The molecular basis of antibiotic treatment failure in chronic urinary tract infections

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Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections and are likely to become recurrent. In young women, the risk of relapse within 6 months is 24%, which may lead to the development of a chronic infection.1 Unlike in the acute condition, chronic UTI patients often fail to respond to antibiotic treatment. Our clinical experience is that antibiotics predicted to be effective on culture may be unsuccessful in the clinical setting, while antibiotics predicted to be unsuitable can succeed. This suggests that phenotypic sensitivity and resistance profiles of strains that are actually causing the infection might differ from profiles obtained in diagnostic laboratory conditions.

Hypothesis

In this study we hypothesized that diagnostic growth media can influence the outcome of sensitivity testing, leading the same strain to show different Minimum Inhibitory Concentrations (MICs) for a given antibiotic depending on the nutrients available. We decided to test this hypothesis using the following approaches:

- The use of a more biologically relevant condition (i.e. urine, human bladder organoid) could reveal sensitivity profiles that are more likely to match what happens in chronic UTI patients.
- The application of Next Generation Sequencing (NGS) techniques could reveal the genomic and transcriptional signatures of pathogens after antibiotic administration.

Results

- Evolution of resistance to amoxicillin-clavulanic acid (AMC) was performed using the clinical isolate Escherichia coli 10129 in either M9, ISO or LB medium. A significant reduction in cell density was observed during incubation in M9 containing sub-inhibitory concentrations of AMC (see Fig. 1) and it was not possible to recover any resistant isolate from agar plates.
- MICs of evolved strains in different media showed very high variability in sensitivity profiles (see Fig. 2).
- Culturing of ancestral and evolved strains in LB and the human bladder organoid showed discrepancies in relative fitness and growth in the two systems (see Fig. 3).

Conclusions

- Type of medium has a direct effect on the exhibition of sensitivity profiles: this finding may have implications for the interpretation of diagnostic testing and for treatment outcome.
- The use of a human bladder organoid and NGS techniques may shed light on why chronic UTIs can be difficult to treat.
- We may need to look beyond the genomic sequence and consider expression profiles when unravelling host-pathogen interactions in the clinical setting.

References
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2 Hubbard A. et al., Front Microbiol. 2019