EXPERT REVIEWS

Economics of antibiotic resistance

Expert Rev. Anti Infect. Ther. 6(4), 523–539 (2008)

Oguz Resat Sipahi
Ege University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Bornova Izmir, Turkey
Tel.: +90 232 390 4510
Fax: +90 232 342 0871
oguz.resat.sipahi@ege.edu.tr

Antibiotics are developed to kill microorganisms; however, microorganisms develop and disseminate resistance as a reaction to antimicrobials in accordance with the laws of evolution and natural selection. Resistant and multidrug-resistant bacterial infections comprise a great problem in both the community and hospital setting. Increasing values of health expenditures, including antibiotics, is a global problem. Antibiotic resistance is not always, but usually, associated with significant morbidity, longer hospitalization, excess costs and mortality. Excess costs associated with resistant microorganisms may be due to: obligation to use more expensive antibiotics, longer hospital stay, higher mortality, delayed appropriate antibiotic therapy or a necessity to perform surgery. Optimal use of existing antimicrobial agents, using alternative treatment options (where possible), reducing the need for antimicrobials by increasing immunity, reducing the use of antimicrobials without providing an alternative form of treatment through education of health professionals and patients, antibiotic policies (including antibiotic stewardship and regulations for restricted use), implementation of infection control measures (e.g., hand washing, screening and isolation) are the strategies aimed at prevention of emergence and spread of antibiotic resistance.

KEYWORDS: *Acinetobacter baumannii* • antibiotic stewardship • community-acquired infection • cost analysis • Enterobacteriaceae • *Escherischia coli* • extended-spectrum β-lactamases • hospital-acquired infection • *Klebsiella pneumoniae* • methicillin-resistant *Staphylococcus aureus* • *Mycobacterium tuberculosis* • net present value • nosocomial • *Proteus mirabilis* • *Pseudomonas aeruginosa* • *Streptococcus pneumoniae* • surveillance • VRE

Isaac Newton's laws of motion are three physical laws that provide relationships between the forces acting on a body and the motion of the body. Briefly stated, the three laws are:

- An object will remain at rest or continue to move at a constant velocity, unless an external net force acts upon it;
- Net force on an object is equal to its rate of change of momentum;
- For every action, there is an equal and opposite reaction [201].

In biology, evolution is a change in the inherited traits of a population from one generation to the next. These traits are the expression of genes that are copied and passed on to offspring during reproduction. Mutations in these genes can produce new or altered traits, resulting in heritable differences between organisms. New traits can also come from the transfer of genes between populations, such as in migration, or between species, such as in horizontal gene transfer. Natural selection is a process that causes heritable traits that are helpful for survival and reproduction to become more common and causes harmful traits to become more rare [202].

Antibiotics are chemotherapeutic agents that inhibit or abolish the growth of microorganisms, such as bacteria, fungi or protozoans, and are developed to kill microorganisms. Microorganisms develop and disseminate resistance as a reaction to antimicrobials in accordance with the rules of physics, evolution and natural selection. In spite of considerable developments in antibiotics, antibiotherapy, science, medicine and medical care, infectious diseases and infectious complications related to resistant bacteria, such as staphylococci, respiratory pathogens (e.g., *Streptococcus pneumoniae*), Gram-negative bacilli, as well as fungi and viruses, remain important causes of human morbidity and mortality. As stated in the very recent last call for action to the medical community from the Infectious Diseases Society of America [1], we are in the midst of an emerging (probably already emerged) crisis of antibiotic resistance throughout the world.

 10.1586/14787210.6.4.523 ISSN 1478-7210

This review will focus on the economics, epidemiology and basic causes of antibiotic resistance (mostly but not entirely in terms of methicillin-resistant *Staphylococcus aureus* [MRSA] and methicillin-resistant coagulase-negative staphylococci [MRCNS], vancomycin-resistant enterococci [VRE], extended-spectrum β-lactamase [ESBL]-positive and/or carbapenem-resistant Enterobacteriaceae, multidrug-resistant [MDR] or pandrug-resistant *Pseudomonas* and *Acinetobacter* spp., MDR-TB and extensively drug-resistant [XDR]-TB) and approaches to prevent antibacterial resistance.

Economics & pharmacoeconomics

Economics is the social science that studies the production, distribution and consumption of goods and services. The term 'economics' comes from the Greek for *oikos* (house) and *nomos* (custom or law), hence 'rules of the house(hold)'. A definition that captures much of modern economics is that of Lionel Robbins in a 1932 essay: 'the science which studies human behavior as a relationship between ends and scarce means which have alternative uses'. The definition of economics in terms of scarcity suggests that resources are in finite supply while wants and needs are infinite [203].

Pharmacoeconomics is a relatively new discipline that consists of a systematic approach to decision analysis to determine the most cost-effective therapy among the available alternatives. In other words, pharmacoeconomics is 'the description and analysis of the costs of drug therapy to healthcare systems and society'. As in the case of economics, pharmacoeconomic reasoning also starts from the point that in any real economic system, resources are scarce in relation to demands and needs. This is also true for both public and private healthcare systems. Therefore, those who plan, receive or pay for health services must make choices among available alternatives [2,3].

The increasing costs of health expenditures is a major and worldwide problem [2–9]. Antibiotics comprise a significant portion of total health expenditures. From the institutional perspective, antimicrobials account for more than 30% of hospital pharmacy budgets. An early estimate of American healthcare costs made by the American Society for Microbiology in 1995 revealed that annual healthcare costs associated with the treatment of resistant infections in the USA are over US$4 billion. A more recent estimate increased this value to US$7 billion; up to US$4 billion of which is for treatment of resistant nosocomial infections [2,5]. In 1996, 26.3% of the total health expenditure in Turkey was spent on drug consumption and 22.4% of all drugs used were antimicrobial agents, which means a value of US$400 million per year [7]. Society pays for the costs of MRSA or other MDR microorganisms through increased tax or insurance charges [10]. Thus, economics of antibiotic resistance is important from the view of the patient, the health system, the country and the world.

Resistance

Most bacteria have multiple routes for acquiring resistance to a drug. Once they acquire the resistance, they can rapidly give rise to vast numbers of resistant progeny. Natural selection favors mechanisms that confer resistance with the least fitness cost. Selection may also favor determinants that prevent their own counterselection and resistant strains with enhanced survival ability or virulence [11].

Antibiotic usage has been shown to have a critical role in the selection of antibiotic-resistant bacteria as the dominant colonizing flora as well as the nosocomial pathogens of hospitalized patients [12]. Regarding this process, at least two mechanisms have been documented. First, antimicrobial-resistant flora may be endemic within the institution and may be transferred to the patient within the hospital setting [12,13]. Second, a small population of antimicrobial-resistant bacteria that are a part of patient's endogenous flora at the time of hospitalization may emerge under the selective pressure of antibiotics and become the dominant flora [12,14].

In the case of TB, the situation is not much different. Misuse of drugs to treat TB, owing to the prescriber or the patient, can lead to the loss of drug sensitivity, giving rise to various forms of drug-resistant TB. Prescription of inadequate regimens, inappropriate supply of drugs and poor adherence may result in resistance. Resistance occuring under drug pressure in a patient initially affected by a drug-sensitive strain is known as acquired drug resistance. Spread of the resistant strain to a previously healthy person results in a phenomenon known as primary drug resistance. MDR-TB refers to bacteria resistant to at least isoniazid and rifampin. XDR-TB refers to resistance to isoniazid plus rifampin plus any fluoroquinolone plus at least one of the following injectable drugs: capreomycin, kanamycin or amikacin [15].

Epidemiology of antibacterial resistance in the hospital

Problems related to antibiotic resistance differ from unit to unit, hospital to hospital and country to country. In Europe, resistant rates tend to increase as one moves southward. Resistance is at its lowest in Scandinavia and highest in Mediterranean countries. Within North America, resistance rates are mostly higher in the USA than in Canada. Some of the highest rates of resistance are found in the newly prosperous countries of Eastern Asia and Southern America [11]. Examples of rates of several resistant bacteria, such as MRSA, VRE, ESBL$^+$ *Escherichia coli* or *Klebsiella pneumoniae*, from different parts of world are given in Table 1.

Of note, the resistant microorganisms do not recognize boundaries between countries; hence, the epidemiology of resistance may be multinational, with some transferable determinants prevalent worldwide. Medical literature on the transfer of resistance from city to city and country to country is not rare [11,16,17].

Table 1. Examples of resistance rates of MRSA, MRCNS, VRE, ESBL$^+$ *Escherichia coli* and *Klebsiella pneumoniae* from different countries.

Bacteria	Country	Number of strains	Resistance rate (%)	Ref.
MRSA	Turkey	941	74.2	[128]
MRSA	USA	22,899	48.1	[142]
MRSA	Turkey	37	88.4	[143]
MRSA	Greece	1019	33 (1994) 50 (2001)	[144]
MRSA	Austria	2587	38.8	[144]
MRSA	Belgium	1587	38.2	[144]
MRSA	Germany	6074	34.5	[144]
MRSA	Spain	1279	38.4	[144]
MRSA	Holland	81	0	[145]
MRSA	France	4385	44.8	[144]
MRCNS	Turkey	93	81.7	[143]
MRCNS	USA	13,553	76.6	[142]
VRE	Turkey	153	7.8	[4]
VRE	USA	14,140	13.9	[142]
ESBL$^+$ *Klebsiella pneumoniae*	Turkey	42	33	[146]
ESBL$^+$ *K. pneumoniae*	Turkey	168	47	[147]
ESBL$^+$ *K. pneumoniae*	Turkey	426	38.9	[129]
Third-generation cephalosporin-resistant *K. pneumoniae*	USA	7529	6.2	[142]
ESBL$^+$ *Klebsiella* spp.	Holland	196	<1	[148]
ESBL$^+$ *K. pneumoniae*	France	6121	11.4	[149]
ESBL$^+$ *K. pneumoniae*	Greece	79	58.3	[150]
ESBL$^+$ *Escherichia coli*	Turkey	51	47	[146]
ESBL$^+$ *E. coli*	Turkey	179	28	[147]
Third-generation cephalosporin-resistant *E. coli*	USA	12,011	1.3	[142]
ESBL$^+$ *E. coli*	Holland	571	<1	[148]
ESBL$^+$ *E. coli*	Greece	124	20.2	[150]

ESBL: Extended-spectrum β-lactamase; MRCNS: Methicillin-resistant coagulase-negative staphylococci; MRSA: Methicillin-resistant *Staphylococcus aureus*; VRE: Vancomycin-resistant *Enterococcus*.

Finally, the evolving problem of antimicrobial resistance in *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *K. pneumoniae* has led to the emergence of clinical isolates susceptible to only one class of antimicrobial agent and, eventually, to pandrug-resistant isolates [18]. *P. aeruginosa* and *A. baumanii* are disseminated widely in the environment and they are prone to the acquisition of novel resistance determinants from environmental species, which they stabilize into their genome [19]. Infections caused by pandrug-resistant strains are associated with significant mortality and treatment is quite challenging [20–22].

Epidemiology of antibacterial resistance in the community

Antibiotic resistance in the community is an emerging global problem [23–29]. The normal individual flora, which is important for the maintenance of individual health, can play a critically important role in infectious diseases [24]. Carriage of resistant bacteria such as MRSA, ESBL$^+$ Enterobacteriaceae and pneumococci may result in infections.

In fact, carriage of such pathogens and infections related to them is not rare in the community. In a study performed in Saudi Arabia, fecal carriage of ESBL$^+$ organisms was detected in 26.1% of 272 in-patients, 15.4% of 162 out-patients, and 13.1% of 426 healthy individuals [30]. In another study performed in Spain, a cross-sectional survey of human ESBL-producing Enterobacteriaceae carriers in the community showed a general prevalence of 6.6% (out of 948 samples) [31]. The ESBL rate of community-acquired urinary tract infections related *E. coli* strains are 7.9% in Turkey and 34.4% in India [23,29]

Not only ESBL$^+$ bacteria, but also MRSA and penicillin-resistant *Streptococcus pneumoniae* have important community reservoirs. Yildirim *et al.* reported 5% nasal MRSA carriage and 8.3% intermediately resistant *S. pneumoniae* carriage in 484 children [24]. MRSA carriage was reported to be 2.6% in 500 healthy adults and 1.9% in 500 healthcare workers [26]. In addition to human reservoirs, MRSA in animals (e.g., pigs) can spread, colonize and infect humans [25].

The WHO estimates that 4% of all new TB cases globally are MDR-TB [15]. MDR-TB prevalence is reported to be 21.5% (n = 900) in Estonia, 5.7% (n = 748) in Germany, 2.8% (n = 2140) in Italy and 7.9% (n = 505) in Turkey [15,32–35]. According to multivariate analysis of a large case–control study, prior TB treatment for 6–11 months (odds ratio [OR]: 7.6; 95% confidence interval [CI]: 2.6–22.4; $p < 0.001$) and for at least 12 months (OR: 13.7; 95% CI: 4.5–41.6; $p < 0.001$), but not

HIV positivity, was associated with MDR-TB [36]. As expected, XDR-TB is usually common in countries where MDR-TB is common. XDR-TB exists in all continents. An analysis of 17,690 strains from 48 countries resulted in 234 strains (6.6% of overall MDR-TB [0.6% in Africa and 15.4% in Korea]) [37].

Cost & other results of antibiotic resistance

Antibiotic resistance is not always [38], but usually, associated with significant morbidity, longer hospitalization (including permanent or temporary sequalae and indirect significant psychiatric issues) and excess costs and mortality. Reported additional costs of ESBL$^+$ versus ESBL$^-$, MRSA versus methicillin-susceptible *S. aureus* (MSSA), VRE versus vancomycin-susceptible *Enterococcus* (VSE), MDR versus non-MDR *Acinetobacter* or *Pseudomonas* spp. infections range between US$7212 and 98,575 and additional length of hospital stay ranges between 2 and 15.3 days (Table 2) [39–47].

Excess costs associated with resistant microorganisms may be due to:

- Obligation to use more expensive antibiotics
- Longer hospital stay
- Higher mortality
- Delayed appropriate antibiotic therapy
- More common necessity to perform surgery [48]

Obligation to use more expensive antibiotics

One of the major consequences of resistant bacterial infections is the obligation to use antibiotics with extended spectrums and (usually) increased expense (Table 3). For example, in the case of MSSA/MRSA the treatment options turn from cefazolin/β-lactam plus β-lactamase combinations to vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin; in VSE/VRE; pencillin or vancomycin to linezolid and quinopristin/dalfopristin, in ESBL$^+$/ESBL$^-$ Enterobacteriaceae: cephalosporins or β-lactam/β-lactamase inhibitor combinations to carbapenems [49–53].

Table 2. Effects of multidrug resistance of several MDR bacteria on mortality, length of stay and cost of hospitalization.

Bacteria	Control	Syndrome	Mortality (%)	Length of stay (days)	Extra cost or cost (US$)	Ref.
ESBL$^+$ *Escherichia coli*, *Klebsiella* spp., *Proteus* spp.	ESBL$^-$ *E. coli*, *Klebsiella* spp., *Proteus* spp.	Bacteremia	35 vs 16	11 vs 5	9620	[39]
ESBL$^+$ *E. coli*, *Klebsiella pneumoniae*	ESBL$^-$ *E. coli*, *K. pneumoniae*	Heterogeneous	15.2 vs 9.1	11 vs 7	66,590 vs 22,231	[40]
MRSA	MSSA	Bacteremia	22.9 vs 19.8	30.6 vs 15.3	21,577 vs 11,668	[41]
MRSA	MSSA	Bacteremia	22.9 vs 19.8	9 vs 7	26,424 vs 19,212	[42]
VRE	VSE	Bacteremia	33.3 vs 11.1	17 vs 3		[43]
Imipenem-resistant *Acinetobacter baumannii*	Imipenem-susceptible *A. baumannii*	Bacteremia	57.5 vs 27.5			[44]
MDR (sensitive to imipenem and sometimes aminoglycosides) *Acinetobacter* spp.	Susceptible	Heterogeneous	19.4 vs 4.5	13	60,913	[45]
MDR (resistant to all penicillins, all cephalosporins, ciprofloxacin, gentamicin and imipenem) *A. baumannii*	Non-MDR *A. baumannii*	Burn patients		36.8 vs 25.6	201,558 vs 102,983	[46]
MDR (resistant to ceftazidime, cefepime, aztreonam, ciprofloxacin, piperacillin and gentamicin) *Pseudomonas aeruginosa*	Non-MDR *P. aeruginosa*	Heterogeneous	21 vs 12	20 vs 10		[47]

ESBL: Extended-spectrum β-lactamase; MDR: Multidrug-resistant; MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-susceptible *S. aureus*; VRE: Vancomycin-resistant *Enterococcus*; VSE: Vancomycin-susceptible *Enterococcus*.

Longer hospital stay

It is not easy to explain the excess cost of resistant bacterial infection only as a result of the consumption of more expensive drugs in all countries. This may be true in a country such as Turkey where drugs are usually more expensive than using a health service. In contrary, longer hospitalization may play a more important role in excess cost of resistant bacterial infections in a country such as USA, where penicillin G can be more expensive than vancomycin or levofloxacin [49].

Mortality

Some of the costs associated with resistance (at least in some bacteria) are also due to increased mortality. In a recent meta-analysis, bacteremia due to ESBL$^+$ Enterobacteriaceae was found to be associated with increased mortality (pooled relative risk [RR]: 1.85; 95% CI: 1.39–2.47; $p < 0.001$) [54]. Another meta-analysis shows that patients with MRSA bacteremia have a RR of death of 2.12 (95% CI: 1.76–2.57) compared with patients with MSSA bacteremia [55]. Why are resistant bacterial infections associated with higher mortality? Existing data do not support the hypothesis 'resistant microorganisms are more virulent than nonresistant ones' in major pathogens, such as *S. aureus* (with the exceptance of community-acquired MRSA), *Enterococcus* or Gram-negative bacilli [48]. The reason may be delayed appropriate or inappropriate therapy [41,48,54].

Delayed appropriate therapy

Some portion of excess mortality/cost/duration of hospitalization in some of the resistant bacterial infections is due to delayed appropriate or inappropriate antimicrobial therapy. Schwaber and Carmeli reported increased incidence of delay in effective therapy in ESBL-associated bacteremia (pooled RR: 5.56; 95% CI: 2.94–10.51; $p < 0.001$) in the aforementioned meta-analysis [54]. MRSA bacteremia patients also have an increased risk of delayed treatment and delayed therapy is reported to be an independent predictor of mortality in this group, too [41]. Mortality rates are higher among patients with ventilator-associated pneumonia who receive inappropriate empirical treatment [48]. Starting inappropriate therapy affects not only mortality but also duration of hospitalization (if patients survive and can obtain appropriate therapy, duration of hospitalization will also increase) and the ecology of hospitals (as inappropriate therapy is prolonged, the likelihood of resistant bacteria arising will increase, which sometimes may result in the occurrence of outbreaks).

Table 3. Daily drug-acquisition costs of several antibiotics.

Antibiotic	Dosage	Cost in Turkey*	Cost in the USA‡
Vancomycin	4 × 500 mg	39.4	15.5
Linezolid	2 × 600 mg	208.5	164
Teicoplanin	2 × 400 mg	144.9	NA
Imipenem	4 × 500 mg	93.7	156
Meropenem	3 × 1 g	148.6	204
Piperacillin/tazobactam	3 × 4.5 g	78.9	72
Ceftriaxone	2 × 1 g	14.7	13.2
Cefepime	3 × 1 g	32.8	108

NA: Not available.
*As the price on 7th January 2007 in Turkey. Prices are converted to US dollars assuming that YTL1.2 = US$1.
‡Adapted from [49].

More common need for surgery

Longer hospital stay and higher costs of care for patients infected with a resistant organism may also result from an increased frequency of surgical interventions required to control infection. Several groups of investigators have documented an increased need for surgery among patients infected with resistant organisms, such as VRE and *P. aeruginosa* [48]. This may also be the case in community-acquired MRSA, which may be susceptible to trimethopirim/sulfomethoxazole or clindamycin but may sometimes need adjuvant surgery for treatment.

Which is worse? MDR Gram-negative or Gram-positive organisms

Although it may vary from country to country, a recent study from Austria suggests that not length of stay and mortality but total costs (GB£26,317 vs GB£14,782) were found to be significantly higher in MDR (not susceptible to more than one antibiotic except colistin) Gram-negatives than MRSA [56].

MDR- and XDR-TB are also associated with significant morbidity and mortality. In a multinational study including Estonia, Germany, Italy and Russia, XDR-TB cases had a RR of 1.58 to have an unfavorable outcome compared with MDR-TB cases resistant to all first-line drugs (isoniazid, rifampicin ethambutol, streptomycin and, when tested, pyrazinamide), and a RR of 2.61 compared with 'other' MDR-TB cases (those susceptible to at least one first-line anti-TB drug among ethambutol, pyrazinamide and streptomycin, regardless of resistance to the second-line drugs not defining XDR-TB) [32]. Another study, from South Africa reported 98.1% mortality in 53 XDR-TB cases (of note, at least 44 were HIV positive) [57].

Problems with the economic evaluation of antibiotic resistance

In calculating the cost of nosocomial infections and/or infections with resistant microorganisms, there are a number of methodological factors to be considered:

- Study design
- Patient group (incidence, prevalence and epidemics)
- Location (hospital and follow-up after discharge)

- Dimension of the study (hospital, country, pathogens and interventions)
- Extra cost and design of length of stay
- Costs (hospital charges, length of stay in the hospital, deaths, antibiotic utilization, antibiotic resistance, environmental damage, loss of productivity, psychological problems and anxiety [if colonization continues or other family members are involved through contact screening], diminished quality of life, and the hospital's reputation as patients perceive [sometimes correctly] that they are often unclean, dangerous places)
- Conclusion statistics (mean, median, percent, total) [2,3,10]

Drug, antibiotic acquisition costs and increased length of stay are widely and well-described parameters. However, control measures, impaired hospital activity and reputation, litigation, morbidity and attributable mortality are poorly described in the medical literature. Extra cost of infection with resistant microorganism and/or nosocomial infection includes the bed, intensive-care unit stay, hematological, biochemical, microbiological and radiological tests, antibiotics, other drugs, extra surgical procedures and working hours [2,3,10].

Antibiotic use versus susceptibility relations

Group-level and individual patient-level analyses of antibiotic use versus susceptibility relations may yield divergent results. The decreased use of an antibiotic at group-level analysis may reveal decreased resistance in some bacteria; in contrast to an increased resistance in others [4,58]. These conflicting results are probably due to distinctions in the selective force of individual antibiotics on different dominant strains in different settings. To evaluate the potential bias of analyzing aggregated data, Harbarth *et al.* separately examined antibiotic exposure and resistance data of 35,423 patients admitted to a university hospital in Utah (USA) from both an individual patient and group-level perspective [58]. From 1994 through 1998, use of defined daily doses (per 1000 patient days) of fluoroquinolones, third-generation cephalosporins, ampicillin–sulbactam, and imipenem increased by 82, 38 and 99%, and decreased by 38%, respectively; whereas, group-level resistance rates of Enterobacteriaceae or *Pseudomonas* spp. changed only minimally. However, in individual patient analyses performed by multivariable proportional hazards regression, exposure to a fluoroquinolone, third-generation cephalosporin, ampicillin–sulbactam, or imipenem was a strong risk factor for resistance to fluoroquinolones (adjusted hazard ratio [AHR]: 4.0; $p < 0.001$), third-generation cephalosporins (AHR: 3.5; $p < 0.001$), ampicillin–sulbactam (AHR: 2.3; $p = 0.008$) and imipenem (AHR: 5.7; $p < 0.001$). In contrast to these findings, Lopez-Lozano *et al.* reported a temporal relationship between hospital imipenem use and the percentage of imipenem-resistant/intermediate *P. aeruginosa* with time-series analysis [59]. In a recent study, time-series analysis performed by Hocquet *et al.* revealed a significant relationship between antibiotic (aminoglycoside, fluoroquinolone and cefepime) use and incidence of MexXY-OprM-overproducing *P. aeruginosa* [60]. In another study performed in 47 French settings by Rogues *et al.*, a statistically significant relationship was found between the rate of fluoroquinolone use and the rate of antimicrobial resistance among *P. aeruginosa* isolates [61]. Hsu *et al.* reported that ciprofloxacin resistance and empirical use of fluoroquinolones are predictors of mortality in patients infected with *P. aeruginosa* in a case–control study [62]. Another study, performed by the same group, also suggests that in settings where high rates of fluoroquinolone resistance exist, use of nonfluoroquinolone-based empirical regimens for *P. aeruginosa* infections improves patient's outcomes and organism susceptibility over time [63].

Theoretically, any particular antibiotic ineffective against MRSA will encourage its acquisition. Overall consumption of penicillins is associated with an increase in MRSA at the group level and fluoroquinolone consumption is associated with an increase in MRSA at the indvidual and group level [61,64].

Colonization and infection with VRE is a complicated issue that has been associated with exposure to antibiotics that are active against anaerobes. In mice that have intestinal colonization with VRE, these agents promote high-density colonization; whereas, antibiotics with minimal anti-anaerobic activity do not. Anti-anaerobic antibiotics with relatively enhanced antienterococcal activity that are excreted in high concentrations in bile (e.g., piperacillin/tazobactam, with a MIC of 625 μg/ml for the VRE test strain) may inhibit establishment of VRE colonization during treatment in mice. Although piperacillin/tazobactam inhibits the establishment of VRE colonization in mice when exposure occurs during treatment, a very recent study suggests that this agent may not prevent acquisition of VRE in patients [65–67].

Well-established data are rare with regards to the effects of antibiotics in the community setting. In a recent randomized, double-blind, placebo-controlled study, both clarithromycin and azithromycin resulted in higher rates of pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers compared with placebo [68]. Of note, the proportion of macrolide-resistant streptococci was higher after azithromycin treatment compared with after clarithromycin use.

Inappropriate antibiotic usage

Adverse drug reactions, emergence of resistant and MDR organisms and excessive strain on already limited pharmacy budgets are major outcomes of inappropriate antibiotic use [4,69].

Inappropriate antibiotic usage is a global problem [6–9,70–72]. Etiler *et al.* found that 43% of antibiotic usage was inappropriate and that the direct cost of inappropriate usage is US$996 per day in Antalya, Turkey [7]. Inappropriate antibiotic usage was reported as 49% in another Turkish tertiary-care educational university hospital and 37.4% in Breda, The Netherlands [6,72].

Inapproriate and/or prolonged surgical antibiotic prophylaxis (SAP) is an important contributor to antibiotic abuse [9,73]. Knowledge about SAP is poor among surgeons [74,75]. Inappropriate SAP

rates are reported as 15% in USA, 72% in Sweden, 58.3% in France and 47.7 to more than 98% in Turkey [76–81]. SAP exceeded 1 day in 80% and 3 days in 68.2% of the 3104 patients in a study from Taiwan [79]. Erdem *et al.* analyzed the SAP practice in 200 patients in a prospective study held in a Turkish State hospital [82]. In total, 50% of 200 patients were reported to receive inappropriate antimicrobial prophylaxis and the nosocomial infection rate was higher in the inappropriate SAP group ($p < 0.05$). Cost of inappropriate SAP was US$10,000. In a study that we performed in our cardiac-surgery intensive-care unit [81], only 0.6% of patients received appropriate SAP (appropriate prophylaxis was defined according to criteria of advisory statement of the American National Surgical Infection Prevention Project [83] and only 1.8% received 1-day-long SAP). Of note, in most of the surgery types, prolonged SAP does not have any benefit in the prevention of nosocomial surgical-site or other infections. Controlled studies suggest a decrease in surgical-site infections when SAP is applied in appropriate durations; however, no preventative measure can replace good surgical technique and asepsis [83].

Microbiologic culture-based or -targeted antibiotherapy is an important factor in decreasing inappropriate antibiotic usage [84]. In a moderately to severely infected patient in an intensive-care unit, antibiotics are usually started empirically. If microbiologic sampling is not performed and there is no clinical response to the initial regimen, the antibiotherapy will be restructured on an empirical basis. If microbiologic sampling yields a pathogen, there will be a chance to tailor the treatment regimen to it. Besides performing cultures, physicians must follow-up the results of the cultures. If this follow-up is not performed adequately, the chance of de-escalating or escalating the initial therapy will be missed [85].

Inappropriate antibiotic usage is common not only in the hospital setting but also in the community. Antibiotic self-treatment is common in countries where antibiotics may be gained without a doctor's prescription [71]. Patients may start antibiotics by themselves in the case of fever or common cold or to overcome malaise, fatigue or pain. Antibiotic leftovers, especially by the point of disappearance of the symptoms, are also common (even in the presence of a prescription by a medical professional) [86,87]. In a multicenter study performed in ten countries [88], overall prevalence of possession of leftovers was reported to be 51.9% in 3649 subjects who obtained antibiotics by filing for a new prescription or received them from a medical professional. The prevalence ranged between 13.5% (The Netherlands) and 90% (China). Countries where antibiotics are dispensed in fixed packs, rather than exact numbers of doses, had the higher prevalence of individuals possessing antibiotic leftovers. Further use of leftover antibiotics in subsequent infection was also very high (70% in 2252 subjects, ranging between 44.4% in The Netherlands and 90.2% in Russia).

'Direct-to-consumer' advertising may also result in increased inappropriate antibiotic usage. In the USA, direct-to-consumer advertising has been expanded since 1997 when the US FDA decided to ease restrictions on TV advertising. The rationale behind direct-to-consumer advertising is that it provides patients with information regarding drug therapies and empowers them to make more rational healthcare decisions. However, balance in advertising may be lacking and an artificial demand for drugs may be created. There is some evidence that physicians are sensitive to requests from patients for particular medicines. As the population of the world increases and health expenditures decrease, physicians need to see as many patients as possible in the shortest period of time with minimal, if any, laboratory or radiologic support and they often feel compelled to prescribe antimicrobial drugs in order to meet patient expectations [69,71,89].

Inappropriate antimicrobial usage is undoubtedly associated with, at least to a certain degree, resistance to science. Resistance to certain scientific ideas derives in large part from assumptions and biases that can be demonstrated experimentally in young children and that may persist into adulthood. In particular, both adults and children resist acquiring scientific information that clashes with common sense intuitions about physical and psychological domains. In addition, when learning information from other people, both adults and children are sensitive to the trustworthiness of the source [90]. During residency or fellowship education, prophylaxis practice or antibiotherapy, choices regarding several clinical conditions are generally learnt from the seniors of the trainees. The seniors, in turn, had learnt from their seniors. Hence, acceptance of new knowledge into traditional practice needs acceptance by at least senior members of this teaching pyramid. Why does such an acceptance occur very rarely (or never in several situations)? The reason maybe due to the belief that the knowledge is not provided via ideal and ethical methods, that is, without any scientific misconduct or simply ignorance of scientific knowledge [90–94].

Last but not least, the active promotional efforts of the drug companies may be influential on inappropriate antibiotic usage [95]; Guldal and Semin reported that promotional gifts affected the drug choice of 43.9% of physicians [96].

How to decrease antimicrobial resistance

Due to the aforementioned reasons, eradication of resistance is impossible and development of resistance to any particular antibiotic is inevitable. Therefore, the suitable interventions may be:

- To contain and/or decrease the already existent resistance
- To prevent further emergence and spread of resistance
- To develop and produce new antibiotics that would avoid having to be concerned about the containment of resistance (i.e., developing less resistance and/or ensuring containment of the resistant bacteria is relatively easy) [5]

Strategies for avoiding the emergence and spread of resistance can comprise of four categories [5]:

- Optimal use of existing antimicrobial agents
- To use alternative treatment options, including antiseptics, probiotics and cranberry juice (for urinary tract infection)

- Reducing the need for antimicrobials by increasing immunity through vaccination, improved nutrition and minimizing the time for which a patient is immunocompromised. In a study performed by Shinefield *et al.,* the use of conjugated *S. aureus* vaccine on hemodialysis patients resulted in a significant decrease in *S. aureus* bacteremia episodes in the first 52 weeks [97]. In another study, a mass conjugated meningococcus C vaccine campaign resulted in a decrease in meningococcus C disease [98]. The use of conjugated pneumococcus vaccine is also associated with a decrease in invasive pneumococcal disease in children and adults, and with penicilin-nonsusceptible and macrolide-resistant *S. pneumoniae* infections [99–103]
- Reducing the use of antimicrobials without providing an alternative form of treatment through education of health professionals and patients, antibiotic policies and regulation, restricting availability [4,5]

Strategies aimed at reducing the transmission of antibiotic resistance:

- Techniques for the early recognition of resistant microorganisms via methods such as more rapid diagnostic techniques, surveillance systems and screening of patients and staff
- Reduction of infectivity through the use of antimicrobials and disinfectants
- Reduction of the chance of spread by isolation of the colonized or infected cases and through improvements in hand hygiene
- Improvements in the spacing of beds in hospitals [5]

Screening & isolation

Screening and isolating (and destroying, such as in MRSA) the MDR organisms is an important issue that is successful both for preventing the introduction of the resistant bacteria to the hospital setting and decreasing the dissemination of already entered microorganisms.

A screen–isolate–destroy strategy is effective in both endemic and epidemic MRSA. As an impressive example for tackling endemic MRSA, Coskun and Aytac reported that by periodical education of hospital staff regarding infection control and hospital hand hygiene, surveillance for nasal *S. aureus* carriage among surgical staff and treatment of the carriers with intranasal antibiotic ointment, use of intranasal antibiotic ointment three-times daily for 3 days for all patients undergoing elective surgery, isolation of all patients admitted from other settings until a MRSA-negative anterior nares culture was obtained and use of chlorhexidine baths for surgical patients the night before surgery, healthcare-associated *S. aureus* (2.8% in 2000 to 1.3% in 2005), MRSA rates (37.1% in 2000 to 0.8% in 2005) and expenditures for glycopeptide usage (US$243,347 in the 2000–2001 period to US$99,473 in the 2004–2005 period) decreased substantially [104]. Identification of MRSA carriers via selective screening and subsequent isolation in an endemic setting was cost effective (in case of a more than 14% decrease in MRSA infection rate without substitution by MSSA) when compared with no screening and standard precautions. This strategy was dominant where MRSA carriage on intensive-care unit admission ranged between 1 and 7% [105].

What about epidemic MRSA? In a 2600 bedded Swedish setting, epidemics of MRSA-16 could be stopped by an intensive control program that included re-admission screening of all patients that had been hospitalized during the outbreak and closure of the ward in the presence of more than one colonized patient. Their strategy was cost saving after 24 months of implementation [106].

How to screen MRSA is a popular question in medical literature. By comparing many methods with complex mathematical models, it was concluded that taking a sample from the nose alone and inoculating directly on to Ciprofloxacin Baird–Parker agar without broth incubation and confirmation by a Pastorex Staph-Plus test without any methicillin-resistance confirmation was the most cost-effective approach in MRSA screening [107]. Interestingly, pooling swabs from different parts of the body was not found to increase the sensitivity and resulted in the missing of 14% of colonized cases [108]. Detection of MRSA by the PCR assay is promising but its cost–efficiency depends on the prevalence of the microorganism. This method for reducing MRSA transmission was found more costly than detection by culture in a Canadian study, which had a relatively low MRSA prevalence (monthly incidence of nosocomial MRSA colonization or infection was 0.37 cases per 1000 patient-days) [109].

Mupirocin is effective in the elimination of MRSA carriage. Intranasal mupirocin three-times daily for 3 days before orthopedic surgery is effective in decreasing the rates of both MSSA and MRSA surgical site infections [110] but resistance to mupirocin both in the community and hospital remains an emerging problem [24,111]. In the study by Yildirim *et al.,* 83.3% of MRSA and 33.3% of MSSA strains isolated from nasal or nasopharingeal samples of school children were resistant to mupirocin [24]. Mupirocin resistance in clinical MRSA and MRCNS isolates is also high. Vardar-Unlu *et al.* analyzed mupirocin resistance in clinical isolates of MRSA and MRCNS [112]. Low-level mupirocin resistance was detected at 31.6 and 10.6% in MRSA (n = 98) and MSSA (n = 85) strains, and at 12.1 and 2.4% in MRCNS (n = 66) and MSCNS (n = 84) strains, respectively. High-level mupirocin resistance was observed in 4.5 and 1.2% in MRCNS and MSCNS, respectively, but not detected in any of *S. aureus* strains tested.

What is the role of screening and isolating in decreasing $ESBL^+$ bacteria rates? Conterno *et al.* found that the use of private rooms for $ESBL^+$ bacteria-colonized or infected patients, along with contact precautions for patients at high risk for transmission, contributed to outbreak prevention but had no impact on the nosocomial ESBL incidence [113]. Routine rectal screening for $ESBL^+$ Enterobacteriaceae was not found to be cost effective in settings with low prevalence of carriers upon admission [114]. If a

center chooses to implement screening and isolation, it may be recommended to search not only on admission but also during the hospital stay, since the chance of being colonized by MDR organisms is associated with length of hospitalization [115].

Recent US CDC Isolation Guidelines recommend contact precautions in settings with evidence of ongoing MDR organism (e.g., MRSA, VRE, VISA/VRSA, ESBL producers and resistant *S. pneumoniae*) transmission or in acute-care settings with increased risk of transmission or wounds that cannot be contained by dressings [204]. The guidelines suggest that definition of MDR organisms may be broadened by an infection control program, based on local, state, regional or national recommendations, to be of clinical and epidemiologic significance.

Going back to economics, is a screen–isolate and/or destroy strategy cost effective? When we consider the results of the studies mentioned previously, we may conclude that the answer of this question is dependent on the background prevalence of MDR organisms and to the degree one can decrease resistance via these interventions [105,106,109,114]. It is worth stating that results of economical/pharmacoeconomical studies cannot be generalized to the whole world; hence, results of an American study may not be valid in Turkey and *vice versa* and so every country must find out its own results.

Last but not least, besides economical evaluations, potential legal problems (varying from country to country) should also be taken into account by infection control practitioners during decision of whether to implement a screen–isolate–destroy strategy.

How to improve antibiotic usage

Several policies have been developed to improve antibiotic usage. Preventing antibacterial resistance and reducing the cost are the main goals of these policies. The ideal is to have all patients treated with the most effective, least toxic and least costly antibiotic for the optimal time [4,27,28,116].

For improving antibiotic usage, there are many strategies, such as guidelines, antibiotic control committees, surveillance, feedback of antimicrobial resistance ratios and prior authorization by an infectious disease specialist (IDS) for selected antimicrobial agents [27,28,116]. Antimicrobial stewardship, which consists of some of these measures and will be detailed in the following section, is another important strategy for improving antibiotic usage.

An IDS consultation service has an important role in the management of nosocomial infections and community-acquired infections requiring hospitalization. IDS consultations may increase the rate of correct diagnosis, ensure appropriate antibiotic usage and decrease the cost of the antibiotics. Antibiotics ordered by IDSs or infectious disease trainees are less likely to be inappropriate [117–123]. It has been reported that the requirement for approval by an IDS for the use of restricted antibiotics is the most effective method for improving antibiotic usage [4,118].

How shall we improve TB treatment? Treatment of TB, including MDR- and XDR-TB, is challenging and needs good laboratory support including data of susceptibility to all first- and second-line treatment options. For a better and targeted treatment for TB (and also decreased rate of MDR- and XDR-TB), we need:

- An availability of culturing;
- An availability of directly observed therapeutic strategies;
- Increased access to second-line drugs;
- Development of techniques that reveals the resistance pattern of the bacteria without the need for culturing [15,35,124,125].

Antimicrobial stewardship

Antimicrobial stewardship is an activity that includes appropriate antibiotic selection, dosing, route and duration of antimicrobial therapy. The terms used to refer to antimicrobial stewardship programs may vary considerably: antibiotic policies, antibiotic management programs, antibiotic control programs and other terms may be used more or less interchangeably. The goals of antimicrobial stewardship are to preserve the effectiveness of current antiinfective agents by reducing resistance and to improve outcomes associated with antimicrobial use [28,116]. A secondary benefit is a reduction in healthcare costs both from direct savings in acquisition costs and from reduced resource utilization with improved outcomes. These terms generally refer to an overarching program that aims to change and direct antimicrobial use at a healthcare institution and may employ any number of individual strategies [27,28]. Recently, the IDSA and several other organizations released a guideline [28] for developing an institutional program to enhance antimicrobial stewardship. The activities that are recommended in the mentioned guideline with A-I and A-II (according to IDSA criteria [126]) level evidence are:

- Formulary restriction and preauthorization requirement (A-II). Carling *et al.* reported a sustained favorable impact of a multidisciplinary antibiotic management program conducted over 7 years [127]. Concomittantly, they had experienced a significant decrease in nosocomial infections caused by *Clostridium difficile* and resistant Enterobacteriaceae. The recent Turkish experience that was started with the enforcement of government is also an interesting example of preauthorization requirement in the developing world. In 2003, the Turkish Ministry of Finance, which is responsible for payback of over 90% of the population's health expenditures, released a new budget application instruction for regulating the usage of parenteral antibiotics inside and outside hospitals. The instruction took effect on 1 March 2003. According to this instruction, the payback of parenteral vancomycin, teicoplanin, meropenem, imipenem, piperacillin/tazobactam and ticarcillin/clavulanate has been restricted without prior approval of IDSs. Payback of ceftriaxone, cefotaxime, ceftizoxime, cefoperazone, ceftazidime, cefoperazone/sulbactam, cefepime, ciprofloxacin, levofloxacin, netilmicin, amikacin and isepamicin was unlimited, when prescribed for the first 72 h of treatment, by all specialists (except general practitioners) but further usage required IDS approval. The other antimicrobials could be prescribed without any restriction by all

medical doctors. After this regulation, we compared 2002 and 2003 March–October periods [4] and saw that this intervention resulted in a US$540,303 (-19.6%) decrease in the total antibiotic cost. Overall mortality was similar. Cumulative nosocomial infection rates in four intensive-care units and two clinics decreased significantly. When hospital-wide microbiologically confirmed nosocomial bacteremia cases during the study period were analyzed, amoxycilline/clavulanate, ciprofloxacin, cefuroxime, cefotaxime and piperacillin/tazobactam resistance and ESBL rate in *K. pneumoniae* decreased significantly ($p < 0.05$). Since our hospital pharmacy could not obtain the antibiotics regularly (i.e., could not record antibiotic usage properly), we could not evaluate the changes in antibiotic use over a longer period. Nevertheless, when we evaluated the resistance patterns of hospital-wide nosocomial bacteremia *K. pneumoniae* and *S. aureus* strains between 2001 and 2005 and compared the 2001–2002 and 2004–2005 periods [128,129], we saw that resistance to amikacin (30 and 19%, respectively), cefuroxime (55 and 37%, respectively), amoxycillin/clavulonate (59 and 46%, respectively), piperacillin/tazobactam (51 and 39%, respectively) and cotrimoxazole (5 and 35%, respectively) in *K. pneumoniae* decreased significantly ($p < 0.05$). The rate of $ESBL^+$ *K. pneumoniae* strains was 49% in the 2001–2002 period, while it decreased to 35% in the 2004–2005 period ($p < 0.025$). The situation was not much different for *S. aureus*; methicillin (70.1% in 2002 to 55.3% in 2005), levofloxacin, gentamicin, clindamycin and erythromycin resistance decreased significantly in the 2004–2005 period. Of note, we did not implement a screen and/or destroy and/or isolate policy in this period (except for VRE). Immediate decrease in antibiotic consumption [121,122,130] and antibacterial resistance in at least some of the bacteria [122] were also shown in other studies performed in other Turkish centers;

- Preauthorization requirement may also result in aggresive negotiations. This system results in consultations only for 'requesting' antibiotics but the act of requesting sometimes gets nearer to a state of 'enforcing' [123]. Arguments with the internists (especially hematologists) and anesthesiologists about the restriction policy in Turkey still continue [131–133];
- Multidisciplinary development of evidence-based practice guidelines incorporating local microbiology and resistance patterns can improve antibiotic usage (A-I) including SAP [134];
- Combination therapy (in certain clinical contexts, including use for empirical therapy for critically ill patients at risk of infection with MDR pathogens, to increase the breadth of coverage and the likelihood of adequate initial therapy [A-II]);
- Optimization of antimicrobial dosing based on individual patient characteristics, causative organism, site of infection and pharmacokinetic and pharmacodynamic characteristics of the drug (A-II);
- A systematic plan for parenteral to oral conversion of antimicrobials with excellent bioavailability, when the patient's condition allows, can decrease the length of hospital stay and healthcare costs (A-I).

Of note, in institutions that use preauthorization to limit the use of selected antimicrobials, monitoring overall trends in antimicrobial use is thought to be necessary to assess and respond to shifts in use. Daily defined dose (DDD) is a good marker used for the evaluation of drug consumption and prevents the patient-number bias. For anti-infectives (or other drugs normally used in short periods), it is often considered most appropriate to present the antibiotic amounts as numbers of DDDs per patient per year [4,28].

Comphrensive antimicrobial stewardship programs are cost effective for both large and small institutions. Unfortunately, evidence-based medicine is not implemented by everybody or every institution. Planning, devoting resources and implementing an antimicrobial stewardship program in an orchestrated and delibarate fashion requires support from all physicians throughout the institution and investment by the institutional administration. Administrators must have the patience to take a long view on their investment and the character to demand nothing less than active participation from all parties [27,28,116].

Effects of antibiotic resistance on industrial antibiotic R&D

The main expense to the drug industry related to resistance is the money spent on R&D on new antibiotics and, unfortunately, there is an absolute decline in the development of new antibiotics by pharmaceutical companies [1]. Aventis, Eli Lilly, Bristol-Myers Squibb, GlaxoSmithKline, Proctor & Gamble, Roche and Wyeth have greatly curtailed, wholly eliminated or spun off their antibacterial research. Not only does this threaten the development of new drugs against existing drug-resistant pathogens, but it also undermines the capacity to respond rapidly to the threat of emerging infectious diseases. Developing an antibiotic is not cheap; the US Department of Health and Human Services provided an estimate based on 2002 data of US$1.7 billion [135,136].

Drug companies choose areas of investment by a parameter known as net present value (NPV). The NPV of antibiotics is not high. A typical NPV for an antibiotic would be 100, compared with 300 for an anticancer drug, 720 for a neurological drug and 1150 for a muscular–skeletal drug. Any drug with a NPV of less than 100 is unlikely to be progressed by a large pharmaceutical company, so antibiotics really are on this borderline [135,136].

The fact that antibiotics are short-course therapies curing their target disease and are low-priced generics is important in contributing to their low NPV [1,135]. The emergence and spread of antimicrobial resistance (which require continuous R&D of antibiotics) also decrease the NPV of antibiotics. Increasing stringency of antibiotic restrictions (including the need for antibiograms [which are not usually available in primary practices] before prescribing [Greece], local guidelines

leading to the omission of newer antibiotics from hospital formularies [UK], quotas for generic substitutions and parallel imports [Germany], prior authorization by IDSs [Turkey]) may decrease the total antibiotic consumption (as well as bacterial resistance) and results in a decreased NPV. Therefore, there is a direct conflict between the two aims of antibiotic management: on the one hand, to restrict the use of these agents to prevent the spread of resistance and, on the other, a call for the development of new agents to fight resistant strains [1,4,135].

Market restriction stifles innovation and investment; fewer antibiotics are developed, leaving us more dependent upon existing agents that may no longer be maximally effective. An increased dependency on a reduced number of antibiotics may also accelerate the development and spread of resistance to these agents [136].

It is worth stating that no government has successfully discovered and developed an antibiotic and it is unlikely that any public body would have the resources or technical ability to do so. Thus, we are essentially dependent on the pharmaceutical industry to provide us with new antimicrobial agents and there needs to be a dialogue between stakeholders, including a balance between public health/clinical needs and commercial realities of drug R&D [1,135,136].

Expert commentary

Antibacterial resistance is inevitable. It exists and will go on existing. Antibacterial resistance is not always but usually associated with higher morbidity, mortality and excess costs. Depending on country, the excess cost related to resistant bacteria may be due to higher antibiotic acquisition costs and/or longer duration of hospitalization and/or extended medical examinations and/or control measures implemented to control the MDR organism. Current methodologies in the cost analysis of antimicrobial resistance have several limitations. Drug and especially antibiotic acquisition costs, in addition to increased length of stay, are widely and well-described parameters; however, control measures, impaired hospital activity and reputation, litigation, morbidity and attributable mortality are poorly described.

Inappropriate antibiotic usage is an important contributor to antimicrobial resistance. The ideal is to have all patients treated with the most effective, least toxic and least costly antibiotic for the optimal time. In a particular indication, the treatment options usually have similar clinical efficacy; hence, using the most cost-effective antibiotic with the least resistance-inducing capacity is of critical importance. Shall we always use narrow-spectrum molecules rather than broad-spectrum ones? The answer probably depends on the basal resistance status of the setting, the syndrome we treat and the clinical presentation of the patient. In a severely infected patient presenting with meningitis, sepsis, endocarditis or intensive-care unit-acquired pneumonia, the initial regimen may be broad spectrum. In these syndromes delayed appropriate therapy (after the 48 h spent developing results of bacteriologic cultures) may have fatal results. In contrast to these diseases, a narrow-spectrum antibiotic may be started in a case with noncomplicated urinary tract infection, pharangitis or sinusitis [49].

Antibiotic stewardship activities and/or antibiotic restriction policies and consultations performed by IDSs improve antibiotic consumption, and this improvement results in less antimicrobial resistance, at least in some of the MDR bacteria. Multidisciplinary development of evidence-based practice guidelines, optimization of antimicrobial dosing based on individual patient characteristics, causative organism, site of infection, pharmacokinetic and pharmacodynamic characteristics of the drug and a systematic plan for parenteral to oral conversion of antimicrobials with excellent bioavailability, when the patient's condition allows, are important and effective interventions to decrease the length of hospital stay and healthcare costs. Implementation of universal infection control measures with strict application of screening and isolation (and destroy whenever possible) are the other effective interventions for tackling MDR bacteria.

Five-year view

Microorganisms will continue developing and spreading resistance and patients will continue dying due to antibiotic-resistant microorganisms. Since resistant microorganisms do not recognize country boundaries, antibacterial resistance will continue to be a global problem.

Although there are promising agents, such as linezolid, tigecycline, quinopristin/dalfopristin, oritavancin, telavancin, dalbavancin, daptomycin and ceftobiprole, for treating MDR Gram-positive organisms [50], the situation is not the same for Gram-negative organisms and TB [15,51,137]. One of the most valuable and important contemporary Turkish writers and philosophers Cetin Altan states "do not hang your heads in sorrow, the world never goes to the bad" [205]. As MDR- and XDR-TB and pandrug-resistant Gram-negative organisms increase in prevalance (at the cost of countless lives), the NPVs of both areas will increase and then the drug industry will start to deal with the subject more eagerly.

Drugs such as fosfomycin and colistin will probably be researched more with regards to their possible use in treating MDR Gram-negatives. Large randomized trials are usually performed only by the support of the industry but these drugs do not have much industrial support. Probably, funders of independent research (e.g., the NIH, EU and governments) will give more support to the research of these old and important drugs.

The importance of phage therapy and associated research may increase proportionately with the incidence of pandrug-resistant microorganisms. Although it may be considered a kind of individualized therapy and may need complex technical equipment, the cost of phage therapy was found to be less than vancomycin, linezolid, teicoplanin and quinopristin/dalfopristin in the treatment of staphylococcal infections [138].

At present the data in the epidemiology and control measures of MRCNS are scarce. This subject will probably be evaluated more comprehensively.

The importance of translational research (which describes research that tries to convert the advances in our understanding of genetic and biochemical processes, which may represent valid pharmaceutical targets, into screening assays against which large compound libraries can be rapidly tested for activity with the aim of identifying candidate drugs) will increase. These compound libraries and the large-scale ultra-high-throughput screening facilities, which are generally sited within large R&D pharmaceutical companies, will decrease the cost of developing new antimicrobials [135,136,139].

The number of countries implementing antibiotic-restriction policies will increase. The epidemiology of resistance will be studied more frequently in the level of plasmids or transposons or hypermutables. Methods and, maybe, drugs or compounds (such as ethidium bromide, acridine orange, acriflavine, surface-active compounds [e.g., sodium dodecyl sulphate], several tricyclic antipsychotic drugs and their derivatives for plasmids [140]) will be sought to decrease their spread. In addition, research on bacteria in the soil that have the ability to use many of the currently used antibacterials as carbon suppliers [141] may increase.

The resistance-inducing capacity of antibiotics will be analyzed more comprehensively and this parameter will probably be a major factor in the choice and marketing of antibiotics (especially among antibiotics with similar clinical efficacy).

Investments on infection control measures and pediatric–adult vaccination will increase in countries where human life is of value and where the fact that letting people become infected or die is not as cost effective as treating them gets generalized acceptance.

Acknowledgements

OR Sipahi thanks Sercan Ulusoy, Tansu Yamazhan, Hilal Sipahi, Elif Hakko and anonymous reviewers for their useful comments for the improvement of the manuscript. OR Sipahi is also grateful to Ebru Akyol and Sevim Sipahi (English teachers) for their English proofreading.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Microorganisms will keep on developing and disseminating resistance as an opposite reaction to antimicrobials in accordance with the laws of physics, evolution and natural selection.
- Multidrug-resistant bacterial infections comprise a great problem both in community-acquired and healthcare-associated infections.
- Antibiotic resistance is usually associated with significant morbidity, longer hospitalization, excess costs and mortality.
- Excess costs associated with resistant microorganisms may be due to obligation to use more expensive antibiotics, longer hospital stay, higher mortality, delayed appropriate antibiotic therapy and more common necessity to perform surgery.
- Optimal use of existing antimicrobial agents, using alternative treatment options (where possible), reducing the need for antimicrobials by increasing immunity, reducing the use of antimicrobials without providing an alternative form of treatment by education of health professionals and patients, antibiotic policies (regulations for restricted use, prior authorization by infectious disease specialists for certain antibiotics), implementation of infection control measures (such as hand washing), screening and isolation are the strategies aimed at prevention of emergence and spread of antibiotic resistance.
- Since the net present value of antibiotics is not high, the drug industry does not invest much in antibiotics. No government has successfully discovered and developed an antibiotic, thus, we are dependent on the pharmaceutical industry to provide us with new antimicrobial agents and there needs to be a dialogue between stakeholders on how this can best be achieved.

References

Papers of special note have been highlighted as:
- • of interest
- •• of considerable interest

▶1 Spellberg B, Guidos R, Gilbert D *et al.* The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clin. Infect. Dis.* 46, 155–164 (2008).

▶2 Yalcin AN. Socioeconomic burden of nosocomial infections. *Indian J. Med. Sci.* 57(10), 450–456 (2003).

•• **Very good review of the pharmacoeconomics of nosocomial infections.**

▶3 Eandi M, Zara GP, Della Pepa C. Application of pharmacoeconomics to the use of antibiotics. *Clin. Microbiol. Infect.* 6(Suppl. 3), 90–92 (2000).

▶4 Arda B, Sipahi OR, Yamazhan T *et al.* Short-term effect of antibiotic control policy on the usage patterns and cost of antimicrobials, mortality, nosocomial infection rates and antibacterial resistance. *J. Infect.* 55(1), 41–48 (2007).

•• **One of the most comphrensive analyses of antibiotic restriction interventions, involving overall mortality, hospital-acquired infection rates and resistance rates of nosocomial bacteremia strains.**

▶5 Coast J, Smith RD. Antimicrobial resistance, cost and containment. *Expert Rev. Anti Infect. Ther.* 1, 241–251 (2003).

• **Comphrensive review of antimicrobial resistance and cost.**

▶6 Tunger O, Dinc G, Ozbakkaloglu B, Atman UC, Algun O. Evaluation of rational

antibiotic use. *Int. J. Antimicrob. Agents* 15, 131–135 (2000).

7 Etiler BN, Saba R, Günseren F, Mamikoglu L. Akdeniz Universite Hastanesi'nde uygunsuz antimikrobiyal ilac kullanimin dogrudan maliyeti karsilastirilmasi. *Turk. J. Hosp. Infect.* 4, 144–147 (2000).

8 Buke C, Sipahi OR, Tasbakan M *et al.* The evaluation of the infections developing in intensive care unit of the internal medicine department. *Turk. J. Infect.* 19, 67–73 (2005).

▶9 Usluer G, Ozgunes I, Leblebicioglu H. Turkish antibiotic utilization study group. A multicenter point-prevalence study: antimicrobial prescription frequencies in hospitalized patients in Turkey. *Ann. Clin. Microbiol. Antimicrob.* 4, 16 (2005).

▶10 Gould IM. Costs of hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) and its control. *Int. J. Antimicrob. Agents* 28(5), 379–384 (2006).

•• **Recent and excellent review of the cost of methicillin-resistant *Staphylococcus aureus* (MRSA).**

▶11 Livermore DM. Bacterial resistance: origins, epidemiology, and impact. *Clin. Infect. Dis.* 36(Suppl. 1), S11–S23 (2003).

•• **Outstanding review of antibacterial resistance and its effects.**

12 Kernodle DS, Kaiser AB. Postoperative infections and antimicrobial prophylaxis. In: *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. Mandell GL, Bennett JE, Dolin R (Eds). Churchill Livingstone, PA, USA, 3177–3191 (2000).

▶13 Archer GL, Armstrong BC. Alteration of staphylococcal flora in cardiac patients receiving antibiotic prophylaxis. *J. Infect. Dis.* 147, 642–649 (1983).

▶14 Kernodle DS, Barg NL, Kaiser AB. Low-level colonization of hospitalized patients with methicillin resistant coagulase-negative staphylococci and their emergence during surgical antimicrobial prophylaxis. *Antimicrob. Agents Chemother.* 32, 202–208 (1988).

▶15 Matteelli A, Migliori GB, Cirillo D, Centis R, Girard E, Raviglion M. Multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis*: epidemiology and control. *Expert Rev. Anti Infect. Ther.* 5(5), 857–871 (2007).

•• **Excellent review of multidrug-resistant and extensively drug-resistant TB.**

▶16 Danel F, Hall LM, Gur D, Akalin HE, Livermore DM. Transferable production of PER-1 β-lactamase in *Pseudomonas aeruginosa*. *J. Antimicrob. Chemother.* 35(2), 281–294 (1995).

17 Tansel O, Kuloglu F, Mutlu B *et al.* Methicillin-resistant *Staphylococcus aureus* outbreak in a new university hospital due to a strain transferred with an infected patient from another city six months previously. *Turk. J. Infect.* 16(4), 457–461 (2002).

▶18 Falagas ME, Bliziotis IA. Pandrug-resistant Gram-negative bacteria: the dawn of the post-antibiotic era? *Int. J. Antimicrob. Agents* 29(6), 630–636 (2007).

▶19 Nordmann P, Naas T, Fortineau N, Poirel L. Superbugs in the coming new decade; multidrug resistance and prospects for treatment of *Staphylococcus aureus*, *Enterococcus* spp. and *Pseudomonas aeruginosa* in 2010. *Curr. Opin. Microbiol.* 10(5), 436–440 (2007).

▶20 Beno P, Krcmery V, Demitrovicova A. Bacteraemia in cancer patients caused by colistin-resistant Gram-negative bacilli after previous exposure to ciprofloxacin and/or colistin. *Clin. Microbiol. Infect.* 12, 497–498 (2006).

21 Akalin H. Colistin. *Ankem Dergisi* 21(Suppl. 2), 26–28 (2007).

▶22 Buke C, Sipahi OR, Yurtseven T, Zileli M. High dose of intrathecal netilmicin in the treatment of nosocomial *Acinetobacter baumannii* meningitis. *J. Infect.* 51(5), 420–422 (2005).

▶23 Akram M, Shahid M, Khan AU. Etiology and antibiotic resistance patterns of community-acquired urinary tractinfections in JNMC Hospital Aligarh, India. *Ann. Clin. Microbiol. Antimicrob.* 6, 4 (2007).

24 Yildirim M, Sahin I, Basak S *et al.* The investigation of nasal carriage and colonization of nasopharingeal pathogens at a primary school in Duzce. *Turk. J. Med. Sci.* 37, 359–365 (2007).

▶25 Huijsdens XW, van Dijke BJ, Spalburg E *et al.* Community-acquired MRSA and pig-farming. *Ann. Clin. Microbiol. Antimicrob.* 5, 26 (2006).

▶26 Cesur S, Cokça F. Determination of nasal carriage rates of methicillin resistant *Staphylococcus aureus* in hospital personnel and in the community. *Mikrobiyol. Bul.* 36(3–4), 247–252 (2002).

▶27 MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. *Clin. Microbiol. Rev.* 18(4), 638–656 (2005).

▶28 Dellit TH, Owens RC, McGowan JE Jr *et al.* Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin. Infect. Dis.* 44(2), 159–177 (2007).

•• **Recent evidence-based guidelines for antibiotic stewardship.**

▶29 Arslan H, Azap OK, Ergönül O, Timurkaynak F; Urinary Tract Infection Study Group. Risk factors for ciprofloxacin resistance among *Escherichia coli* strains isolated from community-acquired urinary tract infections in Turkey. *J. Antimicrob. Chemother.* 56(5), 914–918 (2005).

▶30 Kader AA, Kumar A, Kamath KA. Fecal carriage of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in patients and asymptomatic healthy individuals. *Infect. Control Hosp. Epidemiol.* 28(9), 1114–1116 (2007).

▶31 Mesa RJ, Blanc V, Blanch AR *et al.* Extended-spectrum β-lactamase-producing Enterobacteriaceae in different environments (humans, food, animal farms and sewage). *J. Antimicrob. Chemother.* 58(1), 211–215 (2006).

▶32 Migliori GB, Besozzi G, Girardi E *et al.* Clinical and operational value of the extensively drug-resistant tuberculosis definition. *Eur. Respir. J.* 30(4), 623–626 (2007).

• **Clear effects of resistance on outcomes in TB.**

▶33 Migliori GB, Ortmann J, Girardi E *et al.*; SMIRA/TBNET Study Group. Extensively drug-resistant tuberculosis, Italy and Germany. *Emerg. Infect. Dis.* 13(5), 780–782 (2007).

▶34 Saygan MB, Ocak F, Cesur S *et al.* Susceptibilities of *Mycobacterium tuberculosis* strains collected from regional tuberculosis laboratories to major antituberculous drugs. *Mikrobiyol. Bul.* 41(3), 403–409 (2007).

▶35 Cavusoglu C, Turhan A, Akinci P, Soyler I. Evaluation of the Genotype MTBDR assay for rapid detection of rifampin and isoniazid resistance in *Mycobacterium tuberculosis* isolates. *J. Clin. Microbiol.* 44(7), 2338–2342 (2006).

▶36 Espinal MA, Laserson K, Camacho M *et al.* Determinants of drug-resistant tuberculosis: analysis of 11 countries. *Int. J. Tuberc. Lung Dis.* 5(10), 887–893 (2001).

▶37 Shah NS, Wright A, Bai GH *et al.* Worldwide emergence of extensively drug-resistant tuberculosis. *Emerg. Infect. Dis.* 13(3), 380–387 (2007).

▶38 Pullukcu H, Tasbakan M, Sipahi OR, Yamazhan T, Aydemir S, Ulusoy S. Fosfomycin in the treatment of extended

spectrum β-lactamase-producing *Escherichia coli*-related lower urinary tract infections. *Int. J. Antimicrob. Agents* 29(1), 62–65 (2007).

• **Single-center experience with fosfomycin in the treatment of extended-spectrum β-lactamase-positive *Escherichia coli* urinary tract infections.**

▶39 Schwaber MJ, Navon-Venezia S, Kaye KS, Ben-Ami R, Schwartz D, Carmeli Y. Clinical and economic impact of bacteremia with extended-spectrum-β-lactamase-producing Enterobacteriaceae. *Antimicrob. Agents Chemother.* 50(4), 1257–1262 (2006).

▶40 Lautenbach E, Patel JB, Bilker WB, Edelstein PH, Fishman NO. Extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for infection and impact of resistance on outcomes. *Clin. Infect. Dis.* 32(8), 1162–1171 (2001).

▶41 Lodise TP, McKinnon PS. Clinical and economic impact of methicillin resistance in patients with *Staphylococcus aureus* bacteremia. *Diagn. Microbiol. Infect. Dis.* 52(2), 113–122 (2005).

▶42 Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect. Control Hosp. Epidemiol.* 26(2), 166–174 (2005).

▶43 Vergis EN, Hayden MK, Chow JW *et al.* Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. a prospective multicenter study. *Ann. Intern. Med.* 135(7), 484–492 (2001).

▶44 Kwon KT, Oh WS, Song JH *et al.* Impact of imipenem resistance on mortality in patients with *Acinetobacter* bacteraemia. *J. Antimicrob. Chemother.* 59(3), 525–530 (2007).

▶45 Young LS, Sabel AL, Price CS. Epidemiologic, clinical, and economic evaluation of an outbreak of clonal multidrug-resistant *Acinetobacter baumannii* infection in a surgical intensive care unit. *Infect. Control Hosp. Epidemiol.* 28(11), 1247–1254. (2007).

▶46 Wilson SJ, Knipe CJ, Zieger MJ *et al.* Direct costs of multidrug-resistant *Acinetobacter baumannii* in the burn unit of a public teaching hospital. *Am. J. Infect. Control* 32(6), 342–344 (2004).

▶47 Aloush V, Navon-Venezia S, Seigman-Igra Y, Cabili S, Carmeli Y. Multidrug-resistant *Pseudomonas aeruginosa*: risk factors and clinical impact. *Antimicrob. Agents Chemother.* 50(1), 43–48 (2006).

▶48 Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin. Infect. Dis.* 42(Suppl. 2), S82–S89 (2006).

•• **Well-established review of cost and resistance.**

49 Gilbert DN, Moellering RC, Eliopulos GM, Sande MA. *The Sanford Guide to Antimicrobial Therapy (38th Edition).* Antimicorbial Therapy Inc., VA, USA (2008).

▶50 Loffler CA, MacDougall C. Update on prevalence and treatment of methicillin-resistant *Staphylococcus aureus*. *Exp. Rev. Anti-Infect. Ther.* 5, 961–981 (2007).

•• **Comphrensive review of MRSA.**

▶51 Torres JA, Villegas NV, Quinn JP. Current concepts in antibiotic-resistant Gram-negative bacteria. *Exp. Rev. Anti-Infect. Ther.* 5, 833–843 (2007).

▶52 Paterson DL, Ko WC, Von Gottberg A *et al.* Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum β-lactamases. *Clin. Infect. Dis.* 39(1), 31–37 (2004).

53 Paterson DL, Ko WC, Von Gottberg A *et al.* International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum β-lactamase production in nosocomial infections. *Ann. Intern. Med.* 140(1), 26–32 (2004).

▶54 Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum β-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J. Antimicrob. Chemother.* 60(5), 913–920 (2007).

▶55 Whitby M, McLaws ML, Berry G. Risk of death from methicillin-resistant *Staphylococcus aureus* bacteraemia: a meta-analysis. *Med. J. Aust.* 175(5), 264–267 (2001).

▶56 Daxboeck F, Budic T, Assadian O, Reich M, Koller W. Economic burden associated with multi-resistant Gram-negative organisms compared with that for methicillin-resistant *Staphylococcus aureus* in a university teaching hospital. *J. Hosp. Infect.* 62(2), 214–218 (2006).

▶57 Gandhi NR, Moll A, Sturm AW *et al.* Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 368(9547), 1575–1580 (2006).

▶58 Harbarth S, Harris AD, Carmeli Y, Samore MH. Parallel analysis of individual and aggregated data on antibiotic exposure and resistance in Gram-negative bacilli. *Clin. Infect. Dis.* 33(9), 1462–1468 (2001).

•• **Comparison of the effect of antibiotics on resistance at the group and individual level.**

▶59 López-Lozano JM, Monnet DL, Yague A *et al.* Modelling and forecasting antimicrobial resistance and its dynamic relationship to antimicrobial use: a time series analysis. *Int. J. Antimicrob. Agents* 14(1), 21–31 (2000).

▶60 Hocquet D, Muller A, Blanc K, Plésiat P, Talon D, Monnet DL, Bertrand X. Relationship between antibiotic use and incidence of MexXY-OprM overproducers among clinical isolates of *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* 52(3), 1173–1175 (2008).

▶61 Rogues AM, Dumartin C, Amadéo B *et al.* Relationship between rates of antimicrobial consumption and the incidence of antimicrobial resistance in *Staphylococcus aureus* and *Pseudomonas aeruginosa* isolates from 47 French hospitals. *Infect. Control Hosp. Epidemiol.* 28(12), 1389–1395 (2007).

▶62 Hsu DI, Okamoto MP, Murthy R, Wong-Beringer A. Fluoroquinolone-resistant *Pseudomonas aeruginosa*: risk factors for acquisition and impact on outcomes. *J. Antimicrob. Chemother.* 55(4), 535–541 (2005).

▶63 Nguyen LH, Hsu DI, Ganapathy V, Shriner K, Wong-Beringer A. Reducing empirical use of fluoroquinolones for *Pseudomonas aeruginosa* infections improves outcome. *J. Antimicrob. Chemother.* 61(3), 714–720 (2008).

▶64 Dancer SJ. The effects of antibiotics on methicillin-resistant *Staphylococcus aureus*. *J. Antimicrob. Chemother.* 61(2), 246–253 (2008).

▶65 Donskey CJ, Chowdhry TK, Hecker MT *et al.* Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. *N. Engl. J. Med.* 343(26), 1925–1932 (2000).

▶66 Donskey CJ. The role of the intestinal tract as a reservoir and source for transmission of nosocomial pathogens. *Clin. Infect. Dis.* 39, 219–226 (2004).

▶67 Paterson DL, Muto CA, Ndirangu M *et al.* Acquisition of vancomycin-resistant *Enterococcus* rectal colonization among intensive care unit patients treated with piperacillin/tazobactam versus cefepime-containing antibiotic regimens. *Antimicrob. Agents Chemother.* 52(2), 465–469 (2008).

68 Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet* 369(9560), 482–490 (2007).

•• **Very well-planned and important study evaluating the effects of azithromycin and clarithromycin on the resistance of streptococci in the community.**

69 Garau J. Impact of antibiotic restrictions: the ethical perspective. *Clin. Microbiol. Infect.* 12(Suppl. 5), 16–24 (2006).

•• **Different view based predominantly on the ethical perspective of antibiotic restrictions.**

70 Ntagiopoulos PG, Paramythiotou E, Antoniadou A, Giamarellou H, Karabinis A. Impact of an antibiotic restriction policy on the antibiotic resistance patterns of Gram-negative microorganisms in an intensive care unit in Greece. *Int. J. Antimicrob. Agents* 30(4), 360–365 (2007).

71 Kunin CM. Resistance to antimicrobial drugs – a worldwide calamity. *Ann. Intern. Med.* 118(7), 557–561 (1993).

72 Willemsen I, Groenhuijzen A, Bogaers D, Stuurman A, van Keulen P, Kluytmans J. Appropriateness of antimicrobial therapy measured by repeated prevalence surveys. *Antimicrob. Agents Chemother.* 51(3), 864–867 (2007).

73 Sacar S, Kavas ST, Asan A, Cenger DH, Turgut H. Point prevalence study relating to antibiotic usage in Pamukkale University hospital. *ANKEM Dergisi* 20, 217–221 (2006).

74 Tarhan MO, Cetin GO, Tipirdamaz H, Mutlu A, Biberoglu K. Cerrahide profilaktik antibiyotik kullanimi: bir anket çalismasi ve sonuçlari. *Ilac ve Tedavi Dergisi* 9, 307–310 (1996).

75 Hosoglu S, Sunbul M, Erol S *et al.* A national survey of surgical antibiotic prophylaxis in Turkey. *Infect. Control Hosp. Epidemiol.* 24, 758–761 (2003).

76 Bugnon-Reber A, de Torrente A, Troillet N, Genne D; ETUDAS group. Antibiotic misuse in medium-sized Swiss hospitals. *Swiss Med. Wkly* 134, 481–485 (2004).

77 Bailly P, Lallemand S, Thouverez M, Talon D. Multicentre study on the appropriateness of surgical antimicrobial prophylaxis. *J. Hosp. Infect.* 49, 135–138 (2001).

78 Yalcin AN, Serin S, Gurses E, Zencir M. Surgical antibiotic prophylaxis in a Turkish university hospital. *J. Chemother.* 14, 373–377 (2002).

79 Chen YS, Liu YH, Kunin CM, Huang JK, Tsai CC. Use of prophylactic antibiotics in surgery at a medical center in southern Taiwan. *J. Formos. Med. Assoc.* 101, 741–748 (2002).

80 Dagan O, Cox PN, Ford-Jones L, Ponsonby J, Bohn DJ. Nosocomial infection following cardiovascular surgery: comparison of two periods, 1987 vs. 1992. *Crit. Care Med.* 27, 104–108 (1999).

81 Buke C, Sipahi OR, Basoglu MT *et al.* Evaluation of surgical prophylaxis in heart surgery. Presented at: *15th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)*, Copenhagen, Denmark, 2–5 April, 2005. P1051 *Clin. Microbiol. Infect.* 11(Suppl. 2), 326–327 (2005).

82 Erdem I, Yildirim I, Avkan V, Vahaboglu H. Gereksiz antibiyotik kullaniminin maliyeti: gozleme dayali bir calismanin sonuclarinin analizi. *Ulusal Cerrahi Dergisi* 13, 75–79 (1997).

83 Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin. Infect. Dis.* 38, 1706–1715 (2004).

84 Joffe AR, Muscedere J, Marshall JC, Su Y, Heyland DK; for the Canadian Critical Care Trials Group. The safety of targeted antibiotic therapy for ventilator-associated pneumonia: a multicenter observational study. *J. Crit. Care.* 23(1), 82–90 (2008).

85 Marschall J, Agniel D, Fraser VJ, Doherty J, Warren DK. Gram-negative bacteraemia in non-ICU patients: factors associated with inadequate antibiotic therapy and impact on outcomes. *J. Antimicrob. Chemother.* 61(6), 1376–1383 (2008)

86 Buke AC, Ermertcan S, Hosgor-Limoncu M, Cicekliogl M, Eren S. Rational antibiotic use and academic staff. *Int. J. Antimicrob. Agents* 21(1), 63–66 (2003).

87 Buke C, Hosgor-Limoncu M, Ermertcan S *et al.* Irrational use of antibiotics among university students. *J. Infect.* 51(2), 135–139 (2005).

88 Kardas P, Pechère JC, Hughes DA, Cornaglia G. A global survey of antibiotic leftovers in the outpatient setting. *Int. J. Antimicrob. Agents* 30(6), 530–536 (2007).

•• **Very interesting multinational study evaluating antibiotic leftovers and their usage.**

89 Wagstaff B. Impact of antibiotic restrictions: the patient's perspective. *Clin. Microbiol. Infect.* 12(Suppl. 5), 10–15 (2006).

90 Bloom P, Weisberg DS. Childhood origins of adult resistance to science. *Science* 316(5827), 996–997 (2007).

91 Bilic-Zulle L, Frkovic V, Turk T, Azman J, Petrovecki M. Prevalence of plagiarism among medical students. *Croat. Med. J.* 46(1), 126–131 (2005).

92 Riis P. Scientific dishonestry: European reflections. *J. Clin. Pathol.* 54(1), 4–6 (2001).

93 Korenman SG, Berk R, Wenger NS, Lew V. Evaluation of the research norms of scientists and administrators responsible for academic research integrity. *JAMA* 279(1), 41–47 (1998).

94 Anderson J. Fraud in research, 1986–1992: an annotated bibliography. *J. Infor. Ethics* 3(2), 64–89 (1994).

95 Arda B, Yamazhan T, Sipahi OR, Islekel S, Buke C, Ulusoy S. Meningitis due to methicillin-resistant *Staphylococcus aureus* (MRSA): review of 10 cases. *Int. J. Antimicrob. Agents* 25(5), 414–418 (2005).

96 Guldal D, Semin S. The influences of drug companies' advertising programs on physicians. *Int. J. Health Serv.* 30(3), 585–595 (2000).

97 Shinefield H, Black S, Fattom A *et al.* Use of a *Staphylococcus aureus* conjugate vaccine in patients receiving hemodialysis. *N. Engl. J. Med.* 346, 491–496 (2002).

98 Salleras L, Domínguez A, Cardeñosa N. Impact of mass vaccination with polysaccharide conjugate vaccine against serogroup C meningococcal disease in Spain. *Vaccine* 21(7–8), 725–728 (2003).

99 Whitney CG, Farley MM, Hadler J *et al.* Decline in invasive pneumococcal disease after the introduction of protein–polysaccharide conjugate vaccine. *N. Engl. J. Med.* 348(18), 1737–1746 (2003).

100 Poehling KA, Talbot TR, Griffin MR *et al.* Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. *JAMA* 295, 1668–1674 (2006).

101 Stephens DS, Zughaier SM, Whitney CG *et al.* Incidence of macrolide resistance in *Streptococcus pneumoniae* after introduction of the pneumococcal conjugate vaccine: population-based assessment. *Lancet* 365, 855–863 (2005).

102 Lexau CA, Lynfield R, Danila R *et al.* Changing epidemiology of invasive pneumococcal disease among older adults in

the era of pediatric pneumococcal conjugate vaccine. *JAMA* 294(16), 2043–2051 (2005).

▶103 Kyaw MH, Lynfield R, Schaffner W *et al.* Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N. Engl. J. Med.* 354(14), 1455–1463 (2006).

▶104 Coskun D, Aytac J. The decrease in healthcare-associated methicillin-resistant *Staphylococcus aureus* infections and savings from glycopeptide use. *Infect. Control Hosp. Epidemiol.* 27(10), 1131–1132 (2006).

• **Endemic MRSA may be decreased by infection control measures.**

▶105 Chaix C, Durand-Zaleski I, Alberti C, Brun-Buisson C. Control of endemic methicillin-resistant *Staphylococcus aureus*: a cost–benefit analysis in an intensive care unit. *JAMA* 282(18), 1745–1751 (1999).

▶106 Björholt I, Haglind E. Cost-savings achieved by eradication of epidemic methicillin-resistant *Staphylococcus aureus* (EMRSA)-16 from a large teaching hospital. *Eur. J. Clin. Microbiol. Infect. Dis.* 23(9), 688–695 (2004).

▶107 Kunori T, Cookson B, Roberts JA, Stone S, Kibbler C. Cost–effectiveness of different MRSA screening methods. *J. Hosp. Infect.* 51(3), 189–200 (2002).

▶108 Grmek-Kosnik I, Ihan A, Dermota U, Rems M, Kosnik M, Jorn Kolmos H. Evaluation of separate vs pooled swab cultures, different media, broth enrichment and anatomical sites of screening for the detection of methicillin-resistant *Staphylococcus aureus* from clinical specimens. *J. Hosp. Infect.* 61(2), 155–161 (2005).

▶109 Conterno LO, Shymanski J, Ramotar K *et al.* Real-time polymerase chain reaction detection of methicillin-resistant *Staphylococcus aureus*: impact on nosocomial transmission and costs. *Infect. Control Hosp. Epidemiol.* 28(10), 1134–1141 (2007).

▶110 Coskun D, Aytac J. Decrease in *Staphylococcus aureus* surgical-site infection rates after orthopaedic surgery after intranasal mupirocin ointment. *J. Hosp. Infect.* 58(1), 90–91 (2004).

111 Naz H, Cevik FÇ, Aykin N. Nasal *Staphylococcus aureus* carriage among hospital staff in Eskisehir Yunus Emre state hospital. *ANKEM Dergisi* 20(3), 141–144 (2006).

112 Vardar-Unlu G, Unlu G, Yagmuroglu A. Mupirocin resistance of *Staphylococcus aureus* and coagulase-negative staphylococci isolated from clinical specimens. *ANKEM Dergisi* 20(4), 222–225 (2006).

▶113 Conterno LO, Shymanski J, Ramotar K, Toye B, Zvonar R, Roth V. Impact and cost of infection control measures to reduce nosocomial transmission of extended-spectrum β-lactamase-producing organisms in a non-outbreak setting. *J. Hosp. Infect.* 65(4), 354–360 (2007).

▶114 Thouverez M, Talon D, Bertrand X. Control of Enterobacteriaceae producing extended-spectrum β-lactamase in intensive care units: rectal screening may not be needed in non-epidemic situations. *Infect. Control Hosp. Epidemiol.* 25(10), 838–841 (2004).

▶115 Buke C, Armand-Lefevre L, Lolom I *et al.* Epidemiology of multidrug-resistant bacteria in patients with long hospital stays. *Infect. Control Hosp. Epidemiol.* 28(11), 1255–1260 (2007).

▶116 Martin SJ. Antimicrobial stewardship: the aspirin of the 21st century. *Expert. Rev. Anti Infect. Ther.* 5(2), 159–161 (2007).

▶117 Petrak MR, Sexton DJ, Butera ML *et al.* The value of an infectious diseases specialist. *Clin. Infect. Dis.* 36, 1013–1017 (2003).

▶118 Erbay A, Bodur H, Akinci E, Coplan A. Evaluation of antibiotic use in intensive care units of a tertiary care hospital in Turkey, *J. Hosp. Infect.* 59, 53–61 (2005).

▶119 Hirscman SZ, Meyers BR, Bradbury K, Mehl B, Gendelman S, Kimelblatt B. Use of antimicrobial agents in a university teaching hospital. Evolution of a comprehensive control program. *Arch. Intern. Med.* 148, 2001–2007 (1988).

▶120 Kunin CM. The responsibility of the infectious diseases community for the optimal use of antimicrobial agents. *J. Infect. Dis.* 151, 388–398 (1985).

•• **Classical paper about roles of the infectious diseases community in antibacterial use.**

▶121 Hosoglu S, Esen S, Ozturk R *et al.* The effect of a restriction policy on the antimicrobial consumption in Turkey: a country-wide study. *Eur. J. Clin. Pharmacol.* 61(10), 727–731 (2005).

•• **Multicenter study evaluating short-term effects of the 2003 Turkish antibiotic restriction experience.**

▶122 Ozkurt Z, Erol S, Kadanali A, Ertek M, Ozden K, Tasyaran MA. Changes in antibiotic use, cost and consumption after an antibiotic restriction policy applied by infectious disease specialists. *Jpn. J. Infect. Dis.* 58(6), 338–343 (2005).

▶123 Sipahi OR, Tasbakan M, Pullukcu H *et al.* Accuracy of consultations performed by infectious diseases trainees and factors associated with adherence to them. *Int. J. Infect. Dis.* 11(6), 518–523 (2007).

124 Cicek C, Cok G, Ozhan M, Yaygin E, Bilgic A. Comparison of a Quantiferon-TB test with tuberculin skin test in patients of latent and active tuberculosis infection. *Turk. J. Infect.* 20(1), 15–18 (2006).

▶125 Richeldi L. Rapid identification of *Mycobacterium tuberculosis* infection. *Clin. Microbiol. Infect.* 12(Suppl. 9), 34–36 (2006).

▶126 Kish MA. Guide to development of practice guidelines. *Clin. Infect. Dis.* 32, 851–854 (2001).

▶127 Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect. Control Hosp. Epidemiol.* 24(9), 699–706 (2003).

•• **Long-term effects of antibiotic restrictions.**

128 Sipahi OR, Pullukcu H, Aydemir S *et al.* Changes in antibacterial resistance patterns in *Staphylococcus aureus* strains which are related to microbiologically confirmed nosocomial bacteraemia in a tertiary care educational hospital in Turkey. *Ankem Dergisi* 21(1), 1–4 (2007).

▶129 Tasbakan MI, Pullukcu H, Sipahi OR *et al.* Extended-spectrum β-lactamase production and antimicrobial resistance patterns of *Klebsiella pneumoniae* strains isolated from nosocomial bacteremic patients: evaluation of the results of 2001–2005 period. *Mikrobiyol. Bult.* 42(1), 1–7 (2008).

130 Azap A, Topcuoglu P, Yesilkaya A *et al.* The effect of a nationwide antibiotic restriction policy on antibiotic usage in a stem cell transplantation unit. *Turkish J. Haematol.* 22(2), 87–90 (2005).

131 Akan H. Opinions of the Turkish Society of Hematology on rational antibiotic usage. *Ankem Dergisi* 20, 65–67 (2006).

132 Unal N. Budget application directions and restriction of antibiotic prescriptions from intensivist's point of view: targets, expectations, conclusions and suggestions. *Ankem Dergisi* 20, 55–60 (2006).

133 Sipahi OR, Pullukcu H, Tasbakan M, Yamazhan T, Arda B. Letter to the editor. *Ankem Dergisi* 20, 133–136 (2006).

▶134 Gorecki W, Grochowska E, Krysta M, Wojciechowski P, Taczanowska A, Stanek B. A prospective comparison of antibiotic

usage in pediatric surgical patients: the safety, advantage, and effectiveness of the Surgical Infection Society guidelines versus a common practice. *J. Pediatr. Surg.* 37, 1430–1434 (2002).

135 Projan SJ. Why is big Pharma getting out of antibacterial drug discovery? *Curr. Opin. Microbiol.* 6(5), 427–430 (2003).

• **Critical review about why pharmaceutical companies leave antibiotic R&D.**

136 Power E. Impact of antibiotic restrictions: the pharmaceutical perspective. *Clin. Microb. Infect.* 12(Suppl. 5), 25–34 (2006).

•• **Very good critical review on the reasons pharmaceutical companies leave antibiotic R&D.**

137 Poirel L, Pitout JD, Nordmann P. Carbapenemases: molecular diversity and clinical consequences. *Future Microbiol.* 2(5), 501–512 (2007).

• **Recent review of carbapenemases.**

138 Miedzybrodzki R, Fortuna W, Weber-Dabrowska B, Górski A. Phage therapy of staphylococcal infections (including MRSA) may be less expensive than antibiotic treatment. *Postepy. Hig. Med. Dosw.* 61, 461–465 (2007).

• **Phage therapy is cheaper than conventional therapy in a Polish setting.**

139 Wang J, Soisson SM, Young K *et al.* Platensimycin is a selective FabF inhibitor with potent antibiotic properties. *Nature* 441, 358–361 (2006).

•• **Good example of how and with what facilities antibiotics are developed.**

140 Martins M, Dastidar SG, Fanning S *et al.* Potential role of non-antibiotics (helper compounds) in the treatment of multidrug-resistant Gram-negative infections: mechanisms for their direct and indirect activities. *Int. J. Antimicrob. Agents* 31(3), 198–208 (2008).

141 Dantas G, Sommer MO, Oluwasegun RD, Church GM. Bacteria subsisting on antibiotics. *Science* 320(5872), 100–103 (2008).

142 National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System Report, data summaryfrom January 1992 through June 2004, issued October 2004. *Am. J. Infect. Control* 32(8), 470–485 (2004).

143 Kiremitci A, Durmaz G, Akgun Y, Kiraz N, Aybey A, Yelken B. Frequency of isolation and antimicrobial resistance patterns of the microorganisms isolated from various clinical specimens in an anaesthesia intensive care unit, data of year 2003. *Turk. J. Infect.* 20(1), 37–40 (2006).

144 Suetens C, Morales I, Savey A *et al.* European surveillance of ICU-acquired infections (HELICS-ICU): methods and main results. *J. Hosp. Infect.* 65(Suppl. 2), 71–73 (2007).

•• **Effects of MRSA carriage on MRSA bacteremia are shown clearly.**

145 Wertheim HF, Vos MC, Ott A *et al.* Risk and outcome of nosocomial *Staphylococcus aureus* bacteraemia in nasal carriers versus non-carriers. *Lancet* 364(9435), 703–705 (2004).

146 Celen MK, Ayaz C, Geyik MF, Hosoglu S, Ulug M. Extended-spectrum β-lactamases in Gram-negative bacilli isolated from nosocomial infections. *Ankem Dergisi* 20, 148–151 (2006).

147 Zarakolu P, Hasçelik G, Unal S. Antimicrobial susceptibility pattern of nosocomial Gram negative pathogens: results from MYSTIC study in Hacettepe University Adult Hospital (2000–2004). *Mikrobiyol. Bul.* 40(3), 147–154 (2006).

148 Stobberingh EE, Arends J, Hoogkamp-Korstanje JA *et al.* Occurrence of extended-spectrum β-lactamases (ESBL) in Dutch hospitals. *Infection* 27(6), 348–354 (1999).

149 Albertini MT, Benoit C, Berardi L *et al.* Surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA) and Enterobacteriaceae producing extended-spectrum β-lactamase (ESBLE) in Northern France: a five-year multicentre incidence study. *J. Hosp. Infect.* 52(2), 107–113 (2002).

150 Tzelepi E, Magana Ch, Platsouka E *et al.* Extended-spectrum β-lactamase types in *Klebsiella pneumoniae* and *Escherichia coli* in two Greek hospitals. *Int. J. Antimicrob. Agents* 21(3), 285–288 (2003).

Websites

201 Wikipedia: Newton's laws of motion http://en.wikipedia.org/wiki/Newton_laws (Accessed on 15 December 2007)

202 Wikipedia: evolution http://en.wikipedia.org/wiki/Evolution (Accessed on 15 December 2007)

203 Wikipedia: economics http://en.wikipedia.org/wiki/Economics (Accessed on 15 December 2007)

204 Siegel JD, Rhinehart E, Jackson M, Chiarello L, and the Healthcare Infection Control Practices Advisory Committee. 2007 Guidelines for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings, June 2007 www.cdc.gov/ncidod/dhqp/pdf/isolation2007.pdf (Accessed on 15 December 2007)

205 Altan C. Hersey iyiye gidiyor, enseyi karartmayin. Milliyet (12 July 2002). www.milliyet.com.tr/2002/07/12/yazar/altan.html (Accessed on 22 June 2008)

Affiliation

• Oguz Resat Sipahi
Ege University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Bornova Izmir, Turkey
Tel.: +90 232 390 4510
Fax: +90 232 342 0871
oguz.resat.sipahi@ege.edu.tr