

THE COST OF COMPANIONSHIP

Jared Gillingham and Robert Burlage
Concordia University School of Pharmacy
Mequon, WI

Synopsis: Infectious diseases are always a concern, but when you are a person in an at-risk category the difficulties multiply. You must be aware of the typical pathogens, but also the atypical pathogens that would not be dangerous to healthy people. In this case study we explore an atypical pathogen, *Bordetella bronchiseptica*, in cystic fibrosis patients and the surprising source of that pathogen. We present the case incrementally to develop a model for anticipating potential problems. The issue is not only this pathogen and this at-risk group, but a conceptual model of determining where pathogens may affect many other at-risk groups.

Learning objectives

At the end of this case study students should be able to

- Identify and list the characteristics of an at-risk population as compared to a healthy population
- Describe the molecular nature of cystic fibrosis and the current pharmaceutical treatments (section I and II)
- Describe the pathogenic basis of disease for the *Bordetella* pathogens (section II)
- Recommend methods to avoid, eliminate or alleviate infection in at-risk populations (section II and III)
- Create a cogent argument for the potential of an atypical pathogen to cause illness in a specific at-risk population (see Engering article for in-depth discussion)

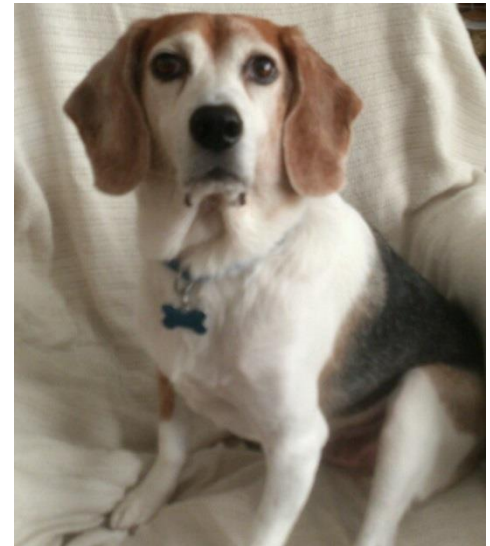


Figure 1. Used with permission from Cooper, the dog. Now throw the ball.

People with cystic fibrosis (CF) face immense health challenges. As a genetic disorder it appears in early childhood. Depending on the type of genetic mutation, the CF patient may exhibit a range of disease symptoms. Many people will correctly associate an increased saltiness of the skin as a symptom of CF. This is because the gene involved is responsible for a chloride transporter in the cell membrane of epithelial cells. When the transporter is malfunctioning the electrolyte balance is disrupted. Affected organs include the lungs, pancreas, intestine, and reproductive organs.

In particular, the lungs suffer from accumulation of thick mucus which clogs the airway spaces. Thick mucus that cannot efficiently be cleared provides an environment for bacterial growth, which results in pneumonias caused by a variety of microbial pathogens. Of great concern is pneumonia caused by *Pseudomonas aeruginosa*, which is often highly resistant to antibiotics. Repeated infections can result in damage to the lungs and reduced respiratory effectiveness. Respiratory failure is the leading cause of death in CF.

Treatment has been improving, including some new, revolutionary drugs (see below), although the life expectancy is still short. It is currently about 36 years for those with the worst genetic mutations. Other mutations which are not as severe give the patient an average life expectancy of 50 years. There is much more to learn about CF and its resulting complications. Here we will use it as an example of a specific at-risk population and the susceptibility of the sufferers.

I. The Nature of CF.

First, describe the cause of CF. Which gene is involved, and which mutations are responsible for the worst cases? What is the normal function of the protein, and what happens when that protein is mutated?

Is there an effective treatment for CF? Describe.

II. The Unexpected Complication

Across the U.S. there are many specialized treatment centers for CF patients. These centers often screen the patients for infectious disease using respiratory samples. A clinic in Minnesota that specializes in CF cases performed a comprehensive study of microbial contaminants associated with their patients. That is, they identified all microbial isolates from the samples.

Interestingly, they identified seven patients who tested positive for *Bordetella bronchiseptica*. This microbe rarely causes human illness, so its presence in the CF patients is very unusual. Consider that the treatment center has an enrollment of only 137 CF patients, making the percentage of affected patients far higher than is found in the general public.

Why is the presence of *Bordetella bronchiseptica* a surprising finding? Which disease is this microbe responsible for? Is it a typical human disease?

How do you think the researchers identified the microbes? What would be the ideal way to specifically identify the suspected microbe in new patients?

How do you think the patients contracted this microbe? How would you create an experiment to test your hypothesis?

Patient	Genes	Animal contact	Bacterial isolates	Treatment	Post-treatment isolates
1	ΔF508/ ΔF508	Dog	MSSA, B. bronchiseptica	Azithromycin	MSSA
2	ΔF508/ ΔF508	Dogs, horses, cats, guinea pigs *	MSSA, B. bronchiseptica, Pseudomonas aeruginosa	Ciprofloxacin	P. aeruginosa
3	ΔF508/ ΔF508	Dogs, cats	MSSA, B. bronchiseptica, Group A Streptococcus, Stentrophomonas maltophila	Trimethoprim/sulfamethoxazole	MSSA
4	ΔF508/Δ1507	Dog, horses*	MSSA, B. bronchiseptica	Meropenem, tobramycin	MSSA
5	ΔF508/ ΔF508	Dogs, cats	MSSA, B. bronchiseptica, Pseudomonas aeruginosa	Ceftazadime, tobramycin, Trimethoprim/sulfamethoxazole	MSSA, Trichosporon
6	ΔF508/unknown	Dogs†	MSSA, B. bronchiseptica, yeast	Clindamycin, ceftazadime	Staphylococcus, Stomatococcus, alpha-hemolytic Streptococcus
7	ΔF508/ ΔF508	Dog*	MSSA, B. bronchiseptica, yeast	Clindamycin, ceftazadime, tobramycin, itraconazole	MSSA, yeast

Based on data from Brady et al. (2014).

*Farm environment

†kennel environment

MSSA – methicillin-sensitive Staphylococcus aureus

The table provides the actual data from the clinic study, listing the seven infected individuals and the results of the analysis. How has your response to the previous question changed in response to these data?

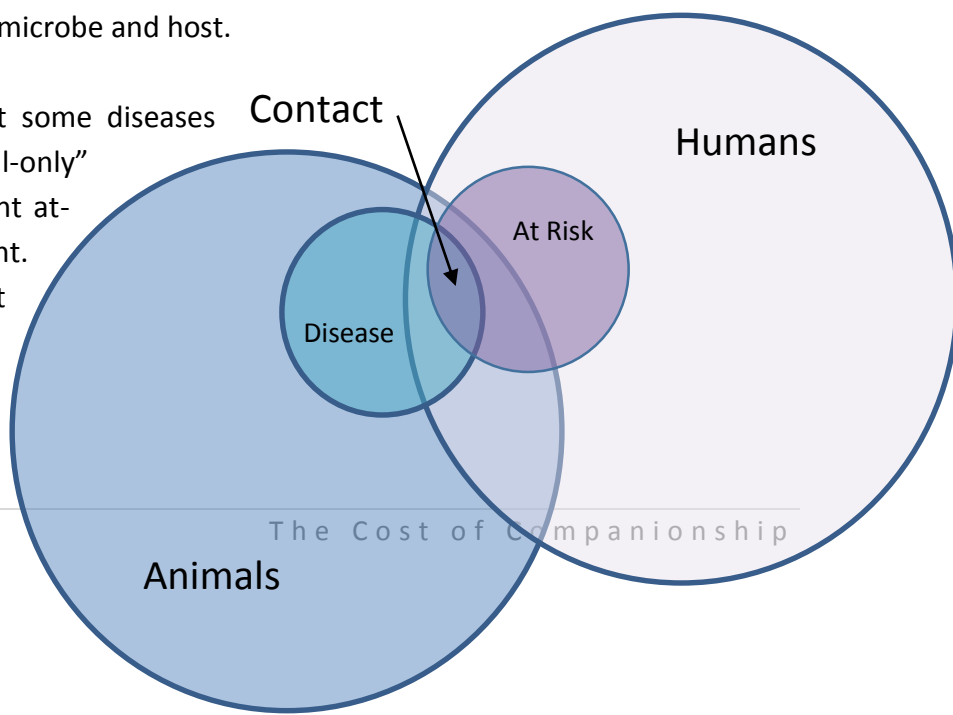
Given what you know about bacterial pathogens, what are some examples of bacterial virulence factors that contribute to symptoms? How would you hypothesize that *B. bronchiseptica* could contribute to pathology in compromised subjects?

Referring once again to the table, note that the CF patients received treatment for the *Bordetella* infection. A post-treatment screening was also performed. What can you conclude about the drug treatments?

III. The Bigger Issue

A zoonosis is an infectious disease of animals which can be passed to humans, where it causes disease. It is easy to see how disease can be passed from animals to humans. Humans have always lived in close proximity with the rest of the animal kingdom. We contact animals through the hunting and cleaning of game, the domestication of many species such as cattle and sheep, and of course the keeping of many other species as pets such as cats and dogs. In our increasingly overlapping habitats, humans and animals also share their respective microbiota and pathogens. While pathogens have evolved to infect a certain species or closely related species based on their physiology and genetics, there is occasional crossover to other species of similar physiology. Random mutations may create changes that result in an increased or decreased interaction between microbe and host.

It is important to note here that some diseases which are considered as “animal-only” may in fact be zoonotic if the right at-risk human population is present. The diagram illustrates that humans and animals frequently come into contact. Subsets of the animal population will have an infectious disease, while a subset



of humans will be at-risk for that disease. Keeping these two subsets apart should be our conceptual objective.

Assume you are responsible for reducing infections from *B. bronchiseptica*, especially in at-risk patients. Describe some of the ways you could achieve your goal. Can you think of any examples where there is physician/vet interaction outside of this example?

Given the information you have collected today, how would you approach a patient who has immune system complications that is interested in getting a pet or service animal? What advice might you give?

Chlamydophila abortus is another potential pathogen of at-risk individuals. Apply the above analysis to research the issue and identify the at-risk groups, the potential harm, and the methods you could employ to reduce risk.

About the authors

Jared Gillingham is a second year student at the Concordia University School of Pharmacy

Robert S. Burlage, Ph.D. is a professor and chairman of the Pharmaceutical and Administrative Sciences Department at the Concordia University School of Pharmacy

References

- A standard microbiology text is sufficient for information about the *Bordetella* species mentioned here as well as other typical animal pathogens that might cross over to humans. We can recommend Medical Microbiology. Murray, P.R., Rosenthal, K.S. and M.A. Pfaller. 7th edition. Elsevier Saunders. ISBN 978-0-323-08692-9.
- Most standard texts on cell biology present a section on cystic fibrosis because it is understood very well.

- Cystic Fibrosis (Oxford Respiratory Medicine Library (O R M L), Horsley, A., Cunningham, S. and J. Alastair Innes (Eds.) 2nd Edition. Oxford University Press. ISBN-13: 978-0198702948. 2015. This book has the latest information about CF and is comprehensive in the treatment of the subject.
- The Cystic Fibrosis Foundation (<https://www.cff.org/>) is an excellent source of information on the disease. CF is described for the layman at <http://www.cysticfibrosisdata.org/>. Note that the data are a little dated.
- Mattoo, S. and Cherry, J.D. 2005. Molecular Pathogenesis, Epidemiology, and Clinical Manifestations of Respiratory Infections Due to *Bordetella pertussis* and Other *Bordetella* Subspecies. Clin Microbiol. Rev. 18(2): 326-382. This is a lengthy review of *Bordetella* species but has very valuable information on *B. bronchiseptica*. It is also worth reading for the instructor.