

Clinical impact of antimicrobial resistance in humans

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Summary

The dramatic rise in the number and spread of resistant bacterial species continues. This involves not only bacteria that cause infections in the healthcare sector but also those that originate in the community. Antibiotic resistance rates are rising in almost all bacterial species, including those that are the most common bacterial pathogens in people (*Escherichia coli* and *Staphylococcus aureus*). Serious infections caused by resistant bacteria do not respond well to therapy and these infections are often associated with worse outcomes, including increased rates of complications, additional expense, higher associated mortality rates and prolonged hospital stays.

Keywords

Antibiotic – Antimicrobial resistance – Community-onset infection – *Escherichia coli* – Healthcare-associated infection – *Staphylococcus aureus*.

Introduction and background

Antimicrobials are essential drugs that are needed to maintain the health and welfare of people. Serious bacterial infections remain common and include bacteraemia, meningitis, pneumonia and peritonitis. In the era before antibiotics, bloodstream infections with *Staphylococcus aureus* and *Streptococcus pneumoniae* were associated with mortality rates of over 80% (23). The most common bacteria to cause serious infections in people are *Escherichia coli*, *S. aureus* and *S. pneumoniae* (3, 11, 12, 19, 21, 26, 36). With the advent of antibiotics, dramatic decreases have been seen in the mortality and morbidity associated with these life-threatening infections. Unfortunately, there continues to be a dramatic rise in both the number of resistant bacteria and the number of resistant bacterial species, as well as a considerable increase in the spread of these bacteria. In particular, there has been an increase in the number of Gram-negative strains that are resistant to broad-spectrum cephalosporins and carbapenems (8, 31, 40, 52). This should be considered as a growing pandemic (6).

Serious infections caused by resistant bacteria do not respond well to medical therapy (6, 16, 38, 39, 42, 53). These infections are often associated with poor outcomes,

including high associated mortality rates and prolonged hospital stays (6, 16, 18, 50). Increased mortality is seen in bacteraemia caused by *S. aureus* if the causative organism is methicillin resistant (MRSA), when compared with episodes caused by methicillin-sensitive strains (16). People infected with cephalosporin-resistant *E. coli* have higher mortality rates and longer hospital stays than those infected with more sensitive strains of *E. coli* (18).

The major issues for patients and for the therapy of any infection caused by bacteria that have become resistant to antibiotics are:

- antibiotics that are much more expensive need to be used (e.g. linezolid rather than ampicillin to treat enterococcal infections)
- antibiotics need to be given intravenously instead of orally (e.g. for *E. coli*, meropenem is required instead of oral cephalexin)
- antibiotics that have lower intrinsic activity are required (e.g. vancomycin compared to flucloxacillin to treat resistant *S. aureus* infections)
- there may in the future be no antibiotic available that is active against the bacteria causing the infection.

These factors result in:

- increased numbers of deaths
- increased complications
- additional expense
- prolonged hospital stays
- additional toxicity
- the need to receive intravenous therapy as an inpatient rather than being able to use oral therapy as a patient based in the community.

With *E. coli*, rapidly increasing rates of antimicrobial resistance are being seen, including multi-resistance (2, 4, 7, 9, 15, 25, 33, 40, 57, 58). This means that there may be few or no antibiotics available for therapy. This is of particular concern because *E. coli* is the commonest cause of bloodstream infections worldwide. In developed countries, rates of between 30 and 60 episodes per 100,000 people occur each year (21, 36). *Staphylococcus aureus* is the next most common cause of bloodstream infections (3, 11, 12, 26).

Increasing resistance is occurring in all medically important bacteria, and this includes resistance to antimicrobials classified as ‘critically important’ for human health (13, 56). Increasing numbers of bacterial infections for which no effective antibiotics are available are being seen in hospitals. This includes infections caused by *E. coli*, *Acinetobacter* spp., *Serratia* spp. and *Enterobacter* spp. (6, 8, 19, 22, 31, 39, 40, 42, 52, 53). Resistance rates in almost all types of bacteria are much higher in developing than in developed countries. Some of these multi-resistant bacteria can be distributed by the water supply (52). For most people who live in developing countries this problem is compounded by poor access to appropriate diagnostic facilities, fewer resources being available to help initiate and maintain appropriate hygiene and infection control practices, and difficulties in accessing adequate and affordable medical care.

Resistant bacteria move readily from person to person, from hospital to hospital and from country to country. When resistant bacteria are carried by people in the community they also cause problems for people in hospitals, especially when people are admitted for medical or surgical therapy and if they are subsequently unlucky enough to develop complications. Resistant bacteria can spread directly among people in the community or can be acquired from other sources such as water contaminated by human waste. Resistant bacteria can also move from food animals to people via water and food, or by direct contamination of people’s hands or skin (1, 13, 17, 24, 30, 34, 54, 55). The bacterial genes that encode antimicrobial resistance can be readily transmitted between bacteria of the same species and also between bacteria of different species (6, 22, 40).

Most antimicrobial classes were discovered decades ago. There have been very few new classes of antibiotics developed in the last 30 years (fluoroquinolones, lipopeptides, oxazolidinones). There have been some developments in classes of antibiotics that have already existed that have led to agents with much improved activity (ketolides and tigecycline). However, these latter agents are just variations of macrolides and tetracyclines, respectively (10).

The problem is that antibiotic resistance is developing much faster than the rate at which new drugs or drug classes are likely to be made available in the near future (48). This is particularly a problem for Gram-negative bacteria, for which there are few promising drugs at the research stage, and none in the development pipeline. The financial rewards received by pharmaceutical companies for the research and marketing of completely new classes of antibiotics is relatively poor when compared with the returns on drugs that are taken continuously by a large percentage of the population, for example cholesterol-lowering drugs (1, 10, 48). Unfortunately this situation is not likely to change in the near future.

Almost all bacteria that cause infections in people show increased rates of antimicrobial resistance when compared with those 10 or 20 years ago. Some infections, however, are relatively common and cause more serious infections in people. The more important of these are discussed below.

Staphylococcus aureus

Staphylococcus aureus is commonly carried asymptotically by people in the community, particularly in the nose and on the skin. It is one of the most common of the virulent bacteria that cause infections, and especially healthcare-associated infections (3, 10, 11, 12, 21, 26). Even now, with good medical support available for patients in hospitals (including intensive care), people with *S. aureus* bacteraemia have a median mortality rate of 25%. If they have MRSA bacteraemia the median mortality rate is 35% (16). These infections are also very common. In Denmark the annual rate of all *S. aureus* bloodstream infections is about 28 per 100,000 inhabitants per year. In the United States it may be as high as 50 per 100,000 per year (or about 150,000 episodes per year) (12, 38). In Australia it is about 30 per 100,000 inhabitants per year (12).

Rates of the more resistant varieties of *S. aureus* (i.e. MRSA) are very high (3, 11, 12, 21, 26). In the United States and in many European countries as many as half of all *S. aureus* isolates that cause bloodstream infections are MRSA. In hospitals the percentage of infections caused by MRSA is even higher. In the United States it is estimated

that there may be more than 100,000 episodes of invasive MRSA infections per year, mainly bacteraemia (38).

Interventions, particularly those designed to improve infection control and antimicrobial use (e.g. decreasing the use of broad-spectrum antibiotics, especially cephalosporins and fluoroquinolones), have made a difference. Antimicrobial stewardship (which includes encouraging the prudent use of antibiotics, providing education that includes heightening awareness of the negative consequences of misusing antibacterial medications, and establishing procedures to limit the amount and types of antimicrobials used) is a major way in which antibiotic usage can be improved. Attempts to implement antimicrobial stewardship programmes are being made. However, both implementation and sustained use are difficult. Such systems can also involve significant increases in expenditure, especially if electronic prescribing and data collection are part of the improved process.

Implementation of improved infection control programmes and surveillance have also helped. In the United Kingdom a national programme decreased the number of episodes of MRSA bacteraemia by over 40% per year from 2003 to 2007 (from 3,955 to 2,376 episodes) (11, 26).

Recent developments have resulted in more agents that are effective against *S. aureus* and other Gram-positive bacteria (10). These have included agents such as linezolid, tigecycline, daptomycin and quinupristin/dalfopristin. However, resistance, associated toxicity and/or high cost have limited their use. These agents also do not appear to be more effective than vancomycin. However, it is known that vancomycin is less active than β -lactam antibiotics against methicillin-sensitive strains of *S. aureus* (MSSA), which means that one other clinical cost of increasing resistance is the need to use drugs that are intrinsically less active in patients with serious disease (10). Thus, while these agents are a welcome addition to the drugs available to treat serious infections (otherwise the infections would be untreatable), they are less effective than some of the older agents against *S. aureus*. This is why there is a continued necessity to limit the development and spread of resistant bacteria such as MRSA.

While most MRSA that affects people is the result of infection acquired in hospitals, there have also been increasing numbers of unrelated strains that cause serious and frequent infections in the community. The MRSA infections that are healthcare associated are often the result of less than optimal infection control practices in hospitals, the overuse of broad-spectrum antibiotics and the crowding of people together in hospitals, often in contact with those who are immunosuppressed (10). However, the increasing number of community MRSA

strains that are not healthcare related is a major concern. These are now causing a large and increasing percentage of community-acquired infections in the United States, Europe and Australia, and elsewhere. In some cities over 50% of community *S. aureus* infections are now MRSA. This means that, for very common infections, it is necessary to use antibiotics that are more expensive, more toxic and less effective than agents that were used successfully in the past. It is fortunate that many of these community MRSA strains can still be treated with oral agents such as tetracycline and clindamycin. However, increasing levels of resistance are being seen even to these agents in community-acquired strains of MRSA. Frequently the only option, even for less serious skin infections, is now intravenous therapy, when previously these types of infection could be treated with oral agents. Other MRSA strains have recently been found (e.g. in the Netherlands and Denmark) that can spread from pigs to humans and cause infections in people (2, 7, 37, 41).

Escherichia coli

As noted earlier, *Escherichia coli* is the commonest cause of serious bacterial infections in people (18, 21, 36, 40, 50, 52); bloodstream infections are common (30 to 60 episodes per 100,000 people per year) and are associated with substantial mortality and morbidity. There are thought to be over two million episodes per year worldwide. *Escherichia coli* also causes large numbers of infections that are not life-threatening, e.g. urinary tract infections. In many developing countries antimicrobial resistance is extensive and widespread and few or no agents may be available for therapy. Intravenous carbapenems, e.g. imipenem, can usually still be used to treat most infections, but resistance appears to be developing rapidly even to these agents. These agents are only available in intravenous forms and are also very expensive. This means that many people cannot access any antibiotics that are effective for these very common infections (6, 10).

The main reservoir for *E. coli* is the bowel and there is a large turnover of the bacterium every day (9, 15, 33). While many *E. coli* strains are relatively specific with respect to where they both live and multiply (e.g. some may be adapted to the pig gut), recent studies show that a large proportion of *E. coli* carried by people are acquired via food, and especially from poultry (9, 33). This is particularly the case for antibiotic-resistant bacteria (33). In developed countries *E. coli* remains largely sensitive to third-generation cephalosporins, fluoroquinolones and/or aminoglycosides, and these agents can generally still be used to treat those with serious infections. However, this is not the case in developing countries (52). Travellers from countries with low rates of resistance to critically important

antimicrobials such as fluoroquinolones and third-generation cephalosporins often acquire resistant bacteria (most likely via food and/or water) when visiting countries with much higher endemic rates of infection. Carriage of these resistant bacteria can be over 50% in travellers and may persist after their return home for over six months (35, 49).

In addition, increasing levels of *E. coli* that carry extended-spectrum β -lactamases (ESBL) are being seen in developed countries, including the United States and Europe. These strains are resistant to all third- and fourth-generation cephalosporins and appear to be community acquired with food as a source. In particular, poultry have been found to be frequently contaminated with multi-resistant *E. coli*. In Hong Kong, the prevalence rate of ESBL in poultry isolates of *E. coli* was found to be 78% (28). There is now a worldwide epidemic in people of resistant *E. coli* carrying genes encoding CTX-M and CMY β -lactamases (2, 7, 44, 58). In Europe there are hundreds of thousands of episodes per year, and isolates obtained from blood in 2009 showed ranges in different countries of 4% to 29% for ESBLs and 9% to 44% for fluoroquinolone resistance. It is of note that ESBL bacteraemia in Europe is associated with a 32% mortality rate within 30 days of the episode of sepsis (18).

Streptococcus pneumoniae

Streptococcus pneumoniae is spread from person to person. It is the commonest cause of pneumonia and meningitis in most countries, and is also a common cause of bloodstream infections. It is also a frequent cause of more common, but less serious, infections such as otitis media (10, 14, 29, 46). It does not appear to have any non-human reservoirs and thus all resistance seen in pneumococci is likely to be the result of antibiotic use in people and/or associated with poor hygiene that allows the spread of this bacterium from person to person. Increasing levels of resistance are seen in these bacteria to all antibiotics, and particularly to penicillins. However, for treatment of infections, intravenous penicillin is usually still effective unless high-level resistance is present. Penicillin resistance in streptococci is mediated by modifications in the targets for penicillins – the penicillin-binding proteins (PBPs). While modified PBPs have variable affinity for penicillins and other β -lactams, for some strains treatment with penicillin is still feasible if high dosages are used.

One antibiotic that can still be relied on in all circumstances to treat serious pneumococcal disease (including meningitis) is vancomycin, although its penetration into cerebrospinal fluid is relatively poor and it is not absorbed when given orally. Other agents, such as

linezolid, appear to be effective because resistance in pneumococci is currently very low. Oral therapy is very important for the treatment of many infections other than meningitis. High dose oral amoxicillin appears to be effective when therapy is needed even if intermediate penicillin resistance is present. However, with respect to other oral agents, unfortunately increasing numbers of pneumococci are developing resistance to tetracyclines, co-trimoxazole and macrolides, which limits therapeutic options for the oral treatment of pneumonia and other conditions (10, 14, 29, 46).

Other Gram-negative bacilli

There are many Gram-negative bacteria that cause serious disease, particularly in healthcare settings (8, 10). Examples include *Enterobacter* spp., *Pseudomonas aeruginosa*, *Serratia*, *Klebsiella* and *Acinetobacter*. Some may be untreatable with any antibiotic, including polymyxins (22). For other examples, including *P. aeruginosa* and *Burkholderia* spp., there are often no effective antibiotics that can be used in patients with serious infections, such as those acquired in intensive care units, and in patients with cystic fibrosis and complicated lung infections. An older and relatively toxic antibiotic (polymyxin) is being used increasingly as intravenous therapy when no other option is available to treat these resistant bacteria (42).

Enterococci

Enterococcus spp., in particular *E. faecium*, are intrinsically resistant to large numbers of antimicrobials. In people most infections are caused by *E. faecalis*, which remains generally sensitive to both ampicillin and vancomycin (10, 27, 45). For some serious infections such as endocarditis, an aminoglycoside needs to be added to ampicillin to achieve bactericidal activity. If high-level resistance to aminoglycosides is present, endocarditis (which in the pre-antibiotic era was associated with 100% mortality) will not usually be curable.

Enterococci are intrinsically resistant to cephalosporins. This is probably an important reason why these bacteria are selected and are increasing in numbers in environments such as hospitals where cephalosporins are frequently used. Enterococci are becoming increasingly important pathogens in hospitals, and cause many serious infections such as bloodstream infections. Of particular concern are vancomycin-resistant enterococci (VRE) because there are only limited options for therapy and the bacteria spread readily within a hospital environment as a result of their lack of susceptibility, both to environmental stressors and to disinfectants and cleaning. There is also the concern

that the genes that encode for vancomycin resistance may spread to more virulent bacteria such as *S. aureus*. Fortunately, compared with 10 years ago, there are now more agents available to treat infections caused by VRE (e.g. linezolid).

In most hospitals, infection control practices are used to limit the spread of these bacteria. Such procedures include isolating patients and requiring increased precautions to be taken by all medical and nursing staff looking after them, e.g. the use of gowns, gloves and isolation rooms. The appearance of VRE is a concern, particularly if they are also found in food, as was the case when avoparcin was used extensively as a livestock growth promoter in the past (2, 10, 27, 45). Other resistant enterococci can also spread via food to humans (27).

Foodborne pathogens

Antimicrobial resistance is increasing in many foodborne pathogens, in particular *Salmonella* and *Campylobacter*. Agents that were very effective in the past, including ciprofloxacin, are now ineffective (2, 10, 20, 32, 43, 47, 51).

Non-typhi *Salmonella*

Infections with non-typhi strains of *Salmonella* are common in developed countries (and even more common in developing countries). In developed countries nearly all these strains are derived from food animals. Increasing antibiotic resistance is an issue in these bacteria as well, and some have been impossible or very difficult to treat. Of particular concern is the development of ESBL; when this occurs there may be no therapy available to treat pregnant women or children if they develop serious infections (e.g. bacteraemia), because third-generation cephalosporins are the drug of choice in that circumstance. *Salmonella* containing ESBL can develop from the use of third-generation cephalosporins in poultry. In Canada a close association has been found between the use of a third-generation cephalosporin (ceftiofur), ESBL *Salmonella* and ESBL *E. coli* (5).

Salmonella typhi

Salmonella typhi is a pathogen that spreads from person to person, usually via contaminated food and water. It has no animal reservoir and thus all resistance is likely to be the result of antibiotics given to people, along with poor hygiene and poor water infrastructure. If improved water supply and sewage infrastructure were introduced in developing countries, it would have a significant effect in decreasing the number of these infections (including antibiotic-resistant infections).

Campylobacter

Campylobacter is the commonest cause of bacterial diarrhoea in developed countries. The main causative organism is *Campylobacter jejuni*, which is mainly derived from poultry as its initial source. Increasing resistance is seen in these strains to both fluoroquinolones and macrolides. For most cases, no antibiotic therapy is needed. However, with more severe disease, fluoroquinolones and macrolides are the agents of choice and therefore resistance is problematic. Wherever fluoroquinolones have been used in poultry, resistance develops and spreads, and it has reached very high rates in countries such as Spain (1, 10). Even in the United States, where only a small percentage of poultry were exposed to fluoroquinolones, resistance rates to ciprofloxacin in campylobacter were as high as 20% in both poultry isolates and those isolates cultured from people (1, 2, 20).

Other issues

In countries that have never allowed the use of fluoroquinolones in food animals, e.g. Australia, there is almost no resistance seen in isolates of *E. coli*, *Salmonella* or *Campylobacter* derived from food animals or in food produced from these animals (10, 51). This includes a lack of resistance to nalidixic acid. It thus appears very likely that the major driving factors for resistance in most foodborne pathogens that are derived from animals are the use of antimicrobials and the types of antimicrobials used in food animals.

In children and pregnant women, fluoroquinolones are contraindicated, and thus for invasive or serious disease involving *Salmonella*, third-generation cephalosporins are the agents of choice. Unfortunately increasing rates of resistance in *Salmonella* make this option difficult. This is a particular problem in developing countries where invasive *Salmonella* infections are much more common. However, it is also a problem for those living in developed countries because these infections can be acquired domestically and also by travellers who have visited countries with much higher endemic rates of infections and/or resistance. In many countries (e.g. Denmark), imported foods may be contaminated with bacteria that are much more resistant than those found on food produced domestically (17).

Common clinical syndromes where resistance is a problem

When a patient presents with a problem to a doctor or healthcare facility, they do it with a clinical syndrome rather than with a label that states that they have *S. aureus* or *E. coli*. Common clinical syndromes include pneumonia,

meningitis, abdominal sepsis and urinary tract infections (36). It is often 24 to 48 h before results from the bacteriology laboratory are available to help doctors decide on the appropriate therapy. In resource-poor areas there may be limited or no microbiological testing available to guide therapy.

Thus, in areas where multi-resistant bacteria are becoming more common, both in the community and in hospitals, empirical therapy is difficult, and broad-spectrum intravenous antibiotics often need to be used while culture and other results are awaited. This means that where MRSA might be common, vancomycin needs to be used as empirical therapy (or another agent effective against MRSA). If resistant Gram-negative bacteria are likely to be present third-generation cephalosporins or carbapenems may need to be used in empirical therapy. This leads to the paradoxical problem that we tend to drive resistance even faster by the use of these empirical broad-spectrum agents because they help to select for more resistant bacteria such as MRSA, VRE and ESBL *E. coli* and/or other resistant Gram-negative bacteria.

People in the community who are carrying resistant bacteria (e.g. ESBL *E. coli* or VRE) may be admitted to a hospital because of trauma or the need for surgery. If during their hospital stay they are given antibiotics, the resistant bacteria will often be amplified because they are given a selective advantage over more sensitive bacteria the patient may be carrying. These resistant bacteria then become likely to cause infections that may complicate the patient's hospital stay and also become more likely to spread to other people within the hospital. Thus, to minimise the risks from resistant bacteria in healthcare settings, it is very important to limit not only the types and numbers of resistant bacteria that are carried by staff and patients in hospitals but also those in the general community.

The issues raised above highlight the need for improved diagnostic tools. This will allow more rapid and accurate determination of whether a bacterial infection is present or not, and the nature of the causative bacteria. We also need much more rapid testing to identify when major resistant determinants are present. This will allow the best targeted antibiotic therapy to be given and thus avoid prolonged therapy with broad-spectrum agents.

Much better surveillance is also needed – locally, nationally and internationally. The results need to be readily available so that it is possible to monitor the development of resistance in different areas, and surveillance must involve both the human and the non-human sectors. This will allow not only a better choice of empirical antibiotic therapy but will also help to target problem areas with preventive interventions, improved antibiotic stewardship and other programmes. This will help to stop or slow the development of resistance in those targeted areas and may even reduce the level of resistance present.

It is also necessary to consider whether more patients should be screened to detect carriage of multi-resistant bacteria. This may involve not only common healthcare-associated pathogens such as MRSA and VRE but also bacteria, such as multi-resistant *E. coli*, that are acquired and carried with increasing frequency in the community.

Conclusion

Antibiotic resistance causes increased numbers of deaths and complications, increased expense, prolonged hospital stays, toxicity and difficulty in delivering therapy in the safest way to patients. Antibiotic resistance is a continuing and growing problem. There are few new classes of antibiotics likely to be available in the next few decades. Therefore it is necessary to preserve the usefulness of those antibiotics we currently have by decreasing their overall use, and especially the use of broad-spectrum agents. It is also necessary to improve our ability to prevent infections and the spread of resistant bacteria wherever they arise or are found. This means improving practices of infection control, hygiene, animal husbandry and the development and delivery of effective and safe vaccines. Failure to do this will result in huge numbers of people entering a 'post-antibiotic era' for too many common infections.



Impact clinique de l'antibiorésistance chez l'homme

P. Collignon

Résumé

La multiplication et la propagation des espèces bactériennes résistantes se poursuivent à un rythme impressionnant. Ce phénomène ne concerne pas seulement les bactéries responsables d'infections associées aux soins de santé, mais aussi celles qui ont une origine communautaire. La proportion de bactéries résistantes aux antibiotiques augmente dans presque toutes les espèces, y compris celles comptant parmi les pathogènes les plus fréquents chez l'être humain (*Escherichia coli* et *Staphylococcus aureus*). Les infections sévères causées par des bactéries résistantes ne répondent guère aux traitements et sont souvent associées à des tableaux plus graves encore, avec une multiplication des complications, une hausse des coûts de traitement et de la mortalité associée et un allongement des séjours à l'hôpital.

Mots-clés

Antibiotique – *Escherichia coli* – Infection associée aux soins de santé – Infection d'origine communautaire – Résistance aux agents antimicrobiens – *Staphylococcus aureus*.



Efectos clínicos de la resistencia a los agentes antimicrobianos en el hombre

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Resumen

Las especies bacterianas resistentes, entre las que figuran no solo bacterias que provocan infecciones en el sector de la atención sanitaria, sino también otras que tienen su origen en los espacios de la vida cotidiana, siguen conociendo una espectacular progresión, tanto en número como en extensión. Los índices de resistencia a los antibióticos van en aumento en casi todas las especies de bacterias, entre ellas las de los patógenos más comunes del ser humano (*Escherichia coli* y *Staphylococcus aureus*). Las graves infecciones causadas por bacterias resistentes no responden satisfactoriamente a los tratamientos, y a menudo vienen asociadas a peores resultados sanitarios, como mayor porcentaje de complicaciones, gastos suplementarios, tasas más altas de mortalidad asociada y hospitalizaciones más prolongadas.

Palabras clave

Antibiótico – *Escherichia coli* – Infección de origen comunitario – Infección asociada a la asistencia sanitaria – Resistencia a los agentes antimicrobianos – *Staphylococcus aureus*.



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