Prevalence of Hypomagnesemia Associated with Proton Pump Inhibitor Therapy in Children with Cystic Fibrosis (HAPPIT Study)

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Background

- Up to 80% of cystic fibrosis (CF) patients have gastroesophageal reflux (GER), with proton pump inhibitors (PPI) considered treatment of choice for moderate to severe GER
- Since 2006, > 30 case reports published implicating hypomagnesemia as a rare potentially serious side effect of PPI
- Potential complications of hypomagnesemia include:
  - Other electrolyte abnormalities, muscle cramps, tetany, abnormal cardiac rhythm, and seizures
- Concomitant proarrhythmic medications commonly used in CF patients: macrolides, prokinetic agents, azole antifungals
- CF team in British Columbia Children's Hospital (BCCH) aims to address uncertainties around whether children with CF receiving PPI should undergo routine serum magnesium (Mg) monitoring

Objectives

Primary: Prevalence of hypomagnesemia in CF patients receiving PPI compared to CF patients not receiving PPI

Secondary: Severity of the hypomagnesemia
- Interventions initiated and/or clinical complications

Methods

- **Design:** Retrospective cohort study approved by institutional research ethics board
- **Inclusion criteria for cohort group:**
  - Diagnosis of CF, received medical care at BCCH CF Clinic, received a PPI between Jan 2008 - July 2012, ≥ 1 serum Mg measured at BCCH
- **Same inclusion criteria for control group, except:**
  - No previous documented use of PPIs
- **Exclusion Criteria:**
  - Serum Mg excluded if drawn when patient receiving oral/IV diuretics or IV amphotericin
- **Statistical Analysis:** Descriptive statistics. Prevalence of hypomagnesemia by risk ratios (RR) at 95% confidence interval
- **Sample size:** 42 cohorts and 84 controls to provide 80% power to detect a RR of 2 for hypomagnesemia

Definitions

Hypomagnesemia:
- <0.66 mmol/L in patients <2 mos
- <0.78 mmol/L in patients between 2 mos to 12 yrs
- <0.74 mmol/L in patients greater than 12 yrs

Proton pump inhibitor (PPI):
- Omeprazole, pantoprazole, esomeprazole, rabeprazole, dexlansoprazole

Results

Table 1: Patient Characteristics

	Cohort (n=42)	Control (n=57)
Patient Age, years (median (range))	8.3 (0.2-17)	8.0 (0.1-18)
Male (%)	57	47
Number of serum Mg per year per patient (median (range))	1.8 (0.4-22.2)	1.0 (0.04-4.6)
Hospitalized when serum Mg drawn (%)	60	36
Aminoglycoside use when serum Mg drawn (%)	28	20
Pancreatic Insufficiency (%)	93	81
Glucose Intolerance (%)	21	12
History of Bowel Resection (%)	7	2
Celiac Disease (%)	2	4

Figure 1: Patients with ≥ 1 Hypomagnesemia Events

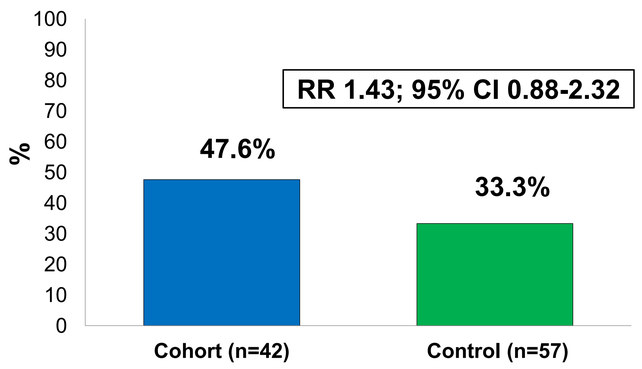

Figure 2: Box Plot of Serum Magnesium Levels

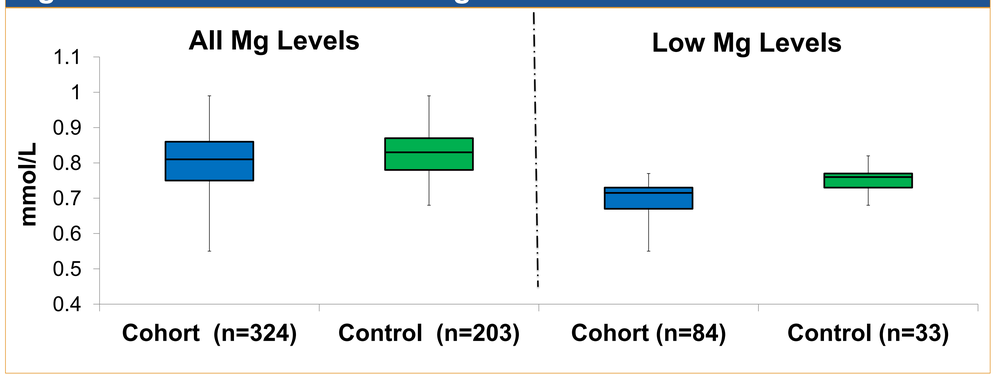

Table 2: Patients with Hypomagnesemia Events

	Hypomagnesemia Cohorts (n=20)	Hypomagnesemia Controls (n=19)
Adverse events potentially attributed to hypomagnesemia (n)	1	0
Mg interventions initiated (n)	2	0
Chronic Mg supplements initiated (n)	1	1
Adverse events + chronic Mg supplementation initiated (n)	1	1

Adverse events reported at the time of low magnesium level:
- **Cohort:** 1 QTc prolongation, 1 dysesthesia/paresthesia
- **Control:** 1 cardiac arrhythmia
- All patients were receiving other medications concomitantly that were felt to be responsible for the adverse events
- None resulted in discontinuation of the PPI

Limitations

- Retrospective review design
- Unable to meet calculated sample size → Risk of type Type II error
- Confounders leading to hypomagnesemia are prevalent in the CF population
- Baseline characteristics indicate more severe CF disease in the cohort group

Conclusions

- This is the first study to our knowledge to explore hypomagnesemia associated with PPIs in children with or without CF
- No statistically significant difference in the prevalence of hypomagnesemia between the cohort and control group, although sample size not achieved
- The risk factors and clinical significance of hypomagnesemia associated with PPI in children with CF are unclear
- Routine monitoring of serum Mg in children with CF receiving PPI may not be needed at this time

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