



Saint Luke's Regional Laboratories Clinical Laboratory Letter



November 2009

More Bad Bugs

Carbapenem antibiotics are used primarily for broad-spectrum coverage and treatment of multiple-drug resistant bacteria and include imipenem, meropenem, ertapenem & doripenem. A new class of beta-lactamase enzymes that hydrolyze & inactivate the carbapenems is being detected in the United States. These carbapenemases are usually plasmid-mediated, which facilitates transfer between bacteria. In addition, these organisms have been responsible for outbreaks within healthcare facilities, primarily in the northeastern United States. Therefore, they have become a serious infection control concern.

Carbapenemases have been detected in a variety of *Enterobacteriaceae*, the bacterial family which encompasses enteric gram-negative bacilli. The most common carbapenemase to date is found in *Klebsiella pneumoniae*, and is hence referred to as KPC. Other enteric bacteria in which this type of plasmid-mediated carbapenemase has been reported include *E. coli*, *K. oxytoca*, *S. marcescens*, *E. cloacae*, *E. aerogenes*, *C. freundii*, and *Salmonella*. The unfortunate clinical significance of the carbapenemase-producing organisms is that they are usually resistant to most other anti-microbials, including all classes of beta-lactam agents, and often aminoglycosides and quinolones as well.

Saint Luke's Microbiology laboratory has instituted recent CDC & Clinical Laboratory Standards Institute (CLSI) recommendations for the detection of carbapenemases. Some gram-negative organisms producing the enzyme may fall within the susceptible range for carbapenems by automated test systems, but will exhibit an elevated MIC to carbapenems. When these organisms are also resistant to a 3rd-generation cephalosporin, such as ceftriaxone, additional testing for carbapenemase production will be performed. This confirmatory testing is called the Modified Hodge Test. Organisms tested by this method will be reported as positive or negative for carbapenemase production. All carbapenems will

be reported as resistant when an organism tests positive. No carbapenemase-producing bacteria have been isolated within Saint Luke's Health System to date.

Virus Culture Not Always Best

Virus culture is no longer the most efficient method for recovery of viruses from many specimen types, including blood and urine. The most likely virus to be isolated from these sources is Cytomegalovirus (CMV). Over the last ten years, Saint Luke's Microbiology has performed 143 viral blood cultures with only 2 specimens growing CMV. Likewise, of 267 viral urine cultures in ten years, only 4 were positive for CMV. PCR has been shown to be more sensitive for recovery of viruses from blood and urine, with a greatly improved turn-around time compared to virus culture. Effective immediately, virus culture on these two specimen sources will no longer be performed. All requests for virus culture on urine or blood will be reflexed to CMV PCR.

Discrepant Point of Care INR Results

Point of care testing on an ISTAT device has been available in the Emergency Department since February 2009. Recently, a member of the medical staff notified the laboratory about a significant discrepancy in INR results between the ISTAT and the laboratory; ISTAT INR was 1.5 and the laboratory value was 2.2. This call prompted a clinical pathologist to review 214 cases in which both ISTAT and lab INR results were available. In 198 cases (7%) both results agreed within 0.2. In 16 cases (7%) the parallel results differed by 0.3 or greater (range 0.3 - 3.0). These discrepancies occurred most commonly when the ISTAT INR was >1.5. There have only been 19 cases with an ISTAT INR >1.5, but 11 of the 19 (58%) differed by more than 0.3. In 7 of the 11 cases, the ISTAT result was higher and in the remaining 4 cases the ISTAT result was lower. This latter category is probably the most worrisome for determining which patients are candidates for TPA therapy.

The results became more discrepant the higher the INR. For example, a difference of 0.9 occurred on two occasions with an INR in the range of 1.7. In one case with an INR of 3.5, the INR differed by 2.1 and in one case with an INR of 4.9, the results differed by 3.1.

After reviewing this data, the laboratory has concluded that ISTAT INR does provide a rapid and reliable result if the INR is 1.4 or lower. However, all INR values of 1.5 or greater should be confirmed by a laboratory INR before any therapeutic decisions are made.

Minimal Change in Lipids after Acute Coronary Syndromes

The MIRACL (Myocardial Ischemia Reduction with Acute Cholesterol Lowering) trial demonstrated that early intervention with statins reduces the subsequent cardiac event rate. Other evidence has indicated that if hospitalized patients do not receive statins during their hospital stay, they are less likely to ever start taking these medications. Nationwide, less than 50% of patients have serum lipids measured within 24 hours of admission. One reason that physicians may not order lipid testing early after an acute coronary syndrome (ACS) is the long held belief that lipid measurements are unreliable during an acute event.

Recently, researchers from the University of Michigan analyzed data from the LUNAR (Limiting UNdertreatment of lipids in ACS with Rosuvastatin) trial to assess lipid changes 1 to 4 days after ACS onset (J Am Coll Cardiol 2008;51:1440-5). The goal of this prospective, multicenter, randomized, open-label, three arm study was to compare the efficacy of rosuvastatin 20 mg and 40 mg with atorvastatin 80 mg in lowering LDL cholesterol over 6 to 12 weeks of once daily therapy. Of the 507 patients available for analysis, 212 were admitted for STEMI, 176 for non-STEMI and 119 for unstable angina.

Before treatment, serum lipids were measured on days 1, 2 and 4 after onset of ACS symptoms. LDL cholesterol levels decreased from an average of 136 to 134 mg/dL during the 24 hour period immediately following admission and then increased to an average of 142 mg/dL over the subsequent 2 days. Total cholesterol followed a similar trend. These changes were not considered

to be clinically meaningful. HDL cholesterol and triglycerides exhibited minimal change during the 4 day period. The same trend was observed in the overall study population as well as in each of the three ACS subgroups.

Lipid	Day 1	Day 2	Day 4
LDL-C	136	134	142
Total-C	200	197	208
HDL-C	39	39	40
Triglycerides	183	177	177

This study suggested that in-hospital lipid determinations are reliable and can form the basis for initiating lipid-lowering therapy.

UGT1A1 Genotyping for Irinotecan

Irinotecan (Camptosar) is a chemotherapeutic drug which is primarily used to treat metastatic colorectal cancer. Irinotecan is slowly metabolized by carboxyesterases into a pharmacologically active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which is 1,000 times more potent than the parent drug. SN-38 is then conjugated by the enzyme UDP-glyucuronosyl transferase 1A1 (UGT1A1) to form an inactive metabolite, SN-38 glucuronide, which is readily excreted in bile and urine.

Irinotecan has a narrow therapeutic window, which is the difference between a therapeutic and a toxic dose. Twenty to 30% of patients who are treated with irinotecan develop severe diarrhea, neutropenia or both, primarily due to toxic levels of SN-38. Elevated SN-38 is usually caused by a polymorphism in the UGT1A1 gene that produces an enzyme variant with decreased activity. The most common allele associated with decreased enzyme activity and irinotecan toxicity is UGT1A1*28. Approximately 10 to 15% of Caucasians and African Americans are homozygous for UGT1A1*28 and these individuals have a 50% higher risk of developing severe neutropenia. Approximately 40% of patients treated with irinotecan are heterozygous for UGT1A1*28 and are also at increased risk of developing neutropenia.

Advanced knowledge of an individual's UGT1A1 genotype provides physicians with the information needed to determine which patients might benefit from a reduced dose of irinotecan.