The Case of the Spring Break Consequences

Hazel reluctantly opened her eyes when her alarm went off. Spring Break was over, and she was definitely NOT ready for the second half of the semester. However, her profs would be ready with assignments and exams - thank goodness she didn't have any exams this first day back. She had really tied one on that last night at the beach, although she had to admit she wasn't too sure of some of the details. Slowly she headed for the shower and then dressed and gathered up her book bag to head to her first class.

![Image](https://example.com/image1.png)

**Figure 1:** Chlamydia inclusion bodies (cytoplasmic vesicles containing RB).

By the next week Hazel was aware of a vague pain in her lower abdomen and a slightly feverish feeling. She might have ignored those symptoms, but when she began to notice a foul-smelling vaginal discharge, she went to Student Health to be tested for STDs. Hazel was diagnosed with pelvic inflammatory disease (PID) caused by *Chlamydia trachomatis* and treated with antibiotics; her symptoms disappeared in a few days. Hazel was advised to finish all her antibiotics and to return to student health in a month to be tested for HIV infection.

Chlamydia is caused by *Chlamydia trachomatis*, an obligate intracellular gram negative bacterium. Chlamydia exists in two forms, infectious **elementary bodies (EB)** and **reticulate bodies (RB)** replicating in cytoplasmic vesicles inside infected cervical epithelial cells in women and urethral epithelial cells of men (**Figure 2**). In the presence of IFN-γ, non-replicating **persistent forms** can survive inside cells and become RB when IFN-γ levels drop. Inflammation at the infection site causes the symptoms, but 30-50% of men and 70-90% of women can be infected without experiencing symptoms. In 20-40% of women, Chlamydia infection can reach the fallopian tubes and cause PID, where it may induce scarring that can result in sterility (11% of women with PID) or tubal pregnancy (9% of women with PID). In a random sampling of young adults in the United States, 4.2% tested positive for *Chlamydia trachomatis* (Brunham and Rey-Ladino, 2005).
Figure 2: Replication of Chlamydia. (Brunham and Rey-Ladino, 2005)
*Chlamydia trachomatis* can also infect the conjunctiva of the eye, resulting in corneal damage and blindness. *C. trachomatis* is the leading cause of blindness in the world. Women infected with sexually transmitted *C. trachomatis* can infect their infants during birth; babies are routinely treated with antibiotic eye drops in the delivery room to prevent infant blindness. Eighteen different serovars of *Chlamydia trachomatis* have been identified, 4 associated with conjunctivitis and the other 14 associated with sexually transmitted disease (*Table 1*).

**Table 1.** (Brunham and Rey-Ladino, 2005)

The immune response to Chlamydia has been studied in mice infected with *Chlamydia muridarum* and in humans infected with *C. trachomatis*. The following factors have been described in immune responses to Chlamydia:

**Cytokines:** Infected epithelial cells produce inflammatory cytokines CXCL1, CXCL8 (IL-8), CXCL16, GM-CSF, IL-1α, IL-6, and TNF. They upregulate secretion of CCL5, CCL7 and CXCL10 that attract lymphocytes. They also secrete IFNα, IFNβ, and IL-12. Infected macrophages secrete TNF and IL-6, while infected fibroblasts secrete IFNα, IFNβ, and nitric oxide (NO). Dendritic cells produce IL-12, as well as CXCL10 (a chemokine that recruits T cells) and CCR7 (a chemokine receptor that allows DCs to migrate to local lymphoid tissues).

**Anatomy:** The lower part of the female genital tract (FGT) has normal flora, while the upper part is normally sterile. The FGT does not have Peyers Patches or M cells like the intestinal mucosa, but it does have small diffuse collections of immune cells in the lamina propria where T and B cells can be activated (*Fig 3*, immune induction sites). DCs can insert dendrites between the mucosal epithelial cells to bind pathogens in the vagina and Fallopian tubes. DCs also carry antigen to nearby lymph nodes for lymphocyte activation, and activated T cells enter the infection site by binding MadCAM1 and VCAM1 that are highly expressed in infected epithelia. Equal amounts of IgA1 and IgA2 are secreted into the FGT; IgA2 is resistant to IgA proteases.
secreted by pathogens such as *Neisseria gonorrhoeae*. Respiratory and upper GI mucosal secretions contain primarily IgA1.

**Cellular responses:** Nude (athymic) mice cannot control *Chlamydia muridarum* infection. Adoptively transferring CD4+ or CD8+ Chlamydia-specific T cells into these mice allows them to successfully control the infection. Adoptive transfer of Chlamydia-specific Th1 but not Th2 cells was protective.

Mice deficient in Class II MHC, CD4, IL-12, IFNγ, or IFNγ receptor cannot control Chlamydia infection. Mice deficient in β2 microglobulin, perforin, or FAS could control Chlamydia infection as well as wild-type mice. However, Chlamydia-specific CD8+ T cells lysed Chlamydia-infected cells in culture, and adoptive transfer of Chlamydia-specific CD8+ T cells protected mice from Chlamydia infection using IFNγ. IFNγ induces infected cells to produce IDO, an enzyme that degrades tryptophan. Tryptophan starvation kills actively replicating intracellular Chlamydia. IFNγ also induces production of NO and activation of Th1 cells.

**Antibodies:** High levels of IgA in the cervical secretions of infected women correlate with low numbers of *Chlamydia trachomatis*. High levels of IgA do not correlate with elimination of infection and do correlate with sequelae such as tubal infertility. In culture, IgA can neutralize Chlamydia. Mice that lack B cells have the same course of primary Chlamydia infection; but mice with normal numbers of B cells but depleted of CD4+ and CD8+ T cells can eliminate Chlamydia in a secondary infection. Mice lacking FcR have more severe secondary infection than mice with FcR.

In spite of these immune responses, infection with *Chlamydia* can be prolonged, probably due to strategies Chlamydia uses to avoid them (see Question 3 below).

**Questions:**

1. Using the information above, list 4 different innate responses, 3 different T cell functions, and 3 different antibody functions involved in the immune response to *Chlamydia*.

2. Using the data supplied above, decide which immune effector is most important for clearing a primary *Chlamydia* infection. List three pieces of evidence given above to support your hypothesis. Then list at least one piece of evidence for each effector that supports the role of two other immune effectors in clearance of or protection from *Chlamydia*.

3. Complete the chart below by describing how each strategy employed by *Chlamydia* to evade immune elimination interferes with the immune system.

<table>
<thead>
<tr>
<th>Immune evasion</th>
<th>Immune Response Inhibited</th>
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<tbody>
<tr>
<td>Many different surface protein serotypes</td>
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<td>Replication within a cytoplasmic vesicle</td>
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<tr>
<td>Blocks apoptosis of host cells</td>
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<tr>
<td>Increased resistance to NO</td>
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<tr>
<td>LPS 100 fold less potent at activating host cells</td>
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</table>
Infected macrophages secrete TNFα, which induces apoptosis of activated T cells

Down regulates host cell expression of MHC Class I and Class II

Develops persistent non-replicating forms that can become RB in the absence of IFNγ

Express genes encoding tryptophan synthetase

Additional Resources:

Chlamydia: CDC Fact Sheet

Evasion of Immune Response

Pelvic Inflammatory Disease: CDC Fact Sheet


Case adapted and Modified from Dr. Janet Deckert at the University of Arizona. Her email is jdeckert@u.arizona.edu and her website is webMic419 Home