Editorial on Penicillin-sensitive bacteria

Penicillin, a serendipitous discovery by Alexander Fleming published by him in the British Journal of Experimental Pathology in June 1929, was regarded at first as a compound that can be used for selecting bacteria from mixed cultures. Ten years later in 1939, Howard Florey, Ernst Chain and their colleagues at the Sir William Dunn School of Pathology at Oxford University worked on different strains of the fungus, penicillium and could finally isolate it in the pure form. In 1941, Albert Alexander, a policeman became the first to be treated with Penicillin for a skin infection that spread to his lungs also, with dramatic relief. For mass production, Florey and his colleagues had to take the help of an American mycologist, Robert Thom of the Department of Agriculture and the department's Northern Regional Research Laboratory in Illinois. The main pharmaceuticals that were involved in the initial production of Penicillin were Merck, Squibb, Lilly and Pfizer who were approached by Florey himself.[1]

The magic of Penicillin is its β-lactam chain structure and the fact that very small quantities of Penicillin are enough to kill major pathogens like streptococci, pneumococci and staphylococci [See Table 1].[2] Natural Penicillins are active against non β-lactamase–producing Gram-positive cocci (*Pneumococci*, *Staphylococci* and *Streptococci*), few Gram-negative cocci (*meningococci* and *gonococci*), Gram-positive bacilli (*Bacillus anthracis*), anaerobes (*Clostridum perfringens*, *C. tetani*) and spirochetes (*Treponema pallidum*, *T. pertenue* and *Leptospira*).

Resistance mechanisms include:

1. Production of β-lactamase that opens the β-lactam ring in *Haemophilus influenzae* and Moraxella. This can be neutralised by a β-lactamase inhibitor like clavulanic acid.
2. Alteration of Penicillin binding proteins (PBPs) in Gram-positive cocci like staphylococci and enterococci. Hence, β-lactamase inhibitors have no role here.
3. Uptake inhibition and efflux mechanisms which are related to the cell membrane are active in Gram-negative bacteria.

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This editorial will concentrate on the use of natural Penicillin in the modern era of multidrug resistant bacteria. It is intended as an eye-opener for clinicians who feel that the oldest antibiotic is now redundant. Let us with the help of current literature, look at the situations where Penicillin in its natural form, i.e. Penicillin G and ampicillin — a modification to increase its spectrum, is still active and serves as a life-saver.

Staphylococci

Staphylococcus aureus was the major pus-forming pathogen to be destroyed very effectively in the early days of Penicillin discovery. Today, approximately 5-10% of community-acquired staphylococcal infections remain sensitive to Penicillin. Staphylococcal infections are distinctively pus-forming and easy to recognise. Hence, it is the tendency of the treating physician to blindly start drugs like cephalosporins, quinolones or if severe, vancomycin or clindamycin, as empirical therapy. In case of a Penicillin-sensitive staphylococcus, Penicillin with its low minimum inhibitory concentration (MIC) of 0.12 mg/L is the drug of choice, penetrating better to sites of inflammation and acting faster at lower concentrations. In an interesting study by Nissen JL *et al.* in Denmark, they concluded that in case of staphylococcal bacteraemia, 'Definitive therapy with cefuroxime was associated with an increased risk of 30 day mortality compared with Penicillin (cefuroxime treatment (39%) versus Penicillin treatment (20%), $P = 0.037$)'.[3] Thus, Penicillin is the drug of choice if the isolate is a sensitive one.

Streptococci

Lancefield groups A, B, C, F and G remain sensitive to Penicillin. Alpha haemolytic streptococci, commensals of the oral cavity, exhibit varied sensitivity patterns. They may appear sensitive, but certain infections like infective endocarditis due to slow growing strains may not respond as the basic mechanism of action needs active multiplication.

Pneumococci

As per Clinical and Laboratory Standards Institute (CLSI) document M100-S21, isolates of pneumococci with Oxacillin zone sizes of ≥20 mm are susceptible (MIC ≤ 0.06 mg/ml) to Penicillin. MICs for Penicillin, Cefotaxime, Ceftriaxone or Meropenem should be determined for those isolates with Oxacillin zone diameters of ≤19 mm, because zones of ≤19 mm occur with Penicillin-resistant, intermediate or certain susceptible strains. For isolates with Oxacillin zones

Table 1: MICs of Penicillin compared among different species of Bacteria according to EUCAST in mg/L

Bacterial species	Penicillin G	Ampicillin
Staphylococcus aureus	0.12	—
Streptococcus groups A, B, C, F, G	0.06*	—
Streptococcus pneumoniae	0.06	0.5
Enterococcus faecalis		4
Haemophilus influenzae		1
Neisseria meningitidis	0.06	0.12
Neisseria gonorrhoea	0.06	
Anaerobic Gram-positive bacteria	0.25	4
Anaerobic Gram-negative bacteria	0.25	0.5

*It may be noted that it needs only 0.06 mg/L of Penicillin in a medium like blood or cerebrospinal fluid (CSF) for killing that species of bacteria. The difference with ampicillin is also significant in some cases.

≤19 mm, a Penicillin MIC test was performed.[4] In India, laboratory resources are still limited, especially access to sheep blood, which is essential for isolation of pneumococci and its sensitivity testing. MIC testing is done only in a few reference labs. On searching literature, it was observed that isolation rates are very low but sensitivity to Penicillin remains almost 100%. In case of resistant strains, it is not mentioned whether MIC was performed for confirmation.[5]

Meningococci

Most of the isolates from an outbreak in New Delhi in 2005-2006 were susceptible to Penicillin, ampicillin, rifampicin and Ceftriaxone. All the isolates were found resistant to cotrimoxazole (MIC >16 mg/mL) and two-thirds were resistant to ciprofloxacin. There is a dearth of information about susceptibility rates in India; however, in the above outbreak, one isolate was resistant to ampicillin.[6]

Gonococci

Treating gonococcal urethritis became relatively easy after the discovery of Penicillin. However, response to Penicillin was seen to be reduced first in 1954, and the first article reporting resistance appeared in 1956 by Thayer *et al*. In India, Chacko and Yogeshwari from Chennai reported 45.6% resistance in 1966, while later in 1971, Moses *et al*. from Mumbai reported 56% resistance.[7] In 1981, the cause of resistance was attributed to β-lactamase enzymes. Later on, Penicillin-binding protein alterations were also noticed. By 1990, Penicillin was no longer a treatment option for gonorrhoea and the era of fluoroquinolones began. As soon as Penicillin was withdrawn, sensitivity rates slowly increased but lack of quality laboratory support has been the major cause for empiric single high-dose therapy in gonorrhoea, and this in turn has led to gonococci acquiring newer modes of resistance.[8]

Enterococci

Ampicillin is the drug of choice. Penicillin shows MICs that are 2-4-fold higher than ampicillin in case of *Enterococcus faecalis*. Though monotherapy may be enough for urinary tract infections (UTI) and skin infections, combination with aminoglycosides is necessary in case of infective endocarditis, osteomyelitis and meningitis in neonates. At present, vancomycin is the alternative therapy recommended in ampicillin-resistant enterococcal infections.

Haemophilus influenzae

Isolating this fastidious bacterium and doing its susceptibility testing is beyond the capacity of the average laboratory in India. A large study involving approximately 8523 strains, in 1999-2000, found that ampicillin sensitivity has shown a slow decline with a rate of 81.9% in the study. However, sensitivity to Ceftriaxone has remained 100%, and 99.6% remain susceptible to amoxycillin-clavulanate even now. The mechanism of resistance is popularly thought to be due to β-lactamase production but there is a group of strains called β-lactamase negative ampicillin-resistant (BLNAR) strains that are also slowly increasing in number.[9]

Bacillus anthracis

Benzyl Penicillin is the treatment of choice in anthrax. For lung infection, fluoroquinolones and tetracyclines are effective alternatives.

Anaerobes

Gram-positive anaerobes like peptostreptococci, *Clostridium tetani* and *C. perfringens* remain sensitive to Penicillin. However, adequate anti-toxin and supportive measures are essential for cure in case of toxin-mediated diseases.

Spirochaetes

It is fortunate that Penicillin retains its potency with respect to agents like *Treponema pallidum* and *Leptospira*. Leptospirosis outbreaks are responsible for keeping the medical community aware of the activity of the oldest antibiotic even now.

The special article in this issue deals with Penicillin-sensitive bacteria in a few centres in India.[10]

This may not be representative of the whole Indian scenario; however, this exercise was intended to increase the awareness of the readers to the continuing usefulness of Penicillin so that it is not dropped from the antibiotic sensitivity testing panels in the laboratories that they serve as clinical microbiologists.

It is our ardent appeal that more laboratories join this simple and interesting exercise of comparing data from

different parts of India in a free and open manner so as to increase co-operation, knowledge and understanding in microbiology. Simply contributing retrospective laboratory data need not compromise any publishing or allied activities.

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