REX HEALTHCARE

# Laboratory Bulletin...

**Updates and Information from Rex Healthcare and Rex Outreach**

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## *VISA: (Hopefully not) Everywhere you want it to be.*

Over the past three decades, *Staphylococcus aureus* has shown increasing rates of resistance to the semisynthetic penicillinase-resistant antibiotics (methicillin, oxacillin, and nafcillin). This has led to increasing reliance on vancomycin for cases of methicillin-resistant *S. aureus* (MRSA). The first case of vancomycin-intermediate *S. aureus* (VISA) was reported in Japan in 1996. Since then there have been eight U.S. cases of VISA confirmed by the Centers for Disease Control and Prevention (CDC). Almost all VISA cases have been MRSA as well. In 2002, two cases of vancomycin-resistant *S. aureus* (VRSA) were reported in the United States (Michigan and Pennsylvania). The method of resistance has been found to be via the vanA gene, the same gene that has been detected in vancomycin-resistant enterococci.

As would be expected, vancomycin has been found to be ineffective in the treatment of VRSA. The CDC also reports that cases of VISA have not responded to vancomycin. Even more worrisome, some technically vancomycin-susceptible organisms with MICs of 4 ug/ml have not responded to vancomycin, most notably in patients with indwelling catheters.

In the initial reports of VISA and VRSA, there have been different classifications based on the minimum inhibitory concentration (MIC) of *S. aureus* growth on vancomycin. In the U.S. the standard definitions used by the CDC and the National Committee for Clinical Laboratory Standards (NCCLS) for laboratory classification are listed below.

> Vancomycin-susceptible *S. aureus* (VSSA): vancomycin MIC $\leq$ 4 ug/ml.
> Vancomycin-intermediate *S. aureus* (VISA): vancomycin MIC= 8-16 ug/ml.
> Vancomycin-resistant *S. aureus* (VRSA): vancomycin MIC $\geq$ 32 ug/ml.

The current methodology at Rex has been to test isolates of *S. aureus* on the Vitek 2 (bioMerieux, Hazelwood, MO), an automated system which reports MICs. Recent information from the CDC has alerted us that one of the VRSA isolates was called susceptible by some of the automated methods. To add an extra layer in detection of these organisms, the microbiology department has added a vancomycin agar screen plate on all cases of *S. aureus*. This plate contains 6 ug/ml of vancomycin, and has been found to detect cases of VISA and VRSA.

Following CDC recommendations, any *S. aureus* with an MIC to vancomycin of 4 ug/ml or greater, or growth of two colonies on a vancomycin screen plate, will be reported to Rex Infection Control and the patient's physician as a possible VISA (or VRSA depending on MIC). The organism will then be rechecked for purity, retested to verify classification as a *S. aureus* and then analyzed by a separate MIC method (Etest). If the MIC is still in the 4-16 ug/ml range, the organism will be reported as a presumptive VISA. If the MIC is >=32 ug/ml, the organism will be classified as VSRA, Infection Control and the physician will be notified, and the organism will be sent to the CDC via the NC State Public Health Laboratory.

To date we have only had one possible case of VISA/VRSA. Upon further testing, we detected contamination with another non-*S. aureus* organism with resistance to vancomycin. The *S. aureus* was confirmed to be vancomycin-susceptible. No confirmed cases of VISA/VRSA have been reported in North Carolina.
All cases of VISA and VRSA have been found to be susceptible to at least some antibiotics. In order to prevent the emergence of more antibiotic resistant organisms such as VISA/VRSA, the CDC has established the Campaign to Prevent Antimicrobial Resistance. Further information can be found in the references below.

*Vincent C. Smith, MD*

*References:*
1. Investigation and Control of Vancomycin-Intermediate and –Resistant *Staphylococcus aureus* (VISA/VRSA). CDC March 2003.
2. Surveillance for Emerging Antimicrobial Resistance Connected to Healthcare (S.E.A.R.C.H.). http://www.cdc.gov/ncidod/hip/ARESIST/SEARCH.htm.
3. VISA/VRSA- Vancomycin-Intermediate/Resistant *Staphylococcus aureus* Fact Sheet. http://www.cdc.gov/ncidod/hip/ARESIST/visa.htm.

## *Elevated AST and ALT: Prevalence and Etiology*

**Introduction:** Chronic liver disease is a major cause of morbidity and mortality in the United States. Dr. Jeanne Clark from John Hopkins University School of Medicine analyzed data on over fifteen thousand adults to uncover the prevalence and etiology of elevated aminotransferases (ALT and AST). [1] These two tests are the most commonly used indicators of liver disease. The prevalence and etiology in the general population were previously unknown. Although chronic viral infections and alcohol consumption account for much of the elevated aminotransferase and chronic liver disease, the underlying cause in many individuals is unknown despite advances in serologic testing for liver disease. Cryptogenic cirrhosis is the third to fourth most prevalent type of cirrhosis in those presenting for liver transplant and the second most prevalent type in obese patients. Other recent studies indicate that nonalcoholic fatty liver disease is the most common cause of cryptogenic cirrhosis. In Dr. Clark's study particular attention was paid to those individuals with unexplained aminotransferase elevations.

**Methods:** The data was collected from the Third National Health and Nutrition Examination Survey on adults >17 years old. An elevation was defined as any value above the normal range. Individuals were classified as having "explained aminotransferase elevation" if either the AST or ALT was elevated in the presence of hepatitis B surface antigen, hepatitis C antibody or transferrin saturation >50% (possibly representing hemochromatosis). Alcohol was considered a potential cause of elevation in women consuming a daily average of one or more drinks or men consuming a daily average of two or more drinks. Finally, individuals were classified as having "unexplained aminotransferase elevation" only if either AST or ALT were elevated in the absence of any of the previously mentioned explanatory factors.

**Results:** The team found that the prevalence of aminotransferase elevation in the United States was 8%. Aminotransferase elevation was more common in men then in women (9.3 vs. 6.6%), in Mexican American (14.9%) and non-Hispanic blacks (8.1%) compared to non-Hispanic whites (7.1%). High alcohol consumption, hepatitis B or C infection and high transferrin saturation were found in only 31% of cases. The majority of cases were "unexplained" (69%). Unexplained aminotransferase elevation was associated with higher body mass index (BMI), waist circumference, triglycerides, fasting insulin, and lower HDL cholesterol levels in both sexes. Type 2 diabetes and hypertension were associated with unexplained elevations in women only.

**Discussion:** The main strength of the study is the estimate of the prevalence of elevated ALT and AST levels (8%) in the general population. Nevertheless, there are several limitations. All of the elevated levels do not necessarily reflect disease and in fact a prior study found that over a 6-month period, elevations were persistent in only one third of cases. It is possible that some of these individuals could have less common causes of liver disease such as $\alpha_1$-antitrypsin deficiency, amyloidosis, Wilson's disease or autoimmune hepatitis. The lack of liver biopsies also precluded the ability to determine whether fibrosis or cirrhosis was present. However, even in the absence of such information, this study is important, as it documents the potential burden of liver disease in the general U.S. population. The association with obesity, high waist circumference, dyslipidemia, high insulin levels, diabetes and hypertension is consistent with other studies that found elevated AST and ALT levels in this population.

**Conclusions:** The researchers concluded, "Aminotransferase elevation was common in the United States, and the majority could not be explained by alcohol consumption, viral hepatitis or hemochromatosis". [1] Unexplained aminotransferase elevation was strongly associated with adiposity and other features of the metabolic syndrome

and thus may represent nonalcoholic fatty liver disease. It may be that successful treatment of the metabolic syndrome could decrease the incidence of cirrhosis.

*Stephen V. Chiavetta, MD*

*References:*
1. Clark JM *et al*. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 2003; 98(5): 960-7.
2. Chiavetta SV. The metabolic syndrome. *Rex Healthcare Laboratory Bulletin,* Issue 78, March 2003.

## *TFTs in Pregnancy and Childhood*

The National Academy of Clinical Biochemistry (in collaboration with a variety of other groups, including the American Association of Clinical Endocrinologists and the American Thyroid Association) recently issued new guidelines for thyroid function testing. [1,2] The recommendations centered on the improved sensitivity of current TSH assays and emphasized the key role TSH plays, both as the initial screening test for diagnosis and in the subsequent management of thyroid dysfunction. ("In general…solo TSH testing is most appropriate in an ambulatory setting and is the approach currently used by most primary care practitioners." [1]) This has been discussed previously and will not be repeated here. [3] In addition, the report presented recommendations for thyroid testing in pregnant women and suggested reference ranges for TSH and free T4 during gestation and childhood. While we have not formally adopted the latter (due to the fact that the assay manufacturer has not validated them), we report the recommendations and suggested reference ranges below to assist in patient management.

**Thyroid Testing in Pregnancy[1]**

- Obtain TSH pre-pregnancy or during 1st trimester
- Refer to Trimester Specific Reference Ranges
- If TSH is above the reference range, obtain a serum thyroperoxidase antibody level. Elevated levels suggest a risk of post-partum thyroiditis
- Follow TSH levels in each trimester to assess response to L-thyroxine therapy

**TSH and FT4 – Gestation and Childhood[1]**

| Age | TSH (mU/L) | Free T4 (ng/dL) |
|---|---|---|
| Pregnancy - 1st Trimester | 0.3-4.5 | 0.7-2.0 |
| Pregnancy – 2nd Trimester | 0.5-4.6 | 0.5-1.6 |
| Pregnancy – 3rd Trimester | 0.8-5.2 | 0.5-1.6 |
| Fetus – Midgestation | 0.7-11 | 0.15-0.34 |
| Term Infant | 1.3-19 | 0.8-1.9 |
| 3 days | 1.1-17 | 1.8-4.1 |
| 10 weeks | 0.6-10 | 0.8-1.7 |
| 14 months | 0.4-7.0 | 0.6-1.4 |
| 5 years | 0.4-6.0 | 0.8-1.7 |
| 14 years | 0.3-5.0 | 0.6-1.4 |
| Adult | 0.3-4.0 | 0.8-1.8 |

*John D. Benson, MD*

*References:*
1. Demers LM. Thyroid testing: What are the implications of the new NACB Guidelines? *Clin Lab News*. April 2003, p. 10-12.
2. Demers LM and Spencer CA. Laboratory medicine practice guidelines: Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 13(1), 2003. (http://www.nacb.org/lmpg/thyroid_lmpg_pub.stm)
3. Benson JD. TFTs for Y2K. *Rex Healthcare Laboratory Bulletin,* Issue 40, August 1999.

## *PSA for Prostate Cancer Screening*

Reproduced below (with some adaptation) is another set of recommendations courtesy of the California Permanente Medical Group regarding prostate cancer screening. The recommendations were compiled by the urologists in the group and published in a column authored by Dr. Seth Haber, *Emeritus Chief of Pathology, Kaiser Permanente Medical Center*, Santa Clara CA. [1]

- Digital rectal exam (DRE) and prostate specific antigen (PSA) measurement should be performed as part of a routine medical examination of men between 50 – 70 years of age.
- DRE and PSA testing should be offered to African American men or men with a family history of prostate cancer, and who are between 40 – 70 years old.
- PSA testing should be performed annually, with more frequent testing if results are abnormal. If the PSA is < 1 ng/mL the test frequency can be decreased.
- Routine DRE does not significantly elevate PSA. The half-life of PSA is roughly 2 days.
- Discovery of an early prostate cancer in men over 70 is unlikely to affect treatment, course or prognosis. Accordingly PSA determinations are not recommended in this age group.
- While not recommended, it may be appropriate to perform DRE and PSA testing in patients who do not fit in the above categories but who "strongly request" testing.
- Many (? too many) physicians apply PSA testing for screening in patients who do not meet the above criteria.
- Transrectal ultrasound is helpful in guiding prostate needle biopsy, but is not recommended as a screening procedure.
- Patients with either an abnormal DRE or PSA > 4.0 ng/mL should be referred to a urologist for further evaluation. Further diagnostic testing could include repeating the PSA after 6 – 12 months, transrectal ultrasound or biopsy.

*John D. Benson, MD*

*Reference:*

1. Haber SL. Innovations in Pathology: Prostate cancer screening. *CAP Today*. December 2002, p. 69.

***What's in a name? (TPFKACLS)***

The pathologists at Rex Hospital, formerly known as Comprehensive Laboratory Services, Inc., have changed their name to Rex Pathology Associates, PA. We hope that this change will enable better recognition of our identity to you, your patients and office staff.

*SVC*

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