Abstract O-07.9: PERSPECTIVE
MAP disease in humans: An inconvenient truth or trivial dalliance?

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Abstract text:
One of the most interesting and challenging questions in MAP research addresses the implication that MAP may be a zoonotic agent. Several human diseases have been linked to this pathogen but it is particularly relevant to the hypothesis that MAP infection triggers Crohn’s disease (CD) just as it does Johne’s Disease (JD). There is an ongoing alarming increase in the prevalence of Crohn’s disease worldwide particularly in paediatric and Asian populations. This is an important emerging issue in public health and if linked conclusively to MAP could represent an inconvenient truth that would have profound consequences for food providers and health strategies around the world. Although still unproven, it remains incumbent on us as experts in this field to assess and plan for such an eventuality with the provision and application of knowledge on all aspects of MAP pathogenesis and disease control.

Current concepts suggest CD does not develop as a result of auto-immunity but from a unique combination of genetic predispositions that importantly always require chronic exposure to environmentally acquired triggers. These drive or enhance immunological dysregulations, eventually releasing a characteristic cocktail of destructive inflammatory mediators which induce phases of gastro-intestinal hyper-responsiveness. Importantly, this is not an acute infectious disease but one that presents with episodes of acute symptoms that are a result of chronic inflammation driven indirectly and possibly distantly from the triggering agent. Presentations can manifest in several biotypes and locations including early and late onset, possibly as a result of the multiple combinations of genetic predisposition, age and triggering agent exposure. As there is no accepted cause we also have no idea of infective trigger dose, nor whether characteristic relapses are a result of re-crudescence from dormancy, re-infection with the triggering agent or even loss of tolerance.

So is MAP the culprit? Is it a lone perpetrator? Or just one of a range of triggers? Contrarily, could it be that previous inconsistencies in MAP isolation from human tissue and the lack of exclusivity in MAP detection from patient samples with and without disease is an indicator that MAP only represents a bystander infection and theories of MAP as a causative agent should be banished to conjecture and tales of coincidence?

The answers to these questions, like in all good detective stories, lies in careful investigation of the manner and motive for the crime; in this case dissecting the critical mechanisms that are required to initiate and maintain CD and demonstrating how candidate triggers may achieve this. Unfortunately, ethics (and health and safety) will no longer let us re-enact the crime! ...but if we are to get a lasting conviction we must aim to show that the suspect had the means and opportunity to deliver, then importantly place them at the scene.

This perspective will discuss the latest evidence in the field for MAP as a causal agent, including new evidence that MAP is widely prevalent in the environment, compounded by low priority treatment of animal waste and persistent in a range of niches, some of which have the capacity to allow MAP proliferation. Further studies prove presence of viable MAP in a variety of both fresh and preserved common food products including meat and dairy, confirming that human exposure
to MAP is beyond doubt a continuous event. Important new evidence suggests viable MAP are also present in food stuffs including dairy products consumed within regions with a low incidence of MAP related disease. If confirmed this could break a long held dogma that MAP is not a credible candidate for triggering because it is not always present in high CD prevalence areas. The current trend for Asian populations to take on Western diets, as seen by recent doubling of demand for milk and dairy products, may in some small way play into this scenario. The reality is that long term exposure of humans to MAP, in the western world at least, is currently inevitable and substantial over long periods, making MAP a triggering candidate with ample opportunity.

As for method, new studies have shown that both CD and JD disease processes develop through significantly similar specific immunological reactivities and share an ever increasing list of host susceptibility gene loci associated with enhancing these pathways. Work in early onset CD correlates particular genetic phenotypes specifically with MAP presence in the gut, whilst interesting studies on late onset CD have linked differing disease biotypes to defined dysbiosis of normal gut flora that associate in a mutually exclusive manner with either MAP or other invasive, persistent bacterial species of as yet undetermined identity.

Definitive proof of causality in this day and age will only come from showing a pathogen specific therapy can prevent progression of the disease. With no cure for CD on the immediate horizon, we must remain speculative. The evidence however is still strongly in favour of an invasive, long term persistent intracellular organism that retains a capacity for dormancy, is prevalent in the environment, remains viable in food and can cause selective dysregulation of innate and adaptive immune processes in a manner highly reminiscent to that of MAP in JD. Finally, suggestions that MAP infection may additionally present specific cellular mimic peptides influencing autoimmune disease linked processes may be a complexity too far, but as we well know, MAP holds its secrets close.