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Review article

Bacteria Resistance to Antibiotics: Recent Trends and Challenges

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ABSTRACT

For several decades, antibiotics have been critical in the fight against infectious disease caused by bacteria and other microbes. Antimicrobial chemotherapy has been a leading cause for the dramatic rise of average life expectancy in the Twentieth Century. However, disease-causing microbes that have become resistant to antibiotic drug therapy are an increasing public health problem. Wound infections, gonorrhea, tuberculosis, pneumonia, septicemia and childhood ear infections are just a few of the diseases that have become hard to treat with antibiotics. One part of the problem is that bacteria and other microbes that cause infections are remarkably resilient and have developed several ways to resist antibiotics and other antimicrobial drugs. Another part of the problem is due to increasing use, and misuse, of existing antibiotics in human and veterinary medicine and in agriculture. When antibiotics are underused, overused or misused, the process of antibiotic resistance is increased. The indiscriminate use of antibiotics, which promotes antibiotic resistance, results from patients' incompliance to recommended treatment and demand, prescribers, irrational use of antibiotics in human, drug advertisement, dispensing doctors and antibiotic use in agriculture, poor quality antibiotics, inadequate surveillance and susceptibility testing. Correcting a resistance problem, then, requires both improved management of antibiotic use and restoration of the environmental bacteria susceptible to these drugs. If all reservoirs of susceptible bacteria were eliminated, resistant forms would face no competition for survival and would persist indefinitely.

1. Introduction

The control of infectious diseases is badly endangered by the rise in the number of microorganisms that are resistant to antimicrobial agents. This is because infections caused by resistant microorganisms often fail to respond to conventional treatment, resulting in prolonged illness and greater risk of death. Antibiotic resistance is a type of drug resistance where a microorganism is able to survive exposure to an antibiotic. The primary cause of antibiotic resistance is genetic mutation in bacteria [1]. Inappropriate and irrational use of antimicrobial medicines provides favourable conditions for resistant microorganisms to emerge, spread and persist.. The greater the duration of exposure of the antibiotic, the greater the risk of the development of resistance, irrespective of the severity of the need for the antibiotic. As resistance towards antibiotics becomes more common a greater need for alternative treatments arises. However, despite a push for new antibiotic therapies there has been a continued decline in the number of newly approved drugs[2, 3]. Antibiotic resistance therefore poses a significant problem.

2.Classifications of Antibiotics

An antibiotic was originally defined as a substance produced by one microorganism, which inhibited the growth of other microorganisms. The advent of synthetic methods has however resulted in a modification of the definition and an antibiotic now refers to a substance produced by a microorganism or to a similar substance, which in low concentrations inhibits the growth of other microorganisms[4,5].Antibiotics are one class of antimicrobials that are relatively harmless to the host. They are small molecules with a molecular weight less than 2000[6]. The various types of antibiotics are:

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2.1 B- lactams

B-Lactams are antibiotics that act as bacteriostatics by inhibiting bacterial peptidoglycan cell wall synthesis[7,8]. B-Lactams includes penicillins and cephalosporins, are narrow spectrum antibiotics, which are highly effective against the Gram-positive genera Streptococcus, Gonococcus, and Staphylococcus[9]. The four-member ring, which all b-lactam drugs feature, is a strained, cyclic amide that is highly susceptible to chemical or enzymatic hydrolysis. The hydrolyzed B-lactam drugs result in an inactive product when the ring is broken. The degradation of B-lactam antibiotics such as penicillin, takes place under acidic and alkaline conditions or by reactions with weak nucleophiles, such as water or metal ions[10]. Alternatively, penicillin can be enzymatically hydrolyzed by b-lactamase enzyme via the same way as acid hydrolysis. B-lactamases are the widespread enzymes in bacteria, and are produced by many species to inactivate the pharmacological effects of the beta-lactamantibiotics [11].

2.2 Sulfonamides

Sulfonamides are bacteriostatic agent that synergistically target and inhibit two pathway steps in bacterial folic acid synthesis [12,13]. Sulfonamide or sulphonamide is the basis of several groups of drugs [14]. Folate derivatives are essential cofactors in the biosynthesis of purines, pyrimidines and bacterial DNA in all living cells. Therefore, blocking this pathway inhibits the production of reduced folates and eventually the synthesis of nucleic acid, which in turn affects bacterial growth. When combined, sulfonamides and trimethoprim afford an effective treatment against a variety of potential bacterial infections.

Sulfonamides are not completely metabolized during use and are excreted via urine into sewage, partly as unchanged parent compounds and partly as metabolites [15, 16]. The major metabolites of sulfonamides entering sewage are biologically inactive N4-acetylated products, for which transformations back to the active parent compounds during sewage treatment has been reported [17]. This phenomenon may have led to apparent negative removal of some sulfonamides, particularly sulfamethoxazole, during biological wastewater treatment[18, 19, 20]. Sulfamethoxazole is among the most frequently detected sulfonamides in municipal sewage[21,22,23].

2.3 Trimethoprim

Trimethoprim is a bacteriostatic antibiotic mainly used in the prophylaxis and treatment of urinary tract infections. It belongs to the class of chemotherapeutic agents known as dihydrofolate reductase inhibitors. Trimethoprim acts by interfering with the action of bacterial dihydrofolate reductase, inhibiting synthesis of tetrahydrofolic acid. Trimethoprim has been reported to occur in raw sewage of a number of countries including the USA[24], Croatia[25], and Mexico[26]. The presence of trimethoprim can generally be correlated to that of sulfamethoxazole[27]. since the two drugs are often administered in combination at a ratio 1:5 [28] reported that the concentration of trimethoprim in the primary effluent of a WWTP was around four times lower than that of sulfamethoxazole, which is relatively consistent with the typical medication ratio.

2.4 Macrolides

The macrolides are a group of drugs (typically antibiotics) whose activity stems from the presence of a macrolide ring, a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached. The lactone rings are usually 14-, 15-, or 16-membered. Macrolides belong to the polyketide class of natural products. Macrolide antibiotics, such as erythromycin, are active against most Gram-positive bacteria by binding reversibly to 50 S ribosomal subunits and inhibiting protein synthesis in microorganisms [5]. After administration, macrolides are largely excreted into sewage in their unchanged forms at excretion rates greater than 60%[29]. The concentration of macrolides in raw sewage from Switzerland vary between 0.01 and 0.6 mg L_1 [30, 31], while WWTP influent in the USA can contain macrolides at concentrations as high as 1.5 mg L_1[32].

2.5 Tetracycline

Tetracycline is a broad-spectrum polyketide antibiotic produced by the Streptomyces genus of Actinobacteria, indicated for use against many bacterial infections. It is a protein synthesis inhibitor. It is commonly used to treat acne today, and, more recently, rosacea, and is historically important in reducing the number of deaths from cholera. They inhibit protein synthesis by blocking the attachment of charged aminoacyl-tRNA. Thus they prevent introduction of new amino acids to the nascent peptide chain [33]. The action is usually inhibitory and reversible upon withdrawal of the drug. Resistance to the tetracycline results from changes in permeability of the microbial cell envelope. In susceptible cells, the drug is concentrated from the environment and does not readily leave the cell. In resistant cells, the drug is not actively transported into the cell or leaves it so rapidly that inhibitory concentrations are not maintained. This is often plasmid-controlled.

2.6Fluoroquinolone

Fluoroquinolones are antibiotics effective against several types of Gram-negative and Gram-positive bacteria [34]. These antibiotics act by inhibiting essential enzyme function for DNA production [12]. The occurrence of fluoroquinolones in WWTP effluents has been reported in countries like Australia, Canada, China, Italy, Mexico, Sweden, and the USA [35-40, 42]. When screening 12 human antibiotics in five WWTPs in Sweden, fluoroquinolones was found to be the most frequently detected antibiotics above analytical quantitation limits [31]. In that study, norfloxacin and ciprofloxacin were detected in 97% and ofloxacin in 50% of the analyzed samples.

2.7Nitroimidazoles

4-Nitroimidazole is an imidazole derivative that contains a nitro group. Several derivatives of nitroimidazole constitute the class of nitroimidazole antibiotics that have been used to combat anaerobic bacteria and parasitic infections [32]. The tetracyclines consist of eight related broad spectrum antibiotics, which are bacteriostatic and are active against Gram-positive and Gram-negative bacteria [13]. Tetracyclines inhibit protein synthesis in the microorganisms by binding to the 30 S ribosome and preventing the access of aminoacyl tRNA to the acceptor site on the mRNA-ribosome complex [33].

2.8 Other antibiotic groups

Aminoglycosidesandionophores are other antibiotic classes of interest. Aminoglycoside antibiotics are widely used in hospitals for treatment very severe human infection by gram-negative and gram-positive of bacteria[34] and in veterinary medicine[35]. Their antimicrobial action is by the inhibition of microorganism protein synthesis[33]. Aminoglycosides are mostly none metabolized after being administered; hence they will be excreted via urine unchanged. The analysis of wastewater from a hospital in Germany revealed that the concentration of aminoglycoside antibiotic gentamicin was between 0.4 and 7.6 mgL_134. There is little other information available on the occurrence and fate of aminoglycosides in wastewater and through treatment processes. However, due to their high absorption properties, it has been suggested that aminoglycoside antibiotics in wastewater would be adsorbed onto solid particles and colloidal organic matter and significantly removed from aqueous phase by filtration.

3.Trends Resistances In Bacteria

Antibiotics have been critical in the fight against infectious disease caused by bacteria and other microbes in the past 60 years. The resistance to antibiotics is increasing at a faster pace than it can be controlled[36]. Antimicrobial chemotherapy is a leading cause for the dramatic rise of average life expectancy in the Twentieth Century. However, disease-causing microbes that have become resistant to antibiotic drug therapy are an increasing public health problem. For instance in the United States, 80 million prescriptions of antibiotics for human use were filled and this equals 12,500 tons in one year[43]. At the present time, about 70 percent of the bacteria that cause infections in hospitals are resistant to at least one of the drugs most commonly used for treatment. Some organisms are resistant to all approved antibiotics and can only are treated with experimental and potentially toxic drugs. An alarming increase in resistance of bacteria that cause community acquired infections has also been documented, especially in the staphylococci and pneumococci (Streptococcus pneumoniae), which are prevalent causes of disease and mortality in most countries. In a study, 25% of bacterial pneumonia cases were shown to be resistant to penicillin, and an additional 25% of cases were resistant to more than one antibiotic[44]. For instance during the last several years, resistance to fluoroquinolones has remained very high among methicillin-resistant *Staphylococcus aureus* strains and in intensive care unit patients, and it has increased among nosocomial isolates of *Klebsiella pneumoniae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*. More worrisome are recent reports of an overall increase in resistance to fluoroquinolones among bacteria responsible for community-acquired infections, such as *Escherichia coli*, *Salmonella species*, *Campylobacter species* and *Neisseria gonorrhoeae.*

About 16 million incidence of typhoid fever and more than 580 000 attributable deaths occur globally each year[5]. The emergence of multidrug-resistant *S typhi* has been associated with an increase in the reported severity of disease[9]. *Shigella flexneri* is responsible for most of the sporadic bacillary dysentery cases in developing countries, and infections can be fatal, particularly in young children[24,25]. Resistance of shigella to ampicillin, tetracycline, cotrimoxazole, and chloramphenicol has also become widespread in Africa, even though these drugs are still used for first-line chemotherapy for dysentery in many parts of the continent [30]. Antimicrobial-resistant *Vibrio cholerae* O1 and, to a lesser extent, O139 isolates are becoming increasingly common[43,44,45]. Of concern is resistance to tetracycline and other agents used for empirical management of the disease in children, for whom tetracycline is contraindicated, or in cases where tetracycline is not available. Resistance patterns in *V cholerae* often mirror those in other enteric pathogens and commensals from the same area[46,47]. This mirroring is potentially because the organisms are under the same selection pressure, but also could be due to the sharing of some resistance genes horizontally[48-50].

Global reports issued in 1997, 2000, and 2004 revealed wide ranges in the prevalence of resistance to antituberculous drugs from place to place [51]. There are at least 17 documented multidrug-resistant tuberculosis hotspots with prevalence above 3%. The top five on the list (prevalence over 9%) are in former Soviet states and China, but hotspots exist in South and Central America, South Asia, the Middle East, Africa, and Europe[52].

Microbial development of resistance, as well as economic incentives, has resulted in research and development in the search for new antibiotics in order to maintain a pool of effective drugs at all times. While the development of resistant strains is inevitable, the slack ways that by which antibiotics are administer and used has greatly exacerbated the process. Unless antibiotic resistance problems are detected as they emerge, and actions taken instantly to contain them, the world could be faced with previously treatable diseases that have become again untreatable, as in the days before antibiotics were developed[50].

4.Mechanism of Bacteria Resistance

Several mechanisms have evolved in bacteria which confer them with antibiotic resistance. These mechanisms can chemically modify the antibiotic, render it inactive through physical removal from the cell, or modify target site so that it is not recognized by the antibiotic[53]. The emergence of resistance to fluoroquinolones in virtually all species of bacteria was recognized soon after the introduction of these compounds for clinical use more than 10 years ago. Various resistance mechanisms, often interdependent, may explain different levels of resistance. Epidemiological factors, local antibiotic policies, patients' characteristics, origin of the strains, and geographic[54] location are among the factors contributing to highly variable resistance rates. The most common mode is enzymatic inactivation of the antibiotic[55]. An existing cellular enzyme is modified to react with the antibiotic in such a way that it no longer affects the microorganism. An alternative strategy utilized by many bacteria is the alteration of the antibiotic target site[56].

4.1.The acquisition and spread of antibiotic resistance in bacteria

The development of resistance is inevitable following the introduction of a new antibiotic. Initial rates of resistance to new drugs are normally on the order of 1%[57]. However, modern uses of antibiotics have caused a huge increase in the number of resistant bacteria. After a widespread use of an antibiotic within 8-12 years, strains were resistant to multiple drugs[58]. Multiple drug resistant strains of some bacteria have reached the proportion that virtually no antibiotics are available for treatment. Antibiotic resistance in bacteria may be an inherent trait of the organism (for instance a particular type of cell wall structure) that renders it naturally resistant, or it may be acquired by means of mutation in its own DNA or acquisition of resistance-conferring DNA from another source[59].

Bacteria may be inherently resistant to an antibiotic naturally[60]. For example, an organism lacks a transport system for an antibiotic; or an organism lacks the target of the antibiotic molecule; or, as in the case of Gram-negative bacteria, the cell wall is covered with an outer membrane that establishes a permeability barrier against the antibiotic. Several mechanisms are developed by bacteria in order to acquire resistance to antibiotics[61]. Antibiotics require either the modification of existing genetic material or the acquisition of new genetic material from another source.

Resistant organisms may become apparent as a result of the destruction of sensitive strains by the antibiotic, allowing naturally resistant strains to colonise the patient. For example, penicillin therapy destroys much of the normal mouth flora and the mouth becomes colonized by penicillin-resistant organisms previously present in small numbers. A genetic mutation may occur during treatment and becomes apparent when the sensitive organisms are destroyed. Mutation occurs more readily with some antimicrobial agents than with others, and especially with streptomycin, rifampicin, and nalidixic acid[62]. Certain organisms may acquire resistance as a result of the activity of phages (bacterial viruses) which incorporate a resistance present in one organism and when released carry the resistance over to an organism which was originally sensitive.

5. Factors Affecting Resistances of Antibiotics

When antibiotics are underused, overused or misused, the process of antibiotic resistance is increased[63]. The indiscriminate use of antibiotics, which promotes antibiotic resistance, results from patients' incompliance to recommended treatment and demand, prescribers, irrational use of antibiotics in human, drug advertisement, dispensing doctors and antibiotic use in agriculture, poor quality antibiotics, inadequate surveillance and susceptibility testing.

Doctors and prescribers are influenced greatly by patients' demand even if they are sure of their diagnosis. Because patients prefer allopathic medicines, many traditional doctors/practitioners are prescribing allopathic medicine instead of herbal medicines. A study in India revealed that many Indians believed in the efficacy of tonics and would not return to a doctor unless a tonic is prescribed as they wish. The doctors prescribe tonics to patients even when they are ineffective because their livelihood depends on the number of patients that attend their clinics[59].

Patient's incompliance to recommended treatment was identified to be one of the causes of microbial resistance to antibiotics. Patients forget to take their medication[64] and some interrupt their treatment when they begin to feel better. In a similar experiment[65], patients may be unable to afford full course of drugs and might also be due to inadequate physician patient interaction. There is irrational use of antibiotics in humans[66].

This is as a result of self medication, which includes unnecessary and inadequate dose. Other patients also misuse the antibiotic due to the fact that it is readily available in the pharmacy and they can buy it without having a prescription[67]. The pharmaceutical companies aid in promoting bacterial resistance to currently available antibiotics. According to an advert by a company, Ciprofloxacin is the appropriate drug of choice for a patient at risk. An advertisement in the Philippines in 1994 and 1995 promoted the use of clindamycin for upper respiratory tract infections and lincomycin for pharyngitis/tonsillitis. The most likely causative agent of these diseases is viral infections that cannot be treated with antibiotics. This is a clear case of antibiotics being advertised for conditions that do not require them.

The actions of physicians also contribute to the microbes developing resistance to antibiotics. This is because physicians over prescribe a broad spectrum of drugs when narrow spectrum are appropriate. Prescribers have different variations in the prescribing of antibiotics and other drugs. It has been shown that 30 to 60% of patients receive twice or more of what is perhaps needed. Wrong prescription and guidelines from unskilled health practitioners also is another important factor. In a similar study it was realized that unnecessary prescription was found in private practitioners[68].

Hospitals and clinics also contribute to the resistance of antibiotic to microbes. This is as a result of poor infection control practices like hand washing, changing gloves among others. Another issue of poor quality antibiotics was raised[69]. This is as a result of the use of expired and counterfeit antibiotics, due to lack of quality compliance and monitoring[70]. There is also the irrational use of antibiotics in animals[71]. Some antibiotics are used for growth and disease control in animals and humans indirectly take these antibiotics when we are eating these animals. Some antibiotics used in treatment of human infections, especially the enterococcal and staphylococcal types, are equally employed in similar infections occurring in plants and animals. The use of penicillin and tetracycline in animal feeds increases the number of resistant organisms within the animal bowel and the existence of such organisms appear to increase the proportion of resistant organisms in man. Surveillance and susceptibility testing conducted on antibiotics is inadequate. Unknown susceptibility pattern of bacterial isolates encourages empirical selection of broad spectrum antibiotics.

6. Challenges of Antibiotics Resistance

Antimicrobial resistance kills[13]. Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness and greater risk of death. Antimicrobial resistance kills hampers the control of infectious diseases[19]. When microbes become resistant to certain microbes, it reduces the effectiveness of treatment because patients remain infectious53 for longer, thus potentially spreading resistant microorganisms to others. Antimicrobial resistance kills threatens a return to the pre-antibiotic era[24]. Many infectious diseases risk becoming uncontrollable and could derail the progress made towards reaching the targets of the health-related United Nations Millennium Development Goals set for 201558.

Antimicrobial resistance kills increases the costs of health care[72]. When infections become resistant to first-line medicines, more expensive therapies must be used. The longer duration of illness and treatment, often in hospitals, increases health-care costs and the financial burden to families and societies. Antimicrobial resistance kills jeopardizes health-care gains to society. The achievements of modern medicine are put at risk by Antimicrobial resistance kills. Without effective antimicrobials for care and prevention of infections, the success of treatments such as organ transplantation, cancer chemotherapy and major surgery would be compromised. Antimicrobial resistance kills threatens health security, and damages trade and economies[73]. The growth of global trade and travel allows resistant microorganisms to be spread rapidly to distant countries and continents.

When a patient receives treatment with antibiotics, both the causative pathogen and the normal nonpathogenic microflora in the body will be affected[13]. The indigenous microflora makes up a complex ecological system of great importance for human health. Besides being essential for the digestion of food and to metabolise drugs, they also produce essential vitamins and are important for the activation and maintenance of the immune system in the gut. Ideally, antibiotics should effectively kill the pathogen responsible for infections and, simultaneously, cause as little disturbance as possible to the microflora of the individual.

7. Measures To Reverses Resistances

In main genetic processes, horizontal gene transfers, the resistant microbe is affected not only in its ability to withstand the antibiotic, but due to the fact that its interaction with the host and its ability to be transmitted between hosts. Usually, it is observed that most resistance mechanisms will confer a reduction in bacterial fitness, which might be expressed as reduced growth and survival inside and outside a host, and reduced virulence or transmission rate from environment to host or between hosts. The observation that resistance is associated with a biological cost has led to the widespread idea that by reducing the volume of antibiotic use the frequency of resistant bacteria in a population can also be reduced. However, this picture is complicated by the fact that bacteria may reduce the costs associated with the resistance through compensatory evolution [1,2,13]. The role of compensatory mutations that maintain the fitness of resistant strains is now well established and increasing levels of biologically competitive resistant bacteria are detected in the community, with no decrease in vitality compared to non-resistant strains.

Physicians, for their part, can take some immediate steps to minimize any resistance ensuing from required uses of antibiotics. When possible, they should try to identify the causative pathogen before beginning therapy[16], so they can prescribe an antibiotic targeted specifically to that microbe instead of having to choose a broad-spectrum product [22]. Washing hands after seeing each patient[44] is a major and obvious, but too often overlooked, precaution.

Two epidemiological studies, of erythromycin resistance in *S. pyogenes*[16] and penicillin resistance in Streptococcus pneumoniae[4], have been suggested as providing support for the reversibility of resistance in community settings. In these cases, the rate and extent of the decline in the frequency of resistance associated with reduced antibiotic use were small, which is in accord with predictions from modeling. In addition, the weak apparent correlation between reduced antibiotic consumption and decreased frequency of resistance could have been caused by many other factors, for example, clonal shifts where a susceptible clone happened by chance to increase in frequency coincidentally with the reduction in antibiotic use. Thus, the epidemiological studies that are available at the moment provide no strong support for reversibility. In addition, several laboratory and epidemiological studies indicate that various processes are predicted to cause long-term persistence of resistant bacteria.

One process is compensatory evolution, where the costs of resistance are ameliorated by additional genetic changes, resulting in the stabilization of resistant bacteria in the population. Even though most resistance is associated with fitness cost, some resistance mutations appear to be gratuitous. The occurrence of such cost-free resistances will also cause irreversibility since the driving force for reversibility is absent. Finally, genetic hitch-hiking between non-selected and selected resistances will confer stabilization of the resistant bacteria. Thus, when two resistance genes are located near each other, on, for example, a plasmid, they tend to be inherited together. As a result, selection for one of the resistance genes tends to cause selection also for the nearby, genetically linked gene. An interesting example of such hitch-hiking was provided by a recent study of sulphonamideresistant E. coli. Here, it was demonstrated that even after a drastic reduction in the use of sulphonamide in the United Kingdom from 1991 to 1999 the frequency of sulphonamide-resistant *E. coli* did not decrease, but actually increased slightly, from 40% to 46%. The explanation for this finding is most likely that the sulphonamide-resistant gene(s) is genetically linked on a plasmid to other resistance genes that were continuously selected during this time period[7]. In conclusion, if antibiotic resistant bacteria have ascended to a high frequency within the community they are likely to remain there for a long time.

In hospital settings the rate and extent of reversibility are much higher than in communities, as shown by both actual experiments and clinical intervention studies as well as by theoretical models[9]. The reason for this difference is that the main driving force for reversibility in hospitals, in contrast to communities, is not the biological cost of resistance. Instead, in hospitals we observe a dilution effect as incoming patients, whether infected or not infected, are in most cases bringing susceptible bacteria into the hospital. To avoid spreading multidrug-resistant infections

between hospitalized patients, hospitals place the affected patients in separate rooms, where they are seen by gloved and gowned health workers and visitors. This practice should continue.

A number of corrective measures can be taken right now. As a start, farmers should be helped to find inexpensive alternatives for encouraging animal growth and protecting fruit trees. Improved hygiene, for instance, could go a long way to enhancing livestock development. The public can wash raw fruit and vegetables thoroughly to clear off both resistant bacteria and possible antibiotic residues. When they receive prescriptions for antibiotics, they should complete the full course of therapy (to ensure that all the pathogenic bacteria die) and should not "save" any pills for later use. Consumers also should refrain from demanding antibiotics for colds and other viral infections and might consider seeking non antibiotic therapies for minor conditions, such as certain cases of acne. They can continue to put antibiotic ointments on small cuts, but they should think twice about routinely using hand lotions and a proliferation of other products now imbued with antibacterial agents. New laboratory findings indicate that certain of the bacteria-fighting chemicals being incorporated into consumer products can select for bacteria resistant both to the antibacterial preparations and to antibiotic drugs.

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