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Microbiological prediction of surgical site infection risk after colorectal surgery: a feasibility study.

Running title: Resistance and colorectal surgery infection

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Sir,

Surgical site infections (SSIs) after colorectal surgery are an important cause of morbidity and mortality.\(^1\) Prevention of these SSIs by antibiotic prophylaxis is an effective intervention, reported to reduce superficial and deep SSI rates from 40% to 10%.\(^2\) Amoxicillin-clavulanic acid is often administered as antibiotic prophylaxis, but resistance to amoxicillin-clavulanic acid has been increasing.\(^3\) It is therefore possible that antibiotic prophylaxis may be becoming less effective.

Currently, there is limited evidence about the impact of Enterobacteriaceae that are resistant to antibiotics on the efficacy of antibiotic prophylaxis in colorectal surgery. To determine the feasibility of research into Enterobacteriaceae resistance and SSI risk, we undertook a prospective feasibility study. The aims of the study were to estimate the recruitment rate of patients to a study that requires pre-operative collection of rectal swabs, and use rectal swabs to estimate the rate of antibiotic resistance in Enterobacteriaceae colonising the rectum of patients due for elective colorectal surgery.

Adults due to undergo elective colorectal surgery, defined as incision, excision or anastomosis of the large bowel, including anastomosis of small to large bowel, at Leeds Teaching Hospitals were eligible to participate in the study. Rectal or stomal swabs were collected from those consenting to participate in the study. Swabs were inoculated on an ISA sensitivity test agar plate with a 30µg amoxicillin-clavulanic acid disc. Enterobacteriaceae growing nearest to the amoxicillin-clavulanic acid disc were subcultured for purity, identified and received susceptibility testing. When more than one species of Enterobacteriaceae was identified in a single patient the most resistant isolate with regard amoxicillin-clavulanic acid was included in subsequent analysis. Retrospective case note review was used to assess for SSIs based on established definitions.\(^4\) SSIs were assessed in participants who had received amoxicillin-clavulanic acid prophylaxis, the recommended standard prophylaxis regimen at Leeds Teaching Hospitals. Resistance was defined according to European Committee for
Antimicrobial Susceptibility Testing (EUCAST) criteria, whereby the minimum inhibitory concentrations (MICs) of amoxicillin-clavulanic acid is >8mg/L.

The study recruited 58% of potential participants (63/108). Enterobacteriaceae were cultured from 55/63 (87%) participants, mostly *Escherichia coli* (47/55, 85%). In total 19% (12/63) of participants were colonised with an Enterobacteriaceae resistant to amoxicillin-clavulanic acid. Amoxicillin-clavulanic acid resistance was present in *E. coli* (n=6) and Enterobacteriaceae other than *E. coli* (6).

SSIs were documented in 7/39 (17.9%) participants who received amoxicillin-clavulanic acid prophylaxis. Within these participants SSIs were documented in 2/7 (28.6%) of those colonised with an amoxicillin-clavulanic acid resistant Enterobacteriaceae. This was a higher rate compared to those colonised with an amoxicillin-clavulanic acid sensitive Enterobacteriaceae, 5/32 (15.6%). Participants colonised with resistant *E. coli* had a higher SSI rate (2/4, 50%) than participants colonised with resistant Enterobacteriaceae other than *E. coli* (0/3, 0%)(Appendix A/B: Detailed methods/Results).

This feasibility study demonstrated it is feasible to recruit patients to an SSI study involving collecting pre-operative rectal swabs. In addition, we have identified that pre-operatively a significant proportion of patients are colonised with antibiotic resistant Enterobacteriaceae. Resistance in this study is based on MICs relevant to the treatment of infection, as opposed to prophylaxis. It is not known whether MIC criteria for the treatment of infections are relevant to the efficacy of antibiotic prophylaxis. It is not our intention that these data should prompt changes to antibiotic prophylaxis regimens. It is though intended that these data should stimulate debate on the contribution of microbiological testing to reducing SSI rates, and stimulate further research in this area.

These are the first data we are aware of that associate rectal colonisation with antibiotic-resistant Enterobacteriaceae to SSI rates in colorectal surgery. We acknowledge that the data are limited by small numbers, as would be expected from a feasibility study; however, the study highlights important questions to be considered in the design of a full trial. In particular, the data raise the
possibility that there may be more of an SSI risk from *E. coli*, compared to Enterobacteriaceae other than *E. coli* which are resistant to antibiotic prophylaxis.

Amoxicillin-clavulanic acid resistance in Enterobacteriaceae colonising the rectum are at rates that, if detected in infections, would lead to consideration of alternative antibiotic regimens. It is feasible, and important, to undertake further research into the impact and prophylaxis of antibiotic-resistant Enterobacteriaceae with regard to surgical site infections.

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**Prior publication:** Some of these data were presented in summary form during an oral presentation at HIS 2014 as part of a wider review entitled "Antibiotic resistance in Enterobacteriaceae: What impact on the efficacy of antibiotic prophylaxis in colorectal surgery?" and a paper based on this oral presentation has been submitted for publication in the conference issue of JHI.

