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PATHOGENESIS OF Corynebacterium pseudotuberculosis INFECTION AND VACCINATION TRIAL AGAINST CASEOUS LYMPHADENITIS IN GOATS

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, In Fulfillments of the Requirements for the Degree of Doctor of Philosophy

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

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November 2016

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Corynebacterium pseudotuberculosis is a Gram-positive bacterium that is responsible for a disease called caseous lymphadenitis (CLA) in goats and sheep. This disease has worldwide distributions and the bacterium can remain in the environment for months. It is difficult to eradicate and can be easily transmitted to naive animals. Furthermore, transmission and the pathology of the disease are not fully understood. Therefore, this experiment was conducted to determine the best route of infection of the disease, the clinical and pathological changes in goats following experimental infection, the humoral immune response via antibody titers shown by the infected goats, and the efficacy of a commercial vaccine in preventing CLA in goats in Malaysia.

Twenty adult healthy goats were selected and divided into 4 groups. All goats of the first 3 groups were infected with 10^7 cfu/mL of live *C. pseudotuberculosis* via three different routes; the intradermal, the intranasal and the oral routes. The last group served as the uninfected control group. The goats were observed daily for clinical signs related to CLA for 30 days experimental period. Rectal temperatures and blood samples were taken periodically. The infected goats from all infected groups were depressed, showed lack of appetite, and increased in body temperature in the first week post-inoculation. The intradermal group had swelling with pus at the site of infection. Blood profile of the goats revealed significant decreased in haemoglobin for the intradermal and intranasal groups. Only the intradermal group showed significantly ($p<0.05$) high total WBC counts, with the increased neutrophils and monocyte concentrations. Generally, goats infected intradermally showed most severe clinical signs and haematology changes.

At the end of 30-day experimental period, all goats were sacrificed. *C. pseudotuberculosis* was re-isolated from most of the intradermally infected goats with 40% of the goats had the bacteria in the liver, 80% in prescapular and 40% in submandibular lymph nodes. Only 20% of goats in the intranasally infected group had the bacteria in the liver. No bacteria were isolated from any organ or lymph nodes from the oral and control goats. Abscessation was the most commonly observed gross lesions, particularly within the lymph nodes of infected goats. Other less common lesions included consolidation of lung lobes, congestion of kidneys and lymph nodes. Histopathological lesions scores revealed significantly ($p<0.05$) much severe overall lesions among goats exposed intradermally.

Following to the initial 30-day experimental trial, a chronic study was eventually conducted. Nine adult goats were similarly infected intradermally with 10^7 cfu/mL of live *C. pseudotuberculosis* and were observed for 3 months. Similarly, all infected goats were less active in week 1 post-infection, developed swelling at the injection site with enlargement of submandibular lymph nodes. The haemoglobin, however, remained within normal value and decresed insignificantly ($p>0.05$) throughout the experimental period. Total white blood cell (WBC) counts were consistently high until day 39 post-infection due to the increased neutrophilic and monocytic counts. The serum IgG increased and exceeded the cut-off value on day 10 post-infection but most significant ($p<0.05$) increase was observed on day 14 post-infection before it gradually decreased until day 53 post-infection and approaching the cut-off value at the end of the 90-day experimental period.

Three goats were sacrificed by slaughtering monthly. *C. pseudotuberculosis* was successfully isolated from all lymph nodes with abscessation, and from the lungs of a goat that was sacrificed 2 months post-infection. Prescapular node abscessation was observed in 2 goats at 1 month post-inoculation, in all 3 goats at 2 and 3 months.There was also abscessation in the submandibular lymph node of a goat at 3 month post-inoculation.The lungs of infected goats showed thickening of interalveolar septa, mild to moderate congestion of the liver with inflammatory cells found scattered in between hepatocytes and presence of mild fatty degeneration of the hepatocytes. The kidneys showed congestion of blood vessels and presence ofurinary cast in the renal tubules.The affected lymph nodes showed typical abscess in which the diameter of the necrotic centre was significantly ($p<0.05$) larger with increase of time post-infection.These results show that the disease progressed with time after infection.

Currently, there is only one commercial vaccine for CLA in Malaysia. However, the efficacy was uncertain. Twenty-seven goats of different serological status were selected from a farm with endemic CLA. Group A consisted of 10 sero-positive goats, group B with 10 sero-negative goats while group C with 7 sero-negative goats that served as control-unvaccinated group. All goats of groups A and B were vaccinated using Glanvac 6^{TM} vaccine twice at 1-month apart. One month after the second vaccination, all goats were challenged with 10^9

cfu/mL of live *C. pseudotuberculosis.*The goats were observed for clinical signs and were killed a month post-infection. The bacterium was most frequently isolated from lymph nodes of goats of group A but the rate of isolation showed no significant ($p>0.05$) difference among all groups. Gross lesion was observed in the prescapular lymph nodes of all groups ($p>0.05$). The goats vaccinated with Glanvac 6^{TM} either with sero-positive or sero-negative still developed signs and lesions of abscessation similar to the unvaccinated goats. Thus, the vaccine was unable to prevent goats from developing CLA.

Keywords: caseous lymphadenitis, *Corynebacterium pseudotuberculosis*, goats

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PATOGENESIS JANGKITAN *Corynebacterium pseudotuberculosis* DAN PERCUBAAN VAKSIN TERHADAP BENGKAK NODUS LIMFA PADA KAMBING

Oleh

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Corynebacterium pseudotuberculosis adalah sejenis bakteria yang bertanggungjawab dalam menyebabkan penyakit bengkak nodus limfa pada kambing dan biri-biri.Penyakit ini tersebar meluas di seluruh dunia dan bakteria tersebut boleh berada di persekitaran selama beberapa bulan. Penghapusan penyakit ini sukar dilakukan dan ianya mudah merebak kepada haiwan-haiwan yang naïf. Penyebaran dan patologi penyakit in tidak difahami sepenuhnya. Penyelidikan ini dijalankan bagi mengenalpasti kaedah terlazim *C. pseudotuberculosis* menjangkiti kambing, kesan terhadap kambing secara klinikal dan patologikal selepas jangkitan serta tahap antibodi yang terbentuk dalam darah kambing, serta keberkesanan vaksin yang berada di pasaran ke atas sebaran dan kawalan penyakit ini pada kambing di Malaysia.

Dua puluh ekor kambing dewasa telah dipilih untuk penyelidikan ini dan dibahagikan kepada 4 kumpulan. Kambing-kambing tersebut telah dijangkiti dengan 10^7 cfu/mL bakteria *C. Pseudotuberculosis* hidup melalui tiga kaedah. Kaedah-kaedah tersebut adalah; melalui kulit, saluran pernafasan dan mulut. Satu kumpulan kambing bertindak sebagai kawalan dan tidak dijangkiti bakteria. Kambing-kambing tersebut diperhatikan selama 30 hari untuk sebarang perubahan yang berkaitan dengan penyakit bengkak nodus limfa. Sepanjang masa itu, suhu badan dan sampel darah diambil mengikut selang masa yang ditetapkan. Pada minggu pertama jangkitan, semua kambing terjangkit kelihatan murung, kurang selera makan, dan suhu badan meningkat. Kambing-kambing yang dijangkiti pada kulit mempunyai bengkak yang mengandungi nanah pada kawasan terjangkit. Kambing-kambing terjangkit melalui kulit dan saluran pernafasan mengalami pengurangan dalam jumlah hemoglobin dalam darah. Hanya kambing terjangkit melalui kulit yg menunjukkan kenaikan bererti ($p<0.05$) dalam jumlah sel darah putih, dengan kenaikan jumlah sel neutrofil dan monosit. Kambing-kambing terjangkit melalui kulit menunjukkan tanda klinikal dan perubahan pada darah yang paling parah.

Selepas 30 hari jangkitan, semua kambing disembelih. Lesi-lesi kasar diperhatikan dan sampel organ-organ dalaman beserta nodus limfa diambil bagi pengasingan semula bacteria dan pemeriksaan histopatologi. Kebanyakkan pengasingan semula bacteria didapati dari kambing terjangkit melalui kulit. 40% kambing terdapat bacteria pada hati, 80% bacteria pada nodus limfa preskapular, dan 40% pada nodus limfa submandibular. Hanya 20% kambing terjangkit melalui saluran pernafasan mempunyai bacteria pada hati. Tiada pengasingan semula bakteria didapati dari kambing terjangkit melalui mulut dan kambing tidak terjangkit. Antara lesi kasar yang dapat dilihat adalah; pembentukan nanah pada nodus limfa, kemerahan pada paru-paru, buah pinggang dan nodus limfa. Lesi histopatologi menunjukkan kambing terjangkit melalui kulit mempunyai lesi yang lebih parah. Melalui penyelidikan ini, didapati nodus limfa yang paling banyak dijangkiti adalah nodus limfa preskapular. Jangkitan oleh *C. pseudotuberculosis* melalui kulit mempunyai lesi keseluruhan yang paling parah.

Berdasarkan keputusan penyelidikan di atas, 9 ekor kambing dewasa telah dipilih untuk penyelidikan seterusnya. Semua kambing dijangkiti melalui kulit dengan 10^7 cfu/mL *C. pseudotuberculosis.* Kambing-kambing tersebut diperhatikan selama 3 bulan untuk sebarang tanda berkaitan bengkak nodus limfa. Suhu badan dan sampel darah diambil mengikut selang masa yang ditetapkan. Semua kambing terjangkit kelihatan tidak aktif pada minggu pertama jangkitan, mempunyai bengkak pada kawasan jangkitan, dan mengalami kenaikan suhu badan. Terdapat juga pembesaran pada nodus limfa submandibular sebesar 3 cm. Pembesaran tersebut dikesan pada seekor kambing pada minggu ke 8 jangkitan. Dalam penyelidikan ini, jumlah haemoglobin dalam darah adalah normal sepanjang 3 bulan penyelidikan, kecuali beberapa hari di penghujung penyelidikan. Jumlah sel darah putih dalam darah adalah tinggi selama 39 hari selepas jangkitan, tetapi kembali ke paras normal selepas itu. Jumlah neutrofil dan monosit dalam darah juga mengalami kenaikan yang sama. Paras IgG dalam serum kambing terjangkit juga di analisis. Paras IgG dalam serum meningkat dan melepasi titik potong pada hari kesepuluh selepas jangkitan. Paras IgG meningkat paling tinggi pada hari ke-14 selepas jangkitan. Bacaan ELISA mula menurun pada hari ke-53 selepas jangkitan dan menghampiri titik potong pada penghujung tempoh penyelidikan.

Tiga ekor kambing disembelih pada setiap bulan. Semasa post-mortem, lesi kasar diperhatikan dan sampel organ dalaman dan nodus limfa diambil untuk pengasingan semula bacteria dan pemeriksaan histopatologi. *C. pseudotuberculosis* berjaya diasingkan dari semua nodus limfa yang bernanah dan dari paru-paru seekor kambing yang disembelih pada bulan kedua selepas jangkitan. Terdapat nanah pada nodus limfa preskapular 2 ekor kambing yang disembelih pada bulan pertama selepas jangkitan. Pada bulan kedua selepas jangkitan, terdapat pendarahan pada paru-paru seekor kambing dan nanah pada nodus limfa preskapular semua kambing. Pada bulan ketiga selepas jangkitan, semua kambing terjangkit mempunyai organ dalaman yang kelihatan normal pada mata kasar. Tetapi, terdapat nanah pada nodus limfa preskapular pada semua kambing terjangkit dan nanah pada nodus limfa submandibular

dalam seekor kambing terjangkit. Pemeriksaan histologi menunjukkan penebalan pada septa interalveolar, kemerahan pada hati, kewujudan sel-sel radang pada hati, degenerasi lemak pada sel hati, kesesakan pada sel darah dalam buah pinggang, dan kast di dalam tubul buah pinggang. Nodus limfa yang bernanah menunjukkan keadaan nanah yang biasa. Nanah tersebut diukur dan didapati bahawa diameter bahagian tengah nanah tersebut meningkat dengan peningkatan masa selepas jangkitan. Keputusan ini menunjukkan penyakit ini bertambah teruk dengan peningkatan masa jangkitan.

Bengkak nodus limfa adalah penyakit yang penting dalam industri kambing di Malaysia, malahan di serata dunia. Oleh itu, pengawalan penyakit ini amat penting. Di Malaysia, hanya terdapat satu vaksin komersial terhadap penyakit ini. Oleh itu, keberkesanan vaksin ini harus dikaji. 27 ekor kambing dengan status serologi yang berbeza telah dipilih untuk penyelidikan ini. Kumpulan A mengandungi 10 ekor kambing sero-positif, kumpulan B mempunyai 10 sekor kambing sero-negatif dan kumpulan C terdiri daripada 7 ekor kambing sero-negatif yang bertindak sebagai kawalan. Semua kambing dalam kumpulan A dan B divaksin menggunakan vaksin komersial tersebut sebanyak 2 kali, dalam jarak 1 bulan. Sebulan selepas vaksinasi kedua, semua kambing dijangkitkan dengan 10^9 cfu/ml *C. pseudotuberculosis.* Kambing-kambing tersebut diperhatikan untuk sebarang perubahan dan disembelih sebulan selepas jangkitan. Kebanyakkan pengasingan semula bakteria didapati dari kambing dalam kumpulan A. Tetapi, tiada perbezaan bererti ($p>0.05$) antara semua kumpulan kambing. Kebanyakkan lesi kasar didapati pada nodus limfa preskapular, dan tiada perbezaan bererti ($p>0.05$) antara semua kumpulan kambing. Lesi kasar menunjukkan bahawa kambing yang divaksin dengan Glanvac 6^{TM} juga akan terjangkit dengan penyakit ini dan mempunyai nanah pada nodus linfa. Oleh itu, vaksin ini tidak berkesan sepenuhnya dalam menghalang penyakit ini kerana keberadaan penyakit ini tidak mempunyai perbezaan yang bererti ($p>0.05$) antara kambing yang divaksin dan kambing yang tidak divaksin.

Kata kunci: bengkak nodus limfa, *Corynebacterium pseudotuberculosis*, kambing

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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CLA:	caseous lymphadenitis
AGPT:	agar gel precipitation test
ELISA:	enzyme-linked immunosorbent assay
PBS:	phosphate buffered saline
BHI:	brain-heart infusion
CFU:	colony forming unit
SD:	standard deviation
CMN:	*Corynebacterium, Mycobacterium, Nocardia*
CBC:	complete blood count
WBC:	white blood cells
RBC:	red blood cells
PCV:	packed cells volume
PCR:	polymerase chain reaction
ANOVA:	analysis of variance
PLD:	phospholipase D
LN:	lymph node
IgG:	immunoglobulin G
bp:	base pairs
ºC:	degrees celcius
µL:	microlitre
g:	gram
p.i.:	post-infection
HE:	Haematoxylin and Eosin stain
rpm:	round per minute

APTT:	activated partial thromboplastin time
PT:	prothrombin time
BUN:	blood urea nitrogen
TP:	total protein
AST:	aspartate aminotransferase
ALP:	alkaline phosphatise
CK:	creatinine kinase
Alb:	albumin
GGT:	gamma-glutamyl transferase
A:G:	albumin and globulin ratio
OD:	optical density

CHAPTER 1

INTRODUCTION

Corynebacterium pseudotuberculosis is the aetiological agent of a disease called caseous lymphadenitis (CLA) or “cheesy gland disease” that affects goats and sheep worldwide. It is a non-spore forming, facultative, intracellular Gram positive bacterium. In stained smears, the rods appear isolated and have pleomorphic form, from coccoids to filamentous rods that grouped in parallel cells or in a format similar to Chinese letters. In sheep blood agar incubated at 37°C, the organism appears as cream-colored colonies with a β-hemolysis zone at 48 h. It has a broad spectrum of hosts and causes clinical disease in sheep, goats, cattle, horses, pigs, deer, camels and laboratory animals, as well as in human (Moore *et al.*, 2010).

CLA is characterized by chronic abscess formation in superficial lymph nodes such as the submandibular, parotid, pre-scapular, subiliac, popliteal and supramammary lymph nodes. The internal lymph nodes are also affected such the mediastinal, bronchial and mesenteric lymph nodes. Occasionally, visceral organs like liver, lung and spleen might have the same abscessation (O’Reilly *et al.*, 2008).CLA has a severe economic impact on the sheep and goat industries due to reduction in wool, meat and milk production and condemnation of carcass and skins (Fontaine and Baird, 2008).Thus, it is important to understand more about the disease and to determine whether the current control and prevention measure is efficient in controlling the disease.

There are few postulated and confirmed routes of infection for the disease. It can occur through direct or indirect contact or through wounds that come into contact with pus from the sick animals. In naturally observed infections, the main portal of bacterial entry is generally accepted to be through the skin, normally as a result of the presence of minor wounds and abrasions (Collett *et al.*, 1994). A respiratory route for transfer of *C. pseudotuberculosis* has been postulated and some researchers suggest that animals with pulmonary lesions may present the major source of exposure to naive animals within a flock (Ellis *et al.*, 1987). In addition, head and neck lesions are thought to arise from bacterial entry via the oral cavity (Ashfaq and Campbell, 1979). To date, no study had been conducted to confirm the best route of transmission of the disease. Therefore, the most efficient route of infection should be determined to better understand the mechanism of the infection.

Vaccination against CLA is one of the ways to prevent infection by *C. psedotuberculosis*. Glanvac 6™ is a vaccine against several important small ruminant diseases that is currently available in Malaysia. It is a multicomponent adjuvanted vaccine containing *C. pseudotuberculosis* and

5 *Clostridium sp.*, which are *Clostridium perfringens* type D*, Clostridium tetani*, *Clostridium novyi* type B, *Clostridium septicum* and *Clostridium chauvoei*. It has been evaluated in many countries such as in Australia, Canada, and Saudi Arabia but not in Malaysia.

This study was conducted to evaluate *C. pseudotuberculosis* infection through different routes of infection. The viscerals organs and lymph nodes were examined for lesions and the commercial vaccine was assessed for efficiency against CLA in goats in Malaysia. The objectives of the present study are:

1. To determine the most efficient route of infection in producing CLA in goats.
2. To assess the clinical and pathological changes in goats following acute and chronic experimental infection by *C. pseudotuberculosis.*
3. To determine the efficiency of Glanvac 6^{TM} vaccine against CLA in Malaysia.

Based on the objectives of the study, the hypotheses are:

1. The most efficient route of infection is via dermal route.
2. Following infection, lymph nodes abscessation is most frequently developed, with involvement of the visceral organs in which the severity increased with increasing time of infection.
3. The Glanvac 6^{TM} vaccine is efficient in preventing caseous lymphadenitis among goatsin Malaysia.

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