The path of least resistance: aggressive or moderate treatment?

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The evolution of resistance to antimicrobial chemotherapy is a major and growing cause of human mortality and morbidity. Comparatively little attention has been paid to how different patient treatment strategies shape the evolution of resistance. In particular, it is not clear whether treating individual patients aggressively with high drug dosages and long treatment durations, or moderately with low dosages and short durations can better prevent the evolution and spread of drug resistance. Here, we summarize the very limited available empirical evidence across different pathogens and provide a conceptual framework describing the information required to effectively manage drug pressure to minimize resistance evolution.

1. Introduction

Since the first introduction of anti-infectives (antibiotics, anti-malarials, anti-virals, anthelmintics) the evolution of resistance to chemotherapy has threatened clinical care, and continues to be a serious global health problem [1,2]. Although almost every anti-infective that has been introduced and regularly used has eventually had its effectiveness diminished by the emergence and spread of drug-resistance, the lag time until drug-resistance evolves differs considerably across drug-pathogen combinations. Consequently, a key question is which strategies are optimal for minimizing or delaying drug resistance for each specific pathogen. Generally, slowing the evolution of resistance in a population is best achieved by
treating as few patients as possible, thereby minimizing the selective pressure for resistance [3,4]. This must be balanced against the benefits of treatment, which can reduce morbidity, mortality and the spread of infections by curing individuals faster (treatment as prevention). Maximizing the good achieved with a drug thus involves a trade-off between curing infections and avoiding the spread of resistance. To attempt to balance these two aims, the traditional recommendation has been to use a drug only when the patient’s condition necessitates, but then to treat an infection as aggressively as possible, using the highest possible dose for as long as it takes to eliminate the pathogen [5]. This approach, which we refer to as aggressive chemotherapy, is fundamentally motivated by the need to cure the patient, but there is also some limited empirical evidence demonstrating that aggressive chemotherapy can prevent the de novo evolution of resistance by ensuring clearance of partially resistant strains that are able to persist at lower drug levels.

In contrast, recent theory and experimental data have suggested that reducing the dosage or the length of treatment may slow the spread of resistance under some conditions [6–9]. This approach, which we refer to as moderate chemotherapy (see glossary) recommends that drug treatment should aim to optimize clinical outcomes but not necessarily to clear the infection, and in fact, has a long history within the literature (e.g. see the concept of premunition in malaria [10]). Moderate chemotherapy may be successful if the host immune system is able eventually to clear the infection [11,12], or if complete eradication of the pathogen from the host is not essential for treatment of the acute illness. In fact, evolutionary ecology suggests that evolution of tolerance is a common strategy of hosts to cope with pathogens [13]. The key concept underlying this approach for resistance management is that the strength of selection for resistance is given by the difference in the relative fitness (see glossary) of drug-sensitive and drug-resistant pathogens, and that this quantity increases with the dosing of the drug. Thus, moderate chemotherapy reduces the advantages of drug-resistant pathogens by being less restrictive to drug-sensitive pathogens that compete against the resistant strains.

Here, we compare these two alternate approaches of aggressive versus moderate chemotherapy from a broad ecological perspective, discuss the factors and mechanisms that can favour one over the other approach, and summarize the still very scarce empirical evidence supporting either moderate or aggressive chemotherapy.

2. Optimal treatment from an evolutionary perspective

The reason that two such different recommendations exist (moderate or aggressive) is that the spread of resistance depends on two processes that react in opposite ways to increasing drug pressure (see glossary) in individual patients. On the one hand, the rate at which resistant mutants are generated depends on the abundance of the pathogen, and is therefore a decreasing function of drug pressure, since drug pressure is generally expected to correlate with numbers of pathogens killed. Furthermore, sufficiently high drug pressures can kill partially resistant strains and thereby prevent the further accumulation of resistance mutations. On the other hand, once resistance mutations are present, the rate with which they increase in frequency in the human population is a function of the selective advantage for resistant organisms, which increases with drug pressure. The reason for this is that more aggressive treatment will be more likely to remove susceptible competitors either at the primary site of the infection or at colonization sites. These drug-sensitive competitors might otherwise limit the spread of the resistant pathogens at these sites [14]—e.g. by depleting resources such as nutrients or space, by directly interfering with the growth of the resistant strain, or by changing the context of immune response—and thus their removal can benefit the resistant strains.

One way to frame the interplay of these two effects is a simple conceptual curve describing the speed of resistance evolution in relation to drug pressure in individual hosts (see [15] for an analogous framework developed in the context of immune escape). Consider the effect of the extremes of drug pressure on a single mutation that confers some finite degree of resistance (for example, it may increase the drug dosage that can be tolerated by the pathogen by a finite amount). In the absence of drug pressure, there is no selection favouring this resistance mutation, which will therefore not increase in abundance (regime 1 in figure 1). At the other extreme, drug pressure is so intense that even the marginally resistant pathogens are cleared and therefore cannot be transmitted (regime 2 in figure 1). This effect will be compounded by a reduced mutational input, because higher drug levels lead to an increased kill rate, which reduces the number of pathogen cell divisions, and thus the probability of resistance emergence during treatment. Since at the extremes of very high and very low drug pressure, resistance mutations do not spread, the rate at which resistance spreads either within a patient or in a population must be maximized at an intermediate level of drug pressure (regime 3 in figure 1). For resistance evolution in in vitro systems or in individual patients, this conceptual curve is related to the pharmacodynamical concept of the mutation-selection window [16–18] (MSW, see glossary).
However, our conceptual curve also applies to the epidemic spread of resistance: all other factors being equal, the speed of resistance spread in a population will depend on the dosing with which the drug is typically administered and the spread will be fastest for intermediate levels of dosing. Moreover, the MSW typically considers the effect of dosing on a single strain, whereas the curve in figure 1 is modulated by co-infection with different strains and even by co-infection with different species (bystander selection, see below).

Medical necessity requires drug pressure to be high enough to guarantee clinically successful treatment of the patient, imposing a lower bound to drug pressure; while avoiding toxic outcomes, imposing an upper bound to drug pressure. It is within this ‘clinically neutral’ range, that drug pressure might be optimized to minimize resistance. As several studies have demonstrated comparable clinical outcomes for short-course (‘moderate’) treatment versus long-course (‘aggressive’) treatment for several infections [19–21], the existence of such ‘clinically neutral’ ranges might be relatively common. The crucial question therefore is how this clinically neutral range of drug pressures maps onto the conceptual curve (figure 1).

— If the clinically neutral range extends to include the range that would clear those resistant strains that are currently present in the human population or that can evolve from them in the short-term, then aggressive chemotherapy is likely to be the best strategy to minimize resistance (scenario a in figure 1).

— Conversely, if levels necessary to clear those strains are considerably beyond the threshold for toxicity or bioavailability (which is, for example, the case if fully resistant strains already exist in the population) then moderate chemotherapy could be the best strategy to minimize the spread of resistance at both the individual and population scale (scenario b in figure 1).

A key challenge consists in assessing the generalizability of a broad clinically neutral range beyond the diseases studied so far. Moreover, it is unclear whether this clinically neutral range includes treatment durations that are so short that treatment does not completely clear the pathogen from the site of infection (but the immune system completes the clearance). Finally, resistant pathogen strains might require higher doses or longer durations of treatment and thereby exhibit a substantially narrower neutral range. Determining the quantitative effects of resistance on the clinically neutral range remains however an open challenge.

The key difficulty in applying this logic is that lack of empirical data and a poor theoretical understanding of the processes underlying the conceptual curve imply that its exact shape is not known for most pathogen–drug combinations (see below). If the conceptual curve is applied to the speed with which resistance evolves at the epidemic (or population) level, there is the additional difficulty that the curve links different scales of pathogen population biology—the $x$-axis corresponds to drug pressure at the within-host scale, whereas the $y$-axis corresponds to the speed of evolution at the epidemic scale—and there is currently a very limited empirical and theoretical understanding of how such within-host effects translate into epidemic scale effects. Nonetheless, framing the problem in this way allows us to identify the key elements likely to affect optimal treatment relative to resistance.

### 3. Determinants of optimal treatment relative to resistance

Several factors determine the optimal choice of treatment (moderate or aggressive) to meet the goals of patient treatment while avoiding the emergence of resistance. These include: the genetic architecture underlying resistance; community levels of resistance, which may be related to the length of time an anti-infective agent has been in use; and patient adherence to therapy.

If the genetic architecture underlying resistance implies that a large number of mutations are required to achieve full resistance, i.e. if the genetic barrier to resistance is high, then the first mutation to spread will probably confer only a moderate level of resistance, meaning that clinically relevant levels of drug pressure will clear the partially resistant mutant [22]. Thus, aggressive chemotherapy may be more advantageous if full resistance is a quantitative trait requiring many mutations, and full resistance has yet to appear within the population. A corollary of this is that combination therapy, which raises the genetic barrier, could increase the advantages of aggressive therapy. Identifying the magnitude of the genetic barrier for a particular drug is, however, a major difficulty, in part because the correspondence between the genetic barrier in vivo and in vitro is not perfect. In the context of combination therapy against bacteria, for example, many mechanisms, such as biofilm formation, states of quiescence, efflux-pumps, or multi-drug-resistant plasmids can confer resistance to many drugs at once [23]. As these mechanisms may play a different role in different settings (in vitro versus in vivo; human versus animal models), their effect will be hard to infer from in vitro tests, or even from small-scale in vivo tests (indeed even such small-scale in vivo tests are extremely scarce; see section Empirical evidence).

The dynamic context of evolution may also mean that the benefit of aggressive or moderate treatment may change as a function of the number of years since the drug has been in use. Drugs that are approved tend to have a high genetic barrier to resistance initially (at least in vitro), and clear infections rapidly. This implies that the range of neutral drug pressures incorporates clearance of the first emerging partial resistance mutations (i.e. scenario a in figure 1), which recommends aggressive treatment. Over time, pathogens are likely to accumulate resistance mutations and the drug pressure necessary to eliminate all pathogens (including the ones that have acquired new mutations) will increase (i.e. scenario b in figure 1). This reflects a shift of the maximum of the conceptual curve to higher drug pressures, thereby broadening the drug pressure range in which moderate treatment is optimal. This implies that adaptive management strategies, which alter the degree of ‘aggressiveness’ through time (e.g. depending on the level of resistance found in cross-sectional surveys), could extend the lifespan of a drug beyond what can be achieved with a uniformly aggressive or moderate treatment strategy.

The benefits of moderate versus aggressive treatment will also depend on the epidemiological context. If the presence of susceptible pathogens within a host limits the replication and transmission of resistant pathogens, then the frequency of co-infection with different pathogen strains will affect the strength of competition and hence the optimal treatment strategy for reducing the spread of resistance. For example, for malaria in high-transmission areas, where co-infection is more frequent [24–27] moderate treatment may be more
beneficial than it would be in low-transmission areas, because in the former case resistant and sensitive strains compete more often within an individual host and hence aggressive treatment is then more likely to cause the removal of a sensitive competitor. However, rapid reinfection by susceptible strains in high-transmission areas may mitigate this disadvantage of aggressive chemotherapy.

Similarly, the complex relationship between colonization and infection with bacteria creates a situation in which any chemotherapy will select for resistance in entire microbial communities occupying a range of tissue types ('bystander' selection) [28]. In particular, such bystander treatment might affect microbial communities both in the tissue occupied by the focal pathogen and in other tissues (for example, orally administered antibiotics can affect the gut microbiota irrespective of the site occupied by the focal pathogen [29]). These unintended consequences might increase the advantages of moderate chemotherapy by reducing the amount of time non-target organisms are exposed to a drug, especially given the possibility of horizontal gene transfer [30].

Finally, optimal treatment with respect to resistance minimization might also depend on variation in patient adherence. Non-compliance with recommended treatment courses by some patients is a general feature of chemotherapy. In addition, there is often substantial variation in the absorption and metabolism of drugs across patients. This suggests that moderate treatment may occur unintentionally even in populations where aggressive chemotherapy is recommended. If low levels of unintentional moderate treatment are a driving force in the emergence of resistance then an aggressive chemotherapy policy's main benefit (of inhibiting the accumulation of resistance mutations) will be hampered [31]. Accordingly, this could change the shape of the conceptual curve to favour moderate chemotherapy. Alternatively, it might imply that even more aggressive chemotherapy should be recommended because higher drug doses might be more robust to imperfect adherence.

4. Empirical evidence

There is surprisingly limited empirical evidence describing how treatment regimes can affect the emergence and spread of resistance (electronic supplementary material, table S1). Even worse, the evidence might be biased because most empirical studies are based on the effect of drug pressure on the de novo evolution of resistance—i.e. on the emergence, establishment and increase in resistance in a single infection or in vitro culture founded by a susceptible strain—and this scenario tends to favour aggressive therapy.

Clinical data for the impact of drug pressure on de novo drug resistance evolution stem mostly from infections requiring long-lasting treatment such as HIV [32–34] and TB [35]. For HIV-1, studies considering resistance evolution in relation to patient adherence suggest that treatment that does not completely suppress pathogen replication facilitates de novo evolution of resistance [32–34,36]. There is some evidence that resistance evolution is maximized at intermediate adherence [37], but the clinical needs of HIV therapy exclude moderate chemotherapy as a strategy. For TB, the main objective of long treatment duration is to prevent relapse of the infection, and the clinical evidence for an increased risk of resistance evolution with short treatment duration is mixed [35]. However, as for HIV, residual replication due to non-compliance or PK/PD variability is considered a risk factor for resistance evolution in TB [38,39].

For a broad range of bacterial pathogens, experimental studies done in vitro or in animal models support the view that aggressive chemotherapy can contribute to resistance management, with most studies finding that high drug pressure/doses prevent the de novo evolution of resistance mutations (see [40], references therein, and electronic supplementary material, table S1). These results support the notion that for concentrations above the mutant prevention concentration (MPC, see glossary), de novo resistance cannot evolve in the target pathogen [41,42]. Interestingly, it has also been shown in animal models that intermediate drug-concentrations can maximize the abundance of resistant strains [43,44] (specifically, Tam et al. [44] found an ‘inverted-U’-shaped relation similar to figure 1). Overall, most experimental findings from infections with drug-sensitive strains indicate that concentrations above the MPC can be reached in vitro and hence the de novo evolution of antimicrobial resistance should be curbed ‘by administering the highest tolerated doses of antibiotic’ [40]. It should be noted, however, that the advantage of high doses might be non-existent if a single and probably point mutation leads to full resistance (e.g. resistance to pyrimethamine or atovaquone in malaria [45]) or if fully resistant mutants are expected to pre-exist even in infections founded by a susceptible strain (e.g., in the past in HIV monotherapy with low-genetic barrier drugs [46]); because in this situation whatever the dose administered, resistant pathogens may persist and cause therapy failure.

The effect of drug pressure/dosing on transmitted resistance (i.e. if an individual infection is founded by a resistant strain, or a combination of susceptible and resistant strains) has received much less attention in empirical studies, even though it constitutes a large part of the global health burden. One study on Streptococcus pneumonia found that low doses of beta-lactams increase the risk of carrying transmitted penicillin-resistant strains [47] (but note: long duration was also associated with resistance in this study). By contrast, experiments where drug-resistant and drug-susceptible malaria pathogen strains are inoculated into mice either singly or in co-infections indicate that the presence of a competitor considerably slows the rate of increase in the resistant pathogens, but this disadvantage disappears in the presence of drugs, and the stronger the drug treatment, the greater the benefit to resistant pathogens [6,9]. Furthermore, there were no health benefits for the mice in aggressive relative to moderate chemotherapy. This suggests that aggressive chemotherapy can promote the spread of resistance once fully resistant strains are present in the population; and moderate chemotherapy may not be associated with any health costs. These two studies consider the effect of treatment strategies on transmitted resistance in individual hosts, but what is completely lacking are studies to assess the comparative effect of aggressive versus moderate in entire transmission chains.

Broadening the focus to the whole pathogen community, there is evidence that chemotherapy will unavoidably affect any other organisms in the vicinity of the targeted pathogen at least for bacterial infections [48] (i.e. bystander selection, see above), and that the prevalence of resistance in the microbiota increases with antibiotic consumption [49] and the duration of treatment [50]. This evidence suggests that use of aggressive chemotherapy with the aim of minimizing mutational inputs into target pathogen populations only makes sense as a resistance management strategy if
mutational inputs are a more important source of de novo resistance than horizontal transfer of resistance factors from non-target microflora such as commensal bacteria.

5. Future directions

Overall, clear unambiguous empirical evidence for either aggressive or moderate chemotherapy in the context of resistance management is still largely lacking. Moreover, all empirical examples concern resistance evolution at the level of the individual host, and it is unclear how dynamics from the within-host scale links to the epidemic level (cross-scale dynamics). The key missing elements for understanding how treatment strength shapes the emergence and spread of resistance are (i) experimental data on both the shape of the conceptual curve (discussed above) and the location of the clinically neutral range of treatments on the drug pressure axis; (ii) a more thorough understanding of the cross-scale dynamics of anti-microbial resistance (see, e.g. [51]); and (iii) consideration of the different pathogen ecologies that determine how much competition between resistant and sensitive pathogens is likely to occur within a host. Quantitative predictions of resistance evolution, including the outcome of greatest public health interest, i.e. the disease burden and the proportion of infections that is no longer treatable due to resistance, require all these elements. Such predictions must be based on models of cross-scale dynamics, encompassing the effect of dosing strategies on within-host dynamics and medical outcomes through to transmission across populations [52]. The following research directions have most potential to engage with these issues.

Given the broad use of chemotherapy in agriculture, these systems could provide unique opportunities for testing the effect of dosing on the evolution of resistance. Experimental animal transmission systems are also a promising direction for testing evolutionary outcomes of dosing strategies [53]. More generally, there is a lack of good animal models to test the in vivo effect of chemotherapy in bacteria (although some progress has been made using other infections, such as malaria models in mice [6,9]). A consequence of this is that genetic barriers to resistance are generally evaluated in vitro. By necessity such in vitro studies do not incorporate the immune system, which is likely to be a key element in the success of moderate chemotherapy [8]. Moreover, it is often unclear how evolutionary processes [54] and drug dosing [55] can be translated from in vitro to in vivo systems. Measurement of resistance evolution in animal models and in semi-realistic animal model populations (e.g. farms) might narrow the gap between experimental predictions and expected genetic barriers in treatment of humans.

Ethical issues generally prevent direct observation of the effects on resistance of a range of drug pressures in humans. However, our understanding of the effect of optimal dosing on resistance could be improved by measuring the effect in clinical trials that are already testing varying drug dosages from a position of equipoise. This is an outcome that is rarely measured [56], and can be crucial in assessing why certain patients do not respond to certain dosages. Moreover, tests of the effects of different chemotherapy strengths in human populations might be ethically implemented in the case of prophylactic use of drugs (e.g. in malaria trials such as [57] or HIV trials such as [58]). A failure to explore the effects of strength of treatment on emergence of resistance via randomized population level trials that are already being conducted for the purposes of prophylaxis would be a missed opportunity.

At the individual scale, generally, decisions on better treatment regimens to contain resistance will be greatly aided by diagnostic tests that can distinguish between drug-sensitive and drug-resistant strains of a pathogen. In the case of mono-infection with either a sensitive or resistant strain, such diagnostic tests can help dictate which therapies have the potential to be effective. In the case of initial co-infection with sensitive and resistant strains, advanced diagnostics could help inform the decision as to whether to use moderate chemotherapy or which drugs to use in combination if aggressive chemotherapy is likely to be more effective [59]. The experience with HIV suggests that baseline resistance testing reduces the problem of transmitted resistance (provided that treatment can be adapted to the infecting strain). Since transmitted resistance is the main reason for moderate therapy, this implies that improved diagnostics can potentially increase the benefits of aggressive therapy. It is, however, unclear whether this effect applies to infections other than HIV. Among the challenges to such an approach are the availability of alternative treatments, the timely determination of the resistance profile (delays caused by resistance testing in bacterial infections often mean that optimal treatment is not administered until resistance is proven), and resistance in the microflora.

Observational studies comparing variability in the effect of the dosing of chemotherapy at different spatial scales (e.g. states, cities) on the emergence and spread of resistance may shed light on the optimal treatment for managing resistance. Most observational/ecological studies so far focus on the correlations between bulk quantities (such as daily defined doses) of drugs used in a given region and the prevalence of resistance [3]. Despite the general limitations of ecological approaches, a key extension of these analyses would be to include information on the dose and timing of treatment in individual patients in addition to the bulk quantities.

Apart from its public health relevance, the question of optimal treatment strength is a real-world illustration of eco-evolutionary interactions. In particular, it illustrates the concept of evolutionary rescue, which deals with the question of how evolutionary adaptation can prevent extinction after environmental changes. Related issues have been discussed in the evolution of virulence, e.g. the work of Gandon et al. [60] on pathogen escape from imperfect vaccines. While little is known about the effect of treatment strength on evolution of resistance, even less is known about the consequence of treatment strategy on the evolution of virulence, though this would be a key direction for future research.

The question of how treatment can be used to minimize the spread of resistance (while achieving goals of patient health) is not purely academic. Recent reports have documented the emergence of malaria parasites with delayed clearance from artemisinins [61]. This delayed-clearance phenotype, while not of clinical significance yet, is the first indication that resistance to artemisinin is beginning to emerge, and may be spreading [62]. Artemisinins are an essential component of combination treatments necessary to clear malaria in many parts of the world, which makes understanding the effects of treatment on artemisinin-resistant strains a particular urgency. The drug policies to manage this and other resistance problems will necessarily consist of several components, including switching to new drugs (if available), combining available drugs, reducing...
unnecessary treatment, and improving compliance with treatment recommendations. The success of any such strategy will, however, eventually depend on the adequacy of the recommended dosing; and both extremes of too high and too low dosing may needlessly accelerate the spread of resistance.

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References


49. Gubler D, Hargis B, Lu X. 2000 Infection and resistance of a given drug or treatment MSW appearance of a mutation that confers resistance within a single host, and its transmission to subsequent hosts number of mutations the pathogen needs to accumulate in order to achieve full resistance the mutation-selection window (MSW) has been defined as the range between the minimal inhibitory concentration (MIC)
and the mutant prevention concentration (MPC), where the MIC is the minimal concentration at which wild-type growth is inhibited and the MPC is the minimal concentration at which growth of resistant single point mutants of the wild-type is inhibited. The MSW is very similar in concept to the curve in figure 1. However, the MSW is typically restricted to \textit{in vitro} or within-host systems and it specifies the range for which growth of the resistant strain is possible (rather than the value for which it is maximized). Recent work has moreover contested the MIC as the lower limit of the MSW as it has been shown that the range in which drug resistance is selected may go considerably beyond this traditional MSW [63].

Moderate chemotherapy treatment where the aim is to maximize host health outcomes while trying to minimize drug doses. This might not mean eliminating the pathogen during drug treatment. Note that moderate treatment may still recommend doses above the MIC as long as they are not sufficiently high or taken for sufficiently long to completely clear the pathogen. Moderate treatment aims to optimize the dosage and timing of treatment of individual patients rather than at coordinating anti-infective use at the population scale (e.g., antibiotic cycling in hospitals). However, the outcome being optimized is typically the same (minimizing the spread of resistance at the population level) in both cases. The approach of moderate chemotherapy contrasts aggressive chemotherapy, which aims to completely clear the pathogen from the patient.

- **Clinically neutral range** range of drug pressures with comparable clinical outcomes for an individual patient (but potentially different outcomes with regard to resistance evolution).
- **Break points** MICs used to identify the degree of resistance possessed by a particular strain (often within the classes ‘susceptible’, ‘intermediate’, ‘resistant’).
- **Emergence** first appearance of a drug-resistant mutation in a focal population following emergence, the drug-resistant pathogens increasing in frequency within the population.
- **Establishment** drug-resistant mutation maintains a consistent equilibrium frequency in the population.
- **Cost of resistance** reduction in fitness experienced by resistant pathogens relative to susceptible pathogens in the absence of the drugs; often caused by mutations in genes key to metabolic processes that are drug targets.
- **Drug pressure** the relative degree to which treatment can reduce abundance of the susceptible pathogens; which can be achieved either through high concentration of treatment or long duration of treatment (provided that the concentration is not too low).
- **Fitness** quantity that quantifies the ability to survive and reproduce and contribute to the gene pool in the next generations.