Host immune response to *Bartonella henselae*

AYOUNG HONG

Host response

Innate response: Phagocytes

- Macrophage
  - Engulf the pathogen for phagocytosis
  - Toll-like receptor 4 (TLR-4): recognize lipopolysaccharide of the pathogen
  - proinflammatory cytokine IL-2 and IL-6: induce inflammatory cell migration
  - anti inflammatory cytokine IL-10: prevents the maturation of macrophage, dendritic cells
- Dendritic cell
  - Present bacterial peptides via MHC class II molecules → activate CD-4 naïve T-helper cells

Adaptive response

- Assist cell-mediated immunity by T-helper cells & cytotoxic T cells
- Stimulate B cell
  - Secrets antibody IgM & IgG
- Immunologic memory
  - B-cell recognition the antigen of *B. henselae*
  - more rapid antibody production in future infection

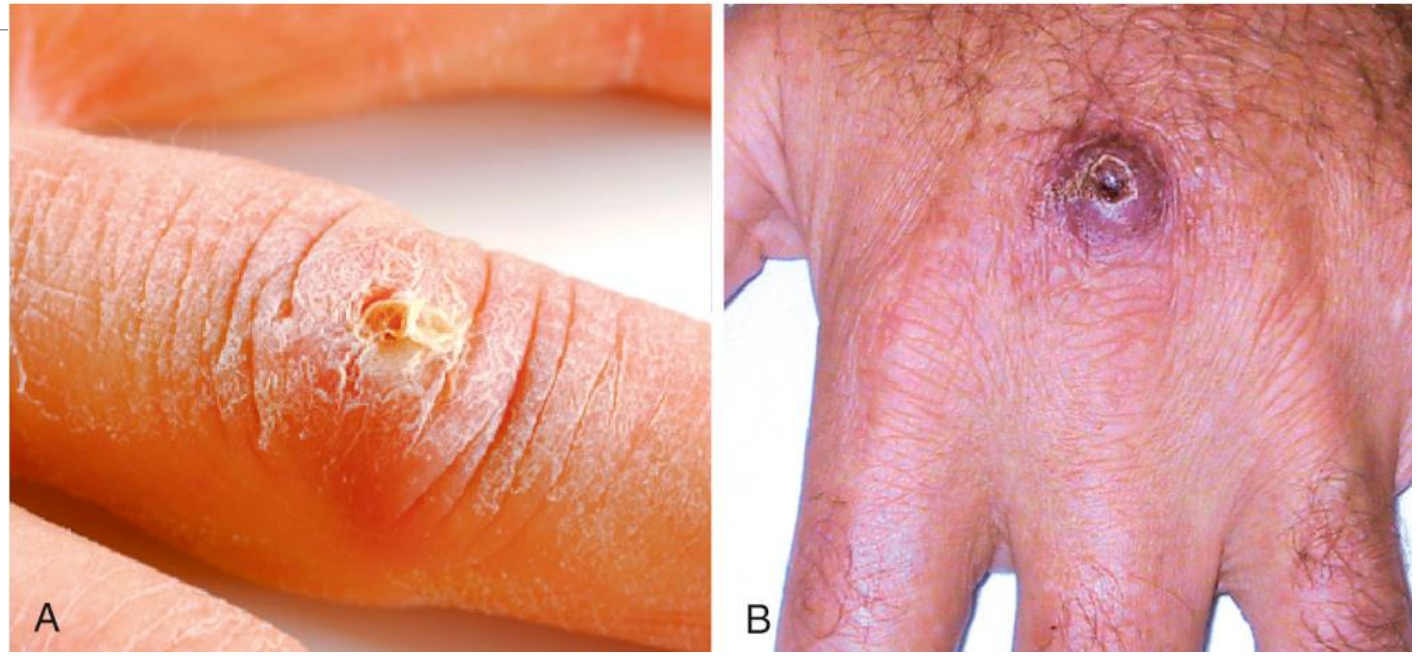
In immunocompetent host

- Innate immunity: *B. henselae* still evades phagocytes and migrate to lymph nodes
  → causes lymphadenopathy
  → granulomatous lesion/papules at the site of inoculation (skin)
- Adaptive immunity: *B. henselae* cannot multiply due to adaptive immune response in the lymph nodes
- Immunocompetent host do not need antibiotic intervention generally. The infection is self-limited and resolve within 1-2 months.
- Immunocompetent host will have antigen specific immunity against possible future re-infection.

Host Immune Response-Associated Damage & Bacterial Evasion

Skin lesion

- cutaneous pustule/papule
- >90% of typical CSD cases
- Starts 3-10 days after animal contact
- Lasts 1-3 weeks

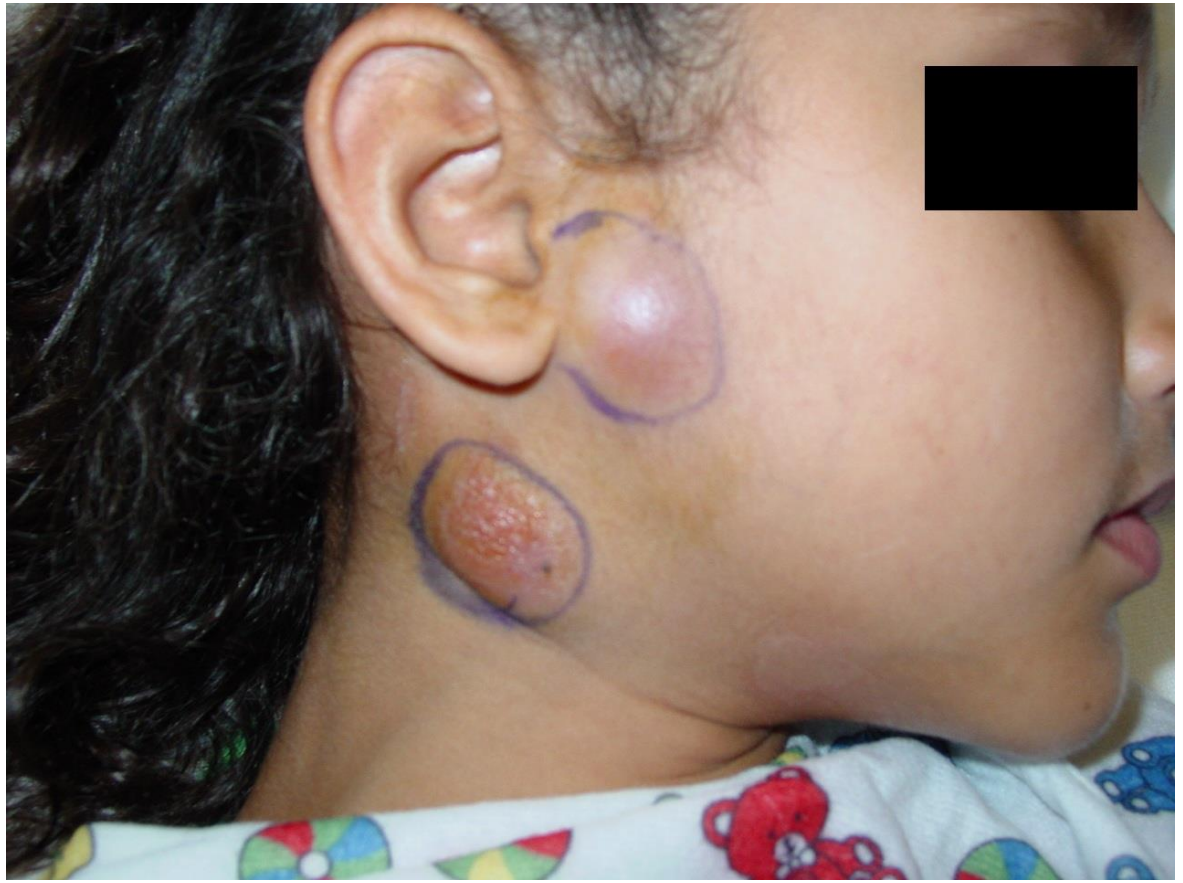


A: papules on the site of inoculation in immunocompetent host, B: granulomas in moderately immunocompromised host (kidney transplant)

Rose SR, Koehler JE. 2020. Bartonella, Including Cat-Scratch Disease, 2824-2843. In Bennett J (ed), Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th ed. Elsevier, Philadelphia, PA.

Lymphadenopathy

- swollen lymph nodes close to the site of inoculation
- Common symptoms of CSD. Single lymph node in 50%, multiple nodes at one site in 20% multiple site nodes in 30%
- Develops in 1-7 weeks



Lieberman, J. M. (2019, January 17). Cat Scratch Disease. Cancer Therapy Advisor. https://www.cancertherapyadvisor.com/home/decision-support-in-medicine/pediatrics/cat-scratch-disease/

Systemic Symptoms

- Low-grade fever in 30-60% patients
- Malaise/fatigue in 25% patients
- Headache, sore throat in 10% patients
- Transient rash in 5% patients

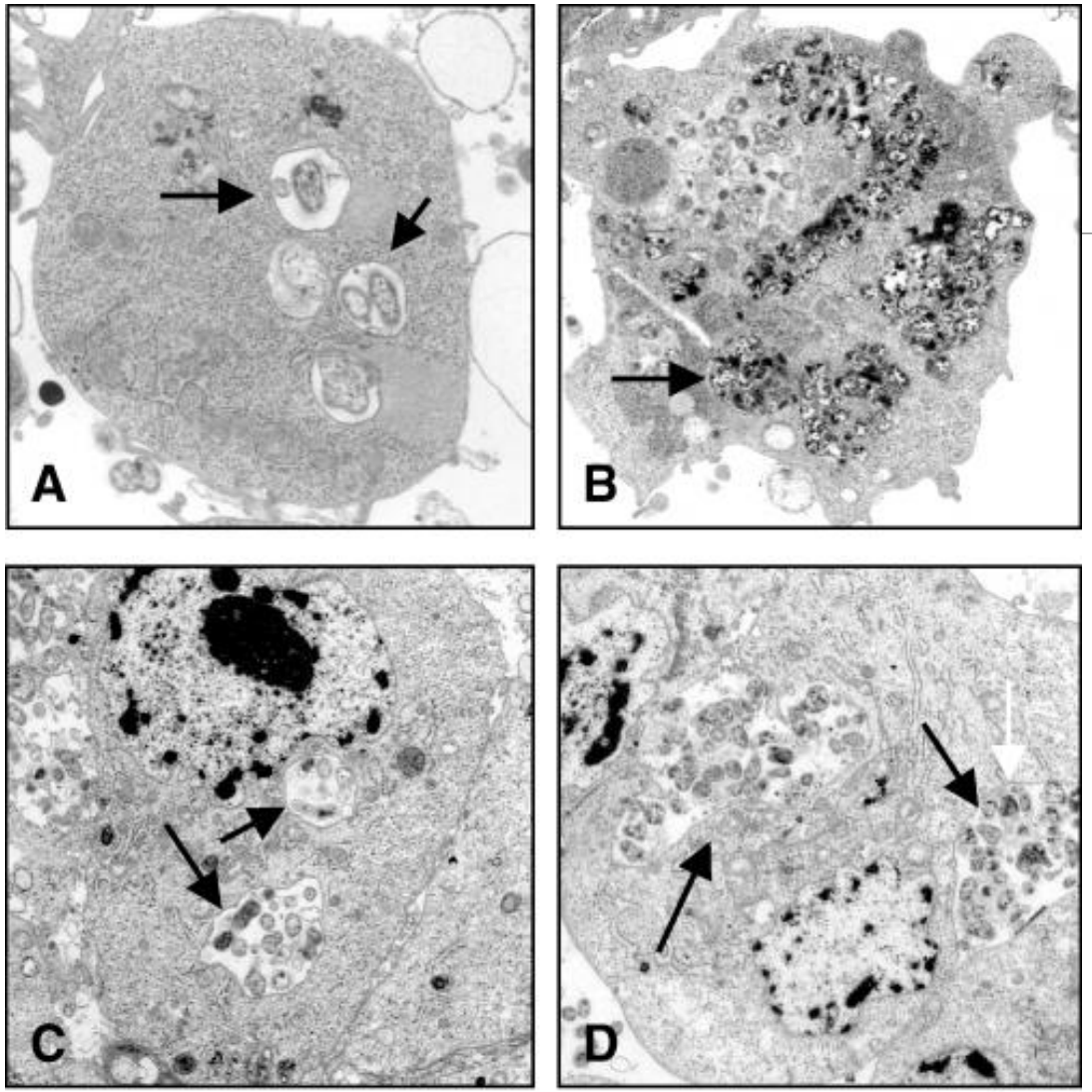
How does *B. henselae* cause symptoms?

- These symptoms (Skin lesion, lymphadenopathy, systemic symptoms) occur during innate & adaptive immune response
- Skin lesion develops due to local immune & inflammatory response

Lymphadenopathy - Evasion of Phagocytes

- Phagocytes as a vehicle
  - In murine model infection, bacteria are found in liver & lymph nodes within 6 hours after intraperitoneal inoculation.
  - *B. henselae* travel in the host system via phagocytes from skin to endothelial cell of blood vessel
- *Bartonella*-Containing Vacuoles (BCV)
  - "specialized non-endocytic membrane-bound vacuole"
  - BCV delays lysosomal targeting and destruction in phagocytes

Evasion of Phagocytes



Transmission electron microscopy

- A: murine macrophage infected with *B. henselae* for 2 hours. Bacteria are in the vacuoles (arrows).
- B: murine macrophage infected with *B. henselae* for 24 hours. Bacteria are degraded.
- C: human endothelial cell infected with *B. henselae* for 2 hours. Bacteria are in the vacuoles (arrows).
- D: human endothelial cell infected with *B. henselae* for 24 hours. Bacteria are in the vacuoles and viable (arrows).

Kyme PA, Haas A, Schaller M, Peschel A, Iredell J, Kempf VA. Unusual trafficking pattern of Bartonella henselae-containing vacuoles in macrophages and endothelial cells. Cellular microbiology. 2005 Jul;7(7):1019-34.

Related Virulence Factors

1. Penta-acylated lipopolysaccharide (Lipid A)
   - LPS and lipid A part: recognized by TLR4
     → *B. henselae* has unusual lipid A with long chain fatty acid without O-chain polysaccharide
2. Unusual structures of flagellin
   - Flagellin: site of TLR5 recognition
     → In *B. henselae*, TLR5-dependent NF-kB activation is suppressed
3. *Bartonella* adhesion A (BadA)
   - "Encodes antigenic variation of repetitive tandem stalk domains to prevent phagocytosis"
   - Prevent complement activation

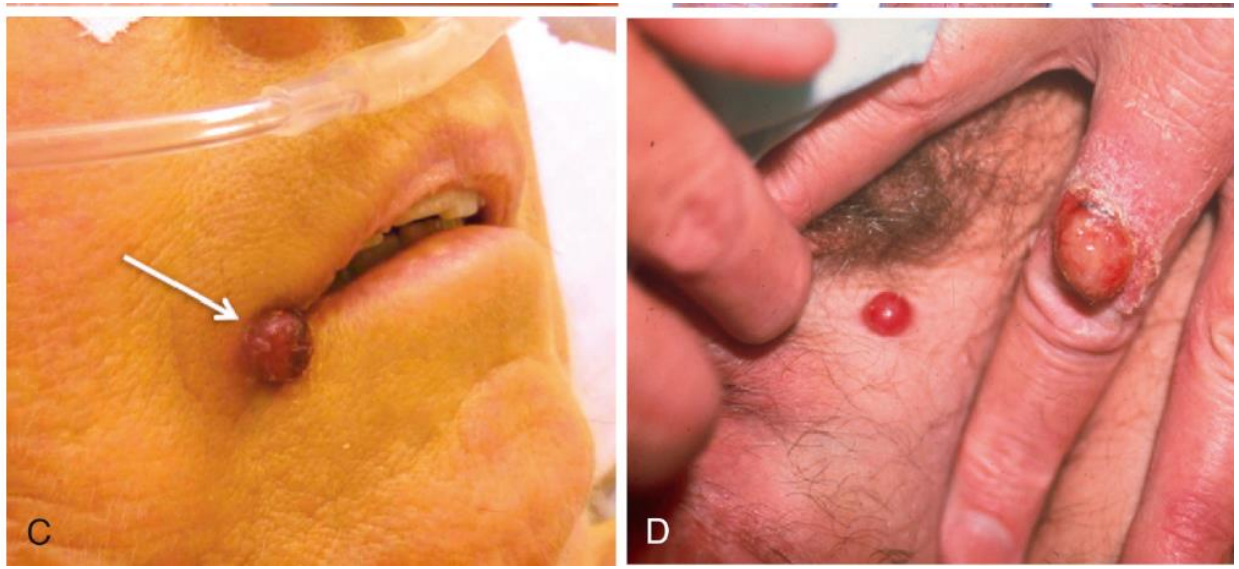
Pathogenesis by evading phagocytes

- Immunocompetent host: adaptive immune response eradicates bacteria
- Immunocompromised host: adaptive immune response fails to remove bacteria

  → Further complications

Bacillary Angiomatosis (BA)

- Vascular proliferation in skin
- First found in AIDS patient. Mostly occur in immunocompromised host, and very rarely in immunocompetent host.
- BA has been identified in a variety of internal organs, including liver, spleen, bone, brain, lung, bowel, and uterine cervix.



C: BA in immunocompromised host (pancreas-kidney transplant),
D: BA in AIDS patient

Rose SR, Koehler JE. 2020. Bartonella, Including Cat-Scratch Disease, 2824-2843. In Bennett J (ed), Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th ed. Elsevier, Philadelphia, PA.

Related Virulence Factors

"Direct mitogenic & antiapoptotic stimulation of endothelial cells + autocrine & paracrine cytokine secretion that synergizes with the direct effects"

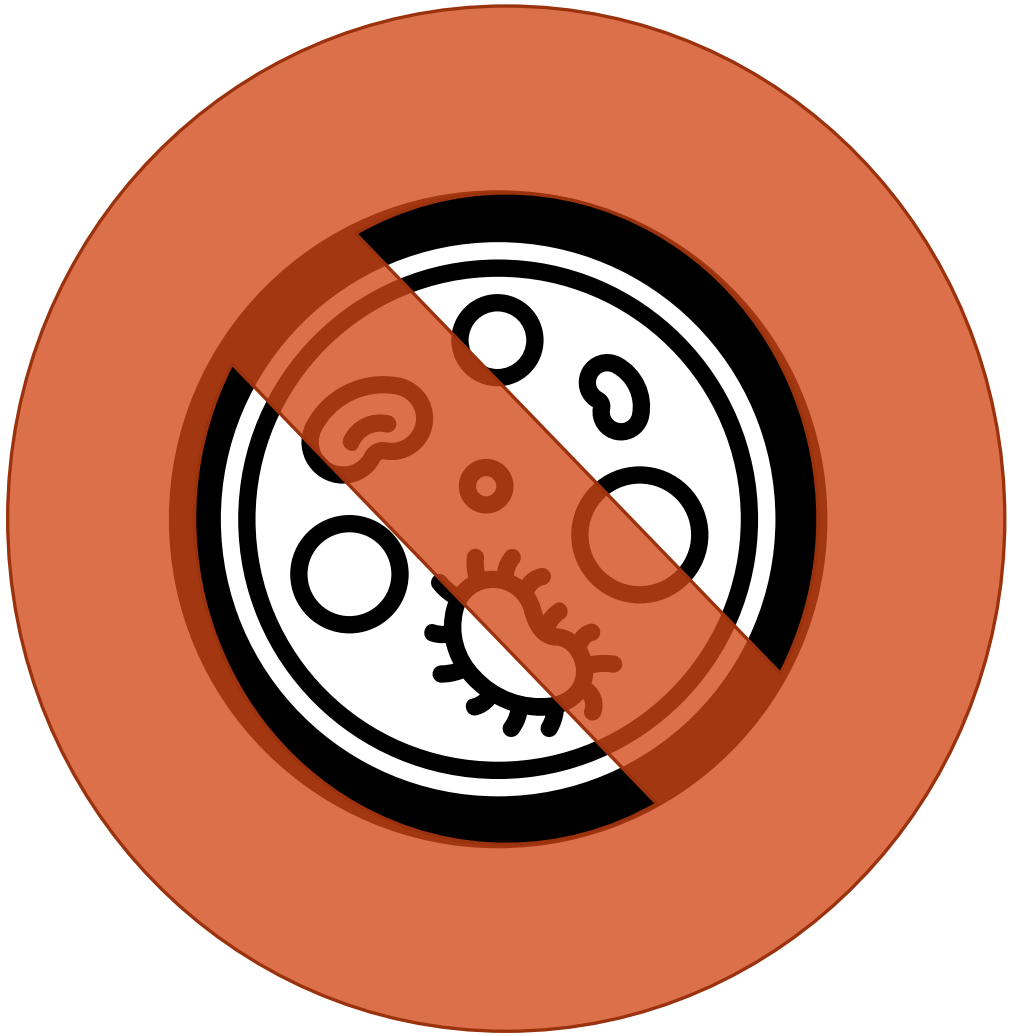
→ Stimulates vascular endothelial growth factor (VEGF)

1. Bartonella adhesion A (BadA):
Activation of NF-KB & secretion of proangiogenic cytokines

2. Outer membrane proteins:
activation of NF-kB signaling & part of pro-angiogenic signaling

Other complications

- Bacteremia
  - Symptoms: malaise, body aches, fatigue, weight loss, progressively higher and longer recurring fevers, headache
- Aseptic meningitis
- Endocarditis
- Occur mostly in immunocompromised patient or individuals with underlying disease (e.g., pre-existing valvular heart disease)



Outcomes

Eradication of Bacteria

- In immunocompetent patient, the pathogen will be eliminated once adaptive immunity is achieved. It is generally self-limiting
- In immunocompromised patient, host immune system fails to achieve adaptive immunity. Bacterial infection will cause further complications.

Patient Prognosis

- Immunocompetent patient with successfully devlopped memory B cells, re-infection will less likely to occur.
- Immunocompromised patient without memory B cells, host immune system will fail to recognize *Bartonella* in possible future infection.

References

1. Rose SR, Koehler JE. 2020. Bartonella, Including Cat-Scratch Disease, 2824-2843. In Bennett J (ed), Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th ed. Elsevier, Philadelphia, PA.

2. Harms A, Dehio C. Intruders below the radar: molecular pathogenesis of Bartonella spp. Clinical microbiology reviews. 2012 Jan;25(1):42-78.

3. Kyme PA, Haas A, Schaller M, Peschel A, Iredell J, Kempf VA. Unusual trafficking pattern of Bartonella henselae-containing vacuoles in macrophages and endothelial cells. Cellular microbiology. 2005 Jul;7(7):1019-34.

4. Deng H, Pang Q, Zhao B, Vayssier-Taussat M. Molecular mechanisms of Bartonella and mammalian erythrocyte interactions: a review. Frontiers in cellular and infection microbiology. 2018 Dec 12;8:431.

5. Resto-Ruiz S, Burgess A, Anderson BE. 2003. The Role of the Host Immune Response in Pathogenesis of Bartonella henselae. DNA Cell Biol. 22:431–440. https://doi.org/10.1089/1044549037676506694.