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Side Effects and Complications of Proton Pump Inhibitors: A Pediatric Perspective

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Proton pump inhibitors (PPIs) are a class of acid suppression medications that block gastric parietal cell acid production by irreversibly inhibiting the luminal H^+/K^+ adenylpyrophosphatase (ATPase).[1] PPIs are used for a variety of conditions involving inflammation of the upper gastrointestinal tract in children, including gastroesophageal reflux disease, erosive esophagitis, gastric and duodenal ulcers, eosinophilic esophagitis, and *Helicobacter pylori* gastritis.[2-4] Alternative uses for PPIs are increasing, and include treatment of various pediatric respiratory symptoms, sleep disorders, and even irritability or excessive crying in infants.[5-8] Prescriptions for PPIs have increased greatly among pediatric and infant populations in recent years. A retrospective study of insurance claims for PPI prescriptions in Belgian children found that the prescribed monthly volume of PPIs increased from 3472 daily defined doses per month in January 1997, to 103 926 daily defined doses per month in June 2009.[9] An American retrospective study of 2469 infants less than 12 months old found a 4-fold increase in PPI use from 2000 to 2003.[10] Although prescriptions and alternative uses for PPIs are increasing, evidence of their efficacy has lagged. Based on the increasing rate of PPI prescriptions, some clinicians have concluded that PPIs are overprescribed in otherwise healthy pediatric patients for cases of over-medicalized physiological infant reflux or functional gastrointestinal disorders.[11]

Although PPIs were initially considered benign, potential safety concerns have arisen.[12] PPI-induced changes are believed to include dysbiosis, bacteria functional and morphological changes, local mucosal secretory alterations, anti-inflammatory effects, and other potential alterations with significant implications toward health maintenance and disease. Additional consideration is needed for young infant and premature populations that may have increased side effects attributable to frequent indiscriminate use of acid suppression therapy, despite potential drug metabolism alterations because of liver immaturity. An article by Rosen et al quantified gastric, lung, and oropharyngeal microbiome alterations associated with PPI use in pediatric patients.[13] Their findings regarding the association between PPIs and alterations to the microbiome provide a starting point from which to explore unanticipated medication side effects and serves as a springboard for review and consideration of well established, newly recognized, and potential side effects associated with PPI use in pediatric populations. In this review, we will consider PPI safety, including infectious diseases, malabsorption, immunological changes, gastrointestinal and cardiovascular risks, and potential effects on the microbiome.

ADMA	Asymmetrical dimethylarginine
AIN	Acute interstitial nephritis
ATPase	Adenylpyrophosphatase
CAP	Community-acquired pneumonia
CDI	*Clostridium difficile* infections
FAP	Familial adenomatous polyposis
FGP	Fundic gland polyp
HAP	Hospital-acquired pneumonia
PPI	Proton pump inhibitor
RAHS	Rebound acid hypersecretion
SBBO	Small bowel bacterial overgrowth
SBP	Spontaneous bacterial peritonitis
VAP	Ventilator-associated pneumonia

Infectious Disease

It is increasingly recognized that PPI use is associated with an elevated risk of infectious diseases. There is growing evidence to explain this association, including decreased gastric acid barrier, altered microbiome and local bacterial overgrowth, altered barrier function of aerodigestive mucosa, attenuation of the immune response, and direct effects on bacteria and decreased effectiveness of antibiotics.

PPI-induced hypochloridia is known to alter the gastrointestinal bacterial motif, allowing certain normally absent or depleted pathogenic microorganisms to survive and proliferate.[14] Small bowel bacterial overgrowth (SBBO) is a clinical manifestation of PPI-induced changes in bacteria quantity. A meta-analysis of 11 adult studies (n = 3134) assessing the risk of SBBO in PPI users found a pooled OR of 2.28 (95% CI, 1.23-4.21) among those treated.[15] When considering only those patients diagnosed with SBBO through duodenal or jejunal aspirate cultures, the risk was even higher (OR, 7.59; 95% CI, 1.81-31.89). A prospective cohort study of 40 children evaluated via glucose breath hydrogen test found that SBBO occurred in 22.5% of children treated with PPIs longer than 3 months.[16] Apart from symptoms related directly to increased quantities of bacteria, the altered microbial profile and quantity is theorized to cause an increased infectious risk.[15,17] A local inflammatory response, which could occur in the setting of a PPI-facilitated invasive

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microorganism infection, may create a microenvironment that favors additional pathogenic microbial colonization, potentially enhancing the risk of disease.[18] In addition to bacteria growth and variety, a retrospective case-control study of 102 patients with cirrhosis suggested that PPIs might facilitate bacterial translocation across gastrointestinal epithelium.[19] Beyond the gastrointestinal system, there is growing evidence that PPI use alters the microbiome and possibly the secretory and antimicrobial properties of other mucosal surfaces.[20,21]

Several in vitro studies provide evidence that PPIs can suppress immune cell surveillance, activation, migration, and function.[22] Additionally, their effects are thought to extend to endothelial and epithelial cell signaling.[23] Incubation with physiological levels of omeprazole caused irreversibly reduced neutrophil chemotaxis and inhibited oxygen-derived free-radical generation and degranulation.[24] PPIs have been shown in vitro to inhibit human neutrophil H^+/K^+ ATPase activity, leading to inhibition of cell migration and intracellular calcium influxes.[25] Additionally, PPIs may suppress polymorphonuclear leukocyte chemotaxis and cytokine production, possibly through the suppression of mitogen-activated protein kinase signal transduction.[26]

PPIs may also affect microbial enzymatic activity and growth and directly alter antibiotic effectiveness.[27,28] The direct effect of PPIs on bacterial proteins or molecular pumps may have implications for the effectiveness of antibiotics that rely on functional bacterial physiology for their uptake or mechanism of action. Previous in vitro studies of PPI exposure in bacterial species that possess multidrug efflux pumps suggest that PPIs do not significantly degrade the effectiveness of tetracycline, ceftazidime, levofloxacin, meropenem, streptomycin, or gentamicin.[29,30] Importantly, the in vitro addition of omeprazole, lansoprazole, and pantoprazole to bacterial isolates in the presence of the antibiotic tigecycline was found to increase the mean inhibitory concentration by 4- to more than 128-fold in a concentration-dependent manner.[31] This study provides evidence that PPIs may play a role in bacterial tigecycline resistance or inhibited effectiveness, even at low concentrations. The potential in vivo effects of PPIs on tigecycline and other antibiotics effectiveness have not been evaluated to date.

Gastrointestinal Infections

Two systematic reviews of general population studies found that PPIs appear to increase susceptibility to multiple enteropathogens, including nontyphoid *Salmonella* species, *Campylobacter jejuni*, and *Clostridium difficile* infections (CDI).[32,33] Several studies have specifically evaluated CDI risk in pediatric patients on PPIs, but currently there are no published large population studies assessing the risk of other pediatric infectious enteritides.[34-36]

The association between PPIs and CDI is well established in adults with a large population meta-analysis.[37] This association recently has been confirmed in children. Turco et al performed a retrospective case-control study of 68 children and found that those exposed to PPI therapy were at higher odds for developing CDI (OR, 4.5; 95% CI, 1.4-14.4).[34] A retrospective self-controlled study of 2437 children with CDI confirmed that infection was more likely to occur during periods when they were prescribed PPIs (relative incidence, 2.36; 95% CI, 2.22-2.52).[35] A retrospective case-control study of 138 pediatric patients with CDI using acid-suppression therapy found that patients on PPIs had an increased risk of infection (aOR, 1.8; 95% CI, 1.0-3.1), with near parity to the risk associated with antibiotic use (aOR, 1.7; 95% CI, 1.1-2.7).[36] Critics have suggested previously that study populations taking PPIs are more ill, but a prospective cohort study of 186 otherwise healthy children found a significant increase in acute gastroenteritis among those treated with PPIs.[38]

Beyond the established risk of adult and pediatric CDI and adult *Salmonella* and *Campylobacter* infections, acid suppressive therapy poses a theoretical threat of gastrointestinal infections with other pathogens. In vivo and in vitro studies have shown alterations of environmental pH can influence the growth of other clinically important microorganisms, including invasive strains of *Escherichia coli, Vibrio cholerae*, and *Listeria*.[33] The potential risk of parasitic infections, including *Giardia* and *Strongyloides*, and viral infections, has been suggested previously by small studies and case reports, but has not been studied extensively.[39]

Lower Respiratory Tract Infections

Refluxing of gastric contents still occurs in the presence of PPI-induced hypochloridia. Microorganisms, along with gastric contents, are refluxed proximally to the hypopharynx and can be aspirated into the lower airways. Aspiration events increase the risk of community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP). The alterations of gastric microorganism contents in the setting of PPIs are a topic of potentially great clinical concern.[13] Microaspiration is common in patients with compromised oropharyngeal protective reflexes. Laryngomalacia, which can cause increased risk of microaspiration, is relatively common in young infants. Recurrent aspiration of pneumoniagenic microorganisms, with greater organism quantities attributable to acid suppression and anti-inflammatory or mucosal alterations, may provide potential mechanisms for increased risk of lower respiratory tract infections in patients on PPIs.

Meta-analyses of 31 studies found an increased risk of CAP associated with PPI use, with an aOR of 1.27 (95% CI, 1.11-1.46).[40] The previously mentioned prospective cohort study of 186 otherwise healthy children aged 4-36 months also confirmed a significant increase in CAP after initiation of PPI therapy.[38] HAP, which is defined as pneumonias acquired ≥48 hours after hospital admission, was associated previously with PPI, but not histamine-2 receptor antagonist use, in a large adult prospective cohort study (OR 1.3; 95% CI, 1.1-1.4).[41] Currently, there are no large population studies assessing the risk of HAP in hospitalized pediatric patients on short- or long-term PPI therapy. VAP, a subset of HAP that occurs ≥48 hours after endotracheal intubation

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