Antibiotic resistance

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Abstract

Antimicrobial resistance continues to increase while the pipeline for new antibiotic development is drying up; after only eight decades of antibiotic use, bacterial infections that once were easily treated are becoming untreatable. Antimicrobials have enabled the advancement of many areas of medical practice. The successful outcomes of many surgical procedures and immunosuppressive treatments depend on antibiotic prophylaxis and the ability to treat infective complications. Antibiotic resistance, therefore, poses a serious threat to much of healthcare as we know it. Areas of particular concern are multiresistant carbapenemase-producing Gram-negative organisms, gonorrhoea and multidrug-resistant tuberculosis.

Antibiotic resistance correlates with antibiotic use, so that improved antimicrobial stewardship, with better prevention and diagnosis of infection, can help to conserve the currently available antimicrobial agents. Significant global action and investment, from both public and private sector funding, is required if the development of new anti-infectives is to keep pace with increasing resistance.

Keywords β-Lactamase; antibiotic resistance; antibiotics; carbapenemase; gonorrhoea; meticillin-resistant *Staphylococcus aureus*; MRCP; multidrug-resistant tuberculosis

Key points

- Intrinsic and acquired resistance mechanisms should be considered when prescribing antibiotics
- Increased antibiotic use leads to antibiotic resistance, so unnecessary use must be avoided
- Antibiotic resistance is of particular concern in Gram-negative bacteria (especially carbapenemase producing Enterobacteriaceae), *Neisseria gonorrhoeae* and tuberculosis
- Use of older drugs, such as colistin, with suboptimal adverse effect profiles is increasing because of the lack of newer safer drugs to treat resistant infections
- Infection control measures are important in reducing the spread of resistant infections
- Antimicrobial resistance is a global problem requiring international action and investment to preserve our existing antibiotics and develop new agents

Definition of antibiotic resistance

Antibiotic resistance in pathogenic bacteria can be defined microbiologically or clinically. Microbiological resistance is the presence of a genetically determined resistance mechanism (acquired or mutated), categorizing the pathogen as resistant or susceptible based on the application of a set cut-off in a phenotypic laboratory test. Clinical resistance is a level of antimicrobial activity that is correlated with a high likelihood of therapeutic failure; in other words, treating a pathogen with a drug to which it has tested susceptible produces a better outcome than is attained with a drug to which the pathogen has tested resistant. The test cut-offs for determining clinical resistance can vary with aspects of the clinical setting, such as the site of infection or the dosage of the drug.[1]

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Antibiotic resistance can be inherent (i.e. characteristic of all isolates of that species) or acquired. Examples of inherent antibiotic resistance include the resistance of all Gram-positive organisms to colistin, the resistance of Enterobacteriaceae to glycopeptides and linezolid, and the intrinsic resistance of *Pseudomonas aeruginosa* to a wide range of antibiotics.

Acquisition of antibiotic resistance

Acquired resistance occurs when naturally susceptible bacteria gain the genes encoding a resistance mechanism via mutation or the transfer of genetic material from other bacteria, of the same or a different species.

The antimicrobial resistance genes are carried on mobile genetic elements; these are either plasmids, which are circular molecules of double-stranded DNA independent of the chromosome, or transposons ('jumping genes'), which are mobile sequences of DNA that can move to different positions in the genome. Transfer can occur by several methods (Figure 1):

- conjugation – direct cell-to-cell contact with plasmid transfer
- transduction – transfer of bacterial DNA by a bacteriophage, a bacterial virus that replicates in the bacterial cell and can incorporate a piece of bacterial DNA in the assembled viral particle, which is then transferred to the next bacterial cell that the virus infects
- transformation – uptake of naked DNA from the environment.

When antibiotics are used, this exerts a selection pressure in favour of bacteria possessing resistance mechanisms, which now have a survival advantage and are able to pass on the resistance genes to other bacteria. Use of antibiotics is correlated with the presence of resistance in both the individual patient and the

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Please cite this article in press as: MacGowan A, Macnaughton E, Antibiotic resistance, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.07.006

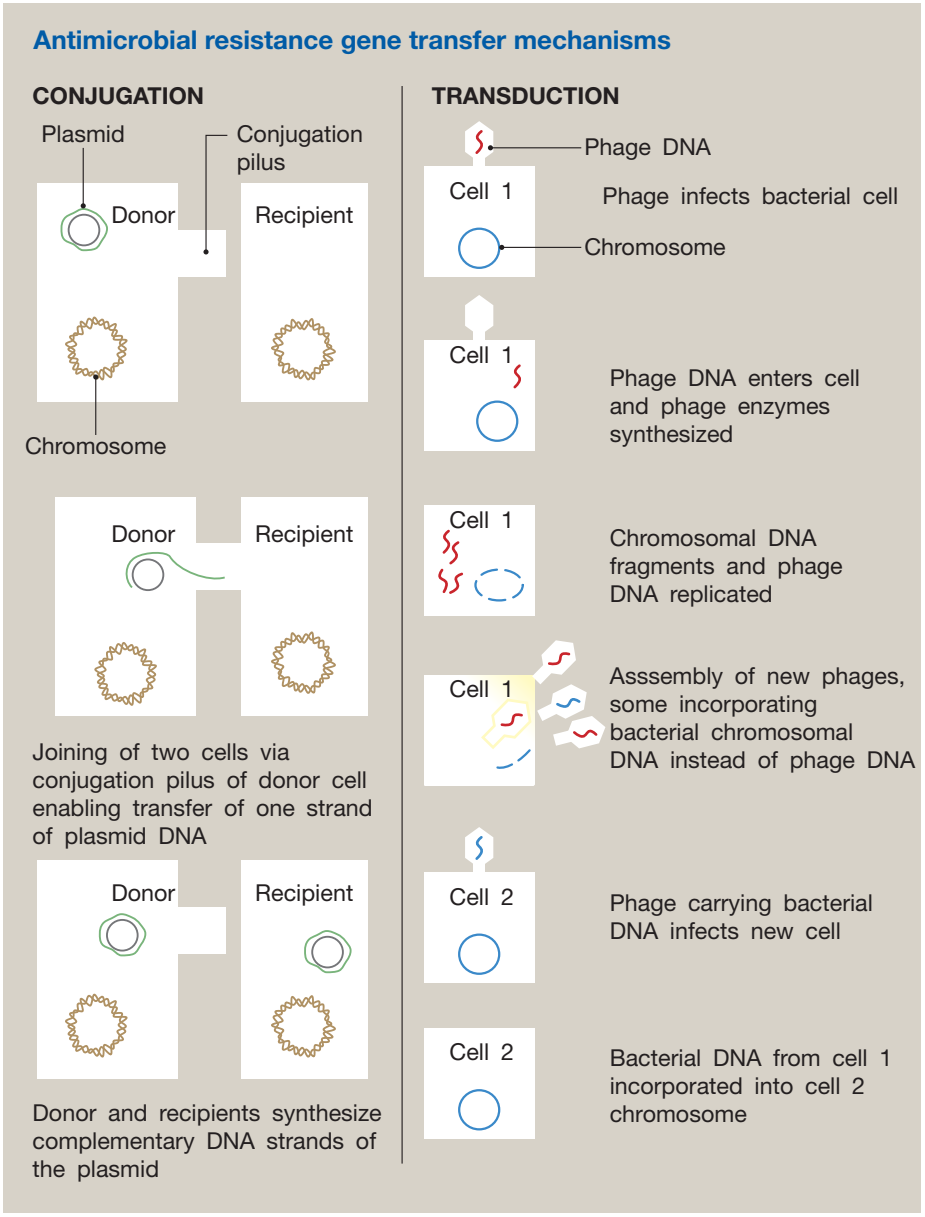

Figure 1

wider community. In the individual patient, studies have demonstrated persistence of resistance to an antibiotic up to a year after exposure, in both the urinary tract (*Escherichia coli*) and the respiratory tract (*Streptococcus pneumoniae*, *Haemophilus influenzae*). The probability of resistance at 12 months was also correlated with exposure to a higher number of antibiotics or for a longer duration.[2]

Mechanisms of antibiotic resistance

The main mechanisms by which bacteria demonstrate resistance to antibiotics are illustrated in Figure 2.

β-Lactamases

Hydrolysis of the β-lactam ring by these enzymes renders β-lactams inactive. There are many different types of β-lactamase that differ in their affinity for the particular β-lactam agents and classes, their structure and their response to β-lactamase inhibitors, such as clavulanic acid.

The rise of the extended spectrum β-lactamases (ESBLs) produced by Enterobacteriaceae (e.g. *E. coli*, *Klebsiella* spp., *Enterobacter* spp.) makes infections with these organisms harder to treat because they confer resistance to penicillins and cephalosporins (first, second and third generation). Resistance to third-generation cephalosporins in *E. coli* and *Klebsiella pneumoniae* increased significantly in the EU in 2012–2015 (>50% resistance for *K. pneumoniae* in many countries, including Italy and Greece; see Figure 3),[3] probably increasing the risk of use of carbapenems, the β-lactams with the broadest spectrum.

Carbapenemases

Carbapenems are stable to ESBL enzymes, but we are now seeing their usefulness threatened by the rising prevalence of

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