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How will I know whether "an apple is ripe or rotten"? A new proposed composite algorithm to predict acute liver failure in patients with drug-induced liver injury

Robles-Diaz M, Lucena MI, Kaplowitz N, et al. Use of Hy's Law and a New Composite Algorithm to Predict Acute Liver Failure in Patients With Drug-Induced Liver Injury. Gastroenterology 2014; 147: 109-18.

Drug-induced liver injury (DILI) is defined as a liver injury caused by various medications, herbs, or xenobiotics, leading to highly variable liver abnormalities ranging from asymptomatic elevation of liver enzymes to acute liver failure (ALF). DILI accounts for 13% of cases of acute liver failure in the US. Antimicrobials and agents for the central nervous system are the most common causes of DILI. The diagnosis is based on exclusion (1).

Currently we do not have a good sensitive and specific biomarker to predict severity and progression of DILI. Hy's Law has been used to determine the risk of a fatal DILI since 1968. Hyman Joseph Zimmerman or "Hy" to all who knew him described Hy's Law according his original clinical observation (2). Hy's Law cases have the following three components; A) The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater AST or ALT elevation above the upper limits of normal (ULN). B) Subjects also show elevation of serum total bilirubin to >2xULN, C) Absence of initial findings of cholestasis (absence of alkaline phosphatase (ALP) activity >2xULN. D) No other reason can be found to explain the combination of increased ALT and total bilirubin levels. This definition has been used by the US Food and Drug administration over the years. In 2011, the consensus criteria adopted was ALT level ≥5xULN, ALP level x≥2xULN or ALT level ≥3xULN + total bilirubin level ≥2xULN. The ratio (R) value (ALT level x ULN / ALP level x ULN) level ≥5 was used. A case was hepatocellular when R was ≥5, cholestatic when R was ≤2, and mixed when R was between 2 and 5 (3).

In the June 2014 issue of Gastroenterology, Roblez-Diaz et al. (4) study was published to optimize the definition of Hy's Law and to develop a model for predicting ALF in patients with DILI. They collected data from 771 patients with 805 episodes of DILI. They analyzed data collected at the initial diagnosis and at the time of peak levels of ALT and total bilirubin. A total of 32 patients developed ALF with hepatic encephalopathy and coagulopathy. They compared different ways to use Hy's Law to predict which patients would develop ALF. Their ALT criteria sensitivity and specificity were 93% and 43%. The R criteria showed 83% sensitivity and 67% specificity. They also used a new ratio (nR) value with AST or ALT level (whichever was highest) x ULN / ALP level x ULN) level ≥5. (nR) criteria sensitivity and specificity were 90% and 63%, respectively. A new composite algorithm base on AST >17.3xULN, total bilirubin >6.6x ULN, and AST: ALT >1.5 identified patients who developed ALF with 80% sensitivity and 82% specificity. As a result, their (nR) criteria for Hy's Law provided the best balance of sensitivity and specificity. The new composite algorithm provided additional specificity in predicting absolute development of ALF. Female gender, high transaminases and total bilirubin levels were predictors of fulminant outcome (4).

Roblez-Diaz et al. (4) improved the definition of Hy's Law and developed a better model. They underlined the value of AST level and AST/ALT ratio to predict a fatal outcome at any time point. Although aminotransferase increase in a traditional concept does not have a prognostic value in acute liver injury. An ongoing increase in AST component exceeding ALT levels looks to be associated with severe outcome in their study.

In contrast to clinical trial DILI studies, most of the patients had advanced liver injury, as 52% required hospitalization and 66% had jaundice. Their new proposal is important as to use a new (nR) value, using either ALT or AST whichever is highest for better ALF prediction in DILI. In contrast to Hy's Law, their new composite algorithm did not show a benefit in excluding patients with ALP >2xULN.

When an apple turns mushy and buggy, it is no longer good to eat and the fruit stock should be replaced. However, we still lack of very sensitive and specific pre-

dictive biomarkers for progressive DILI. The authors' modified Hy's Law criteria with a new (nR) and composite algorithm to improve the assessment of DILI progression and severity looks better than any formula we have so far.

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