Risk Perception and Inappropriate Antimicrobial Use: Yes, It Can Hurt

John H. Powers
Scientific Applications International Corporation in support of the Collaborative Clinical Research Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, and University of Maryland School of Medicine, College Park, Maryland; and George Washington University School of Medicine, Washington, DC

(See the article by Llor and Cots on pages 1345–9)

One of the first principles of medicine since the time of Hippocrates has been to first do no harm. All medical interventions—drugs, biologics, and devices—have the potential to cause unwanted harm, which accompanies the potential for benefit. The safe use of medical interventions relies on using them in situations in which there is substantial evidence of effectiveness to justify any potential harm. In the absence of evidence of benefit, even low-frequency or non-serious harm is not justifiable. However, it seems that various providers sometimes give antimicrobials to patients using the maxim “it can’t hurt”—in other words, even if it does not work as intended, the risk of harm is vanishingly low. This is based on a mistaken assumption that the use of antimicrobials comes at no cost to the patient or to society. However, not only can antimicrobials cause direct toxicity to patients, including serious adverse events, such as anaphylaxis, but inappropriate use spreads antimicrobial resistance to both the persons who receive the drug and those who do not, without providing benefits to either group.

Using antimicrobials properly entails an accurate diagnosis, timely administration of the drug, and use at the optimal dosage and duration. Amazingly, after 80 years of antimicrobial use, we still are not clear on some of these points, such as the appropriate duration of antimicrobial treatment for some diseases (e.g., pneumonia). On the other side of the coin, appropriate use entails avoiding the use of antimicrobials when the harm outweighs the benefits, such as situations in which studies have not reliably and reproducibly demonstrated the benefits of antimicrobials. Appropriate use also entails not using antimicrobials as a substitute for timely follow-up, that is, just in case “something bad might happen.”

Learning from history. Appropriate conditions of use for anti-infective agents is an issue that dates back to the use of serum therapy to treat pneumococcal pneumonia in the early 1900s. Serum therapy caused serious adverse events, such as allergic reactions with attendant hypotension, so it was important to make an appropriate diagnosis by typing organisms prior to administering the serum. With the introduction of sulfa drugs, typing of organisms became less necessary, but this led to use of the drugs in situations in which their benefits did not outweigh their risks in cases of inappropriate diagnosis.

The issue of adverse events with antimicrobials also has a long history. Deaths attributable to the mixing of sulfanilamide with diethylene glycol spurred the passing of the Food, Drug, and Cosmetic Act in the United States in 1938. Theodore Klumpp of the US Food and Drug Administration pointed to the importance of appropriate use in the findings of his investigation of the sulfanilamide tragedy: “I think you would be interested in some of the implications that arise from the observations recorded. I refer particularly to the 105 deaths associated with consumption of the drug…In a hundred instances the drug was administered on a physician’s prescription [for] Bright’s disease [nephritis], bichloride and mercury poisoning, renal colic and backache [2, p. 82].” Based on cases such as these, H. Corwin Hinshaw in 1939 urged that, “For the most
part, sulfapyridine should be used only for patients who are seriously ill. I doubt the advisability of using the drug for patients who have influenza, the common cold, sinusitis, or tonsillitis. In such cases, the treatment may be worse than the disease, not only much more uncomfortable but more dangerous [3, p. 771].” But for all the early concern regarding risk-benefit of antimicrobial use, some clinicians voiced the attitude that still exists today regarding administering antimicrobials, that they should be used “just in case.” In a 1941 presentation to the Virginia State Medical Society, William McIlwaine proudly invoked the military analogies often used to justify inappropriate use of antimicrobials: “And now I am starting to use [sulfa] prophylactically. And why not? It has not been show to work that way! Not scientific you say! Remember, we are front line soldiers; when we see the enemy we do not have to wait for orders from headquarters through a long line of red tape. We must go for him, without waiting for the attack!…Then why not get the jump on those little bacteria? Kill them before they get a foothold [4, p. 410].” This sentiment existed in spite of the fact that a contemporaneous study published in 1943 failed to show the benefits of prophylactic antimicrobial use in upper respiratory tract infections to prevent pneumonia [5].

The above cases point to the challenges when clinicians choose to prescribe antimicrobials in situations in which the benefits are unclear. It seems self-explanatory to us today that Theodore Klumpp would point out that most of the patients who died on elixir of sulfanilamide received the drug by a physician’s prescription. However, prescriptions did not become mandated by law in the United States until the Durham-Humphrey amendments to the Food, Drug, and Cosmetic Act in 1951. Prior to that time, regulations in the United States allowed direct sale of drugs to consumers as long as there was detailed information in the labeling provided to potential patients. However, drug manufacturers could, at their own discretion, substitute the wording: “Caution: To be used only by or on the prescription of a physician (or dentist or veterinarian) [6, p. 110].” However, despite these regulations, the American Pharmaceutical Manufacturers bulletin in 1939 pointed out that over-the-counter sales, particularly of sulfa drugs, continued “to reach the consuming public in considerable quantities and through non-prescription sale [6, p. 110].” The 1951 law, sponsored by Senator Hubert Humphrey, who himself was a pharmacist, was based on the principle that drugs which were potentially habit-forming and those that have particularly serious adverse effects were best prescribed with the aid of a clinician. The clinician could help in making an appropriate diagnosis and, thus, limit unwarranted adverse events in situations in which drugs would provide little to no benefits to the patient.

Modern history. So, is the issue of non-prescription use of antimicrobials a historical curiosity? Recent evidence seems to say no. In this issue of Clinical Infectious Diseases, Llor and Cots [7] present data on the ability of trained actors to obtain antimicrobials without a prescription in Catalonia, Spain. Like in the United States, a prescription is required in Spain before a pharmacist may dispense an antimicrobial. The authors found that the actors were able to obtain an antimicrobial without a prescription in 89 (45%) of 197 pharmacies. Pharmacies dispensed an antimicrobial without a prescription in 79.7% of encounters in which an actress described symptoms consistent with but not diagnostic of a urinary tract infection. An actor received antimicrobials in 34.8% of encounters for supposed sore throat and in 16.9% of encounters for supposed acute bronchitis. The pharmacists failed to provide information to these “patients” regarding dosage and duration of use in ~15% and approximately one-third of patients, respectively. Most concerning, pharmacies failed to inquire about drug allergies in ~83% of encounters.

The data presented by Llor and Cots [7] adds another dimension to the challenges associated with the inappropriate use of antimicrobials, namely, the potential for inappropriate use by obtaining the drugs without a prescription. The acquisition of drugs, including antimicrobials, without a prescription is the standard in some countries around the world. The authors also noted the issues of self-medication, including antimicrobial treatment, in some communities in the United States that is associated with obtaining drugs across country borders [8, 9]. Individuals also have the ability to obtain antimicrobials over the Internet without a prescription.

So why does inappropriate use continue? The willingness of some pharmacists to dispense antimicrobials without a prescription even where it is illegal raises the same question as does inappropriate prescription practices by clinicians: why do people think it is acceptable to use antimicrobials inappropriately? One can only wonder how the same pharmacists would respond if a person stated that they thought they had a malignancy and asked for cancer chemotherapy without a prescription. One would hypothesize that the person would walk away with an admonition to see their clinician to make an appropriate diagnosis before subjecting themselves to the adverse consequences of cancer chemotherapy.

So why does the logic applied to cancer chemotherapy not apply to antimicrobials? Indeed, it appears that clinicians, let alone pharmacists, are challenged when it comes to making a diagnosis on clinical grounds alone for the indications of complicated and uncomplicated bacterial urinary tract infection, group A streptococcal pharyngitis, and pneumonia. These infections are easily mimicked by viral diseases or other forms of bacterial or fungal infections that require different therapies than those routinely prescribed for common bacterial infections. Therefore, without physical examination findings and ad-
The use of antimicrobials in situations where the benefits are not clear seems in part due to the mistaken idea that the risks are so low to the individual that even if the diagnosis is unclear and the benefits minimal that the harms are inconsequential. But why do people hold this view? Although policy makers and public health advocates often think in terms of group risk-benefit analyses and the effect on society as a whole, individuals often think of risk-benefit in terms of the impact on themselves, independent of the impact on society. In the summer, the risk of a group of persons experiencing food poisoning may be much higher on average than the risk of an individual experiencing food poisoning. The silver lining here is that the dispensers seem to have been aware that there is a difference in the risk-benefit of antimicrobial treatment depending on the clinical circumstances. However, the lack of inquiry regarding drug allergies would not rule out the potential for serious adverse events attributable to anaphylaxis or other adverse effects. The lack of information regarding other drugs and complications from drug-drug interactions is also a key concern that was left unaddressed by the pharmacies in the study.

The use of antimicrobials in situations where the benefits are not clear seems in part due to the mistaken idea that the risks are so low to the individual that even if the diagnosis is unclear and the benefits minimal that the harms are inconsequential. But why do people hold this view? Although policy makers and public health advocates often think in terms of group risk-benefit analyses and the effect on society as a whole, individuals often think of risk-benefit in terms of the impact on themselves, independent of the impact on society. In the summer, the risk of a group of persons experiencing food poisoning because of undercooked hamburger may be much higher on average than the risk of being bitten by a shark. However, this same risk-benefit analysis changes for a vegan surfer off the coast of Australia. Evidence shows that the risks of antimicrobial resistance rank low on the list of concerns of both clinicians and patients when they are deciding on antimicrobial use [10]. However, the risks of adverse events with antimicrobials come from studies in groups of subjects. The risk to the individual of experiencing an adverse event is either 100% or 0%—either they will experience the event or they will not. In addition, various factors influence people’s tolerance for risk. People are more tolerant of risk when it comes from a natural occurrence (i.e., being struck by lightning) than when it comes from a human decision (i.e., taking a drug). On the other hand, people are more tolerant of risk when it comes from a voluntary exposure (i.e., driving a car on the highway) than when it comes from an involuntary exposure (i.e., a nuclear accident), even when the risk is greater with the voluntary exposure. People are also more concerned about low frequency, high impact events [11]. In the case of antimicrobials, the risk comes in 2 forms: the low-frequency risk of progressing from the common cold to a more serious illness, such as pneumonia; and the risk of a low-frequency but serious adverse event attributable to the drug. Considering the rate of inappropriate prescribing, it appears that the former risk seems to be of more concern to clinicians, patients, and perhaps pharmacists than the latter. But should it be? For instance, some evidence indicates that the rate of suppurative complications among persons with sore throat is lower than the rate of adverse events attributable to antimicrobials [12].

**Future steps.** Perhaps we can learn from the lessons about how people approach risk analyses and what factors influence inappropriate prescribing to present the data on inappropriate use of antimicrobials in a different light [13]. The evidence shows a lack of benefit of antimicrobials in situations such as viral disease. That means antimicrobial usage in these situations is all risk and no benefit. Drugs are one of the most common causes of anaphylaxis, with antimicrobials ranking as one of the most common causes of drug-induced anaphylaxis [14]. Data from the Centers for Disease Control and Prevention show that an estimate of 150,000 cases per year present to US emergency departments for antimicrobial-related adverse events. Of all drug-related adverse events presenting to emergency rooms in the United States, almost one-fifth are related to antimicrobials. Most visits are for allergic reactions [15]. The rate of anaphylaxis caused by drugs is not as rare as is generally believed [14]. For penicillin, the only drug for which there was data available, anaphylaxis occurs with 0.7%–10% of treatments. The lack of data available for other drugs should not be construed as evidence of a lower rate, and the wide range of rates of anaphylaxis reported for penicillin demonstrates the lack of accurate data available for any drug. Neugut et al. [14] estimated that the number of people in the United States affected by anaphylaxis caused by penicillin could be between 1.9 million to 27.2 million persons each year. There is little evidence regarding the rates of more common adverse events to antimicrobials, such as headache, nausea, and abdominal pain, in situations where there is no benefit to antimicrobial treatment. The adverse event, diarrhea, may be a symptom of a superinfection due to an organism such as *Clostridium difficile*.

Perhaps we can use data from focus groups, which include the concerns of patients and clinicians regarding antimicrobial usage and risk assessments and may allow us to take a different approach toward explaining risks and benefits of antimicrobials by focusing on what they care about most [16]. Rather than assuming that education alone will counter the issues related to inappropriate prescribing of microbials, it would be good to be able to educate people on the issues about which they have the greatest concerns. Programs such as the Center for Disease Control and Prevention’s Get Smart program would be a likely place for this research and a focal point around which in-
terested parties could converge [17]. Future research on the optimal duration of therapy for some infections may limit the emergence of resistance while preserving the benefits of treatment. In addition, better design of clinical trials on infectious diseases would provide clinicians with more useful information on which to base clinical decisions, both in terms of effectiveness and adverse events [18]. Accurate, rapid point-of-care diagnostic assays, with high negative predictive values for bacterial etiologies in diseases most commonly caused by viruses, would provide clinicians with evidence on which to base the withholding of antimicrobial treatments. Cost-benefit analyses for these point-of-care diagnostic assays need to be based on overall outcomes that include the cost savings of prevention of direct adverse events, as well as the risk of antimicrobial resistance, rather than simply comparing the acquisition cost of the drug with the cost of the diagnostic test. Hopefully, this will lead to a greater appreciation of the attendant adverse events, both direct and related to resistance, that may accrue from the inappropriate use of antimicrobials. The inappropriate use of antimicrobials wastes a precious resource and consumes the usefulness of antimicrobials such that they will no longer be effective when we need them most, for serious and life threatening diseases in which they have the greatest health impact. The challenges of inappropriate use have existed since the first treatments with antimicrobials, and we need to find a solution to address the resulting unwarranted harms. In the end, yes, it can hurt.

Acknowledgments

Financial support. National Cancer Institute, National Institutes of Health (contract HHSN261200800001E).

Potential conflicts of interest. J.H.P. has served as a consultant or advisor and received <$10,000 for Acureon Pharmaceuticals, Advanced Life Sciences, Astellas Pharma, AstraZeneca Pharmaceuticals, Basilea Pharmaceutica, Centogen, Cerexa, CoNCErT Pharmaceuticals, Cubist, Destiny Pharma, Forest Laboratories, Great Lakes Pharmaceuticals, LEO Pharma, LifeTech Research, MediQuest Therapeutics, Merck and Co., MethylGene, Mpx Pharmaceuticals, Octopus, Takeda Global Research and Development, Theravance, United BioSource Corporation, and Wyeth Pharmaceuticals and has served as a consultant or advisor and received >$10,000 for Gilead Sciences, Invivodata, and Johnson and Johnson R&D.

References
