The MAP Gap

Bridging The Space Between The Science And You

Human Paratuberculosis Foundation Quarterly Newsletter January 2021

Human Para News

We hope this edition of our quarterly newsletter finds you safe and healthy as we head into 2021. While 2020 was a challenging year, Human Para has been blessed by amazing volunteers and a supportive community which allowed us to continue MAP research projects.

Thank you for supporting our Giving Tuesday fundraiser. We raised **$4,048.25** for MAP research!

The initial portion of our **MAP/Crohn's Testing Study** was published in *Microorganisms* in December and individual participant results were mailed over the summer. The remaining WGS portion on the 40 selected MAP isolates has been put on hold due to COVID, but will be reported when available.

The **pediatric MAP testing pilot study** has also been completed. Results will be released to our community shortly. Our **third MAP study** with Johns Hopkins investigating Antibiotic Susceptibility of Different MAP Strains will begin in January 2021.

If you haven't visited us recently, we invite you to check out **HumanPara.org**. There are many excellent resources for patients and doctors, and we are constantly adding updated articles and features! You can also find real time information on our updated **Facebook page**❖

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Research Corner

Below please find the abstracts for the most relevant research publications on MAP and mycobacteria, including hyperlinks to the full article. While this is not an exhaustive list, we thought these articles were the most relevant to our community this quarter.

Presence of Infection by *Mycobacterium avium* subsp. *paratuberculosis* in the Blood of Patients with Crohn's Disease and Control Subjects Shown by Multiple Laboratory Culture and Antibody Methods. (Dec. 2020)

Mycobacterium avium subspecies *paratuberculosis* (MAP) has long been suspected to be involved in the etiology of Crohn's disease (CD). An obligate intracellular pathogen, MAP persists and influences host macrophages. The primary goals of this study were to test new rapid culture methods for MAP in human subjects and to assess the degree of viable culturable MAP bacteremia in CD patients compared to controls. A secondary goal was to compare the efficacy of three culture methods plus a phage assay and four antibody assays performed in separate laboratories, to detect MAP from the parallel samples. Culture and serological MAP testing was performed blind on whole blood samples obtained from 201 subjects including 61 CD patients (two of the patients with CD had

concurrent ulcerative colitis (UC)) and 140 non-CD controls (14 patients in this group had UC only). Viable MAP bacteremia was detected in a significant number of study subjects across all groups. This included Pozzato culture (124/201 or 62% of all subjects, 35/61 or 57% of CD patients), Phage assay (113/201 or 56% of all subjects, 28/61 or 46% of CD patients), TiKa culture (64/201 or 32% of all subjects, 22/61 or 36% of CD patients) and MGIT culture (36/201 or 18% of all subjects, 15/61 or 25% of CD patients). A link between MAP detection and CD was observed with MGIT culture and one of the antibody methods (Hsp65) confirming previous studies. Other detection methods showed no association between any of the groups tested. Nine subjects with a positive Phage assay (4/9) or MAP culture (5/9) were again positive with the Phage assay one year later. This study highlights viable MAP bacteremia is widespread in the study population including CD patients, those with other autoimmune conditions and asymptomatic healthy subjects.

Kuenstner, J.T.; Potula, R.; Bull, T.J.; Grant, I.R.; Foddai, A.; Naser, S.A.; Bach, H.; Zhang, P.; Yu, D.; Lu, X.; Shafran, I. Microorganisms 2020, 8, 2054..❖

MiR-146a *rs2910164 G > C* polymorphism modulates Notch-1/IL-6 signaling during infection: a possible risk factor for Crohn's disease. (October 2020)

Background

MiR-146a, an effector mediator, targets Notch-1 and regulates the innate and adaptive immune systems response. Recently, we reported that Notch-1 signaling plays a key role in macrophage polarization and response during infection. We employed *Mycobacterium avium paratuberculosis* (MAP) infection in Crohn's disease (CD) as a model to demonstrate the role of Notch-1/IL-6 signaling on MCL-1 based apoptosis and intracellular MAP infection and persistence. This study was designed to investigate the impact of polymorphisms in miR146a on the immune response and infection in our MAP-CD model.

Methods

We determined the incidence of miR-146a *rs2910164 G > C* in 42 blood samples from clinical CD patients and controls. We also measured the effect of rs2910164 on expression of Notch-1 and IL-6, and plasma IL-6 protein levels in our study group. Finally, we analyzed the blood samples for MAP DNA and studied any correlation with miR-146a polymorphism. Samples were analyzed for statistical significance using unpaired tow-tailed t-test, unpaired two-tailed z-score and odds ratio. $P < 0.05$ considered significant.

Results

MiR-146a *rs2910164 GC* was detected at a higher incidence in CD (52.6%) compared to healthy controls (21.7%) *rs2910164 GC* Heterozygous polymorphism upregulated Notch-1 and IL-6, by 0.9 and 1.7-fold, respectively. As expected, MAP infection was detected more in CD samples (63%) compared to healthy controls (9%). Surprisingly, MAP infection was detected at a higher rate in samples with *rs2910164 GC* (67%) compared to samples with normal genotype (33%).

Conclusions

The data clearly associates miR-146a *rs2910164 GC* with an overactive immune response and increases the risk to acquire infection. The study is even more relevant now in our efforts to understand susceptibility to SARS-CoV-2 infection and the development of COVID-19. This study suggests that genetic variations among COVID-19 patients may predict who is at a higher risk of acquiring infection, developing exacerbating symptoms, and possibly death. A high scale study with more clinical samples from different disease groups is planned.

Keewan, E., Naser, S.A. Gut Pathog 12, 48 (2020).❖

Rifabutin-Loaded Nanostructured Lipid Carriers as a Tool in Oral Anti-Mycobacterial Treatment of Crohn's Disease. (Oct. 2020)

Oral anti-mycobacterial treatment of Crohn's disease (CD) is limited by the low aqueous solubility of drugs, along with the altered gut conditions of patients, making uncommon their clinical use. Hence, the aim of the present work is focused on the in vitro evaluation of rifabutin (RFB)-loaded Nanostructured lipid carriers (NLC), in order to solve limitations associated to this therapeutic approach. RFB-loaded NLC were prepared by hot homogenization and characterized in terms of size, polydispersity, surface charge, morphology, thermal stability, and drug payload and release. Permeability across Caco-2 cell monolayers and cytotoxicity and uptake in human macrophages was also determined. NLC obtained were nano-sized, monodisperse, negatively charged, and spheroidal-shaped, showing a suitable drug payload and thermal stability. Furthermore, the permeability profile, macrophage uptake and selective intracellular release of RFB-loaded NLC, guarantee an effective drug dose administration to cells. Outcomes suggest that rifabutin-loaded NLC constitute a promising strategy to improve oral anti-mycobacterial therapy in Crohn's disease.

Rouco H, et al. Nanomaterials (Basel). 2020 Oct 27;10 (11):2138.

Mechanisms of Antibiotic Tolerance in *Mycobacterium avium* Complex: Lessons From Related Mycobacteria. (Sept. 2020)

Mycobacterium avium complex (MAC) species are the most commonly isolated nontuberculous mycobacteria to cause pulmonary infections worldwide. The lengthy and complicated therapy required to cure lung disease due to MAC is at least in part due to the phenomenon of antibiotic tolerance. In this review, we will define antibiotic tolerance and contrast it with persistence and antibiotic resistance. We will discuss physiologically relevant stress conditions that induce altered metabolism and antibiotic tolerance in mycobacteria. Next, we will review general molecular mechanisms underlying bacterial antibiotic tolerance, particularly those described for MAC and related mycobacteria, including *Mycobacterium tuberculosis*, with a focus on genes containing significant sequence homology in MAC. An improved understanding of antibiotic tolerance mechanisms can lay the foundation for novel approaches to target antibiotic-tolerant mycobacteria, with the goal of shortening the duration of curative treatment and improving survival in patients with MAC.
Parker H, et al. Front Microbiol. 2020;11:573983.❖

Putting Crohn's on the MAP: Five Common Questions on the Contribution of Mycobacterium avium subspecies paratuberculosis to the Pathophysiology of Crohn's Disease. (Oct. 2020)
For decades, Mycobacterium avium subspecies paratuberculosis (MAP) has been linked to the pathogenesis of Crohn's disease. Despite many investigations and research efforts, there remains no clear unifying explanation of its pathogenicity to humans. Proponents argue Crohn's disease shares many identical features with a granulomatous infection in ruminants termed Johne's disease and similarities with ileo-cecal tuberculosis. Both are caused by species within the Mycobacterium genus. Sceptics assert that since MAP is found in individuals diagnosed with Crohn's disease as well as in healthy population controls, any association with CD is coincidental. This view is supported by the uncertain response of patients to antimicrobial therapy. This report aims to address the controversial aspects of this proposition with information and knowledge gathered from several disciplines, including microbiology and veterinary medicine. The authors hope that this discussion will stimulate further research aimed at confirming or refuting the contribution of MAP to the pathogenesis of Crohn's disease and ultimately lead to advanced targeted clinical therapies.
Agrawal G, Aitken J, Hamblin H, Collins M, Borody TJ. Dig Dis Sci. 2020 Oct 22:1–11.❖

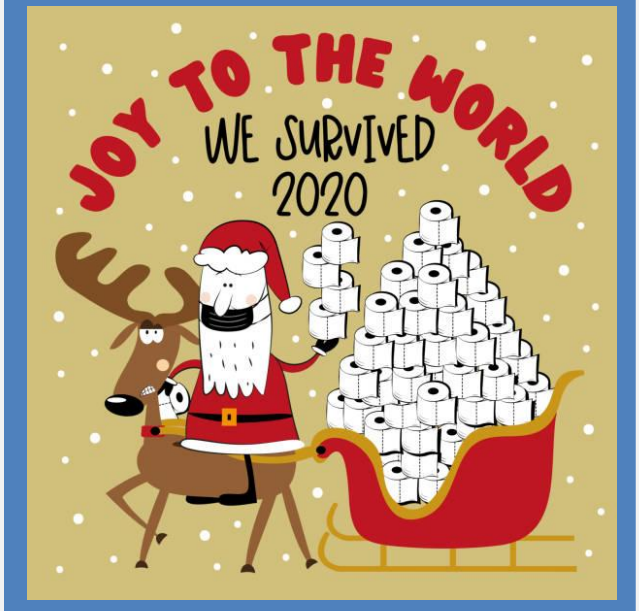
Other News

Ever wanted to know more about MAP? Dr. Marcel Behr and company has recently published a 2nd edition of the comprehensive *Paratuberculosis: Organism, Disease, Control*. This 438 page resource focuses on MAP in a veterinary context, but also addresses the link to Crohn's and human health implications.

The **15th Annual International Colloquium for Paratuberculosis**, slated to be held in 2020, was postponed to June 13-16, 2022 in Dublin. More details on this biennial event, sponsored by the veterinary-focused International Association for Paratuberculosis, to follow.

In case you missed it... A new MAP research study begins in January 2021! Human Para will partner with Johns Hopkins Medicine and Otakaro Pathways to answer the question of the susceptibility of animal and human MAP strains to antibiotic combinations, with a focus on long term safety. Read more about this new research study here! ❖

Just for Fun



Paratuberculosis: A Potential Zoonosis and a Neglected Disease in Africa (July 2020)

The *Mycobacterium avium* subspecies *paratuberculosis* (MAP) is the causative agent of paratuberculosis, which is an economically important disease of ruminants. The zoonotic role of MAP in Crohn's disease and, to a lesser extent, in ulcerative colitis, the two major forms of idiopathic inflammatory bowel disease (IIBD), has been debated for decades and evidence continues to mount in support of that hypothesis. The aim of this paper is to present a review of the current information on paratuberculosis in animals and the two major forms of IIBD in Africa. The occurrence, epidemiology, economic significance and "control of MAP and its involvement IIBD in Africa" are discussed. Although the occurrence of MAP is worldwide and has been documented in several African countries, the epidemiology and socioeconomic impacts remain undetermined and limited research information is available from the continent. At present, there are still significant knowledge gaps in all these areas as far as Africa is concerned. Due to the limited research on paratuberculosis in Africa, in spite of growing global concerns, it may rightfully be considered a neglected tropical disease with a potentially zoonotic role.
Okuni, J.B. et al. Microorganisms 2020, 8, 1007.❖

Genotypic analysis of nontuberculous mycobacteria isolated from raw milk and human cases in Wisconsin. (Jan. 2021)

Nontuberculous mycobacteria (NTM) compose a group of mycobacteria that do not belong to the *Mycobacterium tuberculosis* complex group. They are frequently isolated from environmental samples such as water, soil, and, to a lesser extent, food samples. Isolates of NTM represent a major health threat to humans worldwide, especially those who have asthma or are immunocompromised. Human disease is acquired from environmental exposures and through consumption of NTM-contaminated food. The most common clinical manifestation of NTM disease in human is lung disease, but lymphatic, skin and soft tissue, and disseminated disease are also important. The main objective of the current study was to profile the farm-level contamination of cow milk with NTM by examining milk filters and bulk tank milk samples. Five different NTM species were isolated in one dairy herd in Wisconsin, with confirmed 16S rRNA genotypes including *Mycobacterium fortuitum*, *Mycobacterium avium* ssp. *hominissuis*, *Mycobacterium abscessus*, *Mycobacterium simiae*, and *Mycobacterium avium* ssp. *paratuberculosis* (*Mycobacterium paratuberculosis*). In tank milk samples, *M. fortuitum* was the predominant species in 48% of the samples, whereas *M. chelonae/abscessus* and *M. fortuitum* were the only 2 species obtained from 77 and 23% of the examined filters, respectively. Surprisingly, *M. avium* ssp. *hominissuis*, *M. paratuberculosis*, and *M. simiae* were isolated from 16.7, 10.4, and 4% of the examined milk samples, respectively, but not from milk filters. Interestingly, NTM isolates from human clinical cases in Wisconsin clustered very closely with those from milk samples. These findings suggest that the problem of NTM contamination is underestimated in dairy herds and could contribute to human infections with NTM. Overall, the study validates the use of bulk tank samples rather than milk filters to assess contamination of milk with NTM. Nontuberculous mycobacteria represent one type of pathogens that extensively contaminate raw milk at the farm level. The significance of our research is in evaluating the existence of NTM at the farm level and identifying a simple approach to examine the potential milk contamination with NTM members using tank milk or milk filters from dairy operations. In addition, we attempted to examine the potential link between NTM isolates found in the farm to those circulating in humans in Wisconsin.
Ali ZI et al. J Dairy Sci. 2021 Jan;104(1):211-220.❖

Nicotine Modulates MyD88-Dependent Signaling Pathway in Macrophages during Mycobacterial Infection. (Nov. 2020)

Recently, we reported that cigarette smoking, and especially nicotine, increases susceptibility to mycobacterial infection and exacerbates inflammation in patients with Crohn's disease (CD). The macrophagic response to *Mycobacterium avium* subspecies *paratuberculosis* (MAP) in CD and *Mycobacteria tuberculosis* (MTB) continues to be under investigation. The role of toll-like-receptors (TLRs) and cytoplasmic adaptor protein (MyD88) in proinflammatory response during Mycobacterial infection has been suggested. However, the mechanism of how nicotine modulates macrophage response during infection in CD and exacerbates inflammatory response remain unclear. In this study, we elucidated the mechanistic role of nicotine in modulating MyD88-dependent/TLR pathway signaling in a macrophage system during mycobacterial infection. The data demonstrated that MAP infection in THP-1 derived macrophages was mediated through TLR2 and MyD88 leading to increase in *IL-8* in expression and production. On the other hand, LPS-representing, Gram-negative bacteria mediated macrophage response through TLR4. Blocking TLR2 and TLR4 with antagonists voided the effect of MAP, and LPS, respectively in macrophages and reversed response with decrease in expression of *iNOS*, *TNF-a* and *IL-8*. Interestingly, nicotine in infected macrophages significantly (1) downregulated TLR2 and

TLR4 expression, (2) activated MyD88, (3) increased M1/M2 ratio, and (4) increased expression and secretion of proinflammatory cytokines especially *IL-8*, as seen in CD smokers. We also discovered that blocking macrophages during MAP infection with MyD88 antagonist significantly decreased response which illustrates the key role for MyD88 during infection. Surprisingly, dual treatment of MAP-infected macrophages with MyD88 antagonist and nicotine absolutely impaired immune response and decreased MAP viability, which clearly validate the inflammatory role of nicotine in macrophages through TLR2/MyD88 pathway during infection. This is the first report to describe the mechanism by which nicotine modulates TLR2/MyDD88 and exacerbates inflammation in CD smokers associated with infection.
AlQasrawi, D et al. Microorganisms 2020, 8, 1804.❖

Anti-MAP Triple Therapy Supports Immunomodulatory Therapeutic Response in Crohn's Disease through Downregulation of NF-ϰB Activation in the Absence of MAP Detection. (Nov. 2020)

We previously reported that the triple antibiotic formulation, known as anti-MAP therapy, exhibits unique synergistic antimicrobial activity and should be effective for treatment of Crohn's disease (CD) associated with *Mycobacterium avium* subspecies *paratuberculosis* (MAP). The absence of MAP detection in some CD cases may be linked to poor diagnostics or lack of association with the disease. To understand the therapeutic response of some CD patients to anti-MAP therapy in absence of MAP detection, we investigated the immunomodulatory potency of anti-MAP therapy and its major ingredients, clarithromycin (CLA) and rifabutin (RIF), in THP-1, Caco-2, and Jurkat T-cells. Anti-MAP formulation at 2.0 µg/mL decreased MAP viability in macrophages by 18-fold over 72 h. Additionally, M1/M2 macrophage polarization ratio was reduced by 6.7-fold, and expression and protein levels of TNF-α and IL-6 were reduced by 2.9-fold, whereas IL-10 increased by 5.0-fold in these cells. Mechanistically, the effect of anti-MAP formulation on NF-ϰB p65 activation was dose-dependent and decreased to 13.4% at 2.0 µg/mL. Most importantly, anti-MAP therapy also reversed pro-inflammatory response in lipopolysaccharide (LPS)-induced macrophages, which shows that the anti-inflammatory effect of the treatment is not just due to a decrease in MAP viability. To study the anti-cytotoxic effects of anti-MAP therapy in Caco-2 monolayers infected with MAP or treated with dextran sodium sulfate (DSS), we showed a 45% decrease in lactate dehydrogenase (LDH) activity and an 84% increase in glutathione (GSH) activity, which supports anti-apoptotic activity of the drug. In Jurkat T-cells, anti-MAP therapy decreased T-cell proliferation by 4.8-fold following treatment with phytohemagglutinin (PHA) and by 2.9-fold with MAP purified protein derivative (PPD). Overall, the data demonstrate that anti-MAP therapy plays a significant role in modulating and eliciting a protective immune response in macrophages, endothelial cells, and T lymphocytes, even in absence of infection. This may explain the therapeutic response of some CD patients to treatment, even in absence of MAP detection, infection, or total eradication. The study supports anti-MAP therapy as an alternate treatment option in CD patients, especially in absence of reliable MAP diagnostics.
Qasem A, et al. Biomedicines. 2020 Nov 18;8(11):513.❖

Mycobacterium avium Subspecies *paratuberculosis* Infection in Zoo Animals: A Review of Susceptibility and Disease Process. (Dec. 2020)

Mycobacterium avium subspecies *paratuberculosis* (MAP) is the causative agent of paratuberculosis (ParaTB or Johne's disease), a contagious, chronic and typically fatal enteric disease of domestic and non-domestic ruminants. Clinically affected animals present wasting and emaciation. However, MAP can also infect non-ruminant animal species with less specific signs. Zoological gardens harbor various populations of diverse animal species, which are managed on limited space at higher than natural densities. Hence, they are predisposed to endemic trans-species pathogen distribution. Information about the incidence and prevalence of MAP infections in zoological gardens and the resulting potential threat to exotic and endangered species are rare. Due to unclear pathogenesis, chronicity of disease as well as the unknown cross-species accuracy of diagnostic tests, diagnosis and surveillance of MAP and ParaTB is challenging. Differentiation between uninfected shedders of ingested bacteria; subclinically infected individuals; and preclinically diseased animals, which may subsequently develop clinical signs after long incubation periods, is crucial for the interpretation of positive test results in animals and the resulting consequences in their management. This review summarizes published data from the current literature on occurrence of MAP infection and disease in susceptible and affected zoo animal species as well as the applied diagnostic methods and measures. Clinical signs indicative for ParaTB, pathological findings and reports on detection, transmission and epidemiology in zoo animals are included. Furthermore, case reports were re-evaluated for incorporation into accepted consistent terminologies and case definitions.
Roller M et al. Front. Vet. Sci. 7:572724..❖

Effectiveness of copper ions against *Mycobacterium avium* subsp. *paratuberculosis* and bacterial communities in naturally contaminated raw cow's milk. (November 2020)

Aim: The focus of the present study was to evaluate the copper ions treatment on the viability of Mycobacterium avium subsp. paratuberculosis (MAP) and other bacterial communities in cow's milk.
Methods and results: A copper ions treatment was evaluated in naturally contaminated cow's milk to assay MAP load and/or viability, and relative abundance of other bacterial communities. In addition, physical-chemical analyses of the milk were also performed. All analyses were carried out before and after a copper ions treatment. After copper ions treatment, pH and copper concentration markedly increased in milk; the numbers of viable MAP significantly decreased. The relative abundance of the four target phyla decreased, with the phyla Bacteroidetes and Firmicutes surviving treatment in higher proportions (4 and 2·1% of original populations, respectively). A progressively higher percentage of dead bacterial cells after 5 and 20 min copper ions treatments was found (12 and 35%, respectively).
Conclusion: With the exception of some MAP-tolerant strains, we have once again demonstrated that copper ions have a significant inactivating effect on MAP as well as certain other bacterial communities found in naturally contaminated cow's milk.
Significance and impact of the study: This study showed a significant inactivation of both MAP and other bacteria by copper ions in raw cow's milk, information that could be useful as a tool for MAP control.
Steuer P, et al. J Appl Microbiol. 2020 Nov 5. ❖

Economic Effects Of A Potential Foodborne Disease: Potential Relationship Between Mycobacterium Avium Subs. Paratuberculosis (Map) In Dairy And Crohn's In Humans. (Nov. 2020)

Welfare costs of a potential food shock were estimated by disseminating information to milk drinkers on the prevalence of Mycobacterium avium sub. paratuberculosis (MAP) in the U.S. milk supply, its potential linkage to Crohn's disease in humans, and subsequent government intervention to minimize MAP in the milk supply. We found that 19.6% of milk consumers exposed to MAP information would stop milk consumption at current market prices, and that only 5% of those would return to their original milk consumption levels after the government intervention. Societal costs of the food shock after the intervention were estimated at $18.2 billion.
Chiu, LJ et al. Int. J. Food System Dynamics 11 (5), 2020, 482-502.❖

Crohn's strictures open with anti-mycobacterial antibiotic therapy: A retrospective review. (Dec. 2020)

Background: Medical therapy for strictures is limited and first-line treatment consists of endoscopic balloon dilatation, strictureplasty or surgical resection. *Mycobacterium tuberculosis*, *Helicobacter pylori* and *Streptococcus* can all cause stenosis, for which antibiotic treatment achieves stricture resolution. *Mycobacterium avium ssp. paratuberculosis* is a suspected causative agent in Crohn's disease (CD). Thus, specialized antimicrobial treatment, in particular, anti-mycobacterial antibiotic therapy (AMAT) has been proposed as a potential treatment option. To our knowledge, the opening of CD strictures has not been recorded using any form of antibiotic therapy. We hypothesized that AMAT would resolve strictures in patients with CD.
Aim: To investigate the effect and outcomes of AMAT in a cohort of CD patients with an ileal stricture.
Methods: A single center, retrospective, medical record case review was conducted on an observational cohort of patients with CD who had an ileal stricture on colonoscopy and were treated with AMAT. Forty patients meeting the inclusion criteria were identified from the internal medical database. Thirty (75%) patients had follow-up colonoscopy and clinical data available. The AMAT regimen was prescribed after the initial colonoscopy for a duration of at least six months until follow-up colonoscopy with the attending gastroenterologist. Patient demographics, symptoms, colonoscopy reports, inflammatory serum markers and concurrent medications were recorded at pre-treatment and follow-up between January 1995 and June 2018.
Results: Of the patients that returned for follow-up after > 24 mo of AMAT, twenty (67%) had complete resolution (CR) of their ileal strictures, three (10%) had partial resolution and seven (23%) had no resolution. Irrespective of stricture outcome, 21 patients (70%) demonstrated clinical response to AMAT and there was a statistically significant reduction in inflammatory serum markers C-reactive protein ($P <$ 0.0001) and erythrocyte sedimentation rate ($P =$ 0.04) from pre-treatment to follow-up. It was observed that 11 (37%) patients experienced side effects, but no serious adverse effects were attributable to AMAT. At follow-up there were 26 (87%) patients on concomitant medication for CD and a

statistically significant association between CR and AMAT with a concomitant immunomodulator ($P = 0.02$).
Conclusion: This study demonstrated a high rate of stricture resolution (67%) similar to that seen in tuberculosis strictures (70%), suggesting a shared mycobacterial origin of strictures, and perhaps disease.
Collyer R et al. World J Gastrointest Endosc. 2020; 12(12):542-554.❖

Bovine neutrophils release extracellular traps and cooperate with macrophages in *Mycobacterium avium* subsp. *paratuberculosis* clearance. (Jan. 2021)

Mycobacterium avium subsp. *paratuberculosis* (Map) is the underlying pathogen causing bovine paratuberculosis (PTB), an enteric granulomatous disease that mainly affects ruminants and for which an effective treatment is needed. Macrophages are the primary target cells for Map, which survives and replicates intracellularly by inhibiting phagosome maturation. Neutrophils are present at disease sites during the early stages of the infection, but seem to be absent in the late stage, in contrast to healthy tissue. Although neutrophil activity has been reported to be impaired following Map infection, their role in PTB pathogenesis has not been fully defined. Neutrophils are capable of releasing extracellular traps consisting of extruded DNA and proteins that immobilize and kill microorganisms, but this mechanism has not been evaluated against Map. Our main objective was to study the interaction of neutrophils with macrophages during an *in vitro* mycobacterial infection. For this purpose, neutrophils and macrophages from the same animal were cultured alone or together in the presence of Map or *Mycobacterium bovis* Bacillus-Calmette-Guérin (BCG). Extracellular trap release, mycobacteria killing as well as IL-1β and IL-8 release were assessed. Extracellular trap formation was highest in neutrophils against Map in the presence of macrophages, but without direct cell contact, indicating a paracrine activation. Macrophages were extremely efficient at killing BCG, but ineffective at killing Map. In contrast, neutrophils showed similar killing rates for both mycobacteria. Co-cultures infected with Map showed the expected killing effect of combining both cell types, whereas co-cultures infected with BCG showed a potentiated killing effect beyond the expected one, indicating a potential synergistic cooperation. In both cases, IL-1β and IL-8 levels were lower in co-cultures, suggestive of a reduced inflammatory reaction. These data indicate that cooperation of both cell types can be beneficial in terms of decreasing the inflammatory reaction while the effective elimination of Map can be compromised. These results suggest that neutrophils are effective at Map killing and can exert protective mechanisms against Map that seem to fail during PTB disease after the arrival of macrophages at the infection site.
I Ladero-Auñon, et al. bioRxiv 2020.12.30.424791.❖

Winter is coming! Clinical, immunological, and practical considerations for vaccinating patients with IBD during the COVID pandemic. (Oct. 2020)

In 2020, though, we face a new and formidable foe: the severe acute respiratory syndrome novel coronavirus-2 (SARS-CoV-2). Discriminating coronavirus disease-2019 (COVID-19) from influenza or other respiratory infections based on symptoms alone will be difficult and concomitant infection with SARS-CoV-2 and other respiratory pathogens will likely increase morbidity and mortality. In this commentary, we outline the usefulness and rationale for existing practices related to vaccine-preventable illnesses in IBD, and discuss the emerging science and ethical challenges related to the highly anticipated vaccines against SARS-CoV-2.
Melmed GY, et al. Gastroenterology. 2020;S0016-5085(20) 35251-3.❖

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