Oral Antibiotic Treatment for Infective Endocarditis: an In-vitro Study.

Karin Bacova[1,2], Katherine Mather[2], Fiona Price[2], Simon Eccles[2], Lisa Coulthwaite[1]

[1]Department of Healthcare Science, Manchester Metropolitan University, UK. [2]Manchester Medical Microbiology Partnership, Manchester University NHS Foundation Trust, UK.

Introduction:

Infective endocarditis (IE) is a rare but life-threatening infection of the heart's endothelium which mainly affects the heart valves or intracardiac devices. Annually, there are 3-10 cases per 100,000 people in the UK, and the mortality rate is 30% at 1 year which increases with time (Cahill and Prendergast, 2016). The prevalent cause of IE is by bacterial organisms entering the bloodstream, such as those of viridans group *Streptococcus* (VGS) *spp.* and *Enterococcus spp*. (Rajani and Klein, 2020).
Treatment currently involves administering IV antibiotics for up to 6 weeks however, there was a partial oral treatment of endocarditis (POET) trial conducted in 2019 which concluded that switching to oral antibiotic treatment after stabilisation was non-inferior to continuous IV antibiotic treatment (Iversen *et al*., 2019).

Aim:

The aim of this study was to evaluate in-vitro susceptibility profiles of local clinical isolates and determine the prevalence of resistance mechanisms to antibiotics moxifloxacin and rifampicin in viridans group *Streptococcus spp.* and norfloxacin in *Enterococcus spp.* to support changes in clinical treatment practice at Manchester University NHS Foundation Trust (MFT) to implement oral regimes.

Methods:

- Archived frozen isolates; 75 viridans group *Streptococcus spp.* and 60 *Enterococcus spp*. (135 total) were selected from positive blood cultures over a 12-month period from patients with either IE or bacteraemia.
- Isolates were recovered on Columbia Blood agar (CBA: E&O, Scotland) and checked for purity after incubation at 35-37°C for 18-24 hours in either CO2 conditions (for VGS) or O2 conditions (for *Enterococcus spp.).* Figure 1 displays plates after incubation.

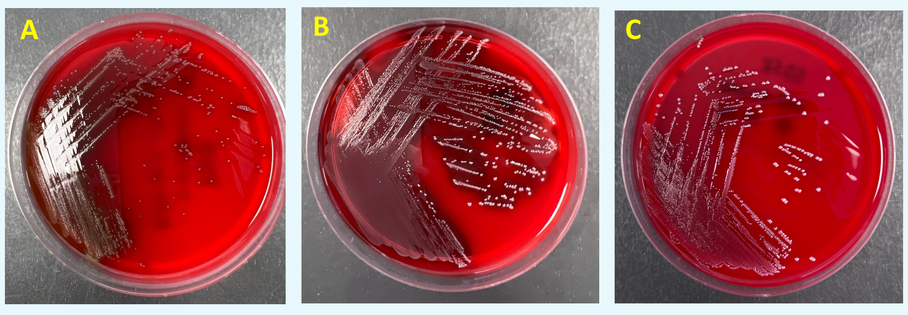

Figure 1. Viridans group *Streptococcus spp.* (A), *Enterococcus faecalis* (B) and *Enterococcus faecium* (C) on Columbia Blood agar.

- Following incubation, bacterial suspensions were made to the 0.5 McFarland standard as per EUCAST guidelines.
- A Mueller-Hinton agar (E&O) for *Enterococcus spp*. or Mueller-Hinton with blood agar (E&O) for VGS was inoculated with the bacterial suspension for susceptibility testing (Fig.2). This included a norfloxacin disc (for all *Enterococcus spp.* isolates), rifampicin E-test (for 50 of the VGS isolates) or moxifloxacin E-test (for the remaining 25 of the VGS isolates).
- Norfloxacin disc zone sizes were measured to the nearest mm whilst rifampicin/moxifloxacin E-test minimum inhibitory concentrations (MICs) were measured by eye through reading in double dilutions. These measurements were recorded, and the isolate was considered devoid of resistance mechanisms if; the disc zone size was =/>12mm for norfloxacin or MIC was </=0.25mg/L for rifampicin and </=0.5mg/L for moxifloxacin (EUCAST, 2025).

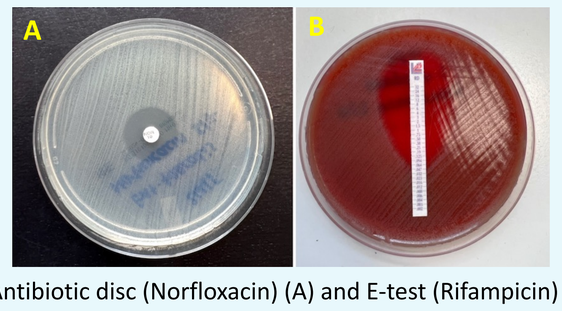

Figure 2. Antibiotic disc (Norfloxacin) (A) and E-test (Rifampicin) (B) on agar.

Results:

All VGS isolates tested were devoid of resistance mechanisms for both rifampicin and moxifloxacin (Figs. 3 and 4). The majority of VGS isolates (94.7%) fell below the EUCAST clinical breakpoints for both antibiotics. However, a small number of isolates (5.3%) reached the breakpoint for rifampicin (Fig.3) or closely approached the breakpoint (28%) for moxifloxacin (Fig.4).

Figure 3. The distribution of rifampicin minimum inhibitory concentration (MIC) for viridans group *Streptococcus spp*. EUCAST clinical breakpoint at the time of the study are indicated on the figure.

Figure 4. The distribution of moxifloxacin minimum inhibitory concentration (MIC) for viridans group *Streptococcus spp*. EUCAST clinical breakpoint at the time of the study are indicated on the figure.

For norfloxacin, all *E. faecalis* isolates tested were devoid of resistance mechanisms with zone sizes above the EUCAST clinical breakpoints (Fig.5). In contrast, all *E. faecium* isolates tested were not devoid of resistance mechanisms with zone sizes significantly below the 12mm breakpoint (Fig.6).

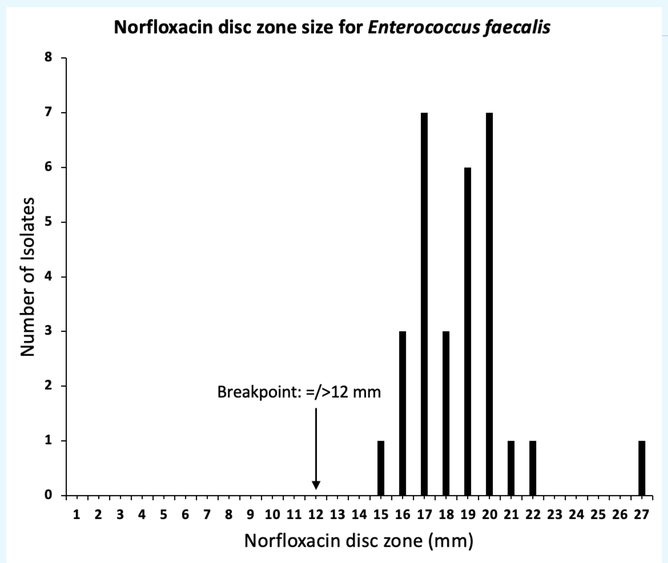

Figure 5. The distribution of norfloxacin disc diffusion zone sizes for *Enterococcus faecalis.* EUCAST clinical breakpoint at the time of the study are indicated on the figure.

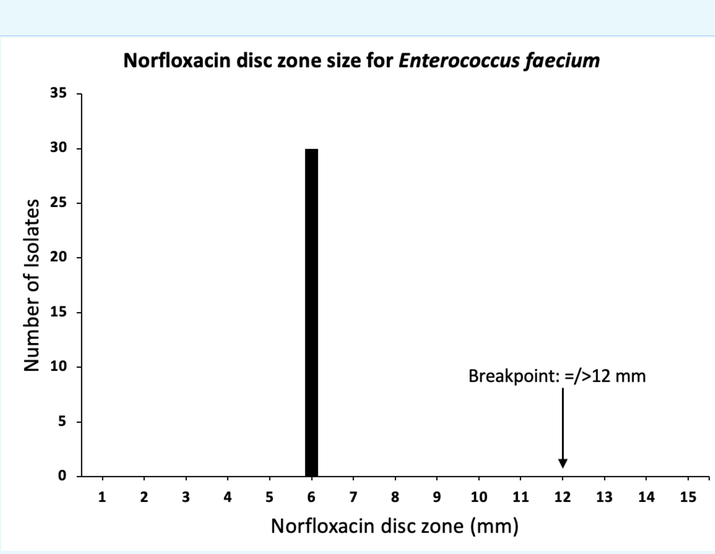

Figure 6. The distribution of norfloxacin disc diffusion zone sizes for *Enterococcus faecium*. EUCAST clinical breakpoint at the time of the study are indicated on the figure.

Discussion:

- Both rifampicin and moxifloxacin were 100% effective against VGS species and norfloxacin was 100% effective against *E. faecalis,* indicating that all have a high susceptibility potential clinically. These are not viable options against IE caused by *E. faecium* due to the significant resistance.
- The small number of isolates that reached/closely approached the breakpoint suggest reduced susceptibility or early signs of resistance developing. Thus, combination therapy of either of these antibiotics with another from a different drug class may be more suitable for treatment of IE to prevent the risk of resistance developing and treatment failure (Rakholiya et al., 2013, pp. 165-179).
- The results of this study agree with the outcomes of the POET trial by Iversen *et al*., (2019), as moxifloxacin and rifampicin were effective against *Streptococcus* and *Enterococcus spp.* and used successfully in combination therapy. The most frequent and recommended regimes used were amoxicillin and rifampicin or amoxicillin and moxifloxacin.

Conclusion:

Oral antibiotics could be a viable treatment option of IE caused by viridans group *Streptococcus spp.* and E. *faecalis* due to the high susceptibility potential presented by both. This along with the positive outcomes of the POET trial means that the microbiology consultant team at MFT can support an oral switch in treatment and start implementing oral regimes in future patients. This may lead to downstream efficiencies in finance and hospital bed management.

References:

Cahill, T. J. and Prendergast, B. D. (2016) 'Infective endocarditis.' *The Lancet*, 387(10021) pp. 882-893.
Rajani, R. and Klein, J. L. (2020) 'Infective endocarditis: A contemporary update.' *Clinical Medicine*, 20(1), pp. 31-35.
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