Colo-Pro Pilot: A pilot randomised controlled trial comparing standard bolus dosed, to bolus-continuous infusion dosed, cefuroxime prophylaxis, for the prevention of infections after colorectal surgery

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Introduction

100,000 colorectal operations take place annually in the UK
Up to 27% develop surgical site infections[1] (SSI)

- → Increased morbidity
- → Longer hospital stay
- → Costing up to £2000[2]

Standard bolus doses of antibiotic prophylaxis intra-operatively may be suboptimal in inhibiting growth of resistant commensal colonic bacteria[3, 4]
A solution may be a continuous administration of antibiotic throughout surgery, aiming to maintain concentrations of antibiotic that inhibit bacterial growth throughout surgery.

Aims

To pilot a study to:

- Evaluate the effect of continuous infusion of cefuroxime intra-operatively, aimed at maintaining an intra-operative cefuroxime concentration of 4 x MIC90 for Enterobacteriaceae (MIC90=16)[5], i.e. 64mg/L, on post-operative SSIs
- Identify the prevalence of colonic cefuroxime resistant *Enterobacteriaceae* using 2 methods

Method

This was a single centre randomised-controlled trial including patients undergoing colonic incision, excision or, anastomosis, with surgery lasting ≥ 2 hours

Prophylactic antibiotic dosing

Patients undergoing colorectal surgery were randomised to receive the following, plus metronidazole:

- **Intervention**: Continuous renal function adjusted cefuroxime infusion
  - Two regimens were used to target concentrations of 4x MIC90 of Enterobacteriaceae (64mg/L), these were a formula based (non-compartment) model and a population pharmacokinetic two compartment model
- **Control**: 1.5 gram bolus of cefuroxime at induction and 4 hourly

Blood samples were collected intra-operatively, up to four samples per patient, to determine serum cefuroxime concentrations

Screening for resistant Enterobacteriaceae

Rectal swabs were taken pre-operatively
Two methods were used to determine cefuroxime resistance (figure 1)
Method 1: Resistance in the numerically predominant *Enterobacteriaceae*

- CLED agar plates were streaked for isolated colonies

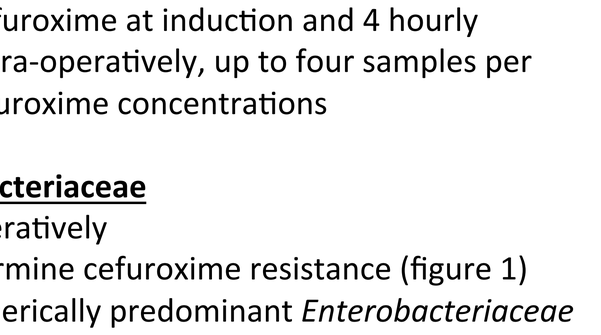
Method 2: Resistance in the most cefuroxime resistant *Enterobacteriaceae*

- CLED agar plate swabbed for confluent growth, and a cefuroxime disc placed centrally; Growth closest to the disc was cultured to purity;

MICs were defined by the cefuroxime gradient MIC method. Resistance was defined as a cefuroxime MIC >8mg/L

Primary outcome: SSI at 30 days
Secondary outcomes: SSI type, other infection, readmission, post-operative antibiotic use and death.

Figure 1: *Methods 1 (left) and 2 (right) for detecting Cefuroxime resistance*



Results

262 patients screened → 196 eligible → 90 consented → 80 analysed as per protocol

Figure 1: recruitment

Between August 2015 and April 2017, 90 patients were recruited (figure 1). Baseline characteristics are shown in table 1.

	Control	Intervention
Number	43	37
Mean age (S.D.)	59	61
Gender female (%)	44	30
Indication cancer (%)	72	78
Rectal resection (%)	54	52

Table 1: baseline characteristics of the control and intervention group

Primary and secondary outcomes are shown in figure 2. There was no significant difference in outcomes between the intervention and control group, although rates of SSI, all infections and readmission were non significantly lower in the intervention group. There was no mortality in the 30 day follow up.

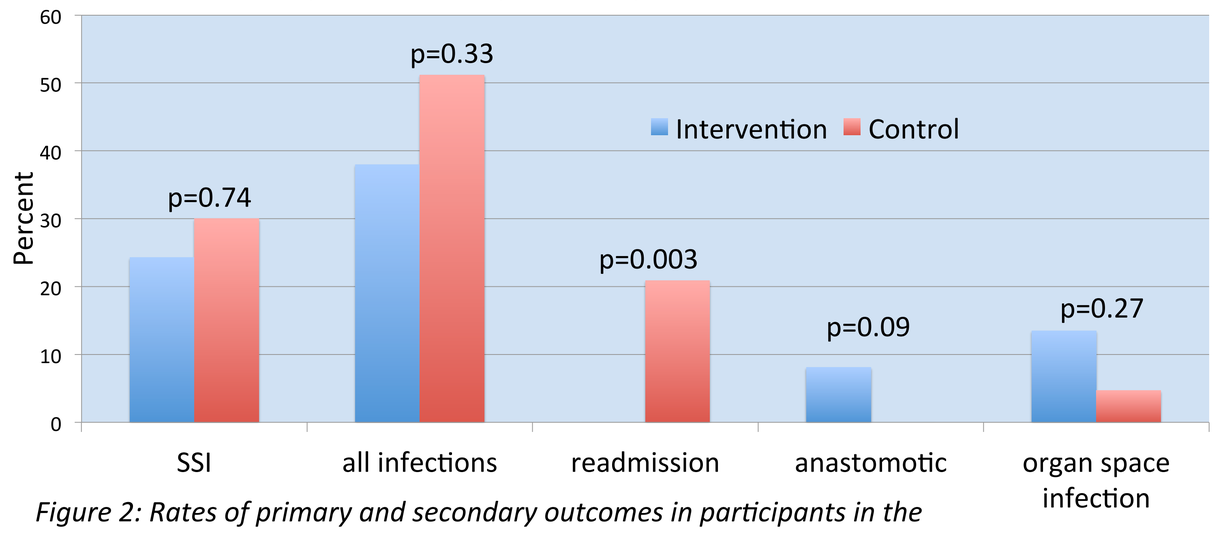


Figure 2: Rates of primary and secondary outcomes in participants in the control and intervention group

Enterobacteriaceae resistance screening

The MIC of colonising bacteria was different depending on the method used. Method 1 (most predominant) found a lower rate of resistance than did method 2 (most resistant) (figure 3)

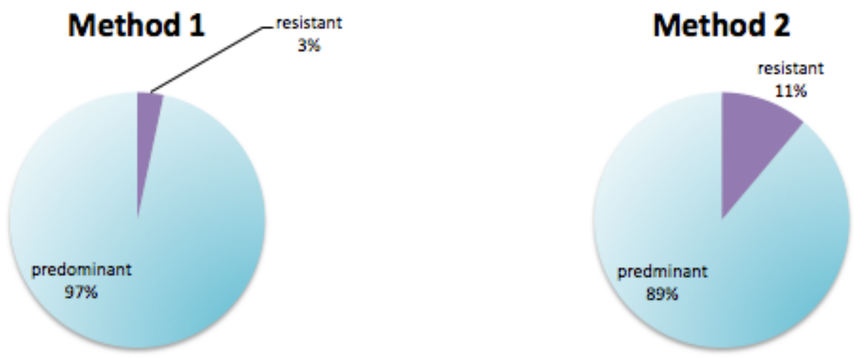


Figure 3: rates of resistant Enterobacteriaceae pre-operatively using two methods

Pharmacokinetics

58 patients intra-operative blood samples were collected. Target concentrations of 64mg/L were achieved using the compartment model, and the non-compartment model achieved higher serum cefuroxime concentrations than standard dosing (figure 4).

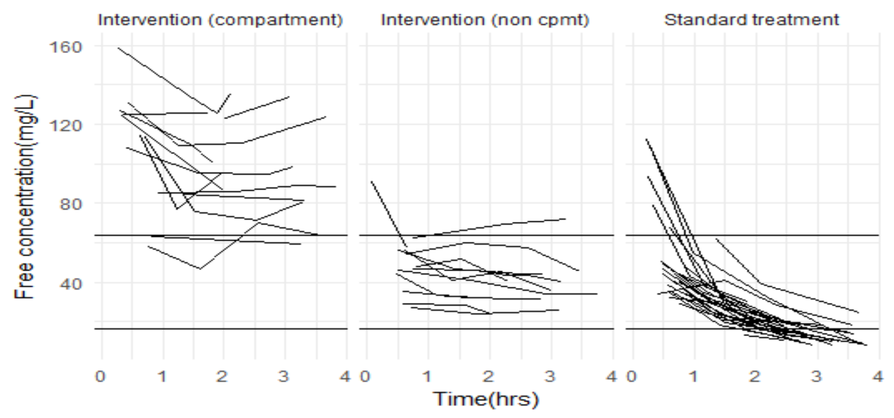


Figure 4: free serum concentrations for patients according to intervention treatment (compartment and non-compartment) and standard dosing regimens. Horizontal lines represent 64mg/L and 16mg/L.

Conclusion

This pilot study demonstrates the feasibility of conducting a trial of the use of bolus continuous infusion of cefuroxime prophylaxis targeting pre-specified serum concentrations. This is a novel intervention that can achieve continuous targeted concentrations of antibiotic prophylaxis. Clinical trials are required to determine the efficacy of this intervention in the prevention of post-operative SSIs as well as the use of pre-operative screening for colonisation with resistant *Enterobacteriaceae*.

References:
(1) Kirby A, Burnside G, Bretsajn L, Burke D. Postoperative infections following colorectal surgery in an English teaching hospital Infectious diseases 2015;47(11):825-9
(2) Coello R, Charlett A, Wilson J, Ward V, Pearson A, Borriello P. Adverse impact of surgical site infections in English hospitals. J Hosp Infect 2005;60:93-103
(3) Barbour A, Schmidt S, Rout WR, Ben-David K, Burkhardt O, Derendorf H. Soft tissue penetration of cefuroxime determined by clinical microdialysis in morbidly obese patients undergoing abdominal surgery. Int J Antimicrob Agents. 2009;34(3):231-5.
(4) Telliant A, Gandra S, Barter D, Morgan DJ, Laxminarayan R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modeling study. Lancet infect dis 2015; 15(12);1429-37
(5) Kirby A, Bretsztajn L, Santoni N, Patel H, Burke D, Horner C. Microbiological prediction of surgical site infection risk after colorectal surgery: a feasibility study. Journal of Hospital Infection. 2015; 90(3):271-272.