

# The Antibiotic Paradox

Ian M. Gould

**Abstract** Antibiotics are one of the great medical advances of all time, but their success has brought advanced warnings of their demise due to over-use. The story of antibiotics is full of paradoxes, from over-reliance leading to poor infection control practice, to over-use leading to resistance and spread of new resistant clones. These clones don't necessarily just replace susceptible clones but might bring additional burden of infection, leading to a net increase in numbers of infections. This chapter will investigate the implications of this for the control of healthcare acquired infection, with several examples of common hospital pathogens, showing not only increased prevalence but also virulence in some cases.

**Keywords** Resistance • HAI • Toxins • Virulence • MRSA • ESBL

## Introduction

Antibiotics are arguably, the greatest discovery of the twentieth century but their very success has brought huge problems, which might be described as paradoxes. Firstly, this success has brought huge overuse and consequent resistance. While 20 years ago many might have argued about the links between use and resistance, these are now generally accepted as direct and irrefutable. Secondly, introduction of novel antibiotics immediately leads to calls for restrictions on their use, in order to delay the onset of resistance. This disincentivises Pharmaceutical companies from crucial (but expensive) research to discover new classes of antibiotics. Thirdly, for all their success in battling infection and becoming the backbone of modern medical practice, it is increasingly evident that antibiotics are actually increasing the number of infections, and maybe even their severity, certainly in hospitals and possibly also in the community. It is this third paradox that I will discuss in this chapter.

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## Infection Control

The era of evidence based infection control really gained ground in the late nineteenth century with the Golden era of Bacteriology although the epidemiological basis had been laid over the proceeding century, arguably starting with the work of Alexander Gordon in Aberdeen, who in 1795 published his thesis on the contagious nature of puerperal fever (Gould 2010). Certainly, by the time the era of antibiotics started, in the 1930s, hospital hygiene, aseptic practices, patient isolation and disinfection were firmly established as major parts of good hospital practice (Williams 2008).

Who would have expected that now, in 2010, we are suffering the highest recorded rates of Hospital Acquired Infection (HAI), within living memory, and possibly since the nineteenth century when major surgery could not advance because of the problem of post operative infections (Lister 1867). Accurate statistics are not available of course, but since surveillance became fashionable, deaths from HAI in the USA have increased approximately sevenfold, from around 13,000 in 1992 to around 100,000 today (<http://www.idsociety.org/>). Moreover, public perception of this problem is real (Washer et al. 2008), antibiotic resistance has never been a bigger problem, and many, if not the majority of HAIs are caused by antibiotic resistant bacteria.

What is causing this undoubted increase in HAI at a time when concern about it has never been higher and resources spent on it are second to none? Possibly it is because we forgot the lessons learnt in the past, relying on antibiotics instead. To quote the US surgeon general “we can close the book on infectious diseases and declare the war on pestilence won” (Spellberg 2008). Or is it because antibiotics are somehow causing infections and countering our best efforts at infection control? (IC) (Gould 2008) Maybe it is a bit of both. Certainly there is plenty of evidence of poor IC practice in hospitals, albeit outside the operating theatre (Gould 2009). But what is the evidence that antibiotics are actually increasing the number of infections and maybe even their severity and why might this be the case and what is the evidence we can reverse these trends with antibiotic stewardship?

## Antibiotics Are Increasing the Number of Infections

The most obvious example where antibiotics are increasing the number of infections is antibiotic associated diarrhoea, and in particular *Clostridium difficile* infection (Karas et al. 2010). This organism is most usually associated with prior antibiotic therapy and has seen big increases in the past decade, often associated with epidemics of multi-resistant, hypotoxin-producing strains. In particular, acquired resistance to quinolones and macrolides/lincosamides and natural resistance to cephalosporins has helped this organism to succeed at a time when these antibiot-

ics are amongst the most commonly used classes in most hospitals. The relationship between resistance and disease is not as clear as that between total use and disease as co-amoxiclav, another very commonly used agent is also associated with *C. difficile* disease although the organism remains susceptible.

## MRSA

MRSA is currently causing a worldwide epidemic of the most notable proportion, possibly the biggest since the 1918–1919 flu pandemic, although it is actually comprised of many different epidemics due to different strains. There are currently separate strains causing major community epidemics in humans in the USA (Gould 2006) and in pigs and pig farmers in Holland and Denmark (Voss et al. 2005). Their relationship to antibiotic use is also probable if not proven. It is quite clear, at least in hospitals, that MRSA is an additional burden of infection. MSSA rates have not declined so if a hospital records its MRSA rate as 50%, then this usually means a doubling in the number of serious staphylococcal infections (HAI Newsletter 2010). While much of the spread of MRSA can correctly be attributed to poor IC practices, the influence of antibiotic use is now clear, not only in the selection and maintenance of such strains, but also in their spread, making IC all the more difficult (Monnet et al. 2004).

Numerous studies now document strong associations between prior antibiotic use and MRSA at an individual patient level and at an ecological level both in hospitals and communities. Simply put, if we did not use antibiotics, we would not have any problem with MRSA as it would have no survival advantage (Gould 2008).

What will happen with vancomycin resistance in *S. aureus*? We are seeing a slow but inexorable rise in low level resistance but there is little data yet to say that these strains will be an additional burden of infection, although they may already be showing more virulence and increased ability to cause chronic infection through tolerance, adherence and biofilm formation (Gould 2008).

## Other Gram-positive Infections

The other Gram-positive organisms causing major problems in HAI are enterococci and coagulase negative staphylococci (CNS). It is no surprise that these organisms are mainly evident in multi resistant forms, enterococci often resistant to penicillins, macrolides and quinolones, always resistant to cephalosporins and increasingly glycopeptide and aminoglycoside resistant (<http://www.rivm.nl/earss/>). Similarly, CNS are methicillin resistant in the great majority of cases (<http://www.eucast.org/>). Fungi, in particular yeasts, should not be forgotten in this context either, broad spectrum antibiotic use being a well established predisposing factor. Antifungals too can select for different strains of emerging fungi.

## Gram-negative Infections

*Pseudomonas aeruginosa* has long held a reputation as a common problem in hospitals, due to its innate antibiotic resistance. Other innately multi-drug resistant (MDR) organisms like *Burkholderia cepaciae* (Avgeri et al. 2009) and *Stenotrophomonas maltophilia* (Gabriel et al. 2004) are also causing increases in HAI rates usually associated with severe immunosuppression in individual patients. More convincingly perhaps, *Acinetobacter* is currently epidemic in many hospitals around the world and it is no coincidence that these epidemic strains are multi resistant, commonly including carbapenem resistance and sometimes Pan-resistance. Indeed, *Acinetobacter* has been described as the “Gram-negative MRSA” and certainly seems to have a unique ability to acquire resistance determinants (Fournier et al. 2006).

Comparative genomics of MDR *A. baumannii* French epidemic strain AYE show an 86-kb resistance island, the largest identified to date, with 45 resistance genes including 19 new putative resistant genes and a 20 kb genomic island “switch” flanked by transposases allowing acquisition of most of the genes recently acquired from *Pseudomonas*, *E.coli*, and *Salmonella*.

Arguably, the most significant development in Gram-negative resistance in the past 10 years has been the widespread transfer of mobile resistance elements determining cephalosporin, quinolone and/or carbapenem resistance in some of the most common human hospital pathogens, *E.coli*, *Klebsiella* spp. and other *Enterobacteriaceae* (Gould 2009; Kumarasumy et al. 2010). The spread of these resistances seems to have taken on an unanticipated importance such that talk of Pan-resistant bacteria is widespread and there are no anticipated new classes of agents in development in the foreseeable future. Other chapters in this book will address some of these bacteria in detail.

An important, and as yet unanswered question is whether these very worrying changes in susceptibility are associated with increases in the total number of infections, as discussed above, or whether as may commonly be assumed, they are merely replacing infections previously caused by susceptible strains. Unfortunately, we do not have robust surveillance systems in place to be able to answer these questions. Such surveillance systems usually collect only snapshots of organisms and describe the percentage resistance. Some such as EARSS (<http://www.rivm.nl/earss/>) and some National systems collect blood or invasive isolates and could calculate a denominator but these systems are usually voluntary so do not have a robust denominator. In any case, they also usually only report percentage resistance so it is difficult to abstract data on actual number of infections.

Looking at data from my own hospital laboratory, which serves a population of 500,000, we can obtain robust denominator data for bacteraemia and all clinical isolates, single episode per patient. Table 1 lists rates for 2008 as a percentage of 2001 levels (the earliest years data available). Any value over 100 is an increase. Only *S.maltophilia*, and *Citrobacter* show a decline while *E.coli*, *P.aeruginosa*, *Klebsiella*, *Enterobacter* and *Serratia* show at least a doubling. These latter species are amongst these demonstrating the greatest changes in resistance, during the past few years, in the Grampian region.

**Table 1** Grampian. Unique clinical isolates per species 2008

Species	Specimen type	% of 2001 level
<i>E.coli</i>	bc	140
	all	400
<i>P.aeruginosa</i>	bc	150
	all	200
<i>Klebsiella</i>	bc	200
	all	200
<i>S.maltophilis</i>	bc	50
	all	100
<i>B.cepaciae</i>	bc	100
	all	100
<i>Acinetobacter</i>	bc	100
	all	30
<i>Enterobacter</i>	bc	100
	all	200
<i>Citrobacter</i>	bc	100
	all	100
<i>Serratia</i>	bc	300
	all	200

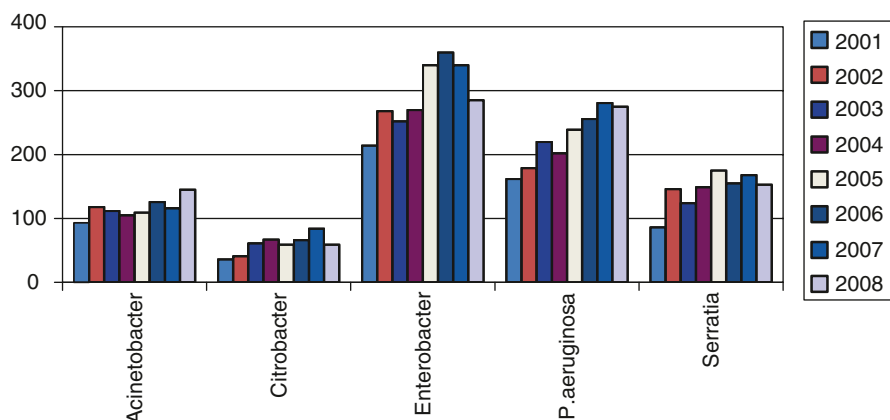
*bc* blood culture*all* all types of specimens

On studying EARSS data for the years 2001/2002 versus 2007 the only comparable data publicly available is for *E.coli*. In 2001/2003 20 countries reported 13,263 episodes of *E.coli* bacteraemia. The reporting laboratories covered 240,000 beds and received 1.3 million blood cultures. Comparable data for 2007 were 30 countries (50% increase), 46,524 episodes of *E.coli* bacteraemia (3–4-fold increase), 350,000 beds (almost 50% increase), 2.8 million blood cultures (approximately twofold increase) (<http://www.rivm.nl/earss/>).

Unpublished data from the Scottish Voluntary National Surveillance of blood cultures, which seems to have had consistent methods of adherence to reporting between 2001 and 2008 (Camilla Wuffe personal communication) are seen in Figs. 1 and 2 and cover a population of just over 5 million and 27 reporting laboratories. While the data cannot be considered robust, it gives great cause for concern and requires much more robust surveillance to be performed in future. In particular, *E.coli* and *Klebsiella* bacteraemia doubled between 2001 and 2008. Similar data from England is shown on the HPA website (<http://www.hpa.org.uk>).

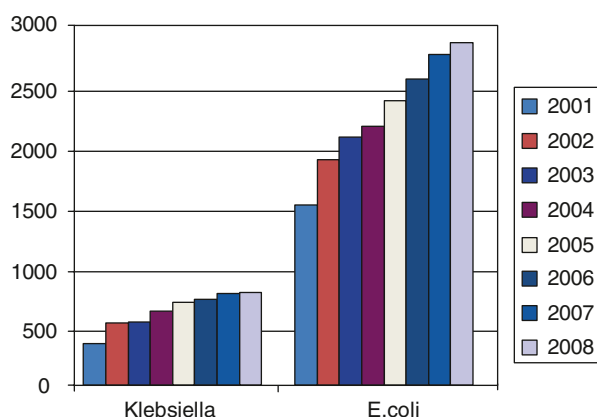
## Antibiotics Are Increasing the Severity of Infections

When a new antibiotic resistance manifests, it is often claimed that the fitness cost to the organism is too great for the strain to be pathogenic (Levin 2001). Unfortunately, time and again this proves to be short lived optimism, as genetic adaption al-



**Fig. 1** Health Protection Scotland reported bacteraemia

**Fig. 2** Health Protection Scotland reported bacteraemia



lows compensatory mutations. *Clostridium difficile*, MRSA, especially PVL strains and perhaps glycopeptide intermediate *S.aureus* are examples where virulence factors can be associated with resistance determinants, sometimes on pathogenicity islands (Lindsay and Holden 2004).

Moreover, the inability to deliver adequate empiric therapy is increased in resistance, more so where there is (linked) multi resistance, encoded for on integrons and other mobile genetic elements. Outcomes are poorer and mortality higher (Kumar et al. 2006). Worse still, alternative therapies may not be so efficacious, even if administered in a timely manner. Again the example of glycopeptides and MRSA springs to mind (Lodise et al. 2007). It is well established that the glycopeptides are sub-optimal therapy when compared with semi-synthetic penicillin for the treatment of methicillin susceptible *S.aureus* (MSSA). Two meta-analysis suggest mortality from MRSA infection is double that of equivalent MSSA infection (Whitby et al. 2001; Cosgrove et al. 2003). No wonder that mortality from HAI is increasing.

## Why Is HAI Increasing in Frequency and Severity?

The easiest explanation for the data I have presented is that it is either false (the surveillance systems are not robust) or that the increasingly aged and immunosuppressed hospital population is more susceptible to infection. Possibly, we have not fully rediscovered good IC practice, having lost ground in the golden antibiotic era when we were lulled into a false sense of security, thinking that antibiotics had infection diseases beaten. I clearly remember one of my mentors in the 1980s telling me we had little need for isolation rooms in modern hospitals. There may be elements of truth to this, but I do not think it's the full explanation. If that were case, then why have HAIs due to susceptible organisms not shown an increase rather than just remained stable? Perhaps also, blood culture systems are better or more blood cultures are being submitted but this is not the case in our own laboratory [unpublished] and it is hard to credit that *E.coli* or *Klebsiella* are better isolated in new blood culture systems.

More plausibly antibiotics not only select for and maintain resistance, but they also can increase transmissibility, colonization and pathogenicity (Gould 2008). Increased transmissibility of antibiotic resistant organisms in patients on antibiotics has long been appreciated (Berntsen and McDermott 1960). More recently, carriers of MRSA in Hong Kong in 2008 were shown to have increased numbers of MRSA in their noses if they were receiving quinolones or cephalosporins, both of which the MRSA isolates were resistant to (Cheng et al. 2008). Simplistically, such antibiotics will ablate the normal (protective) bacterial flora, allowing colonisation and an overgrowth with resistant invaders such as MRSA (in the nose) or ESBL producing *E.coli* in the gut. Other possible mechanisms that may operate to increase colonization and pathogenicity and can be attributed to commonly used antibiotics are listed in Table 2 and a proposed biological model for the vicious cycle of exposure, colonization, infection and death is illustrated in Fig. 3. Not least, the simplistic notion that simple infections not responding to first line treatment, will develop into more serious, often invasive infections, should not be discounted.

Are we in danger of completely negating the antibiotic miracle in our overuse of antibiotics? In other words, are we seeing such a rise in resistant infection that it will ultimately completely counter the beneficial effects of antibiotics?

## What Can We Do?

Clearly more is required than standard IC responses. In some isolated examples, dedicated and targeted IC can work e.g. on catheter care to reduce *MSSA* and MRSA bacteraemia and surveillance cultures for MRSA on admission to hospital as a guide to isolation and decolonisation strategies (Reilly et al. 2010). But these strategies can be expensive. Arguably they are akin to firefighting.

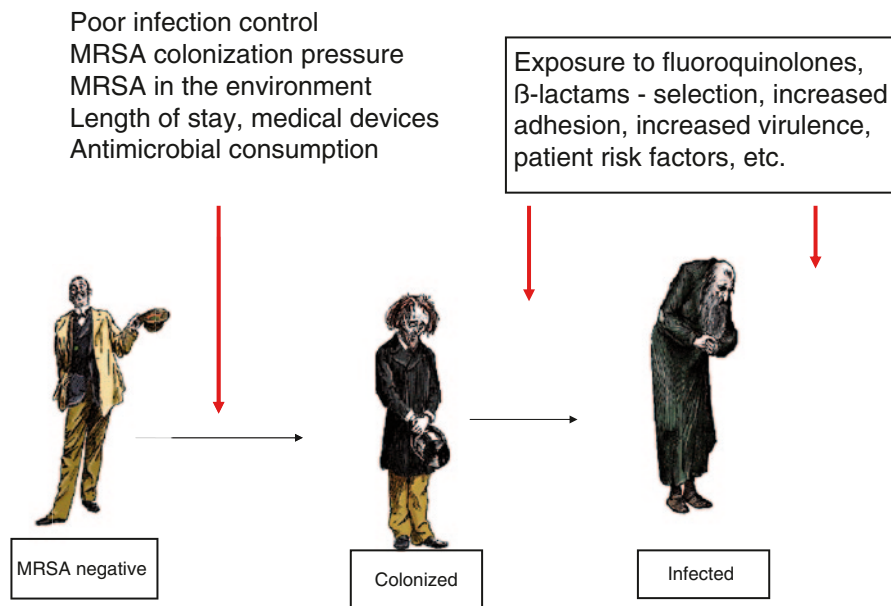
**Table 2** Causes of increased transmission, adherence and pathogenicity of MRSA when exposed to antibiotics

<ul style="list-style-type: none"><li>• Biofilm formation</li><li>• Small colony variants</li><li>• Efflux</li><li>• Hypermutation</li><li>• Skin/RT colonization → transmissibility</li><li>• Fibrinectin-binding protein</li><li>• Toxin production eg <math>\alpha</math>, TSST-1</li><li>• SOS response → horizontal gene transfer</li><li>• Phage induction</li><li>• Quorum sensing</li><li>• Agr expression</li><li>• Autolysis</li><li>• Intracellular persistence</li></ul>
<i>RT</i> respiratory tract
<i>TSST</i> Toxic shock syndrome toxin
<i>Agr</i> Accessory gene regulation

What is required is tackling of the problem at its root cause, namely the gross over use of antibiotics. The Cochrane review on prescribing interventions to control resistance in hospitals was very limited in the robust evidence it found (Davey et al. 2005) but there has been a significant increase in the number of good quality studies published since 2002. There is now reasonable evidence that rates of MRSA, *C.difficile*, VRE and multi resistant Gram-negatives can be reversed by modulating use of key agents such as cephalosporins and quinolones, notwithstanding the particular problems posed by integrons carrying multiple resistant determinants (Gould 2008; Davey et al. 2005).

The real problem for the future, of course, is how to do this without “squeezing the balloon”, transferring the resistance selection pressure to other classes of agents. This highlights another paradox, that of current antibiotic policies which tend to lead to a lack of diversity of use of different classes of antibiotics. Diversity of use is probably one of the best strategies to delay emergence of resistance, although a lack of choice of truly different drug classes makes its implementation problematic. Moreover, the holy grail, and the most difficult thing is to achieve total reduction in prescribing while not compromising patient outcomes. Again, this isn’t something current strategies are good at achieving. This takes us full circle to Volume 1 of this series and the methods of stewardship. In the absence of a good pipeline of new drugs, it is the balance between the individual patient and society as a whole, otherwise known as the ecological perspective, that has to be clearly established and debated. We need to get clever, quickly. Some examples might include only using surgical prophylaxis when it is clearly established to lead to an overall reduction in antibiotic use. This, of course, will mean accepting the occurrence of a certain number of potentially avoidable infections. The potential severity of the infection will also





**Fig. 3** A reasonable biological model? (Adapted from Monnet 2006)

have to be taken into consideration. A graft infection is very different from a superficial wound infection. Similar difficult, long term, decisions will have to be taken in other areas e.g. primary care and the prophylaxis strategies used for highly immunosuppressed patients. Quinolone prophylaxis in haematological malignancy is a good example, with lives saved, but an uncertain future due to resistance.

In conclusion, there are many difficult decisions to be made. The medical profession is certainly more receptive to the problems since the advent of MRSA and the current crop of virulent strains of *C.difficile*, but much more debate and education has to follow to change attitudes and beliefs in order that real changes in prescribing practice can be instituted and maintained. And it isn't just the medical profession that is responsible or needs to lead on this. Society, at all levels in all countries of the world needs to act on the problems of antibiotic use and abuse. Otherwise, current trends of increasing antibiotic use worldwide will only get worse, and with them the current problems of antibiotic resistance and HAI will only seem like the beginning.

Essentially we need new strategies for disease prevention less reliant on antibiotics. Vaccines are the obvious area to expand. By their nature, antibiotics are only a short term strategy, particularly if overused in the current fashion. They are truly a victim of their own success.

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