Antimicrobial resistance: are we losing the war?

Sasha Jaksic MD(Belgrade) FRCPA

Sasha Jaksic was born in the former Yugoslavia, graduated from the University of Belgrade Medical School and completed her postgraduate training in Clinical Microbiology. She worked in the USA for a short time and then in Australia for 10 years. She is a Fellow of the Royal College of Pathologists of Australasia (FRCPA). Sasha has been in New Zealand since February 2002 working as a clinical microbiologist for Medlab in Tauranga. She has a special interest in antibiotic resistance.

The problem

Antibiotics are among medicine's most powerful tools and have significantly contributed to the improvement of public health in the last 50 years. However, their very success and popularity are their Achilles heel – the more antibiotics are used, the more they promote bacterial resistance that undercuts their effectiveness. As a result, clinicians are increasingly using newer and broader-spectrum agents for empiric treatment, thereby expanding the cycle of resistance.[1,2]

In addition to human medicine, antibiotics have also been extensively used for disease prevention and growth promotion in animal, plant and fish farming and this practice has had a strong impact on development of resistance not only in plant and animal bacteria, but also in bacteria associated with people.[3]

An important but largely disregarded aspect of antibiotic use is the fate of antibiotics excreted into the environment following treatment. Tetracyclines, for example, are not inactivated by bacteria and are quite stable in faeces at room temperature.[4] Therefore the tons of tetracycline, yearly used as animal growth promoters or prescribed to patients, probably remain in nature and continue their action on bacteria. More importantly, they are diluted in soil and water to low concentrations known to encourage the selection and transfer of resistance. Regrettably, little or no data exist on the impact of antibiotic residues on the microflora in different ecosystems.

The amount of antibiotics consumed by the antibiotic market worldwide (100 to 200 x 10^6 kg) creates a formidable selection pressure. If we consider the global number of bacteria associated with man and animals, which is possibly in the region of 10^{28},[5] and the ease with which bacteria become resistant, it is not surprising that antibiotic resistance is now a global public health problem. 'Miracle drugs' are destroying the miracle and the worrying vision of a 'post-antimicrobial era', in which these agents will no longer be effective, may soon become a reality.

Lessons learned

In the face of this escalating problem, a few underlying principles (Box 1), may be of value in understanding the issue and approaching a solution.[6]

Common antibiotic-resistant organisms

Most concerns about antibiotic resistance have in the past focused primarily on hospitals without much apparent relevance to family physicians in the developed world. However, the problem is now increasing at an alarming rate in community practice (Box 2). Consequently, family physicians are facing complicated therapeutic choices and increased risk of patient morbidity and mortality.

Box 1. What we have learned

1. Development of resistance to antibiotics is inherent to their use (given sufficient drug and sufficient time, it will emerge).
2. Antibiotic resistance evolves from low to intermediate to high level – it is progressive.
3. Organisms resistant to one antibiotic class are likely to become resistant to other classes (multiresistant).
4. There are no counterselective measures against resistant bacteria (even complete removal of an antibiotic from general consumption will not necessarily result in a decline of resistant strains and the return of susceptible ones).
5. The use of antibiotics by any one person affects others (housemates of patients treated with antibiotics for acne had large numbers of drug-resistant flora on their skin[7]).

Inappropriate prescribing compounds the problem

As we have seen, given enough antibiotic and enough time, resistance to it will appear. The penicillin-resistant *Streptococcus pneumoniae* took 25 years and fluoroquinolone-resistant Enterobacteriaceae took 10 years to emerge clinically. Recently vancomycin-resistant *Staphylococcus aureus* has been reported.[8] The emergence of resistance will inevitably happen even with the appropriate use of antibiotics,[9] but their inappropriate use makes the problem much worse.

In 1992, the US Centers for Disease Control and Prevention (CDC) estimated that more than 40% of antimicrobial courses prescribed in physicians' offices were inappropriate.[10] This is the result of multiple factors influencing antibiotic prescribing.[2,11] Antibiotics may be seen as a way to meet patient expectations. Although physicians are primarily motivated by perceived clinical benefits, they also face strong personal, economic and legal incentives to improve patient satisfaction and maximise their own efficiency. In addition, they may not fully understand the etiology of, and treatment principles for, common infections, or may not be familiar with local resistance patterns and therefore may tend to prescribe newer, broad-spectrum agents to reduce the risk of treatment failure. Pharmaceutical marketing can also substantially influence prescribing. In 2001, the 14 largest pharmaceutical companies spent US$9 billion on marketing all of their products, including antimicrobials, to primary care physicians. No marketing is undertaken for narrow-spectrum agents, such as penicillin, amoxycillin and erythromycin, which are no longer under patent protection.[10]

Box 2. Resistant organisms

Hospitals	Community
Staphylococcus aureus (MRSA,VISA,VRSA)	Streptococcus pneumoniae (PI/R, MDR. FQR)
Enterococcus spp. (VRE)	Group A streptococcus (Macrolide-resistant)
Gram-negative bacilli (IBL, ESBL)	Neisseria gonorrhoeae (PenR, TRNG, FQR)
	E. coli (TrimR, FQR)

MRSA, methicillin-resistant S. aureus; VISA, vancomycin-intermediate S. aureus; VRSA, vancomycin-resistant S. aureus; VRE, vancomycin-resistant enterococcus; IBL, inducible beta-lactamase; ESBL, extended-spectrum beta-lactamase; PI/R, penicillin-intermediate or resistant; MDR, multidrug-resistant; FQR, fluoroquinolone-resistant; PenR, penicillin-resistant; TRNG, tetracycline-resistant N. gonorrhoeae; TrimR, trimethoprim-resistant

Appropriate prescribing

In 1995, the CDC launched a campaign to promote appropriate antimicrobial use (Box 3), emphasising not only the need for reduction of overall antibiotic prescribing in order to combat increasing resistance, but also the need for using targeted (narrow-spectrum) agents at the right dose and for the right amount of time.[10]

The following infections commonly treated in a community practice setting represent an area in which more restrictive administration of antibiotics is advisable.

Respiratory tract infections (RTI)

In the US in 1992, 51% of patients with cold, 52% with upper RTI and 66% with bronchitis received antibiotic treatment , amounting to a total of two million antibiotic prescriptions for these infections.[12]

According to the clinical practice guideline for uncomplicated acute bronchitis, routine antimicrobial treatment is not recommended, regardless of the duration of the cough.[13] Most cases of acute bronchitis are viral in nature, self-limiting and benign. A critical review of the literature regarding antibiotic use in acute bronchitis concluded that symptomatic treatment directed at cough control is sufficient for the majority of patients.[14] Moreover, patient satisfaction with care received for acute bronchitis mostly depends on physician-patient communication and not on the prescription of an antimicrobial.[15] This clinical practice guideline reassures clinicians that patients will be receptive to an explanation of why an antimicrobial prescription is unnecessary.

The guidelines also suggest that antimicrobials not be used for the treatment of non-specific upper respiratory tract infections in previously healthy adults.[16] In the past, the change of nasal discharge from serous to purulent was considered a sign of bacterial superinfection and antibiotics were requested by patients and prescribed by physicians. We know now that purulent (green coloured) sputum and nasal secretions do not predict either bacterial infection or benefit from antibiotics. According to these guidelines, antimicrobial treatment of adults with non-specific upper respiratory tract in-

Box 3. Appropriate antibiotic use according to CDC

1. Prescribing antimicrobials only when they are likely to be beneficial to the patient
2. Selecting agents that will target the likely pathogens
3. Using these agents at the correct dose and for the proper duration

fection neither enhances illness resolution nor prevents complications.

Guidelines for appropriate antibiotic use for acute sinusitis in adults[17] also recommend avoiding antibiotic treatment, especially if symptoms are mild and moderate. Antibiotics should be used only for patients with severe or persistent moderate symptoms and specific findings of bacterial sinusitis (persistent purulent nasal discharge and facial pain and tenderness in patients who are not improving after seven days or those with severe symptoms regardless of duration). Narrow-spectrum agents (amoxycillin, amoxycillin/clavulanate, doxycycline) are reasonable first-line choice.

Most cases of pharyngitis are viral in nature and the only treatment required is fever and pain relief. However, differential diagnosis between viral and, for example, pharyngitis caused by group A streptococcus, for which antibiotic treatment is always indicated, often cannot be reliably made clinically, so microbiological confirmation is advised. As a major goal of antimicrobial therapy for streptococcal infection is to prevent sequelae, antibiotics can be safely postponed until results of throat swab culture are available.[18]

Box 4. Antibiotics in RTI

Generally NOT INDICATED for:

- Acute uncomplicated bronchitis
- Common cold
- Most cases of non-streptococcal pharyngitis
- Non-specific upper RTI

Box 5. Plan for combating the increase in antibiotic resistance

1. Do not indulge patient demands for unneeded antibiotics
2. Educate patients (and parents) on appropriate antibiotic use
3. Identify the pathogen
4. Choose narrow-spectrum antibiotics, appropriate dose and duration of treatment
5. Use antibiotics for prophylaxis prudently
6. Use local susceptibility data
7. Consult local experts (Clinical Microbiologist, Infectious Diseases Physicians)
8. Observe infection control principles
9. Encourage patients to get vaccinated

Urinary tract infections (UTI)

These infections are among the most common problems for which women seek medical advice. Many family physicians tend to prescribe a costly, broad-spectrum agent, fluoroquinolone (norfloxacin), for acute uncomplicated cystitis. However, increasing concerns over resistance associated with the use of fluoroquinolones should discourage an over-reliance on these agents. Current US guidelines for treatment of UTI in women[19] recommend that fluoroquinolones not be used universally as first-line agents for acute uncomplicated cystitis, but considered only in areas with high levels of resistance to other antibiotics. Monitoring of regional resistance trends by microbiology laboratories and availability of these data to local family physicians can help optimise drug choices.

The question I am often asked relates to prescribing antibiotics to patients with indwelling urinary catheters when urinalysis has revealed the presence of bacteria. One must remember that bacteria colonising the surface of catheters create biofilm that protects them from the flushing effect of urine and this facilitates the development of catheter-associated bacteriuria (CAB). As the incidence of CAB is 3–10% per day,[20] when catheterisation is long-term, bacteriuria eventually occurs in almost all patients. Prophylactic antibiotic regimens are not effective in these patients, as biofilm protects embedded bacteria also from antibiotics, causing treatment failure and promoting development of antimicrobial resistance.[21]

In general, the presence of bacteria in urine specimens from indwelling urinary catheters is not an indication for antibiotic therapy in asymptomatic patients. Treatment has little benefit in such patients and may result in serious side effects. It drives the cost of care and the emergence of resistant bacteria in the patient and in the health care facility.[22] Exceptions to this include patients undergoing renal transplantation, urologic or gynaecologic surgery, or surgery involving a foreign body implantation.[20]

For all other patients, antimicrobial therapy, with catheter removal/replacement when possible, is indicated only if symptoms of infection are present.

Current status – some good and some not so good news

Throughout the 1990s in the US, many efforts were made to reduce the volume of unnecessary antibiotic prescribing. Physicians seem to have responded and last year McCaig and colleagues[23] reported that between 1989 and 1990, and 1999 and 2000, community-based prescribing of antimicrobials to children decreased by 47%. Good news indeed! But we have bad news as well. In 2003, Steinman and colleagues[11] looked more closely at the second component of appropriate antimicrobial use, targeted antimicrobial therapy, and noted a significant trend towards using broader-spectrum agents.

Apart from economic implications, there are public health consequences of this shift from targeted therapy. Broad-spectrum agents apply selective pressure to many groups of bacteria, thus encouraging the emergence of resistance outside the organism causing infection they are intended to treat.

For example, in Canada, the increase in prevalence of *S. pneumoniae* with reduced susceptibility to fluoroquinolones paralleled the increase in the number of fluoroquinolone prescriptions.[24] The prevalence of resistance was highest in patients 65 years of age or older, the age group in whom antimicrobial use was the greatest. The majority of patients in this study received ciprofloxacin, which is known to have inadequate activity against *S. pneumoniae*. This study clearly demonstrates the association between antimicrobial use and the development of resistance. To minimise selective pressure and the development of resistance, if a patient requires antibiotic treatment, then a narrow-spectrum agent with potent activity against the most likely infecting organism (targeted therapy) is preferred. We must consider broad-spectrum antimicrobials as precious, limited resources because for many agents, once resistance becomes prevalent in the community, there may be no going back.[25]

Action plan (Box 5)

There is a theoretical possibility of reducing antibiotic prescribing by family physicians by at least 40%.[5] If we are to do so, educating all prescribers on appropriate antibiotic use may not be enough. We also have to reassure the public that withholding antibiotic treatment would not harm patients. To achieve this, we will have to change public knowledge and opinion on the use of antibiotics, and that means creating, and sustaining, lay media's interest in this problem.[10]

Even if we were successful in changing both prescribers' attitude and public opinion on antibiotic use, the question remains of the impact of these changes on reduction of antibiotic resistance. It has to be admitted that information on antibiotic resistance and use in the community is modest but what there is offers some encouragement.[26] However, if we cannot significantly lower the already high levels of resistance to some antibiotics, we must at least try to preserve the efficacy of antibiotics to which current resistance levels are low, by using them prudently and appropriately.

Unless we are happy to live in a world without antibiotics, inactivity is not an option.

References

1. Piccirillo JF, Mager DE, Frisse ME, Brophy RH, Goggin A. Impact of first-line vs second-line antibiotics for the treatment of acute uncomplicated sinusitis. JAMA 2001; 286:1849–56.
2. Avorn J, Solomon DH. Cultural and economic factors that (mis)shape AB use: the non-pharmacological basis of therapeutics. Ann Intern Med 2001; 134:506–8.
3. van den Bogaard AE, Stobberingh EE. Drugs 1999; 58:589–607.
4. Levy SB. Microbial resistance to antibiotics. An evolving and persistent problem. Lancet 1982; 2:83–8.
5. Wise R. Antimicrobial resistance: priorities for action. J Antimicrob Chemother 2002; 49: 585-6.
6. Levy SB. Multidrug resistance – a sign of times. N Engl J Med 1998; 338:1376–8.
7. Miller YW, Eady EA, Lacey RW, Cove JH et al. Sequential antibiotic therapy for acne promotes the carriage of resistant staphylococci in the skin of contacts. J Antimicrob Chemother 1996; 38:829–37.
8. [No authors listed] Vancomycin-resistant Staphylococcus aureus. Pennsylvania, 2002. Morb Mortal Wkly Rep 2002; 51:902.
9. Lipstich M, Samore MH. Antimicrobial use and antimicrobial resistance: a population perspective, Emerg Infect Dis 2002; 8:347–54.
10. Besser RE. Antimicrobial prescribing in the United States: good news, bad news (editorial). Ann Intern Med 2003; 138:605–6.
11. Steinman MA, Gonzales R, Linder JA, Landefeld CS. Changing use of antibiotics in community-based outpatient practice, 1991–1999. Ann Intern Med 2003; 138:525–33.
12. Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. JAMA 1997; 278:901–4.
13. Gonzales R, Bartlett JG, Besser RE et al. Principles of appropriate antibiotic use for treatment of uncomplicated acute bronchitis: background. Ann Intern Med 2001; 134:521–9.
14. Orr PH, Scherer K, Macdonald A, Moffat ME. Randomised placebo-controlled trials of antibiotics for acute bronchitis: a critical review of the literature. J Fam Pract 1993; 36:507–12.
15. Pflomm J. Strategies for minimizing antimicrobial resistance. Am J Health-Syst Pharm 2002; 59 (Suppl 3): S12–15.
16. Snow V, Mottur-Pilson C, Gonzales R et al. Principles of appropriate antibiotic use for treatment of non-specific upper respiratory tract infections in adults. Ann Intern Med 2001; 134:487–9.
17. Snow V, Mottur-Pilson C, Hickner M. Principles of appropriate antibiotic use for acute sinusitis in adults. Ann Intern Med 2001; 134:495–7.
18. Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH. Diagnosis and management of group A streptococcal pharyngitis: a practice guideline. Infectious Diseases Society of America. Clin Infect Dis 1997; 25:574–83.
19. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America. Clin Infect Dis 1999; 29:745–58.
20. Warren JM: Catheter-associated urinary tract infections. Infect Dis Clin N Am 1997; 11(3):609–22.
21. Stamm WE, Hooton TM. Management of urinary tract infections in adults. N. Engl J Med 1999; 329:1328–34.
22. Bennett JB, Brachman PS (eds). Hospital Infections, 4th edition, 1998, Lippincott-Raven Publ, PA, pp477–86.
23. McCaig LF, Besser RE, Hughes JM. Trends in antimicrobial prescribing rates for children and adolescents. JAMA 2002; 287:3096–102.
24. Chen DK, McGeer A, de Azavedo JC et al. Decreased susceptibility of Streptococcus pneumoniae to fluoroquinolones in Canada. Canadian Bacterial Surveillance Network. N Engl J Med 1999; 341:233–9.
25. Levin BR. Minimizing potential resistance: a population dynamics view. Clin Infect Dis 2001; 33 Suppl 3:S161–9.
26. Seppala H, Klaukka T and Vuopio-Varkila J. The effect of changes in consumption of macrolide antibiotics on erythromycin resistance in Group A streptococci in Finland. N Engl J Med 1997; 337:441–6