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Review Article

# The IDI Crohn's Disease Treatment Protocol Recommendations

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## Abstract

In 2001, Infectious Diseases Incorporated (IDI), an infectious disease thinktank, entered into a strategic agreement with the University of Florida to investigate the role of a veterinary pathogen, Mycobacterium avium subspecies *paratuberculosis* (MAP) in disease induction. The alliance identified the pathogenesis of Johne's disease (a chronic inflammatory disease of the gastrointestinal tract of domestic milk-producing herbivores). The knowledge derived from the study of the natural history of Johne's disease laid foundation to understanding MAP's unique ability to induce affixed, dysfunctional, anti-MAP immune response. The deciphering of the pathogenesis of Crohn's disease identified therapeutic intervention points that have been translated into IDI's Crohn's Disease Recommendations.

The proposed management protocol is primarily the product of IDI's unpublished and published intellectual property, its digest of the literature, and the collaborative research done with the University of Florida.

**Keywords:** Infectious Diseases Incorporated (IDI); Crohn's Disease

Sigell-Boneh., *et al*. achieved clinical and sustained remissions in 70% of children and adults with Crohn's disease who had failed biological therapy using plant-based dietary manipulations [1,2]. Chiba., *et al*. demonstrated that 94% of Crohn's afflicted individuals who had achieved remissions on a semi-vegetarian diet remained in clinical remission if dietary guidelines were adhered to [3]. Thirty-free percent of individuals who abandoned their vegetarian diet relapsed.

### Why?

Crohn's disease is stated to be a clinical entity with no cure; yet rare cures have been individually achieved by strict adherence to a vegetarian diet.

### Why?

The answers are now in evidence. Crohn's disease is an inappropriately treated immune-mediated disease. Its proinflammatory immune response is directed against a specific antigen, *Mycobacterium avium* subspecies *paratuberculosis* (4). The pathogenesis of Crohn's disease per the Hruska Postulate explains the genesis of every fact known about the natural history of Crohn's disease and why failure to contain adulteration of milk and milk products by MAP have transformed a once rare disease into a global pandemic in less than a decade [5,6].

Initial therapies of Crohn's Disease were largely the product of trial and error. One important observation emerged that formed the conceptual foundation for Crohn's disease therapy. Anything (corticosteroids, antimetabolites, etc.) that effectively disrupt the immune system's proinflammatory Th1 response could induce varying degrees of clinical amelioration. Adalimumab (Humira®), an inhibitor of tumor necrosis factor- alpha, was initially developed and marketed by Abbott Laboratories. To attain Food and Drug Administration licensure, adalimumab (Humira®) had only to demonstrate statistically significant clinical superiority over placebo in a randomized, blinded comparative trial. Double blinded, randomized comparative studies against placebo have long allowed industry to bring to market suboptimal therapeutic solutions. Its U.S, Food and Drug Administration filing identified adalimumab induced temporary clinical remissions having occurred in 40% of study individuals versus 17% for subjects receiving a placebo [7]. At 56 weeks post-drug therapy termination, 36% remained in remission compared with 12% of individuals receiving the placebo [1], Adalimumab failed to induce temporary remissions in 60 % of treated individuals and ultimately, permanent remissions in 100% of treated individuals. The newer biologics that have replaced adalimumab as advocated therapy for Crohn's disease impact on the same basic mechanism of action and presented comparable therapeutic efficacy data for their FDA licensures.

## The hruska postulate

In 2015, IDI's Hruska Postulate was introduced (4). It stated that Crohn's disease was an immune-mediated and not autoimmune disease. Its induction phase required a newborn to experience a meaningful MSAP infectious challenge. To abort continued MAP replication, the newborn's inherent immune system can be so stressed as to cause fixation of its proinflammatory response to MAP within immunological memory. For disease to develop, MAP had to become so widespread in a nations' food supply for cytokine/antigen interactions to be repetitive and intense to overcome gastrointestinal mucosal integrity in the location of maximum fecal stasis. The loss of mucosal integrity creates the second mechanism within Crohn's disease, the gastrointestinal microbiota's invasion beyond the lamina propria. The incubation of mononuclear cells from individuals with Crohn's disease with selected MAP antigens results in the release of cytokines.

## Therapeutic issues

The pathogenesis of Crohn's disease identified two key therapeutic objectives: 1) restoration of mucosal integrity and 2) addressing submucosal presence of the gastrointestinal microbiota. The latter requires reasonably accurate assessment of what stage the disease process is currently in. When adalimumab did work, it did so by precluding focal cytotoxic cytokine destruction, which in turn allowed the gastrointestinal mucosa to self-heal or establish a degree of mucosal integrity. The degree of mucosal healing determined the time to relapse after drug discontinuation.

The advocate therapy of Crohn's disease centers on removal from di*et a*l food substances that potentially could have been adulterated by MAP (milk, and meat from herbivores). When permanent remissions have been documented, they occur in individuals committed to vegetarian or near vegetarian diets.

- **Restoration of Mucosal Integrity**: That biologics work to the degree that they do has been documented to be due to their ability to prevent the release of cytotoxic cytokines at mucosal sites of MAP attachment.
- **Gastrointestinal Microbiota:** That 70-80% of the body's immune system serves the gastrointestinal tract underlies its importance in preserving the status quo. Even without antibiotics, site immunity can handle a certain level of sub lamina propria microbiota replication. The initial submucosal microbiological environment favors facultative anaerobic bacteria. Once the initial submucosal infection alters the microbiological environment, bacterial replication order shifts towards progressively more obligatory anaerobic bacteria favors the more anaerobic bacteria. The permanent sequela of Crohn's disease, fistula. strictures, loop to loop anastomosis, and bowel penetrations, are fundamentally physician failure to effectively treat the second mechanism of Crohn's disease. Initial bowel penetration occurs in the ileocecum. Bowel adherence within the cul-de-sac allows the microbial-driven inflammatory process to attain a fistulous cutaneous connection.

An estimated 25% of individuals with Crohn's disease reputedly will require one or more operations for removal of diseased bowel. With displacement of the small intestines, subsequent bowel penetration results primarily in either adherence to another loop of bowel, creating bowel-to-bowel anastomosis or rupture into the peritoneal cavity. This latter event is associated with significant mortality.

## Pre-Treatment issues

**Diagnosis:** In most cases, the diagnosis of Crohn's disease is usually achieved by exclusion of alternative etiologies of regional intestinal inflammation. Current diagnosis relies on documentation of site of disease or immune-histological confirmation of the presence of MAP in diseased tissue. Misdiagnosis of Crohn's disease is an ongoing problem.

## Staging disease

Once the diagnosis is determined, the stage of disease needs to be assessed to properly select an appropriate antimicrobial regimen.

The duration of symptomology to date coupled with evaluation of inflammation status determine the degree to which the body is responding to the process. The need for supplement, short-term antibiotic therapy separates Stage I A from Stage I B. Prior removal of bowel constitutes Stage II.

## IDI recommendation for treatment of Crohn's disease

### Initial therapy of Stage I has three components:

### Immediate avoidance of all milk and milk-based products

Dietary manipulation is central to re-establishing mucosal integrity by precluding antigen/antibody cytotoxicity at MAP's sites of mucosal attachment. It is IDI's belief that avoidance of antigen challenges by MAP in adulterated milk products (and possibly meat from herbivores) is the key to induction of long-term remissions and possible cures.

The cost of implementing a randomized, blinded comparison between biologic versus short term antibiotic therapy and exclusion diet is something that is unlikely to be ever funded by the man-

ufacturers of biologics or the National Crohn's and Colitis Foundation. The cross-over studies cited, plus others [1-3], have addressed the question of the effectiveness of dietary manipulation. Adoption of vegetarian-like diets induced not only clinical remissions. Once induced, vegetarian-like diets have demonstrated the ability to sustain such remissions at comparatively minimal cost [1-3,8,9].

## Restoration of dietary elements that affect host immunity

The disease induced alterations of the gastrointestinal structure and function are often such as to cause deficiencies in vitamins, minerals, and selected amino acids that are essential for effective immune system function. The body has no specialized system to store key contributors, particularly zinc and vitamin C. Individuals with Crohn's disease have been demonstrated to have zinc deficiency impairment [10]. Zinc plays a role in the catalytic activity of an estimated 100 enzymes involved with immune function and DNA synthesis. Zinc deficiency causes Th1 and Th2 cytokine shifts [11-13].

Like zinc, vitamin C is not stored by the body. Through its antioxidant mechanisms, Vitamin C plays a central role in containment of mycobacteria [14]. Vitamin C regenerates vitamin E from its oxidized form, which influences the immune functions of selenium and secondarily impacts on zinc and copper utilization [15].

Vitamins C, D, E, zinc, and intermittent selenium coupled with adequate diet protein are deemed essential by IDI for restoration of optimal immune function in Crohn's disease. (The incorporation of a dietician into the therapeutic team is strongly recommended.).

If the second mechanism of Crohn's disease is not in play, it is IDI's conviction that long-term remission can be attained simply through adherence to dietary exclusion of foods that have the potential of adulteration by MAP.

## Initial antibiotic selection and duration of administration

Antibiotic therapy is needed to address the second mechanism of Crohn's disease: submucosal infection by the gastrointestinal microbiota. The permanent sequala of Crohn's disease (fistula, loop-to-loop anastomosis, strictures, bowel perforations, etc.) are the consequences of lack of or inadequate antibiotic coverage for the second mechanism of Crohn's disease [2,3].

Exact antibiotic coverage is largely a function of the stage of disease identified and the laboratory evidence of possible concomitant infection. The duration of symptomology to date coupled with evaluation of inflammation status needs to be part of Stage determination.

Stage IA: Untreated Crohn's disease of recent onset- CRP, ESR, WBC, temperature within normal parameters.

With 70-80% of the body's immune system in service of the gastrointestinal tract, antimicrobial therapy can be optional if all parameters of inflammation are within normal limits. The principal concern is the potential presence of a facultative anaerobe with enhanced virulence which can make the status transformational.

Stage 1B: Untreated Crohn's disease of recent onset: A 1A individual with one or more abnormal parameters indicative of active infection.

Antibiotic therapy whose spectrum encompasses the Enterobacteriaceae, and the principle facultative anaerobic spectrum is advocated. Therapy is sustained until the abnormal parameter is within normal range. The most utilized combination therapy involves oral administration of ciprofloxacin and metronidazole. Ciprofloxacin's extensive use has diminished its overall efficacy. To address possible participation of tissue-adherent Enterobacteriaceae, one -two-day administration of an aminoglycoside should be considered in individuals over the age of fifteen.

Stage 1C: Untreated Crohn's disease of recent onset: A 1B individual with an elevated temperature.

Therapeutic focus needs to cover cell-adherent *Enterobacteriaceae*. Antibiotic spectrum coverage focuses on potentially more pathogenic spectrum of the facultative anaerobic progression. Inclusion of aminoglycoside therapy is not optional. Tissue damage caused by Enterobacteriaceae with enhanced virulence heals primarily by fibrosis.

Stage 2: individuals who have had clinical disease for a prolonged period, failed prior therapy with biologics, experience recurrent disease manifestation after a short remission, or have an elevated ESR.

Aggressive therapy needs to be focused on the obligatory anaerobic spectrum of the **anaerobic progression.** Incorporation of an infectious disease specialist is highly encouraged.

Stage 3. Individuals who have had prior removal of diseased bowel.

Initial bowel perforation from adherent ileocecal area into the cul-de-sac results in fistula extension of the inflammatory process. Surgery displaces the site of fecal stasis such that subsequent bowel perforation, unless is buttressed by adherent bowel, it empties into the peritoneal cavity resulting in gram-negative sepsis and possible death.

The therapy for Stage 3 should consider the addition of a gastrointestinal surgeon.

## Crohn's disease as a curable entity

Based upon its veterinary studies., IDI firmly believes that dietary and supplemented enhancement of host immunity over time has the potential to destroy the MAP templates which exist as MAP

in its cell-wall free, cytoplastic form. The concept originates from observations derived from a cow with terminal Johne's disease. Johne's disease is a chronic granulomatous, inflammatory disease of the gastrointestinal tract of herbivores caused by millions of replication MAP organisms. Based upon the animal's condition, her demise was anticipated within two to three weeks. To obtain additional high tittered anti-MAP sera for research use, working with a group of veterinary nutritionists, a diet was formulated to enhance the animal's cell-mediated immunity. Instead of dying, over the next three months, the cow refused to die. She regained all her original weight and some. The serological markers of MAP progressively diminished. At necropsy, her gastrointestinal tract had normal configuration. Analysis of initial histological slides and subsequent recuts sections (reviewed separately by two pathologists) failed to reveal a single acid-fast bacillus [16]. What was identified was the immune mechanism by which identified how the body destroys mycobacteria [17].

MAP had long been proposed as the cause of Crohn's disease. Naser., *et al*. cultured MAP from the blood of 50% of patients with Crohn's disease, 22% of individuals with ulcerative colitis and 0% of individuals without inflammatory bowel disease [18]. In a follow up study, MAP was identified in the blood of 22 out of 40 individuals with inflammatory bowel disease, but also from 4 of 18 subjects with other problems [19]. Sechi., *et al*. Bull., *et al*. and Autschack., *et al*. all identified a positive correlation between demonstration of MAP in diseased tissue and Crohn's disease [20-22].

MAP cannot be recovered from diseased tissue containing MAP DNA. MAP cannot be demonstrated using special stains. These two facts inferred that MAP DNA in diseased tissue is the spheroplast form of MAP. The IDI/UF cow study and follow-up studies demonstrated that enhanced host immunity can be effectively weaponized to destroy MAP. It is IDI's contention that the ability to destroy MAP is not limited to MAP organisms with intact cell wall and that MAP spheroplasts are the immunological templates that drive the dysfunctional immune response directed at MAP and creates Crohn's disease [23].

## Conclusion

For Crohn's disease, a single therapeutic regimen does not adequately encompass embedded, compounding issues. The IDI Treatment Protocol Recommendations are constructed to address the three important variables that influence clinical outcomes in Crohn's disease: the cell-adherent Enterobacteriaceae, the second mechanism of Crohn's disease (establishment of submucosal infection by the gastrointestinal microbiota), and the potential significance of repositioning small bowel by prior surgery.

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