

# CLINICAL UPDATE

Updates on study findings in essential therapeutic areas of gastroenterology and hepatology

## Selective Intestinal Decontamination in Portal Hypertension

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**N**orfloxacin, a broad-spectrum antibiotic of the fluoroquinolone class, produces selective intestinal decontamination (SID) by inhibiting aerobic gram-negative intestinal flora while preserving the anaerobic flora of the gastrointestinal tract. The importance of this process in patients with cirrhosis is underpinned not only by a well-documented reduction in infective complications, but also by reports of improvement in regional and systemic hemodynamics with norfloxacin therapy. These outcomes are achieved by reducing bacterial translocation and endotoxemia. Many of the hemodynamic changes associated with this therapy are thought to be mediated by modulation of nitric oxide (NO) production, although the precise mechanism by which this occurs is still the subject of active research.

### Background

The migration of bacteria, known as bacterial translocation, and other antigens across the gut wall is thought to be important to the healthy development of the immune system. This process, when regulated by a healthy host, is known as “oral tolerance.”<sup>1</sup> It has been hypothesized that dysregulation of this system, as can occur in the elderly, immunosuppressed, or critically ill, can result in sepsis and systemic inflammatory response syndromes.<sup>2,3</sup> In cirrhosis, the prevalence of bacterial translocation is related to the severity of the liver disease as determined by the Child-Pugh grade<sup>4</sup> as well as the degree of hepatic inflammation.<sup>5</sup> This phenomenon results in a number of frequently encountered complications of cirrhosis and portal hypertension including spontaneous bacterial peritonitis (SBP) and hyperdynamic circulation in cirrhosis.<sup>6,7</sup> It seems intuitive therefore that SID could be effective in managing these complications, and indeed the use of norfloxacin has been shown to be effective as both

### Keywords

Portal hypertension, bacterial translocation, nitric oxide, selective intestinal decontamination.

primary<sup>8</sup> and secondary prophylaxis<sup>9</sup> of SBP, although there are conflicting reports regarding the effect of SID on the bacterial translocation rate in murine models.<sup>10,11</sup> Despite its effectiveness in preventing infective complications of cirrhosis, a role for SID in modulating cirrhotic hemodynamics and portal pressure and its influence upon portal hypertension remain to be determined.

### Selective Intestinal Decontamination and the Hyperdynamic Circulation in Cirrhosis

The hyperdynamic circulation in cirrhosis is characterized by a high cardiac output, low systemic vascular resistance, and a low mean arterial pressure.<sup>12</sup> Chin-Dusting and associates<sup>13</sup> demonstrated a reduction in basal forearm blood flow with a 4-week course of norfloxacin 400 mg twice daily in cirrhotic patients, as well as increased response in patients treated with N<sup>G</sup>-monomethyl-L-arginine, indicating up-regulation of nitric oxide synthase (NOS) in this population. In addition to showing that norfloxacin can improve hemodynamics in patients with cirrhosis (including improving mean arterial pressure and increasing peripheral vascular resistance), our group has shown that SID results in a reduction in serum endotoxin and cardiac output<sup>14</sup>—indicative of reversal of the hyperdynamic circulation in cirrhosis. In this patient population, a trend (although not statistically significant) toward reduction in hepatic venous pressure gradient was seen, possibly contributing toward the reduction in variceal rebleeding risk<sup>15</sup> and increased patient survival<sup>16</sup> previously reported with antibiotic therapy. In addition, in ascitic cirrhotic patients with significant increases in lipopolysaccharide binding protein (LBP), a marker of immune and hemodynamic derangement, norfloxacin was shown to ameliorate these abnormalities, supporting the hypothesis that enteric bacteria or their products are a primary cause of the process.<sup>15</sup> These findings suggest that SID may be most effective in the subset of cirrhosis patients with elevated LBP, a case well-argued in the commentary by Zucker.<sup>17</sup>

Although the ability of SID to alter regional and systemic hemodynamics appears well established, the mechanism underlying these changes and the relative influence of NO derived from endothelial and/or inducible NOS (eNOS, iNOS) remain controversial. Earlier studies demonstrated increased hepatic macrophage production of tumor necrosis factor alpha (TNF $\alpha$ ) with endotoxin stimulation<sup>18</sup> and a significantly elevated inflammatory cytokine profile in cirrhosis.<sup>19</sup> Shortly thereafter it was postulated that inflammatory cytokines such as TNF $\alpha$  play a role in the development of the hyperdynamic circulatory syndrome in cirrhosis.<sup>20,21</sup> Indeed, a recent study<sup>22</sup> demonstrating increased serum TNF $\alpha$  in ascitic cirrhotic patients with high LBP confirmed that norfloxacin treat-

ment normalized serum TNF $\alpha$  levels. The significance of this finding is that TNF $\alpha$  increases in proportion to the degree of bacterial translocation. Additionally TNF $\alpha$  has been reported to stimulate NO production through both iNOS<sup>23</sup> and eNOS—the latter via stimulating tetrahydrobiopterin (BH<sub>4</sub>)<sup>24</sup> likely through GTP-cyclohydrolase-1, a key enzyme in BH<sub>4</sub> synthesis.<sup>25</sup> This provides a mechanism by which bacterial translocation and LBP can initiate an inflammatory/cytokine cascade resulting in overproduction of NO. The potential importance of inflammatory mediators such as TNF $\alpha$  and interleukin (IL)-6 in determining patient outcomes with chronic liver disease is evidenced by the independent association of soluble TNF $\alpha$  receptor 1 with patient mortality.<sup>26,27</sup> Furthermore, anti-TNF $\alpha$  therapy administered to a cirrhotic rat model significantly reduced NO and hepatic NOS activity by 20–25% and 15–30%, respectively,<sup>28</sup> and partially reversed the cirrhosis-induced increase in stroke volume, cardiac output, and portal pressure.

In order to examine the relative importance of iNOS and eNOS in mediating vascular tone and the hyperdynamic circulatory syndrome in portal hypertension, iNOS and eNOS knockout mice models have been studied.<sup>29</sup> In iNOS, but not eNOS, knockout portal hypertensive mice, reduced potency of  $\alpha$ -adrenoceptor agonists in the mesenteric artery have been observed, indicating involvement of iNOS in the normal vascular response to portal hypertension. While it has traditionally been thought that iNOS was the enzyme responsible for NO production with exposure endotoxins and cytokines, recent evidence has indicated an important contribution of eNOS to total NO production with lipopolysaccharide exposure<sup>30</sup> by ensuring efficient arterial expression of iNOS. The pathway involved is thought to be eNOS-derived NO-dependent activation of nuclear factor kappa B (NF- $\kappa$ B), which in turn activates transcription of the gene encoding iNOS. The role of NF- $\kappa$ B in this process is interesting considering its ability to both activate and be activated by TNF $\alpha$ .<sup>31</sup>

Although the role of enteric-derived vascular and inflammatory cytokines facilitating and maintaining the hyperdynamic circulation in cirrhosis is interesting in elucidating the pathophysiology of this disease process, a translation of this into a demonstrable clinical benefit for patient outcomes remains to be evidenced. Thus far only mild reductions in portal pressure have been reported with SID,<sup>14,32</sup> despite reductions in systemic blood pressure, cardiac output, LBP, TNF $\alpha$ , and IL-6. Possible explanations for this limitation are that portal hypertension has both fixed and dynamic components with the reversible, dynamic aspects only accounting for up to 40% of the intrahepatic resistance. It may also be that SID is particularly effective only in patients who demonstrate elevated

inflammatory markers.<sup>32</sup> Finally, it cannot be discounted that this disease process results from a complex interplay of many other vasoactive substances including endothelin,<sup>34</sup> norepinephrine, angiotensin II, and possibly urotensin II, and it would be naive to expect that a silver bullet exists in SID. Having said that, it is the authors' opinion that SID may well prove to be useful adjunct therapy in a disease where current clinical management is severely limited.

## The Future

A well-tolerated and noninvasive method of manipulating portal pressure would be an extremely useful clinical agent. The use of traditional vasoactive agents such as  $\beta$ -blockers and nitrates is limited by patient tolerability and their efficacy is only apparent in a minority of patients.<sup>35</sup> SID through the use of fluoroquinolone antibiotics is an attractive option. These medications are tolerated well,<sup>36</sup> and side effects necessitating withdrawal are uncommon. There are, however, serious concerns regarding the development of quinolone-resistant bacterial strains in those taking prophylactic norfloxacin therapy,<sup>37</sup> leading to suggestions that the use of SID should either be restricted to highly selected patients<sup>38</sup> or that alternative manipulation of the gut flora is indicated. Toward this end, alternative interventions demonstrated to reduce or alter intestinal bacterial overgrowth such as oral bile acids,<sup>39</sup> lactulose,<sup>40</sup> or probiotics<sup>6</sup> may prove worthy of further exploration in this context. In addition, further studies are needed to increase our understanding of how SID improves patient mortality, variceal rebleeding, and systemic hemodynamics. How much of this improvement is related to altered expression of inflammatory mediators, endothelin, or NO<sup>41</sup> remains to be determined. Also of interest will be future studies to determine the effect of SID upon other vascular mediators in portal hypertension and cirrhosis such as urotensin II<sup>42</sup> and anandamide and cannabinoid receptors<sup>43</sup> particularly in the context of adjunct or synergistic therapy.

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