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Limited Value of Magnesium Levels in ICU Patients

Magnesium (Mg) is an important co-factor in several intracellular biochemical reactions. Almost 99% of the body's Mg stores are intracellular. Extracellular Mg is predominantly protein bound, although a free ionized form exists – and is believed to correlate with intracellular ionized magnesium. Gastrointestinal absorption and renal excretion regulate total body Mg stores. Traditionally laboratories have measured "total" serum Mg, although instruments are now commercially available permitting measurement of ionized magnesium (iMg). In addition, methods for measurement of intracellular Mg have been developed. Total Mg levels may be helpful in reflecting acute changes in Mg intake and/or excretion, but correlate poorly with total body magnesium stores.

Several papers have been written in the past discussing the prevalence of hypomagnesemia in critically ill patients (20-65%) and the association of this finding with increased mortality. [1] Two recent papers suggest that measurement of total, ionized or even intracellular Mg levels offers little useful information in the diagnosis of functional hypomagnesemia. Furthermore, the finding of hypomagnesemia did not correlate with patient outcome. Hébert *et al* reported a double-blind randomized trial of 44 consecutive critically ill patients admitted to a tertiary care ICU. [1] A variety of baseline laboratory measurements (including total and ionized Mg levels were obtained.) The study group underwent a magnesium-loading test (7.5 g [30 mmol] of $MgSO_4$ intravenously qd x 3 days) while the control group received saline. Magnesium excretion was measured by 3 consecutive 24-hr. urine collections. The mean control magnesium excretion (4.8 mmol/day) was adopted as the basal excretion rate for both groups. Within the magnesium loading group, magnesium retainers (excreted < 70% of magnesium load + basal excretion [30 + 4.8]) were identified as functionally Mg deficient. Those who excreted > 70% (of the 30 mmol load and 4.8 basal excretion rate) were considered to have adequate Mg stores. The Mg deficient patients all excreted > 70% prior to the end of the study, indicating replenishment of Mg stores by the loading therapy. In this relatively small study, the prevalence of Mg deficiency as defined here was 63%. However, serum Mg and iMg levels did not correlate with functional Mg deficiency. The sensitivities of Mg and iMg levels were both 16.7%, while the positive predictive values were both 66.6%. While the association of hypomagnesemia with mortality was not explicitly evaluated in this study, the authors concluded, "…the lack of correlation between serum magnesium assays and the magnesium-loading test suggests that hypomagnesemia is a marker of disease severity rather than directly contributing to excess mortality." [1]

A different type of study reached a similar conclusion. Huijgen *et al* studied 115 consecutively admitted ICU patients in 2 tertiary care centers who were expected to stay more than 2 days.[2] The only patients excluded were those being treated with Mg. Baseline measurements included serum total Mg, iMg, intracellular RBC Mg and intracellular mononuclear WBC Mg. An APACHE II score was obtained within 24 hr. of admission and the 1-month mortality rate was determined. In this patient population, 51.3% had a serum Mg level below the reference range. In 71% of the hypomagnesemic patients, the iMg was normal. No patient had an intracellular Mg

level below the reference range. There was no correlation between any measured Mg value and clinical outcome. The authors suggested that hypomagnesemia may be an epiphenomenon, perhaps related to low albumin levels. They suggested that neither serum nor intracellular Mg levels reliably reflect true functional Mg status and "routine" use of these tests is not recommended. They suggest that Mg-loading test is the only reliable test to confirm hypomagnesemia, but caution that no large scale tests on ICU type patients have been reported.

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1. Hébert P *et al*. Functional magnesium deficiency in critically ill patients identified using a magnesium-loading test. *Crit Care Med* 25:749-755, 1997.

2. Huijgen HJ *et al*. Magnesium levels in critically ill patients. What should we measure? *Am J Clin Pathol* 114:688-695, 2000.

Pneumocystis

An immunocompromised patient, who acquires respiratory symptoms with fever and an abnormal chest x-ray should be evaluated for Pneumocystosis. However, these same symptoms may be produced by a lengthy list of infectious and noninfectious agents, thus the diagnosis of *Pneumocystis carinii* pneumonia has relied on cyto- or histopathologic demonstration of the organisms in sputum, bronchoalveolar lavage fluid, bronchoscopic or open lung biopsies. A variety of stains have been used to identify Pneumocystis carinii in such specimens: Methenamine silver, toluidine blue and calcafluor white stain the wall of the organism, whereas Wright-Giemsa (or diff-Quick®) allow visualization of all *Pneumocystis carinii* developmental stages as well as the host cells. The Papaniclaou stain used by all cytopathology laboratories provides an expedient way to screen for the characteristic foamy exudate surrounding this organism in infected patients. However, all stains are less useful in immunocompromised cancer patients, in which the organisms are embedded in hyaline membrane like material that adheres to the alveolar septal walls, and does not appear in induced sputum samples as the foamy exudate seen in AIDS patients. Immunohistochemical stains with monoclonal antibodies have shown a greater degree of sensitivity than histologic stains, but are balanced by an increased cost per test. DNA amplification by polymerase chain reaction has shown increased sensitivity without a significant decrement in specificity, when carefully controlled conditions for testing have been maintained. A diagnostic dilemma develops when the organism cannot be detected by other measures and the polymerase chain reaction test is positive. This result may indicate a false positive PCR, or a true positive reaction due to a subclinical infection or a patient recently treated with anti-pneumocystis medications.

Specimen collection is an essential component for the diagnosis of *Pneumocystis carinii* pneumonia. **The more invasive the procedure, the better the diagnostic yield.** *Pneumocystis carinii* is only rarely identified in expectorated sputum, but induced sputum has emerged as the simplest noninvasive technique used to screen for *Pneumocystis* pneumonia. The diagnostic yield from this type of sample has been reported as ranging from 40-90% at different medical centers. Fiberoptic bronchoscopy is the most commonly performed invasive procedure and may result in a diagnostic yield in greater than 90% of cases. Bronchoalveolar lavage offers greater sensitivity than bronchial washings and brushings, and lower morbidity than bronchial biopsies. Open lung biopsy has been considered the reference standard for diagnosing

Pneumocystis carinii pneumonia, but is less frequently performed than in the past due to the effectiveness of less invasive techniques.

At Rex, we have relied on the methenamine silver stain to diagnose *Pneumocystis carinii* pneumonia in both cytologic and histologic specimens because of familiarity with the interpretation of this stain, ease of performance, and the ability to detect fungal organisma, in addition to *Pneumocysti*s. In the past, many sputum samples collected for *Pneumocystis* screening were designated "inadequate", since they did not reflect lower respiratory tree cellular elements in the associated Papanicolou stained smears. However, this situation does not currently appear to be the case. Reviewing 18 months of data on sputum samples collected for *Pneumocystis* screening, only 6 out of 49 (12%) cases were interpreted as "inadequate", while 2 of 43 (5%) were positive for *Pneumocystis carinii*. We are currently evaluating immunoflourescent monoclonal antibody kits to determine if this test can increase sensitivity in our laboratory. The sputum gram stain will be used as the quality check for specimen adequacy and inadequate specimens will be rejected for immunoflourescent testing.

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References:

1. Montaner JS, Zala C. The role of the laboratory in the diagnosis and management of AIDS-related *Pneumocystis Carinii* pneumonia. In: Sattler, FR, Walzer PD, eds, *Pneumocystis Carinii*. London: Bailliere Tindall; 1995: p 471-485.

2. Kroe DM, Kirsch CM, Jensen WA. Diagnostic strategies for *Pneumocystis Carinii* pneumonia. *Semin Respir Infect*. 1997; 12: 70-78.

Gut Check #2 – Reactive Gastropathy

"Gastric antral bx. – r/o Helicobacter" We receive many gastric antral biopsies in patients suspected of having *H. pylori* associated gastritis. Many of these have the characteristic "chronic active gastritis" appearance of increased plasma cells, lymphocytes, esosinophils and neutrophils in the lamina propria with the associated gull-shaped bacteria present along the surface mucosa or within superficial gastric pits. Some biopsies are essentially normal, apart from mild superficial vascular congestion, lacking inflammation or bacteria. Occasional biopsies have a third pattern that has been referred to as **reactive gastropathy**. Histologic features may include some or all of the following: mucosal erosions, foveolar gland hyperplasia, regenerative epithelial changes, and an "empty, pink" lamina propria **devoid** of inflammatory cells. This lack of inflammation explains why the term "gastropathy" is favored over "gastritis". This histologic pattern is not specific and may be observed in the setting of microvascular ischemia due to non-steroidal anti-inflammatory drugs (NSAIDS), chemotherapy, radiation therapy, or portal hypertension. Direct irritation (e.g. bile reflux or alcohol) may also produce a similar appearance. The endoscopic appearance is likewise, nonspecific – patchy erythema, mucosal erosions or small punctuate ulcers. In cases where regenerative hyperplasia is pronounced, polypoid mucosal elevations indistinguishable from true gastric polyps can occur. The endoscopic and histologic appearances are nonspecific AND the histologic changes can be varied and, at times, quite subtle. As a result, the diagnosis can be missed if the endoscopist and pathologist don't consider carefully the clinical history – in addition to the endoscopic and microscopic findings. *"Second verse, same as the first…"*

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1. Emory TS et al. *Atlas of Gastrointestinal Endoscopy and Endoscopic Biopsies*. AFIP, Washington, DC, 2000, p. 103.

2. Herman's Hermits. "I'm Henry VIII I Am". *Herman's Hermits On Tour*. July 1965. (Legend has it Peter Noone improvised this lyric during one take and it was left in the final master.)

Data Mining in the Laboratory

In the near future, a project will begin in the Laboratory to promote data mining in Anatomic Pathology and Clinical Microbiology. We anticipate completion in four to five months, prior implementation of a new Anatomic Pathology Information System (CoPath).

In Clinical Microbiology, the new software will act as an umbrella over the microbiology section of our laboratory information system to collate data generated by this system. We are currently able to perform only simple searches and anticipate this new system will provide a way to perform complex searches of the database to identify trends within the hospital. For example, we would increase our capability of monitoring bloodstream or other types of infection by patient location, physician, specimen source or specific types of isolates.

In Anatomic Pathology, we will begin with an institutional review of our data regarding breast, lung, prostate and colon cancers. Upon completion of this phase of the project, we will create an expanded database with two other private pathology practices (Anderson, SC and Knoxville, TN) within a network of pathologists (Pathology Service Associates). Privacy protected data will be sent to a central server to develop a "best practice" scenario for the above mentioned cancer types.

We are excited about the impact that this project will have in both the Clinical Microbiology and Anatomic Pathology. I would like to personally acknowledge the work and effort demonstrated by the following individuals at Rex Kimberly Guy (Administration); David Rowley, Andy Gilbert , Diana Skrutskie and Vineeta Khemani (Information Technology); and Sharon Logue and Timothy Carter,MD (Laboratory). I also appreciate the support of the Cancer Center Grant Funding Committee (Vicki Byler, Peter Hoffman, MD and Mark Yoffe, MD). Thank you for giving us the opportunity to develop this project for our patients.

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