2013-07-26-058 Paratuberculosis databases updated (2013-07-25)

A special service of the OIE World Organization for Animal Health Reference Laboratory for Paratuberculosis, Brno, Czech Republic to registered members of the Biomedical Technology, Epidemiology and Food Safety network.
How to request full papers from PTB databases

CENTAUR GLOBAL NETWORK INFORMATION Vol. 17, 2013, issue 058 is distributed to: (04) Mycobacterial diseases; (12) Scientific Information, research and education; .

****

New publications in the PARATUBERCULOSIS database (1468-1472)

1468 O'Brien, C. , Kuseff, G., McMillan, E., McCowan, C., Lavender, C., Globan, M., Jerrett, I., Oppedisano, F., Johnson, P., Fyfe, J.

Mycobacterium ulcerans infection in two alpacas
Australian Veterinary Journal, (2013) 91, 296-300
Background An ulcerative dermopathy caused by Mycobacterium ulcerans is described in two alpacas (Vicugna pacos) domiciled in endemic areas of Victoria, Australia. Results The diagnosis was confirmed in both cases by PCR targeting the M.ulcerans-specific insertion sequence, IS2404. Extensive wound debridement and bandaging was effective in controlling local disease in one alpaca, although the animal was eventually euthanased because of suspected disease recurrence at other anatomical sites. Treatment was not undertaken in the second animal, but the results of a complete necropsy are described. Investigation of the environs of the second animal yielded low levels of M.ulcerans DNA associated with a variety of samples. The potential use of adjunctive antibiotic therapies directed against M.ulcerans infection in this species is discussed. Conclusion Mycobacterium ulcerans infection should be suspected in alpacas domiciled in endemic areas and presented with ulcerative skin disease.

1469 Lu, Z., Schukken, Y.H., Smith, R.L., Grohn, Y.T.

Using vaccination to prevent the invasion of Mycobacterium avium subsp paratuberculosis in dairy herds: A stochastic simulation study
Preventive Veterinary Medicine, (2013) 110, 335-345
Paratuberculosis, or Johne's disease (JD), is a chronic enteric disease of ruminants infected by Mycobacterium avium subsp. paratuberculosis (MAP) that causes a significant financial loss in dairy industry. To reduce prevalence and transmission in dairy herds infected with MAP, control programs have been implemented, including test-based culling, improved calf rearing management, and vaccination. The important issue of preventing MAP invasion into a MAP-free herd has been less investigated, however. The objective of this study was to examine whether vaccination was able to prevent MAP invasion in dairy cattle using a stochastic simulation approach. We developed a MAP vaccination model in which calves were vaccinated with a vaccine that is both imperfect in reducing the susceptibility of the host ('leaky') and that does not successfully immunize all calves ('failure in take'). Probability of MAP persistence and the number of infected animals in herds were computed for both control and vaccinated herds over a ten-year period after introduction of an initial infected heifer. Global parameter sensitivity analyses were performed to find the most influential parameters for MAP invasion. Our results show that vaccination of calves is effective in preventing MAP invasion, provided that the vaccine is of high efficacy in both reduction of susceptibility and 'take' effects; however, there is still a small chance (<0.15) that MAP can be sustained in herds over a long time (>10 years) due to vertical transmission. This study indicates that reduction in the transmission rate of high shedders (>50 CPU), the number of infected heifers initially introduced to herds, and vertical transmission are important to further decrease the probability of MAP becoming endemic and the overall number of infected animals in endemic herds. The simulation work is useful for designing vaccination programs aimed at preventing MAP invasion in MAP-free herds.

1470 Naser, S.A. , Thanigachalam, S., Dow, C.T., Collins, M.T.

Exploring the role of Mycobacterium avium subspecies paratuberculosis in the pathogenesis of type 1 diabetes mellitus: a pilot study

Gut Pathogens, (2013) 5, Article Number: 14 DOI: 10.1186/1757-4749-5-14 Published: JUN 13 2013-Background: Although the etiology of Type 1 Diabetes mellitus (T1DM) has not been determined, genetic polymorphism in key genes, including SLC11A1, and association with Mycobacterium avium subspecies paratuberculosis (MAP) have been reported. We hypothesize that molecular mimicry between MAP Heat shock protein 65 K (Hsp65) and human Glutamic Acid Decarboxylase 65 K (GAD65) may be the trigger leading to autoimmune destruction of beta cells in patients exposed to MAP. Method: Peptide sequences of MAP Hsp65 and human GAD65 were investigated for amino acid sequence homology and cross reactivity. A total of 18 blood samples from T1DM and controls were evaluated for the presence of MAP. Results: Peptide BLAST analysis revealed a 44% overall identity between MAP Hsp65 and GAD65 with 75% positives in a 16 amino acid region. PyMOL 3D-structural analyses identified the same 16 amino acid region as a potential epitope for antibody binding. Preliminary data suggests a cross reactivity between MAP Hsp65, and a healthy rat pancreatic tissue homogenate against plasma from T1DM patients and rabbit polyclonal anti-MAP IgG. Long-term culture of human blood resulted MAP detection in 3/10 T1DM and 4/8 controls whereas MAP IgG was detected in 5/10 T1DM samples and 3/8 non-diabetic controls. Conclusion: The high degree of homology between GAD65 and MAP Hsp65 in an antigenic peptide region supports a possible mycobacterial role in triggering autoimmune destruction of pancreatic cells in T1DM. Reactivity of T1DM patient sera with MAP Hsp65 supports this finding. Culture of MAP from the blood of T1DM patients is intriguing. Overall, the preliminary data are mixed and do not exclude a possible role for MAP in T1DM pathogenesis. A larger study including well-characterized controls is needed to investigate the intriguing question of whether MAP is associated with T1DM or not?

1471 Rindi, L., Buzzigoli, A., Medici, C., Garzelli, C.

High phylogenetic proximity of isolates of Mycobacterium avium subsp hominissuis over a two decades-period

Infection Genetics and Evolution, (2013) 16, 99-102

The genetic diversity of 47 human isolates of Mycobacterium avium subsp. hominissuis (MAH) was determined by MIRU-VNTR genotyping. Sixteen unique VNTR patterns and eight clusters including a total 39 isolates were detected; six clusters included strains isolated during at least a 15-year period. Minimum spanning tree analysis showed that 14 VNTR patterns, occurring either as clustered or unique isolates, differed from the nearest one for one allelic variation and that the remaining two patterns differed,for two allelic variations. The high phylogenetic proximity of the isolates, even over a long time period, indicates that the MAR genotype is highly homogeneous and conserved.

1472 McSpadden, K., Caires, K., Zanella, R.

The Effect of Mycobacterium avium subspecies paratuberculosis Exposure on Animal Health

Acta Scientiae Veterinariae, (2013) 41, Article Number: 1095 Published: JAN 3 2013-Background: Johne's disease is an incurable wasting condition that affects ruminant and non-ruminant animals. Each year, Johne's is responsible for losses in the billions of dollars in the United States cattle industry alone. Mycobacterium avium subspecies paratuberculosis (MAP) is the microorganism responsible for Johne's disease. MAP can spread very fast among animals, and this patogen has been isolated across the world and in several different animal species including humans. Therefore, MAP is classified as having a major impact on both animal and human health, and therefore the economy. MAP has also been associated with Crohn's disease in humans, which necessitates great concerns regarding public health. The objective of this literature review is to identify problems and challenges associated with this illness and highlight possible approaches to minimize the economic losses and the incidence of Johne's, two avenues to reduce human exposure with this pathogen. Review: Following ingestion and exposure to MAP, the bacterium will infect the host through the ileum and than it will proliferate inside of host-cells; MAP can therefore be considered an intracellular parasite. After infection, this pathogen goes to a latency period that can be from months to several

years without causing the presence of clinical signs in the host. This bacteria can cause an inflammatory response in the intestine, decreasing the ability of the animal to absorb nutrients. Depending on the level of infection bacteria strain and the genetic composition of the animal, individuals can become or not infected, if infected they can shed variable levels of MAP into the environment, increasing the exposure to other animals. Thus, it is of importance to eliminate MAP infected animals from herds; aiming to reduce the environment contamination with this bacteria. Several chromosomal regions have been associated and linked with MAP infection in cattle. It is proposed that Johne's disease has a polygenic effect with multiple genes involved in the process of susceptibility and tolerance to the disease. Selection for animals that are tolerant to Johne's disease has also been proposed, whereby tolerance was defined as the ratio of MAP tissue infection and MAP fecal shedding. Animals that are shedding low or no levels of MAP in the environment were considered tolerant, thus are preferred in comparison with the ones that are eliminating high levels of MAP. Some positional and functional candidate genes have being identified and explored. The major problem with genetic studies with Johne's disease is the correct classification of the phenotype. ELISA, PCR and fecal culture are methods of testing for Johne's disease but variation exists regarding the degree of accuracy and effectiveness for each test, as discussed further within this review. Discussion: In this study, we presented the importance of preventive control of MAP transmission amongst animals and humans, respectively. Several approaches to reduce the incidence of this illness among animals were evaluated; however the number of infected animals is still increasing annually, especially within dairy herds. Genetic selection for animals that are less susceptible might be one solution to reduce the spread and contamination of other animals with these bacteria. This necessitates the better understanding of the genes involved with host-immune-defense mechanisms for development of an accurate selection method. Questions related to the zoonotic potential of MAP, the causative agent of Johne's disease, and Crohn's disease in humans is still of great concern to the population, therefore efforts to control and eradicate this disease are needed.

New publications in the CROHN'S DISEASE AND PARATUBERCULOSIS database (817-819)

817 To, K.W., Reino, J.J.G., Yoo, D.H., Tam, L.S.

Tumour necrosis factor antagonist and tuberculosis in patients with rheumatoid arthritis: An Asian perspective
Respirology, (2013) 18, 765-773
Rheumatoid arthritis (RA) is a systemic autoimmune disease in which inflammation of the joints is one of the dominant clinical abnormalities resulting in serious morbidity. Over the past decade, tumour necrosis factor (TNF) antagonist has revolutionized the treatment of RA. However, the subsequent increased risk of developing tuberculosis is one of the major drawbacks of this otherwise effective treatment. Latent tuberculosis infection (LTBI) is an asymptomatic form of tuberculosis that is confined by the host's immune system. Active tuberculosis may develop when the immune status weakens. This risk is much higher in patients receiving TNF antagonist. Traditionally, tuberculin skin test (TST) is used to diagnose LTBI. Unfortunately, TST cannot distinguish bacillus Calmette-Guerin (BCG) vaccination from tuberculosis making it difficult to use as a reliable diagnostic tool. In addition, possible anergy and interaction of the altered autoimmune status in rheumatological diseases further complicate the interpretation of TST results. Although interferon-gamma release assay (IGRA) has improved the diagnosis of LTBI in immunocompetent individuals, its respective sensitivity/specificity values are unknown in patients with autoimmune disease due to variable pretest probability and lack of confirmatory test for LTBI. Thus, the use of IGRA for screening LTBI is variable among different countries. This review explores the prevalence of tuberculosis in patients receiving TNF antagonist in countries with different tuberculosis disease burdens and the potential mechanisms for variation in the incidence of tuberculosis with different TNF antagonists, the current practice guidelines for assessing the risk of LTBI in different countries, and the possible solutions for improving diagnosis, monitoring and management of LTBI.

818 Naser, S.A., Thanigachalam, S., Dow, C.T., Collins, M.T.

Exploring the role of Mycobacterium avium subspecies paratuberculosis in the pathogenesis of type 1 diabetes mellitus: a pilot study

Gut Pathogens, (2013) 5, Article Number: 14 DOI: 10.1186/1757-4749-5-14 Published: JUN 13 2013-Background: Although the etiology of Type 1 Diabetes mellitus (T1DM) has not been determined, genetic polymorphism in key genes, including SLC11A1, and association with Mycobacterium avium subspecies paratuberculosis (MAP) have been reported. We hypothesize that molecular mimicry between MAP Heat shock protein 65 K (Hsp65) and human Glutamic Acid Decarboxylase 65 K (GAD65) may be the trigger leading to autoimmune destruction of beta cells in patients exposed to MAP. Method: Peptide sequences of MAP Hsp65 and human GAD65 were investigated for amino acid sequence homology and cross reactivity. A total of 18 blood samples from T1DM and controls were evaluated for the presence of MAP. Results: Peptide BLAST analysis revealed a 44% overall identity between MAP Hsp65 and GAD65 with 75% positives in a 16 amino acid region. PyMOL 3D-structural analyses identified the same 16 amino acid region as a potential epitope for antibody binding. Preliminary data suggests a cross reactivity between MAP Hsp65, and a healthy rat pancreatic tissue homogenate against plasma from T1DM patients and rabbit polyclonal anti-MAP IgG. Long-term culture of human blood resulted MAP detection in 3/10 T1DM and 4/8 controls whereas MAP IgG was detected in 5/10 T1DM samples and 3/8 non-diabetic controls. Conclusion: The high degree of homology between GAD65 and MAP Hsp65 in an antigenic peptide region supports a possible mycobacterial role in triggering autoimmune destruction of pancreatic cells in T1DM. Reactivity of T1DM patient sera with MAP Hsp65 supports this finding. Culture of MAP from the blood of T1DM patients is intriguing. Overall, the preliminary data are mixed and do not exclude a possible role for MAP in T1DM pathogenesis. A larger study including well-characterized controls is needed to investigate the intriguing question of whether MAP is associated with T1DM or not?

819 Uzel, G., Sampaio, E.P., Lawrence, M.G., Hsu, A.P., Hackett, M., Dorsey, M.J., Noel, R.J., Verbsky, J.W., Freeman, A.F., Janssen, E., Bonilla, F.A., Pechacek, J., Chandrasekaran, P., Browne, S.K., Agharahimi, A., Gharib, A.M., Mannurita, S.C., Yim, J.J., Gambineri, E., Torgerson, T., Tran, D.Q., Milner, J.D., Holland, S.M.

Dominant gain-of-function STAT1 mutations in FOXP3 wild-type immune dysregulation-polyendocrinopathy-enteropathy-X-linked-like syndrome

Journal of Allergy and Clinical Immunology, (2013) 131, 1611-DOI: 10.1016/j.jaci.2012.11.054 Published: JUN 2013

Background: Mutations in signal transducer and activator of transcription (STAT) 1 cause a broad spectrum of disease, ranging from severe viral and bacterial infections (amorphic alleles) to mild disseminated mycobacterial disease (hypomorphic alleles) to chronic mucocutaneous candidiasis (CMC; hypermorphic alleles). The hypermorphic mutations are also associated with arterial aneurysms, autoimmunity, and squamous cell cancers. Objective: We sought to investigate the role of STAT1 gain-of-function mutations in phenotypes other than CMC. Methods: We initially screened patients with CMC and autoimmunity for STAT1 mutations. We functionally characterized mutations in vitro and studied immune profiles and regulatory T (Treg) cells. After our initial case identifications, we explored 2 large cohorts of patients with wildtype forkhead box protein 3 and an immune dysregulation-polyendocrinopathy-enteropathy-X-linked (IPEX)-like phenotype for STAT1 mutations. Results: We identified 5 children with polyendocrinopathy, enteropathy, and dermatitis reminiscent of IPEX syndrome; all but 1 had a variety of mucosal and disseminated fungal infections. All patients lacked forkhead box protein 3 mutations but had uniallelic STAT1 mutations (c.629 G>T, p.R210I; c. 1073 T>G, p.L358W, c.796G>A; p.V266I; c.1154C>T, T385M [2 patients]). STAT1 phosphorylation in response to IFN-gamma, IL-6, and IL-21 was increased and prolonged. CD4(+) IL-17-producing T-cell numbers were diminished. All patients had normal Treg cell percentages in the CD4(+) T-cell compartment, and their function was intact in the 2 patients tested. Patients with cells available for study had normal levels of IL-2-induced STAT5 phosphorylation. Conclusions: Gain-of-function mutations in STAT1 can cause an IPEX-like phenotype with normal frequency and function of Treg cells.

****