Review

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The potential impact of coinfection on antimicrobial chemotherapy and drug resistance

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Across a range of pathogens, resistance to chemotherapy is a growing problem in both public health and animal health. Despite the ubiquity of coinfection, and its potential effects on within-host biology, the role played by coinfecting pathogens on the evolution of resistance and efficacy of antimicrobial chemotherapy is rarely considered. In this review, we provide an overview of the mechanisms of interaction of coinfecting pathogens, ranging from immune modulation and resource modulation, to drug interactions. We discuss their potential implications for the evolution of resistance, providing evidence in the rare cases where it is available. Overall, our review indicates that the impact of coinfection has the potential to be considerable, suggesting that this should be taken into account when designing antimicrobial drug treatments.

Classifying mechanisms of pathogen interactions

The spread (see Glossary) of chemotherapy-resistant pathogens is a serious global problem [1], affecting our ability to control pathogens ranging from parasites to viruses. Infected individuals are often coinfected, either by multiple strains of the same pathogen or by different species of pathogen. Classic examples include the multiplicity of strains typically identified in malaria infections [2] and coinfections involving human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (TB) [3]. Here, we present an overview of the potential ways by which coinfection might affect the outcome of chemotherapy, focusing on the question of the evolution of drug resistance.

One way to classify the diversity of possible interactions between pathogens is to set them on a spectrum of synergistic to antagonistic. In synergistic interactions, the within-host growth rate of one parasite will increase in the presence of the other, while in antagonistic interactions, the presence of one pathogen will limit the growth rate of the other. Examples of the former might include HIV–hepatitis C virus (HCV) [4] and HIV–malaria [5–7]; examples of the latter might be multiple strains of malaria [8]. It is also possible that coinfecting pathogens do not interact, but as this is unlikely to affect the evolution of resistance it is not discussed further in this review. It should be noted, however, that the degree to which pathogens interact is

Glossary

Coinfection: for the purposes of this review, the term coinfection is used in a broad sense, covering all combinations of infection with more than one pathogen or strain. We consider coinfections with multiple strains of the same species as well as infections with multiple species of pathogen (following [48]). This includes simultaneous infection (two pathogens or strains transmitted together), superinfection (one pathogen or strain infects a host where another is already present), and sequential infection (one pathogen or strain infects after a previous infection has cleared, potentially leaving residual changes in the immune or resource landscape that would affect the second pathogen).
Emergence: the emergence of a resistance mutation within a pathogen is generally the result of a *de novo* mutation. For bacteria, other possibilities include acquisition from other strains or species present in the vicinity of the pathogen, that is, via horizontal gene transfer.
Fitness cost: frequently, mutations conferring some degree of resistance are associated with a fitness cost in terms of reduced pathogen within-host growth rate, which translates into a reduction in transmission of the resistant pathogen. Such costs are often mediated by competition with other coinfecting pathogens, via direct competition, or apparent competition mediated by the immune system. Even mutations that apparently have no cost, for example, mutations involved in conversion of efflux pumps, will be affected by the presence of susceptible strains, purely in the fraction of transmission dominated.
Focal pathogen: we use the term focal pathogen to mean the pathogen initially targeted for treatment. Often, but not always, this can mean the pathogen causing either more severe or more recognizable disease.
Spread: once a *de novo* resistance mutation has emerged, it must spread within the population. This requires both successful replication within a host, and then spread through the population via transmission to other hosts.

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Table 1. Interactions at the scale of the individual[a]

	Beneficial	Neutral	Detrimental
Beneficial	HIV–HCV[b] [4] HIV–TB[c] [3]	Helminths beneficial for bacteria/viruses [17,18]	Cheating/cooperation in siderophore-sharing bacteria [28,29] HIV–GB virus C[d] (detrimental to HIV) [74]
Neutral	–	Non-overlapping: *tinea pedis*, influenza	Fever-promoting: malaria detrimental for syphilis[75], *Helicobacter pylori* restricting (detrimental for) TB infection [26]
Detrimental	–	–	Competing strains: malaria (depending on strains) [38]

[a]Row labels correspond to the impact on one pathogen of the coinfection, while column labels correspond to the impact of the coinfection on the other.

[b]Hepatitis C virus.

[c]Mycobacterium tuberculosis.

[d]Formerly known as Hepatitis G virus or HGV.

often unclear, and the available evidence is possibly controversial. The type of interaction broadly determines the impact of coinfections on resistance evolution: while synergistic interactions tend to promote resistance, antagonistic interactions hinder the evolution of resistance (see below).

This review is organized around the two main mechanisms that might shape the outcome of chemotherapy: (i) immune modulation (whereby the presence of the coinfecting pathogen can affect immune function), and (ii) resource modulation (where the coinfecting pathogen can have effects on resource availability for the focal pathogen) – Table 1 and Figure 1 give examples. For both mechanisms, we provide an overview of their potential to affect the emergence and spread of drug resistance across a range of pathogens, distinguishing between synergistic and antagonistic interactions where possible. It is important to note that for many pathogens, multiple mechanisms may apply; additional, less clearly classified mechanisms may also be involved (Boxes 1 and 2). Finally, while there may be clear evidence of interaction, the exact mechanism in play is frequently unknown.

Immune modulation

Pathogens attacking hosts are confronted by the immune system, and often the immune responses stimulated by one pathogen interact with those stimulated by a coinfecting pathogen. This type of interaction can be either synergistic or antagonistic, depending on pathogen identity and type of immune response.

Synergistic interactions: immune-mediated facilitation

When coinfection occurs, one or both pathogens may suppress the immune response. This suppression may facilitate the spread of drug-resistant mutants of the coinfecting pathogen via several routes. First, reduced immune-mediated killing of pathogens may lead to higher pathogen replication, which can increase the probability of the emergence of *de novo* resistance (e.g., HIV–malaria coinfection [5]). Second, the reduced efficacy of the immune system may increase the frequency of symptomatic infections (in the absence of immunopathology) and hence the use of antimicrobials (e.g., HIV–herpes simplex virus 2 coinfection [9]), which will increase the selective pressure for resistant mutants and potentially the spread of resistant pathogens. Third, reduced immune-mediated killing may allow the replication of drug-resistant strains bearing a high fitness cost (which would otherwise be outcompeted by fitter sensitive strains, e.g., HIV–TB coinfection [10]). Similarly, impaired immune control may increase the danger of a recrudescence of partially resistant pathogen populations after therapy has ended. Such partially resistant pathogen populations are often selected for during therapy, and might be present after treatment [11]; with an effective immune response they would be rapidly eliminated, but an immunosuppressive coinfection may allow for their proliferation [12]. The impact of HIV coinfection on drug-resistant TB and malaria, on which recent major strides in research have been made, are classic examples of how an immunosuppressive pathogen can exacerbate resistance problems.

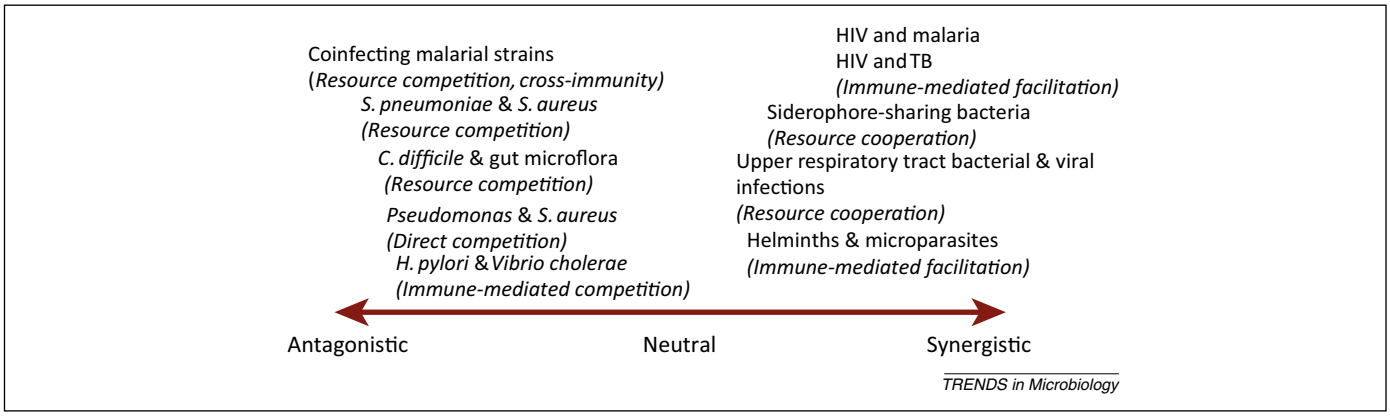

Figure 1. Antagonistic to synergistic coinfections. Coinfection can have effects on focal pathogen density and replication. Different interactions, ranging from antagonistic to synergistic, can then have differing effects on chemotherapy and resistance. Species referred to in the figure: *Streptococcus pneumoniae, Staphylococcus aureus, Clostridium difficile, Pseudomonas* sp., *Helicobacter pylori* and *Vibrio cholerae*. Abbreviation: TB, *Mycobacterium tuberculosis*.