Broad-spectrum antibiotics alter the microbiome, increase intestinal fxr, and decrease hepatic steatosis in zebrafish short bowel syndrome.

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Public Summary:
Short bowel syndrome (SBS) is associated with changes in the intestinal microbiome and marked local and systemic inflammation. There is also a late complication of SBS, intestinal failure associated liver disease (IFALD) in which hepatic steatosis progresses to cirrhosis. Most patients with SBS arrive at massive intestinal resection after a contaminating intraabdominal catastrophe and have a history of exposure to broad-spectrum antibiotics. We therefore investigated whether the administration of broad-spectrum antibiotics in conjunction with SBS in zebrafish (ZF) would replicate these systemic effects observed in humans to identify potentially druggable targets to aid in the management of SBS and resulting IFALD. In zebrafish with SBS, broad-spectrum antibiotics altered the microbiome, decreased inflammation, and reduced the development of hepatic steatosis. After two weeks of broad-spectrum antibiotics, these fish exhibited decreased alpha diversity, with less variation in microbial community composition between SBS and sham fish. Additionally, administration of broad-spectrum antibiotics was associated with decreased expression of intestinal toll-like receptor 4 (tlr4), increased expression of the intestinal gene encoding the Farnesoid X receptor (fxr), decreased expression of downstream hepatic cyp7a1, and decreased development of hepatic steatosis. SBS in zebrafish reproducibly results in increased epithelial surface area as occurs in human patients who demonstrate intestinal adaptation, but antibiotic administration in zebrafish with SBS reduced these gains with increased cell death in the intervillus pocket that contains stem/progenitor cells. These alternate states in SBS zebrafish might direct the development of future human therapies.

NEW & NOTEWORTHY In a zebrafish model that replicates a common clinical scenario, systemic effects of the administration of broad-spectrum antibiotics in a zebrafish model of SBS identified two alternate states that led to the establishment of fat accumulation in the liver or its absence. Broad-spectrum antibiotics given to zebrafish with SBS over 2 wk altered the intestinal microbiome, decreased intestinal and hepatic inflammation, and decreased hepatic steatosis.

Scientific Abstract:
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