
The MAP Gap

Bridging The Space Between The Science And You

TheCrohnsInfection.org Quarterly Newsletter

October 2016

Site News

Welcome! As we begin the last quarter of the year, we look forward to a period of transition for The Crohn's Infection. We are in the midst of reworking the site to make it more user friendly, and will have some **BIG** news by the end of the year. Over the summer, our doctors and researchers were busy attending conferences and seeing patients, but they still found time to send us some excellent articles to keep our readers up to date on the latest happenings in the field. If you haven't had a chance, check them out on the [Presenter Blog](#). As always, we welcome comments and suggestions on what you would like to see on the site in the future.

We added a few pages on [Traditional Crohn's Medications](#), including prednisone, 6-MP and AZA. Looking ahead, we'll continue to report on any new Crohn's and mycobacteria research, and will begin a new series shortly. You can find real time information on site happenings by joining our private [Facebook Group!](#) ❖

INSIDE THIS ISSUE

1 Site News

1-4 Research Corner

3 Other News

1 Just for Fun

Research Corner

Below we have summarized some recent mycobacterial research articles. While we've written the content in an attempt to make it accessible to everyone, we've also provided links if you'd like to view the source and read the full article/abstract. While this is not an exhaustive list, we thought these articles were the most pertinent to the focus of the site this quarter.

Dysbiosis of the Fecal Microbiota in Cattle Infected with *Mycobacterium avium* subsp. *paratuberculosis*. (August 2016)

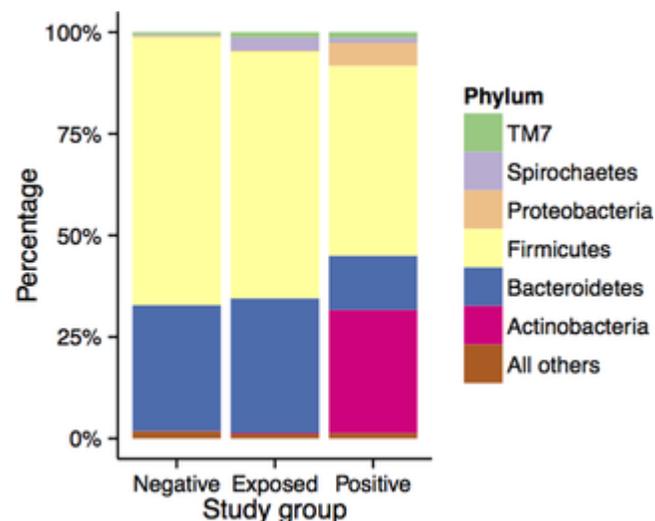
While dysbiosis of the microbiome has been demonstrated in Crohn's disease patients, this study is the first to look at dysbiosis in cattle infected with MAP vs. healthy controls. The bacterial communities from the fecal samples of 20 MAP infected cows, 25 of their herdmates and 25 non-herd MAP negative cows were analyzed. In the MAP positive group, the *Actinobacteria* class was highly abundant compared to the other two groups. The *Bacteroidetes* and *Firmicutes* groups decreased in the cows with MAP vs. the other two groups, where they made up 95% of the bacterial population. Additionally, there were bacterial strains that were found in the MAP infected

Just for Fun

Take pred they said,
You'll be fine they said...



group that were absent in the other two groups. The presence of the *Anthrobacter* genus in the MAP infected group was of interest since it may have a synergistic interaction with MAP to produce disease, but more research is necessary. This shift from bacterial with anti-inflammatory properties found in healthy controls to bacteria with pro-inflammatory properties in MAP infected cattle is similar to what is seen in humans with Crohn's disease.



[Fecteau M-E, et al. PLoS ONE 11\(8\):e0160353. doi:10.1371/journal.pone.0160353](https://doi.org/10.1371/journal.pone.0160353) ❖

Cognitive Impairment in Crohn's Disease is Associated with Systemic Inflammation, Symptom Burden and Sleep Disturbance. (August 2016)

Crohn's disease patients often complain of cognitive dysfunction, which is often ignored by health care providers. The researchers in this study administered the industry standard Subtle Cognitive Impairment Test (SCIT) to 49 patients with Crohn's disease and 31 healthy controls. Not only did the Crohn's disease patients have higher depression scores, they had poorer sleep quality scores, despite sleeping for a longer duration than healthy controls. Response times were also significantly slower for Crohn's patients. Interestingly, clinical measures of inflammation such as CRP level and increased abdominal pain correlated significantly with slower response times. The researchers compared the degree of cognitive impairment in Crohn's patients to greater than the impairment found in healthy controls who have a blood alcohol concentration of .05g/100ml (which is over the legal driving limit in Australia and most of Europe.) These findings support the anecdotal observations that Crohn's

patients have more difficulty with concentration, clouded thought and memory lapses than healthy controls.

[Langenberg, D. et al, United European Gastroenterology Journal 2050640616663397](https://doi.org/10.20506/40616663397) ❖

Temporary and Intrinsic Factors of Rifampicin Tolerance in Mycobacteria. (June 2016)

By studying *Mycobacterium smegmatis*, researchers were able to show that when mycobacterium grow and divide, they do not divide symmetrically. Because of this asymmetry, certain cells are more resistant to rifampicin, a first line tuberculosis antibiotic. The cells that were smaller at birth or at the beginning or end of their cell division cycle were more likely to be killed by rifampicin. However, the larger, longer cells with mature growth poles in the middle of a division cycle were more resistant to rifampicin.

[Richardson, K et al, Proc Natl Acad Sci USA;113\(29\):8302-7.](https://doi.org/10.1073/pnas.1513291113) ❖

Humoral Response Against Host-Mimetic Homologous Epitopes of *Mycobacterium avium* subsp. *paratuberculosis* in Japanese Multiple Sclerosis Patients. (June 2016)

Both the Epstein-Barr virus (EBV) and MAP are thought to be potential pathogenic triggers in the onset of multiple sclerosis, and it has been hypothesized that pathogens such as MAP and EBV could act synergistically in genetically susceptible patients to cause disease. The researchers found that one MAP protein was highly reactive, and found in 30% of the 50 MS patients tested. When compared to the MS Map studies done by the Italian group, the researchers here noted that the antibody response to MAP may be altered between MS patients of different ethnic backgrounds. Also of note: MAP antibodies were just as prevalent in the group experiencing their first demyelinating episode as in the group with MS. Since there is currently no test to diagnose early MS, these results could be of clinical importance for future diagnostics.

[Cossu, Davide et al, Sci Rep. 2016; 6: 29227](https://doi.org/10.1038/srep29227) ❖

Bacteriome and Mycobiome Interactions Underscore the Microbial Dysbiosis in Familial Crohn's Disease. (Sept. 2016)

The gut bacteria of 9 family clusters containing Crohn's patients were analyzed via fecal samples and compared to

the gut bacteria of 4 healthy family clusters. This study attempted to reduce the environmental and genetic differences between patients by looking at family units. Specifically, the researchers looked at the bacterial species (bacteriome) and the fungal communities (mycobiome). The researchers found that the Crohn's patients and their relatives had a more diverse bacteriome but a less diverse mycobiome while the opposite was found for health controls. In Crohn's patients the harmful bacterial species *S. marcescens* and *E. coli*, and the fungus *Candida tropicalis*, were more prevalent while helpful bacterial strains were lower than in the healthy controls. When these three pathogenic species combined, the biofilm they produced together was significantly greater than each species alone, and the species were about to communicate in the biofilm.

[Hoarau G, mBio 7\(5\):e01250-16. doi:10.1128/mBio.01250-16.](https://doi.org/10.1128/mBio.01250-16) ❖

Combining HLA-DRB1-DQB1 and Mycobacterium Avium Subspecies Paratuberculosis (MAP) antibodies in Sardinian multiple sclerosis patients: associated or independent risk factors? (August 2016)

Sardinians have a different genetic predisposition to multiple sclerosis than other populations. Here, researchers analyzed the human leukocyte antigen (HLA) variations of 531 Sardinian MS patients. HLA is the region of DNA responsible for regulating immune system. Certain versions of HLA are either protective of or predisposing to MS. Here, the researchers looked for MAP antibodies and whether the MS patient had a genetic predisposition to MS. While there was no association between the presence of MAP antibodies and a predisposition to MS, there was a significantly lower presence of MAP antibodies in MS patients who had at least one the protective HLA gene. A protective HLA type may protect against MAP and MS.

[Frau J, et al. BMC Neurology. 2016;16\(1\):148. doi:10.1186/s12883-016-0669-1.](https://doi.org/10.1186/s12883-016-0669-1) ❖

Other News

The Crohn's Infection would like to extend a huge **CONGRATULATIONS** to Prof. Thomas Borody for his recently published [DSc](#) thesis which chronicles his 30 years of research, beginning with *H. pylori*, detailing the MAP research in Crohn's disease, and finishing with his research into fecal matter transplants. The full thesis can be viewed [here](#). The Crohn's Infection will summarize this thesis in an exclusive article shortly, so sign up for our mailing list to get it as soon as it's released! Thank you to Prof. Borody for his immense 30 year contribution to gastroenterology research.

News from **RedHill Biopharma** about the progress of [RHB-104](#) in both Crohn's disease and multiple sclerosis: The estimated primary completion date has been changed to September 2017, with study completion estimated to be April 2018. The reason for this shift, as detailed in a [RedHill press release](#), was to complete full enrollment and to review "a possible amendment to the Phase III MAP US study protocol intended to further enhance the overall robustness of the study, provide a more precise assessment of RHB-104's treatment effect, collect additional endoscopic mucosal healing data, further evaluate the Crohn's disease population enrolled and address retention and early terminations." RedHill remains blinded to the ongoing results.

RedHill has also received a European patent for the use of RHB-104 in multiple sclerosis, and [announced the last patient visit](#) in their Stage IIa multiple sclerosis trial. 18 patients were enrolled in this stage of the trial, and final results are expected in the last quarter of 2016. ❖

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Serum BAFF levels, Methyprednisolone therapy, Epstein-Barr Virus and Mycobacterium avium subsp. paratuberculosis infection in Multiple Sclerosis patients. (July 2016)

Elevated B lymphocyte activating factor (BAFF) has been found in MS patients and it plays a role in the maintenance of inflammation and has been indicated in the strength of antibody response to infectious agents. This study looked at BAFF levels and the presence of MAP antibodies, and found that lower BAFF levels were associated with higher MAP antibody response rates. This supports the hypotheses that higher BAFF levels could be associated with more stable disease.

[Mameli G, et al. Scientific Reports. 2016;6:29268. doi: 10.1038/srep29268.](https://doi.org/10.1038/srep29268) ❖

Soluble BAFF Level Is Not Correlated to Mycobacterium avium Subspecies Paratuberculosis Antibodies and Increases After Interferon-β Therapy in Multiple Sclerosis Patients. (Sept. 2016)

This study looked at B lymphocyte activating factor (BAFF) levels in MS patients before and after interferon-β therapy and measured the MAP antibody response to see if it was related to increased BAFF levels. While the researchers found that interferon-β therapy increased BAFF levels, there was no change in the MAP antibody levels. Therefore, interferon-β therapy does not alter the immune response to MAP in MS patients.

[Mameli G, et al. J Mol Neurosci. 60\(1\):91-3. doi: 10.1007/s12031-016-0787-7.](https://doi.org/10.1007/s12031-016-0787-7) ❖

Development of vaccines to Mycobacterium avium subsp. paratuberculosis infection. (July 2016)

Currently, while there are commercially available vaccines against MAP for cattle none are fully effective, although there are many researchers currently interested developing new vaccines for MAP. The authors of this article recap the history and current status of a development of a vaccine for cattle against MAP. The three types of vaccines discussed are (1) whole-cell, (2) subunit and (3) DNA vaccines. Going forward, the focus should be on creating

vaccines that can induce both adaptive and innate immunity.

[Park H-T et al, Clinical and Experimental Vaccine Research. 2016;5\(2\):108-116. doi:10.7774/cevr.2016.5.2.108.](https://doi.org/10.1007/s12031-016-0787-7) ❖

Detection of Mycobacterium avium subsp. paratuberculosis in Iranian patients with type 1 diabetes mellitus by PCR and ELISA. (August 2016)

29 T1D patients and 29 healthy controls provided blood samples to be tested for MAP antibodies and DNA. **The IS900 series of MAP was found in slightly over 50% of T1D patients, but was absent in all of the healthy controls.** Anti-MAP antibodies were found in 31% of T1D patients but were found in only one healthy control. However, the anti-MAP humeral immune response did not match the presence of MAP DNA. The researchers conclude that the T1D patients had been exposed to MAP, which may be considered a trigger of T1D.

[Hesam Shariati, S. et al. The Journal Of Infection In Developing Countries, 10\(08\), 857-862. doi:10.3855/jdc.7473.](https://doi.org/10.3855/jdc.7473) ❖

Inflammatory Bowel Disease Incidence is on the Continuous Rise Among All Paediatric Patients Except for the Very Young: A Nationwide Registry-based Study on 28-Year Follow-up. (August 2016)

Researchers studied all pediatric IBD cases (less than age 20) diagnosed between 1987-2014 in Finland, which was a total of 5,415 patients. Between 1987-1990, 7 of 100,000 children had IBD. However, that rate increased for the years of 2011-2014 as 23 of 100,000 children had IBD. Looking for rates of increase, they found that the highest increase in cases was for ulcerative colitis cases in adolescents ages 16-19. The rate of change was unchanged in patients under 10.

[Virta, LJ et al. J Crohns Colitis. pii: jjw148.](https://doi.org/10.1007/s12031-016-0787-7) ❖