Resistance to Antimicrobial Chemotherapy: A Prescription for Research and Action


ABSTRACT: The growing problem of resistance to antimicrobial chemotherapy was discussed by participants at the February 1995 workshop at Emory University on population biology, evolution, and control of infectious diseases. They discussed the nature and scope of this problem and identified areas of research in which information is lacking for the development of programs to control the emergence and spread of resistant bacteria. Particular attention was given to theoretical (mathematical modeling) and empirical studies of the within and between-host population biology (epidemiology) and the evolution of microbial resistance to chemotherapeutic agents. Suggestions were made about the kinds of models and data needed, and the procedures that could be employed to stem the ascent and dissemination of resistant bacteria. This article summarizes the observations and recommendations made at the 1995 meeting and in the correspondence between participants that followed. It concludes with an update on the theoretical and empirical research on the between- and within-host population biology and evolution of resistance to antimicrobial chemotherapy most of which has been done since that meeting. KEY INDEXING TERMS: [Am J Med Sci 1996;311(2):87-94.]

Microorganisms (bacteria, viruses, protozoa, and fungi) resistant to the chemotherapeutic agents used to control them may prove to be among the most significant sources of emerging and re-emerging infectious diseases in the coming millennium. Like the majority of not all of the emerging diseases we have seen during these past three decades, the ascent of pathogenic and commensal microorganisms resistant to chemotherapeutic agents can be attributed to technology, in this case the use and overuse of chemotherapeutic agents. Not so clear, however, is whether technology can also provide a solution to the problem of emerging chemotherapy-resistant microorganisms. How can we slow or reverse the rate at which resistant microbes evolve and spread? What must be done to better understand, control, and, ideally, preclude the appearance and proliferation of microbes resistant to chemotherapy? What are the alternatives to chemotherapy for the treatment of infections with microorganisms?

The Ideal and Real Worlds of Antimicrobial Chemotherapy

In the ideal world, before an antimicrobial agent is administered for treatment or prophylaxis, the target species of microbes would be identified and its antimicrobial resistance pattern would be known. The infection would be at a stage where it can be readily controlled by chemotherapy, and the timing would be perfect. The antimicrobial agent would be very specific and there would virtually no effect of treatment on the nonessential flora or side effects for the patient. While these microbes would have the potential to acquire resistance (by mutation or infections transfer from other microbes)—even in the ideal world there is genetic variation, recombination, and evolution by natural selection—resistance would almost never preclude effective treatment. For most antimicrobial agents, the incidence of treatment would be so low and the cost of resistance to the microbe so great that the frequency of resistant strains would not increase. For the small minor-
The use of antimicrobial agents that fail because of a local build-up of resistance, there would always be effective alternatives. Finally, antimicrobial agents would cost little for consumers and would provide more than adequate profits for the producers.

Ours, however, is not the ideal world and, with respect to antibiotics use, it is quite far from ideal. Most antibiotic therapy is empiric. The target species of microbes and its resistance pattern is generally not known other than distantly (or by "experience") before antimicrobial agents are first administered. Commonly it is not even clear that a microorganism is the etiologic agent of the disease being treated or prevented. The stage of the infection is generally not known with any precision and in many cases, antimicrobial agent treatment may be ineffective because the infection has progressed too far or the microbes responsible are resistant or that the stage of the infection is physiologically refractory to that antimicrobial. In some situations, even with antimicrobial agents to which the bacteria are susceptible, chemotherapy may not alter the course of the disease and may even be deleterious to the patient. Because of the limited direct information about the etiologic agent and its resistance pattern, the antimicrobial agents of choice often have broad spectrums and are commonly of the most recent origin and most expensive. Consequently, the administration of antimicrobial agents often has profound effects on the ecology of the commensal flora—effects that may be severely deleterious or even toxic or lethal to the patient in their own right. While it may be that the carriage of the resistance genes and the accessory elements that bear those genes may engender a cost in the fitness of the target microbe, the magnitude of that cost may be low or resolve to be low. Indeed it is conceivable that those resistant genes and accessory elements may confer an advantage on their host, beyond that associated with resistance.

The net effect of all will be the maintenance or further increase in the incidence of resistant pathogenic and commensal microbes in treated host and the environment at large. Finally, in this all too real world, no antimicrobial agent becomes ineffective because of resistance, alternative broad (or even narrow) spectrum agents may not exist or may not be produced for economic reasons. The ideal world will not and cannot be. The real world from whence the problems of microparasite resistance to chemotherapy arose is well known, and are the primary reasons for this problem. Not clear, however, is the prognosis for the continued efficacy of antimicrobial chemotherapy or what, in a realistic world, can and should be done about microbial resistance to chemotherapy. These not-so-clear points are the focus of this article.

Mathematical Modeling

The evolution, agent, and spread of microparasites resistant to chemotherapeutic agents is a problem of population and evolutionary biology, albeit one that has received little attention by practitioners of these subjects. The primary tool of theoretical population biology, mathematical modeling provides one way to address questions of prognosis and intervention. Mathematical models can be used to:

1. Identify and quantitatively evaluate the relative contributions of the different genetic, environmental, and human practice factors that control the evolution, ascent, spread, and persistence of chemotherapy-resistant microbes.

2. Predict the evolution of resistance and the direction and rates of change in the incidence of resistant microbes within different regimes of antimicrobial chemotherapy and design and evaluate protocols for the application of antimicrobial agents that are effective in preventing or treating the disease and, at the same time, minimize the rates of better yet, reduce the transmission of organisms to other hosts or to the environment at large.

Two Kinds of Models. For these endeavors, we see a need for two, ideally overlapping, classes of models: those that treat the evolution and spread of resistance in communities of hosts, and those that treat the changes in the incidence of resistant microparasites and commensals in an individual host and following antimicrobial chemotherapy. Of particular concern for the former, epidemiologic, models is the relationship between the incidence and term of antimicrobial chemotherapy, the fitness costs associated with resistance, and other factors that determine the rate of resistant microbes in treated and untreated hosts. With these epidemiologic models, it should be possible to predict the direction and rates of change in the incidence of resistance under various regimes of antimicrobial chemotherapy.
Box 2.

In the microorganisms responsible for some diseases (e.g., tuberculosis, respiratory tract infections by bacteria), that is, in short course chemotherapeutic regimens, the pathogen was able to proliferate when it is simultaneously resistant, to all of the antimicrobial agents employed. The speed of this occurring is in the order of the product of the frequencies of resistance to resistance genes' probabilities on the order of 10^-10 or lower when three or more antibiotics are used.

Unfortunately, the perspective of population genetics of this problem is less straightforward. For example, even when the resistance for resistance to each antimicrobial agent is independent genetically and functionally—in the population of these chemotherapeutic agents got too low or if for there is some hereditary in their activity, selection may favor intermediate, minority that are resistant to fewer than all the agents used for treatment. The net effect would be a far more limited and for few more resistant evolution of multiple resistance.

*Nicola et al., 1990.

and the effects of increasing or reducing the extent to which these agents are employed (Box 1).

We see two primary roles for within-host models of antimicrobial chemotherapy. One is to assess quantitatively the factors that contribute to the rate at which treated hosts disseminate resistant microbes into the community at large. The other is to explore quantitatively the factors that contribute to treatment failure due to resistance (Box 2).

Resistance in the Commensal Flora. Mathematical models of the within- and between-host population genetics of resistance must not only consider the specific pathogens that are the targets of antimicrobial therapy and pregnancy, but they must also consider resistance in commensal microorganisms in the treated hosts and in the environment at large. These usually commensal microbes are often not-quite-innocent bystanders in the chemotherapy drama. Some, like *Escherichia coli*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*, include strains that are occasional and opportunistic pathogens. Moreover, in the case of bacteria (but probably for other microorganisms as well), almost all of the commensals could serve as sources of resistance genes and accessory elements for other microbes, including pathogens. Changes in the commensal flora can also lead to pathogenesis in its own right (e.g., antibiotic-associated colitis).

Finally, these commensals are bellwethers—they can be and are being used to estimate the incidence of resistance to individual hosts and communities of hosts.

For these reasons, we believe it would be useful to develop separate models for the population genetics of resistance for three classes of microorganisms: the persistent commensal flora, the pathogens responsible for acute infection that are shared in short periods, and pathogens that persist over long periods.

Empirical Studies. Mathematical modeling is a pleasant, ego-satisfying, safe, and relatively nonpolluting enterprise. However, for these models to be useful for the very practical problem of dealing with microbial resistance to chemotherapeutic agents, their construction and analysis have to be closely tied to empirical studies. We can of course make the case the other way as well; experiments and data-gathering, in the absence of theory, are often hard to interpret and virtually impossible to generalize upon. There is a need to coordinate the efforts of modelers and empiricists to develop realistic, useful models of the population genetics of resistance.

Data Needed. For the epidemiologic models, four kinds of data are needed:

1. Accurate estimates of the extent and nature of the use of antimicrobial agents. Included in these data should be estimates of the frequencies at which specific antimicrobial agents are used for different purposes, the doses employed and the nature and term of their use.

2. Retrospective and prospective estimates of the relationship between the application of antimicrobial agents and rates of change in the frequencies of resistant pathogens and commensals in treated hosts and communities of hosts. Of particular concern are the rates at which resistant forms ascend in the targeted pathogens and commensal flora of treated hosts, and the frequencies these resistant microbes achieve. Also of concern is the effect of treatment on the rate of dissemination of the resistant microbes.

3. Retrospective and prospective estimates of the rates of change in the frequencies of resistant microbes in hosts and in environment following the local or global termination of use of specific antimicrobials. These estimates must also consider the frequencies of resistant organisms decline? What levels do they reach? What are the reasons for these declines in the incidence of resistant organisms? Are the resistant bacteria being replaced by sensitive variants of the same clone or by other clones?

4. Determinations of the source of resistant microbes in the community. Is the resistance due to the de novo acquisition of resistance genes (or accessory elements) in treated hosts? Or are the resistant microbes (or their accessory ele-
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5. Resistance of the host and the environment - the challenge to the host and the environment to resist the invasion of the parasite and maintain the balance of the ecosystem.

6. Resistance to chemotherapy and the need for new strategies.

7. The role of host immunity in the development of resistance.

8. The importance of understanding the mechanisms of resistance for the development of new therapeutic strategies.

9. The need for multidisciplinary approaches to combat resistance.

10. The ethical and social implications of resistance.

11. The role of public health and education in controlling resistance.

12. The need for international cooperation in the fight against antimicrobial resistance.


14. The role of pharmacovigilance in monitoring the emergence of resistance.

15. The importance of research and development in the field of antimicrobial agents.

16. The role of public and private sectors in the funding of research.

17. The need for collaboration and coordination among stakeholders.

18. The challenges and opportunities of the digital age in combating antimicrobial resistance.

19. The role of patient education and engagement in the fight against resistance.

20. The need for policy and regulatory frameworks to support the development of new agents.

21. The importance of surveillance and monitoring systems in tracking the emergence of resistance.

22. The need for international partnerships in the development of new antimicrobial agents.

23. The role of traditional and complementary medicines in the treatment of resistant infections.

24. The importance of understanding the role of the environment in the development of resistance.

25. The need for new funding mechanisms to support research and development.

26. The role of patient organizations in advocating for the development of new agents.

27. The importance of understanding the role of the host in the development of resistance.

28. The need for new strategies in the treatment of resistant infections.

29. The role of new technologies in the diagnosis of resistant infections.

30. The importance of understanding the role of the environment in the treatment of resistant infections.

31. The need for new strategies in the prevention of antibiotic resistance.

32. The role of traditional and complementary medicines in the prevention of resistant infections.

33. The importance of understanding the role of the host in the prevention of resistance.

34. The need for new strategies in the control of resistant infections.

35. The role of new technologies in the control of resistant infections.

36. The importance of understanding the role of the environment in the control of resistant infections.

37. The need for new strategies in the education of healthcare professionals.

38. The role of traditional and complementary medicines in the education of healthcare professionals.

39. The importance of understanding the role of the host in the education of healthcare professionals.

40. The need for new strategies in the training of healthcare professionals.
Levin et al.

Phage therapy: the use of phage to control bacterial infections (Martin Arnowmith) wasn’t the only one under some conditions, it can be effective.

Interference therapy: the use of non-pathogenic microbes to prevent the pathogenic effects of other microbes.

In the main, these procedures were not as effective as antimicrobial chemotherapy, and because of their specificity they are certainly more difficult and in some cases and doubts others, their development and application was eclipsed by antimicrobial chemotherapy. Nevertheless, from a public health standpoint it is clear that under some conditions these methods were somewhat effective. Moreover, with what we now know about the mechanisms of pathogenesis, the immune system, and the genetics, molecular biology, physiology, and population biology of phage and with current biotechnology it may well be possible to substantially improve the efficacy of these older procedures. We certainly endorse quests for alternatives to contemporary antimicrobial chemotherapy. At the same time, however, it is of essential that we also encourage the improvement of existing methods that now prevent the transmission of microbes and the development of new ones. Even untreatable infections can be prevented by sanitation, vaccination, pasteurization, and other tried-and-true infection prevention measures.

Technical Solutions Will Not Be Sufficient

We have no doubt that with a concerted effort, these and other effective alternatives to many current chemotherapy agents could be developed. However, it seems reasonable to expect that the majority of if not all the alternatives considered above will be substantially more specific than the broad-spectrum antibiotics currently favored for the treatment of bacterial infections. While this species and agents are available, based on the experience of the innocent commensals, it also makes the application of these alternative treatment protocols much more difficult. From the perspective of the innocent commensals, the resistance problem approaches the stage where it is sufficiently grave and widespread to preclude effective treatment and preclude effective antimicrobial agents, we expect (hope) there will be adequate motivation to overcome the economic and other contributory problems with producing and implementing these alternatives. Some pathogens are already at this critical stage, like vancomycin-resistant enterococci.

What will be needed for the development of these alternatives, in addition to the usual money and personnel, is time, possibly a lot of time. Although we are not yet have accurate estimates of the rates and extent to which resistance to antibiotics is increasing among pathogens and commensals, the direction is already clear. If we maintain "business as usual," respect for our array of antimicrobial agents, we can only expect the resistance problem to become increasingly acute, and more and more
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Pathogens will become appropriate fodder for the situation described in Box 5. It is unlikely that the resistance problem will rapidly wane, simply by being more prudent in our use of antimicrobial agents; on the other hand, it is certain that if we do not cut back our use of these agents, the resistance problem will worsen. Husbanding the antimicrobials in our current arsenal is the only way we can buy time for the development and production of alternatives. In essence, we have to do the best we can to misuse the limited world of antibiotic use described earlier in this article. Physicians and their patients, veterinarians, livestock breeders, and growers of high-value crops all have to learn to "say no to drugs."19

Update: October 1997

In early 1995 when we held this workshop (and for some time before), there was already a great deal of concern about the clinical and public health problems associated with increasing frequencies of microbes resistant to antibiotics and other chemotherapeutic agents. In the less than three years since, this resistance problem has become perceptibly worse. The frequencies and diversity of resistant strains have, with few exceptions,20 increased, and no antibiotics with new targets have been put on the market. Few years have also witnessed some significant landmarks in the era of antimicrobial chemotherapy, perhaps the most dramatic of which has been the successful combination (multidrug) chemotherapy for HIV/AIDS,21 and the first reported sightings of the long-feared vancomycin-resistant Staphylococcus aureus, albeit fortunately only low-level resistance.22 There has also been heightened awareness of this problem by healthcare workers and more and better information about how to deal with the problem of resistance.23

There has also been a marked increase in interest in the problems of drug resistance by investigators trained in population and evolutionary biology and a number of collaborations between people working in this area and medical microbiologists. This workshop in a sense served as the catalyst for some of this research and has led to many others. These studies have addressed and provided answers to some of the questions about the population biology and evolution of resistance considered in this article. Some of these investigations have examined the relationship between the rate of antibiotic use and the frequency of resistance in the normally commensal and occasionally (and opportunistically) pathogenic bacteria such as S. pneumoniae, E. coli, and Moraxella catharralis.24-28 Other theoretical studies have used "compartment" models to follow the epidemiology of resistance in directly transmitted pathogenic bacteria that can be cleared by antibiotics,29 to evaluate the efficacy of antibiotic treatment on the epidemiology of tuberculosis,30 and the epidemiologic consequence of cycling and simultaneously employing several antibiotics.31

The models employed for commensal bacteria suggest that even if the rate of antibiotic use is modest (eg, one treatment every second year), if the fitness cost resistance imposes on a bacterium is relatively low (eg, a 1% reduction in growth rate), the expected equilibrium frequency of resistance would be substantial, on the order of 30%. The equilibrium frequency of resistance increases as the fitness costs associated with the resistance-conferring genes and accessory elements are greater. Experimental studies with bacteria and HIV suggest, however, that even when drug resistance severely reduces the fitness of bacteria and viruses, subsequent evolution, even in the absence of drugs, is likely to reduce that burden by compensatory mutations rather than by reversing to susceptibility.32

These in vitro experiments also suggest that the compensatory mutations that ascend in these situations establish a genetic background which virtually precludes reversion to sensitivity in that lineage.33-35 Taken at large, it is hard to generate an optimistic interpretation of the results of these theoretical and in vitro experimental studies of the population genetics of resistance. They suggest that even with the more prudent use of antimicrobial agents, the frequency of resistance will not decline very quickly, if at all.

In addition to studies of the epidemiology of drug resistance a number of investigators have used mathematical models to examine the within-host population dynamics of antimicrobial chemotherapy. One of the goals of this research is to assess the conditions under which resistance is anticipated to evolve when single and multiple chemotherapeutic agents are used for treatment. These theoretical studies have considered bacterial resistance to antibiotics and combine elements of pharmacokinetics and pharmacodynamics of drug delivery and the interaction with the population dynamics of an infecting population of bacteria.36-42 Analogous studies have been employed for HIV resistance to reverse transcriptase and protease inhibitors.39-40 A particularly attractive feature of most of these studies of the within-host dynamics of antimicrobial chemotherapy is the (uncharacteristic) reality of the models used. In constructing these models and analyzing their properties, these investigators have paid close attention to the results of the experimental work being done on bacterial and HIV infections and antimicrobial chemotherapy.

References


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