) by Real-Time-PCR
Replacement	364	Chlamydiales species (*Chlamydophila pneumoniae, Chlamydophila psittaci,* and *Chlamydia trachomatis*) by Real-Time PCR
Discontinued	321	Brucella Genus by Qualitative PCR (*B. abortus, B. melitensis, B. ovis, B. suis)*
Replacement	359	Brucella species (*B. abortus, B. canis, B. ovis, B. melitensis,* and *B. suis*) by Real-Time PCR
Discontinued	579	*Candida glabrata* azole resistance (CDR1) by Quantitative PCR
Replacement	582	*Candida glabrata* fluconazole resistance by X-Plate Technology™ (#559) Req.

Continued from ..... pg 1

brief. These findings support the need for early detection strategies to prevent progression of the disease.

Risk Factors:
There are several risk factors for the development of bladder cancer including bacteria, parasites, fungal infections, bladder stones, certain chemotherapeutic agents, and exposure to chemicals such as cigarette smoking, coffee, analgesics, and artificial sweeteners.

Data suggests that approximately 20% of the bladder cancers in the US are due to occupational exposure. Occupations reported to be associated with increased risk of this disease include car workers, painters, truck drivers, drill press operators, metal and leather workers, dry cleaners, paper manufacturers, rope makers, dental technicians, barbers and beauticians, and physicians. Aniline dyes, used to color fabrics, as well as combustible gases and soot from coal, and certain aldehydes used in the rubber and textile industry have also be shown to be urothelial carcinogens.

Cigarette smokers have up to a four-fold higher rate of bladder cancer than people who never smoked. The risk correlates to the amount of cigarettes smoked, as well as the length of time in which they were smokers. Although the risk is reduced once smoking stops, it can take up to 20 years for this increased risk to reach zero. It has been estimated that one-third of bladder cancer cases are associated with cigarette smoking.

Women treated with radiation therapy for cervical or uterine cancer have a two- to four-fold increased risk of developing bladder cancer. This risk is higher if chemotherapy was also used. The risk in this group continues to rise after 10 years and is characteristically high grade and locally advanced at the time of diagnosis.

Chronic cystitis, such as in the presence of indwelling catheters or bladder stones, is also associated with bladder cancer, but most typically this presents as the more aggressive and lethal squamous cell carcinoma. Around 5% to 10% of paraplegic persons with indwelling catheters develop bladder cancer, which also are mostly squamous cell carcinoma.

Schistosomiasis of the bladder is also associated with squamous cell carcinoma, although transitional cell carcinoma may also occur. Renal transplantation is associated with an increased risk for bladder cancer, most likely the result of immunosuppression.

While heredity plays a role in many tumors, there has been no strong evidence to-date implicating genetic mechanisms as a cause for bladder cancer.

Histology and Cytology:
The urothelium is made of several layers of transitional cells that are sometimes covered by umbrella cells. This layer is resistant to the chemicals of urine, but conditions such as interstitial cystitis are thought to be due to infiltration and inflammation of this lining. Dysplasia of the urothelium suggests epithelial changes between normal

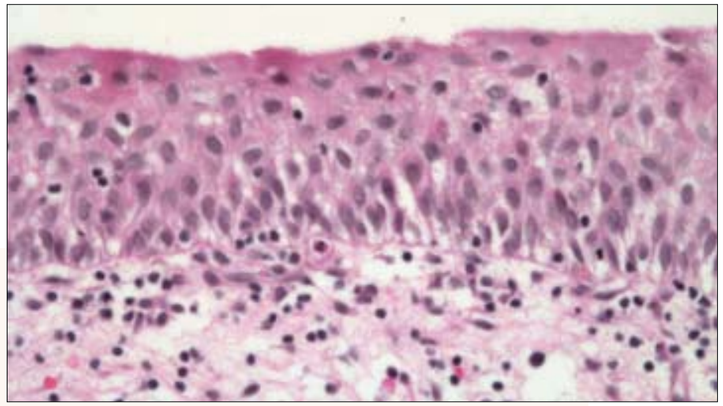

Figure 1: Normal Urothelium
(Photos courtesy of Rebecca Thomas, MD)

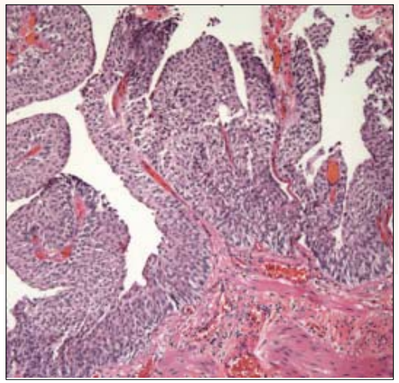

Figure 2: Papillary Transitional cell carcinoma

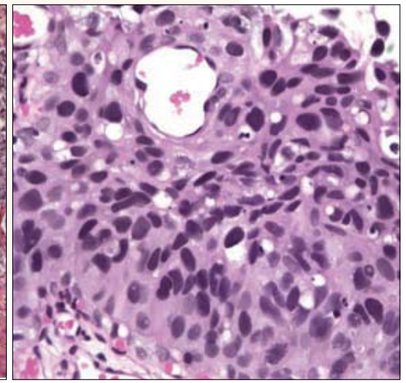

Figure 3: Carcinoma *in situ* (CIS)

cells and carcinoma *in situ* (CIS), but it is still not cancer. CIS may appear as elevated, velvety red patches on the bladder wall which are composed of poorly differentiated transitional cells on the urothelium that are confined and not muscle invasive. Sometimes these lesions may be invisible on cystoscopic exam, and are only suggested by suspicious or positive cytology 80% to 90% of the time. CIS may produce severe symptoms such as increased urinary frequency, urgency, and dysuria. This high association of CIS and muscle invasion of bladder cancer suggests that CIS may be a precursor of muscle invasive bladder cancer (Figures 1, 2, and 3)

Treatment
To the patient and the urologist, the two most important parameters that have prognostic value for bladder cancer treatment are histology grade and stage. Simply put, the best prognosis is for those patients who have a low grade, low stage, non-muscle invasive transitional cell carcinoma.

For low grade, non-muscle invasive TCC, treatment is usually with intravesical Bacillus Calmette-Guerin (BCG) or Mitomycin C. These agents are instilled and to be held in the bladder for two hours weekly over a six week period. They are not without risk, and the BCG should never be instilled into the bladder if there is a traumatic catheterization, as BCG absorbed into the bloodstream could lead to BCG sepsis.

Table I

1. 55% of bladder cancers are low grade and non-invasive to muscle.
2. 45% of bladder cancers are high grade, with the majority invasive to muscle.
3. Most common presenting sign of bladder cancer is hematuria.
4. Urine cytology is positive in high grade tumors, but still has a 20% false negative rate.
5. Early detection should be aimed at low grade cancers with less morbid treatment.
6. Increased fluids, smoking cessation, and a low fat diet are recommended.

Table II TNM Staging 1997 AJCC-UICC

1.	Ta	Paillary, epithelium confined.
2.	Tis	Flat carcinoma *in situ*.
3.	T1	Lamina propria invasion.
4.	T2a	Superficial muscularis propria invasion.
5.	T2b	Deep muscularis propria invasion.
6.	T3a	Microscopic extension into perivesical fat.
7.	T3b	Macroscopic extension into perivesical fat.
8.	T4a	Cancer invading pelvic viscera (e.g. prostate, vaginal wall, rectum, uterus).
9.	T4b	Cancer extension to pelvic sidewalls, abdominal walls, or bony pelvis.

The specificity and predictive value of urine cytology is high as long as the highly suspicious cell is considered positive. Urine cytology is more sensitive in patients with high grade tumors or CIS. However, cytology may be falsely negative 20% of the time.

While the cure rate of superficial bladder cancer using intravesical chemotherapy has been reported to be as high as 60% to 80%, in a subset of cases, intravesical therapy merely delays the inevitable; namely, progression into invasive bladder cancer. Treatment options then require dissection, radical cystectomy and urinary diversion.

Whereas pelvic node dissection for prostate cancer is considered more a diagnostic procedure to see if there is spread of the disease, pelvic node dissection for bladder cancer is both diagnostic and therapeutic. Even with micro-metastatic spread to the lymph nodes, a thorough pelvic lymph node dissection combined with adjuvant chemotherapy has improved overall survival.

The one year survival rate of muscle invasive bladder cancer treated by cystectomy is only 50%. Therefore, the treating urologist straddles the “tightrope” between treating the patient with superficial disease with intravesical chemotherapy, and the risk of having the disease progress to muscle invasion and undergoing radical surgery. Therefore, the patients with superficial disease are under careful surveillance every three months to determine the response to intravesical chemotherapy. The frequency of recurrence and/or persistence of low grade, low stage bladder cancer under surveillance will determine if it is progressing; if so, the urologist and the patient must determine whether another course of intravesical chemotherapy is warranted, or to proceed with radical surgery. Therefore, it is important to determine new innovative techniques and preventive measures for this insidious process.

Figure 4: Normal urine cytology

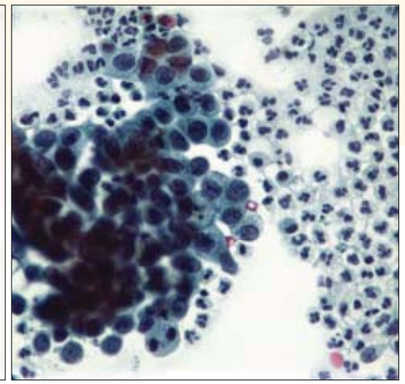

Figure 5: Abnormal urine cytology

Table III
Treatment for low grade, non-muscle invasive bladder cancer

1. Transurethral resection (TURBT) of all visible tumors.
2. If a tumor is high grade, repeat resection to rule out muscle invasion.
3. Reduce recurrence by giving intravesical chemotherapy shortly after resection.
4. If low grade bladder tumor is detected in late term pregnant patient, wait until she delivers, then resect.
5. Initial response of CIS to BCG is 80%. Those failures have 50% tumor progression.
6. If patient fails two six week courses of BCG, recommend cystectomy.

Treatment for muscle invasive bladder cancer

1. Partial cystectomy if solitary, new tumor that allows 1-2 cm margin of bladder resection. Not for CIS or multiple site tumors. Need good capacity bladder.
2. Radical cystectomy if recurs after chemo, or too large for partial, or multiple sites.
3. Male cystectomy: bladder, prostate, seminal vesicles, urethra, if indicated.
4. Female cystectomy: bladder, uterus, fallopian tubes, anterior vaginal wall.
5. Preoperative irradiation not effective for overall survival.
6. Thorough pelvic lymph node dissection diagnostic and therapeutic.
7. For non-surgical candidates: TUR + chemo + XRT.

Prevention
High fat diets and high cholesterol diet have been correlated with an increased relative risk of developing bladder cancer in several studies. Vitamin A has been found to prevent induced bladder cancer in laboratory animals. Soy products have also been shown to inhibit angiogenesis and neoplasia. Perhaps most importantly, dilution of carcinogenic agents in the urine by increased fluid intake can protect against bladder cancer.

Conventional urine cytology and commercially available tests in the US have a relatively poor sensitivity for well and moderately differentiated bladder tumors. An inability to detect more than 20% of high grade cancers would compromise the ultimate goal of screening for bladder cancer and reduce mortality. Although several studies have shown some promise for early bladder cancer detection, including nuclear matrix proteins, telomerase, microsatellite repeat analyses, and methylated DNA assays, evidence shows that neither alone nor in limited combinations are these tests sufficiently sensitive to replace cystoscopy in the evaluation of hematuria or surveillance.

New inroads are being made into discovering new urine tumor markers that may be utilized in a nomogram in the future. Certainly no one can predict whether surveillance cystoscopy will ever be replaced by a combination of tumor marker assays. The ideal tumor marker is one which is positive in the presence of a clinically significant tumor, and is negative in the absence of tumor. Hopefully, future investigations for bladder cancer markers will provide us with better screening, earlier detection, and overall better survival rates for this disease. Knowledge of the contributing environmental factors may also help in lowering the incidence of bladder cancer.

Table IV Urine tumor markers

1. Survivin
2. Telomerase
3. BCL2
4. Death Associated Protein Kinase (DAPK)
5. CDKN2A
6. TERT

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4. **Chang SS, Cookson MS**. 2005. Radical cystectomy for bladder cancer: the case for early intervention. *Urol Clin North Am*. **32**:147-155.

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JOURNAL WATCH

Maurer P, Koch B, Zerfaß I, Krauß J, Linden M, Frère J, Contreras-Martel C, Hakenbeck R. 2008. Penicillin-binding Protein 2x of *Streptococcus pneumoniae*: Three New Mutational Pathways for Remodeling an Essential Enzyme into a Resistance Determinant. *J Mol Biol*, 376 **(5):**1403-1416.

This study investigates the structure/function relationship of one of the major resistance determinants in *S. pneumoniae*, PBP2x by analyzing PBP2x proteins of cefotaxime-resistant laboratory mutants, which are derived from the penicillin-sensitive laboratory strain *S. pneumoniae* R6, with a known set of mutations. Each of these mutants contains a distinct PBP2x variant with three to four mutations. It was demonstrated that the mutational sites of the PBP2x variants are scattered throughout the penicillin-binding domain, illustrating the importance of alterations in the protein within 20-Å radius from the active-site S337. In all the mutants, at least one mutation is located close to the active-site S337 or introduces a negative charge into the active-site cavity. Transformation experiments using PBP2x genes with up to four mutations confirmed that some of the mutations decrease cefotaxime susceptibility in the wild-type background, without the context of mutations in other genes that occur during the selection procedure. Other studies have also shown that when PBP2x mutants are studied in combination with deletion mutants in the regulatory system CiaRH, a slower growth rate and rapid lysis during stationary phase are observed, and the severity of the effect apparently depended on the type of the PBP2x mutation. This work also showed that the apparent effect of two of these mutations is a reduced amount of the protein in the cell. But also in the other mutants, where PBP2x are present in wild-type quantities, additional mutations in *ciaH* are present, and it is unlikely that the *cia* regulon is affected differently in the two mutants producing lower levels of PBP2x. It could be that individual mutations affect the stability of the protein; whereas, it seems unlikely that mutations within the structural gene affect the expression level.

Menard JP, Fenollar F, Henry M, Bretelle F, Raoult D. 2008. Molecular quantification of *Gardnerella vaginalis* and *Atopobium vaginae* loads to predict bacterial vaginosis. *Clin Infect Dis*, 47**(1):** 33-43.

Bacterial vaginosis (BV) is the most common vaginal disorder among women of reproductive age. BV is defined by a transition in the vaginal flora from the predominant Lactobacillus species to other bacterial species such as *Atopobium vaginae* and *Gardnerella vaginalis*. BV is routinely diagnosed in the clinic by Amsel criteria and in the laboratory by Nugent score, which involves microscopic evaluation of gram-stained vaginal samples. Stating that these tools are unreliable, the authors use quantitative Real-Time PCR methods to diagnose BV from cytobrush samples in comparison to Nugent scoring. Eight BV-associated organisms and the human albumin gene (to control for the presence of DNA) were targeted with specific primers and Taqman probes, a sensitive method for measuring DNA amplification during a PCR reaction. The numbers of organisms were measured as copies of microorganism DNA (as compared to a dilution series of a plasmid containing the target sequence of each PCR) per 1ml of vaginal suspension. A total of 231 samples were analyzed during the development of the test. Not surprisingly, the authors found the DNA of BV-associated organisms in women diagnosed with BV by Nugent score more frequently. However, the only statistically relevant associations with BV diagnosis were seen for the molecular quantification of *A. vaginae* (greater than or equal to 10^8 copies/ml) and *G. vaginalis* (greater than or equal to 10^9 copies/ml). Using these defined cutoff values the test achieved 95% sensitivity, 99% specificity, 95% PPV and 99% NPV. The authors then applied the quantitative test prospectively to 56 new vaginal samples and achieved a 96% PPV and 99% NPV. Based on this study, quantitative molecular detection of *A. vaginae* and *G. vaginalis* may be a reliable method to objectively analyze vaginal flora and BV.

Truzzi JC, Almeida FM, Nunes EC, Sadi MV. 2008. Residual urinary volume and urinary tract infection-when are they linked. *J Urol*, 180**(1)**:182-5.

Women who are unable to fully void their bladder during urination are predisposed to urinary tract infections. This study set out to determine if this same predisposition occurs in men. The investigators measured residual urine volume after spontaneous voiding in 196 men. 27% of these patients had a positive urine culture and a mean post-void residual volume of 257 milliliters (ml) compared to only 133 ml in patients with a negative urine culture. The positive predictive value for bacteriuria at a post-void residual volume of 180 ml or was 87.0% and the negative predictive value of 94.7%. This study indicates that, similar to women, men with substantial post-void residual urine volume are at high risk of bacteriuria. These patients should be monitored closely in case they require antibiotic treatment for urinary tract infection or surgery to improve bladder voiding.

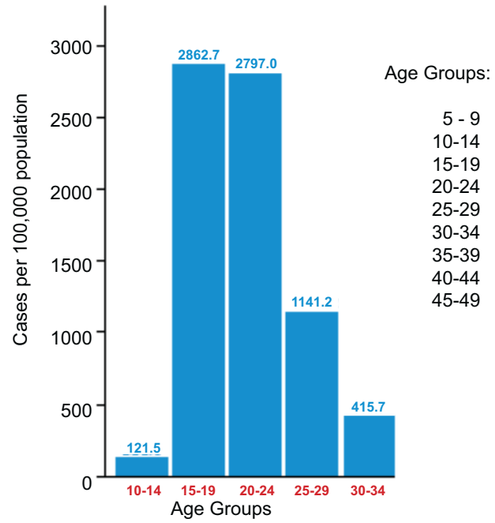
Weissenbacher T, Witkin SS, Ledger WJ, Tolbert V, Gingelmaier A, Scholz C, Weissenbacher ER, Friese K, Mylonas I. 2008. Relationship between clinical diagnosis of recurrent VVC and detection of Candida species by culture and polymerase chain reaction. *Arch Gynecol Obstet.* Published online May 28, 2008.

VVC is a common infection in women which 75% will experience once in their lifetime with 5% experiencing recurrent infections. A study was recently conducted looking at the clinical diagnosis of recurrent VVC by either PCR or traditional culture methods. Out of 104 patients, 29.8% were positive by culture compared to 42.3% by PCR. It was concluded the PCR is more sensitive and rapid than culturing in detecting Candida species in the vagina. The authors also did mention that further investigation into negative tests needs to be performed.

e-Quiz

For results to the electronic Epidemiology Quiz, please visit www.mdlab.com and click on the e-Quiz link.

1. Below is a graph detailing Chlamydia rates among Females for 2006. Place the correct age group underneath the appropriate bar.



Age Groups:

5 - 9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49

2. True or False: Nearly 90% of bladder cancers affect people over the age of 55.

3. Fill in the blank: The incidence of intrauterine growth restriction (IUGR) is estimated to be approximately ____ % of the general obstetric population.

4. The Center for Disease Control and Prevention (CDC) estimates that approximately _____ new sexually transmitted infections occur each year.

   a. 5 million
   b. 9 million
   c. 19 million
   d. 25 million

Recent Publications

Medical Diagnostic Laboratories, L.L.C.

Abstracts

Hedges SR, Smith WL, Kaunitz AM, Adelson ME, Dorak MT, Mordechai E, Trama JP. Variations in the distribution of fastidious vaginal microorganisms in a general gynecologic population. Oral Presentation at the 35th Annual Scientific Meeting of the Infectious Diseases Society for Obstetrics and Gynecology, Seattle, WA. August 14-16, 2008.

Prasad A, Mordechai E, Adelson ME, Gygax SE. Penicillin tolerance in Group B Streptococcus. To be presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy Meeting, Washington, DC. October 25-28, 2008.

Peer-Reviewed Papers

Walsh P, Overmyer CL, Pham K, Michaelson S, Gofman L, DeSalvia L, Tran T, Gonzalez D, Pusavat J, Feola M, Iacono KT, Mordechai E, Adelson ME. 2008. Comparison of respiratory virus detection rates in infants and toddlers using flocked swabs, saline aspirates and saline aspirates mixed in UTM-RT. *J Clin Microbiol*, **46(7):**2374-6.

McCool TL, Hoey JG, Montileone F, Goldenberg HB, Mordechai E, Adelson ME. 2008. Discovery and analysis of *Bartonella henselae* antigens for use in clinical serologic assays. *Diagn Microbiol Infect Dis*, **60(1)**:17-23.

Walsh P, Tran T, Kimmel L, Rosengreen M, Pham K, Feola M, Emery K, Pusavat J, Mordechai E, Adelson ME. Prevalence of *Bordetella pertussis* and *Bordetella parapertussis* in ED patients with bronciolitis. *Pediatr Emerg Care*, Accepted for publication 4/21/08.

Hilbert DW, Paulish T, Trama JP. O serotypes, phylogeny, and virulence factors of cervicovaginal and rectal *Escherichia coli* isolates. *Eur J Clin Microbiol Infect Dis,* Accepted for publication 5/23/08.

Walsh P, Kimmel L, Feola M, Pusavat J, Nguyen T, Emery K, Rosengreen M, Michaelson S, Mordechai E, Adelson ME. Prevalence of *Bordetella pertussis* and *Bordetella parapertussis* in samples submitted for RSV screening. *Pediatr Emerg Care*, Accepted for publication 5/16/08.

Gygax SE, Vermitsky JP, Chadwick SG, Self MJ, Mordechai E, Adelson ME, Trama JP. 2008 Antifungal resistance of *Candida glabrata* vaginal isolates and the development of a qRT-PCR-based azole susceptibility assay. *Antimicrob Agents Chemother*, **52(9):**3424-6.

HUMIGEN, L.L.C.

Peer-Reviewed Papers

Mancini G, Kan S, Gallagher G. A novel insertion variant of the human IL-23 receptor-α chain transcript. *Genes Immun*, Accepted for publication.

Kan S, Mancini G, Gallagher G. Identification and characterization of multiple splice forms of the human interleukin-23 receptor alpha chain in mitogen-activated leukocytes. *Genes Immun*, Accepted for publication.

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Quality Assurance Q&A

Q: 1. Why were there two gonorrhoeae tests run for my patient and what does 'Wild-type' mean?

A: Test No. 145 *Neisseria gonorrhoeae* by Real-Time PCR (Reflex to ciprofloxacin resistance by Pyrosequencing) is set up as a reflex test. If the Real-Time PCR is positive, we automatically perform an additional assay to determine an antibiotic resistance profile. We perform this additional testing via the Pyrosequencing method as a courtesy at no charge. This assay also serves as a secondary confirmation of a positive result. The purpose of this additional antibiotic resistance profile is to assist the clinician in the selection of appropriate antibiotic therapy due to the fact increasing reports of ciprofloxacin resistant strains of *N. gonorrhoeae* in the United States. Wild-type is the most common form of the organism. If the report reads 'Wild-type: Sensitive to ciprofloxacin', this indicates susceptibility to ciprofloxacin.

If you have a question you would like addressed in future issues, please email your question(s) to QAQ&A@mdlab.com