

Microbiology

Antibiotic treatment and susceptibility testing

J R Kerr

A 60 year old tale

The concept of attacking invading microorganisms without harming the host was first introduced by Paul Ehrlich. In 1910 he discovered "salvarsan", which he announced as a magic bullet for the treatment of syphilis. Penicillin, produced by the fungus, *Penicillium notatum*, was first discovered by Alexander Fleming in 1928, purified by Florey and Chain in 1940, and shown to have wide applicability in the treatment of infection caused by a variety of bacteria. With the help of colleagues in the USA, it was produced in sufficient quantity to be a miracle cure for wound infections during the Second World War. But within several years, resistance had developed in bacteria that were formerly thought to be uniformly susceptible, and it became increasingly recognised that for optimal treatment and cure, it was important to test the infecting bacterial culture for susceptibility to antibiotics, and to treat only with antibiotics that were active in vitro against the infecting organism.

The disc technique was used by various workers for this assay because it was relatively easy to set up, and the result could be ascertained the next day from interpretation of the zone size that was obtained. The test was performed by instillation of a standard amount of antibiotic into a paper disc that was, after drying, placed on to the bacterial inoculum in a Petri dish, and was then incubated at a temperature suitable for the growth of the bacterium. It was elegant in that it could use the very organism that caused infection in a particular patient, and could produce a list of possible treatments based on the results. And, apart from a few pitfalls that were important to avoid, the test was quite reproducible.

A paper describing early attempts to standardise this method appeared in the *Journal of Clinical Pathology (JCP)* in 1950.¹ In this paper, BA Thompson reports that after experimenting with various sized discs: "a 9 mm disc cut from No. 633 Hayle Mills blotting paper would absorb the whole volume of one drop (0.02 ml) from a 50-dropping pipette". Dr Thompson also states that

"neither the size of the inoculum nor the degree of moisture on the plates seems to have an appreciable effect on the zoning". Correct placement of the discs to avoid complete inhibition of the sparsely inoculated part of the plate and disc placement not less than 15 mm from the edge of the plate was also recommended.

Although the above method as described is rudimentary and various aspects have now been better understood as confounding variables and standardised (for example, the inoculum density and the degree of moisture on the plate!),² the fundamental principles of this susceptibility system are still in regular use today in clinical microbiology laboratories. The susceptibility results generated by these tests are essential to inform the correct and timely management of infected patients.

Antibiotics have revolutionised the management of many clinical syndromes caused by infection. The beneficial effects were so dramatic that we rapidly came to take them and their effectiveness for granted and they were increasingly used in ways we would later regret—for example, indiscriminate prescribing, inappropriate dosing and duration of treatment, over the counter availability of antibiotics to the general public, use in animal husbandry to maximise the growth of farmed animals, and use to control potential infections in horticulture. Such complacency has contributed to the rise of antibiotic resistance among various common human pathogens, threatening the central purpose for which antibiotics were developed in the first place.³

A second and also important use of antibiotic sensitivity data is to keep track of antibiotic resistance levels in different organisms in different countries and throughout the world. This so called surveillance of antibiotic resistance levels has enabled us to realise that the levels of resistance have risen greatly over recent years, and to recognise particular problem pathogens that are multiresistant and able to spread. However, such knowledge on a national and global scale allows us to tailor local

antibiotic policy according to those antibiotics that are most likely to be useful in different clinical situations. It alerts us to the importance of developing new antibiotics and antibiotic classes, and alternative strategies to the management and prevention of infectious diseases.

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The disc sensitivity test has therefore been the main method by which we have determined antibiotic susceptibility for organisms and by which we have kept a track on resistance itself. The particular disc method in current use in most laboratories in the UK is called the "modified Stokes method" and, although improved since 1950, it still suffers from being prone to unwanted variation as a result of variability in several factors. Much has been done recently to standardise the performance of this method, including more extensive guidance on the method and interpretation of zone sizes⁴ and semi-automated reading using a digital camera linked to the laboratory computer—for example. However, despite criticism of the method and the need to standardise antibiotic sensitivity testing on a global scale, it might be quite some time before it is superseded by other more automated, but more expensive, methods, such as those recommended in the USA,⁵ as has been proposed.⁶

The disc sensitivity test has certain clear advantages over more automated methods in certain situations, such as its use in primary testing (that is, inoculated from the specimen itself which may contain a mixed flora as opposed to the use of a pure culture), where the effect on the colonial morphology of the inoculum can be observed, which may be useful, and because of the opportunity to observe more complex effects of two antibiotic discs in combination on the test organism (either for the purpose of β lactamase testing or to gain an informal picture of possible synergy or antagonism).

In conclusion, both the disc sensitivity test and *JCP* first appeared 60 years ago and have served us well. Both have since been vastly improved and standardised and are likely to be around for a long time to come.

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