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Within-host dynamics of mycoplasma infections: Conjunctivitis in wild passerine birds

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ABSTRACT

The host–pathogen interaction drives infectious disease dynamics at the individual, population and community levels. Here I present and analyze a model of the vertebrate immune response to mycoplasma infections, and use it to identify which pathogen and host immune characteristics drive patterns of *Mycoplasma gallisepticum* (MG) infections in the house finch (*Carpodacus mexicanus*) and other passerine birds. I also address which host and pathogen characteristics most affect host infectiousness and survival. These results imply that much of the observed variation in the house finch likely arises from variation among birds in the effectiveness of their non-specific immune response to MG, and that the host and pathogen characteristics most likely to influence host infectiousness and survival are the intrinsic pathogen growth rate, the strength and efficiency of the non-specific immune response and characteristics affecting the effectiveness of the specific response. These findings suggest that molecular-level study of how MG and other mycoplasmas interact with a host's non-specific and inflammatory responses should reveal much about the relationships between host infectiousness, pathogen load, and disease symptoms in these systems.

1. Introduction

The host–pathogen interaction is at the core of every infectious disease system, and provides an important foundation from which to study infectious disease at the individual, population and ecosystem levels. Central to this interaction is the interplay between the pathogen and the host's immune defenses, which can largely determine (1) both short and long term consequences of infection for the host and (2) host infectiousness and pathogen transmission. The immune–pathogen interaction also mediates how various external factors act to shape the progression and consequences of an infectious disease.

The motivation for this paper is a bacterial disease caused by the pathogen *Mycoplasma gallisepticum* (MG), which has been the focus of many studies since its appearance in wild passerine birds in eastern North America around 1993 (Luttrell et al., 1996; Fischer et al., 1997; Dhondt et al., 1998; Hartup et al., 1998; Luttrell et al., 1998; Hochachka and Dhondt, 2000; Hartup et al., 2001a, 2001b; Altizer et al., 2004a, 2004b; Faustino et al., 2004; Hosseini et al., 2004; Kollias et al., 2004; Dhondt et al., 2005; Farmer et al., 2005; Hawley et al., 2005, 2005a; Hotchkiss, 2005; Lindstrom, 2005; Sydenstricker et al., 2005; Altizer et al., 2006; Cherry et al, 2006; Dhondt et al., 2006; Hawley et al., 2006; Hochachka and Dhondt, 2006; Ley et al., 2006; Sydenstricker et al., 2006; Cooper et al., 2007; Dhondt et al., 2007a; Dhondt, 2007b; Hawley, 2007; Dhondt, 2008; Grodio, 2008; Hurtado, 2008; Hawley, 2010; Grodio et al., 2011). Originally known as a respiratory pathogen of domestic poultry, MG has been well studied prior to its jump to passerine hosts in the early 1990s. Its primary host is the house finch (*Carpodacus mexicanus*), a widespread species introduced into eastern North America from southern California in the early 1940s (Elliott and Aribib, 1953; Aldrich and Weske, 1978). MG can also infect the American goldfinch (*Carduelis tristis*) and other Cardueline finches, and has been detected in various other bird species (Fischer et al., 1997; Mikaelian et al., 2001; Hartup et al., 2001a, DeCoste et al., pers. comm.). Disease symptoms include severe inflammation of the conjunctiva (the mucosal surface of the eye), lethargy, and in some cases death (Luttrell et al., 1998; Dhondt et al., 2005).

There are multiple reasons to study *M. gallisepticum* in wild birds. First, this disease shares many of the hallmarks of mycoplasmal infections in other organisms including some model organisms (rodents), other wildlife (e.g., some ungulates), domestic poultry, pigs and humans (Brown et al., 2005; Marco et al., 2009; Baseman and Tully, 1997; Hu, 2009; Messick, 2004). Second, this wildlife disease is relatively easy to study *in situ* since disease symptoms can be visually observed in wild birds and also since these organisms can be studied in captivity. Third,

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this system provides an opportunity to study host–pathogen coevolution during the emergence of a novel infectious disease. Following its appearance during the early 1990s MG led to significant declines in the eastern population of the house finch and today continues to spread into western North America. The genomes of some MG strains have been sequenced and the functional genomics of MG and other mycoplasmas are fairly well understood (Papazisi et al., 2003; Blanchard and Browning, 2005). Furthermore, recent evidence shows that strains of MG circulating among house finches differ in virulence, which has changed over time.

Fig. 1 illustrates the range of disease progression among house finches using data from experimentally infected captive birds (Grodio, 2008; Grodio et al., 2011; Hawley, 2010). The typical course of infection in the house finch ranges from a very mild acute illness to a more persistent disease with prolonged severe inflammation. Symptomatic infections begin with a brief asymptomatic period followed by mild to severe inflammation of the mucosal tissues surrounding the eye and inside the eyelids (the conjunctiva). This diseased state may clear within a week or two, however in some individuals it can persist for months or may be so severe as to result in death (Sydenstricker et al., 2006; Kollias et al., 2004; Roberts et al., 2001). These persistent infections are typically symptomatic, although the existence of chronic asymptomatic infections has been put forth as one possible mechanism for interannual persistence of MG in wild house finch populations. Observations thus far suggest that the resolution of symptoms typically (though not exclusively) follows a reduction in pathogen load by the host's immune response.

The goal of this paper is to develop and analyze a dynamic model of the vertebrate immune response to a localized mycoplasma infection and use it to answer the following questions about *M. gallisepticum* in wild passerine birds. First, empirical study of this system has shown significant variation in the progression of *M. gallisepticum* infections within and between host species. Such variation is common in wildlife disease systems with multiple host species. To what extent can this variation be explained by a relatively simple model of the pathogen and host immune interaction? What aspects of this variation may result from factors not included this model? Second, preliminary data suggest that there has been some evolutionary change in virulence (i.e., the severity of host symptoms) among circulating strains of *M. gallisepticum* (Hawley et al., pers. comm.). Virulence evolution in this system is likely shaped by pathogen load, which drives host infectiousness (pathogen fitness), and by host disease symptoms, which drive host mortality risk and thus survival (host fitness). Which pathogen and host immune characteristics most affect host infectiousness and host mortality risk? Can likely targets for empirically detecting virulence-driven selection in the host or pathogen be identified using this model?

Mycoplasma infections are typically quite persistent and induce severe inflammation by eliciting a frustrated and ineffective host immune response. To quote Simecka (2005), "it is likely that almost every component of the host immune system is involved in the response to mycoplasma disease." In particular, both specific and non-specific immune responses are involved in controlling infections, and mycoplasmas may manipulate the host

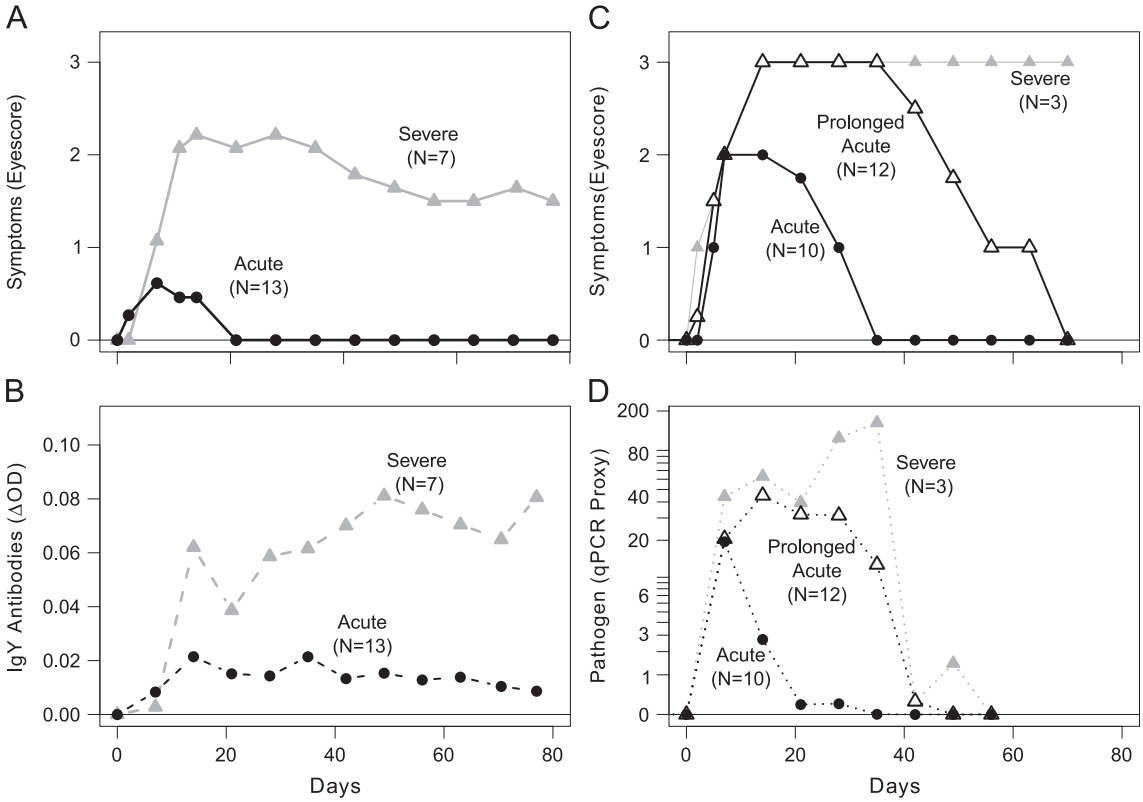

Fig. 1. *Mycoplasma gallisepticum* infections in the house finch (*Carpodacus mexicanus*) range from very mild to very severe. Panels on the left show symptoms (A) and antibody levels (B) for 20 individuals from the common garden experiment described in Hawley (2010) and Grodio et al. (2011). The means for groups are shown: the seven most severe infections from that experiment ($N=40$) and 13 that resolved symptoms of infection from the group ($N=20$) infected with a 2006 isolate of *M. gallisepticum*. Panels on the right show average symptoms (C) and approximate pathogen load (D) from a second experiment (Grodio, 2008; Grodio et al., 2011). Here the median values for three qualitatively similar groups are shown: mild acute infections, prolonged acute infections, and severe infections characterized by persistent, severe symptoms over the duration of the experiment. "Eye Score" is a standard measure of the severity of conjunctivitis (Kollias et al., 2004; Sydenstricker et al., 2006) and IgY is the avian equivalent of mammalian IgG.