UGI Bleeding: New and Old Risk Factors

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Introduction:

Upper gastrointestinal Bleeding (UGIB) is defined as bleeding arising from a source proximal to the ligament of Treitz. In most hospital settings, 80-90% of UGIB is of a non-variceal origin, with gastric and duodenal ulcers accounting for the majority of these bleeding lesions. In the United States there are over 400,000 hospital admissions for UGIB per year. Bleeding peptic ulcers are more common among the elderly, with 68% of the patients with bleeding ulcers aged over 60 yrs. Surprisingly, the mortality from UGIB has remained steady at 5-10% for the last several decades even with the introduction of effective endoscopic techniques for hemostasis.

The most common etiology of ulcers is infection with Helicobacter pylori, causing 80% of duodenal ulcers and 50% of gastric ulcers, see Figure 1. The long term risk of a person infected with helicobacter pylori to develop an ulcer is ~15%. Aspirin and/or NSAIDs use are next most common causes of ulcers. Additional risk factors for the development of NSAID-induced ulcers are shown in Figure 2. Even low-dose aspirin use clearly increases the risk for NSAID-related ulcer complications. The combination of NSAID use and H. pylori infection has been shown to be a strong additive risk factor for ulcer complications. Eradication of H. pylori in patients at high risk for NSAID-related ulcers does reduce the risk of subsequent ulceration and a primary prevention strategy of H. pylori eradication has shown to be cost-efficient using a Markov model for patients above the age of 50 years. However, the utility of a “strategy of test and treat for H. pylori” for all persons needing long term NSAIDs is not a consensus recommendation. Additionally, H. pylori eradication is not sufficient for total prevention of all NSAID-related ulcers.

The risk for ulcers, UGIB, and even related death among the elderly on chronic NSAIDs is significant and has lead to development anti-inflammatory drugs with less GI toxicity. The selective cyclooxygenase (COX-2) inhibitors have effective anti-inflammatory properties without COX-1 inhibition of gastric cytoprotection. Unfortunately, the selective COX-2 agents have been shown to exhibit greater risk for cardiovascular events leading to removal and/or restricted use of COX-2 agents in the US market place.

Prevention of NSAID-induced ulcers is complicated by variable risk of NSAIDS (combined COX-1 and COX-2 inhibitors) and selective COX-2 drugs to cause GI or cardiovascular harm, and by cost and tolerance of co-therapies. Of importance is that naprosyn is only the NSAID that does not appear to increase the risk...
of cardiovascular events.\textsuperscript{21} When patients prescribed long term NSAIDs are at high risk for ulcer complication, then co-therapy with either a PPI or misoprostol is effective for prevention of both gastric and duodenal ulcer complications.\textsuperscript{22} Unfortunately, gastrointestinal side effects have limited the widespread use of misoprostol.\textsuperscript{23} Standard-dose histamine-2 receptor antagonists are a very attractive, cost-effective option to prevent duodenal ulcers, but have not been shown to prevent NSAID-related gastric ulcers.\textsuperscript{24,25} Lanza, F, et al, have recently developed a comprehensive guideline to help prevent NSAID GI toxicity.\textsuperscript{26} Using several key risk factors they identify the patients at highest risk and suggest options for primary prevention, \textit{Figures 3 and 4.}

Confounding the recent ACG Guidelines for prevention of NSAID Induced Ulcers is the emergence of literature suggesting that Selective SEROTONIN Reuptake Inhibitors (SSRIs) are a significant, independent risk factor for UGIB.\textsuperscript{26,27,28,29} Inhibition of serotonin transporters found on platelets is thought to lead to depletion cytosolic serotonin and loss of platelet cohesive properties, \textit{Figures 5 and 6.} The nested, retrospective study by Targownik identified a modest risk for UGIB among patients receiving SSRIs that was significantly reduced by co-administration of PPI, but did not seem to be a significant additive risk factor for NSAID-related UGIB.\textsuperscript{28} However, an extensive population-based case-control study from Denmark suggested that SSRIs should be prescribed with caution for patients with high risk for UGIB and that risk was increased by co-administration of aspirin and NSAIDs, \textit{Figure 7.}\textsuperscript{27}

\textbf{CONCLUSION:}

Risk for UGIB is clearly associated with aspirin (all-doses), NSAIDs, SSRIs and infection with H. pylori. The presence of additional risk factors, see \textit{Figure 2}, further increase the risk for UGIB and should remind clinicians to consider institution of co-therapy to mitigate this risk, \textit{Figure 4.} Although the recent ACG Guidelines on prevention of NSAID-related ulcer did not include SSRIs as an independent risk factor in UGIB, we would suggest that the patients taking SSRIs should prompt clinical concern and justify further prospective study of how to most safely employ these very effective drugs among patients at risk for ulcer and UGIB.

\textbf{References:}


4. Gralnek IM, Barkun AN, and Bardou M. \textit{Management of Acute Bleeding}


