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Antibiotic resistance in Enterobacteriaceae: What impact on the efficacy of antibiotic prophylaxis in colorectal surgery?

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Summary

Antibiotic prophylaxis, introduced in the 1940s, brought in an era of relatively safe colorectal surgery. This was achieved in part due to the prevention of Enterobacteriaceae Surgical Site Infections (SSIs). Since then, Enterobacteriaceae have become increasingly resistant to antibiotics commonly used for prophylaxis. The impact of being colonised pre-operatively with a resistant Enterobacteriaceae on the efficacy of colorectal SSI prophylaxis, if any, is unknown. It is also difficult to predict the likely impact of resistance as the exposure-response relationships are not determined for antibiotic surgical prophylaxis. Neither is it known which is the right test to determine if resistance is present as the importance of the concentration of Enterobacteriaceae in the colon, the ability of different species of Enterobacteriaceae to cause SSIs, and the comparative ability of MIC or presence of a resistance mechanism in predicting SSI risk have yet to be established. Clinical research is urgently needed to answer these questions.

Keywords: Enterobacteriaceae; Resistance; Prophylaxis, Surgical Site Infection, Colorectal.

Introduction

Antibiotic prophylaxis for many types of surgery has proven to be an effective means of reducing Surgical Site Infection (SSI) rates. But with the increase in Enterobacteriaceae antibiotic resistance and the adverse effects this is having in the treatment of infection, the impact of this resistance on surgical prophylaxis is now being questioned. To understand the impact Enterobacteriaceae resistance may have on SSI rates we have reviewed the literature on SSI prophylaxis in colorectal surgery.

An overview of antibiotic prophylaxis in colorectal surgery

Antibiotic prophylaxis for colorectal surgery was introduced at a time when "the stakes were high, with 10% mortality, and 80-90% suppurating wound infections". In 1938, with Escherichia coli identified from surgical wound infections, sulphonamides were investigated as antibiotic surgical prophylaxis. In 1943, 123 colorectal operations with sulphonamide prophylaxis were reported with 4% mortality, lower than the previously reported 10%. New potential agents continued to be investigated, including by feeding dogs meatballs containing investigational compounds and measuring impacts on colonic flora. In 1949, with the discovery of neomycin, a second effective class of antibiotics for "intestinal antisepsis" was available. Interestingly, rapid resistance to neomycin was identified, resulting in combination neomycin and sulphonamide surgical prophylaxis. Thus antibiotic prophylaxis was established as a routine part of perioperative care (1).

In the 1960s Burke carried out animal experiments to understand how the timing of antibiotic prophylaxis was related to surgical wound infections (SWIs). Surgical wounds inoculated with Staphylococcus aureus demonstrated that antibiotics were most effective when administered pre-operatively, and were increasingly ineffective afterwards, being entirely ineffective if administered 4 hours after surgical wound incision/closure (2). It is unclear why antibiotic prophylaxis should be ineffective if delayed, but these data have been supported by clinical studies which have shown no benefit from multiple post operative dosing of antibiotic prophylaxis (3). There is though some evidence that intra-operative re-dosing is associated with reduced SSI rates in colorectal surgery e.g. a retrospective study by Morita et al reported reduced SSI rates with intraoperative redosing at 4 hours compared to no re-dosing, 8.5% (4/47) vs. 26.5% (13/49) (P = 0.008) (4).

In the 1970s and 1980s randomised controlled trials of a heterogeneous collection of antibiotic regimes versus placebo were carried out which demonstrated antibiotics reduced the risks of colorectal surgical wound infections (RR 0.34, 95% confidence interval 0.28 to 0.41). Studies in the 1970s to 1990s demonstrated that aerobic cover, in addition to anaerobic cover, reduced surgical wound infection (SWI) rates (RR 0.44, 95% C.I. 0.29 to 0.68), and that addition of anaerobic cover to aerobic cover reduced SWI rates (RR 0.46, 95% C.I. 0.30 to 0.69). Given the main group of aerobes associated with colorectal SWIs are Enterobacteriaceae, the reduced SWI rate (6.6% with aerobic cover vs 14.4% without), is an example of the prophylaxis efficacy potentially to be lost due to antibiotic resistant Enterobacteriaceae (3). Other studies investigated the efficacy of both intravenous and oral antibiotics in the prevention of SSIs. A Cochrane review determined that oral and intravenous prophylaxis reduced SSI rates compared to intravenous alone (3). These oral antibiotic regimes were administered alongside bowel cleansing agents, which are now not routinely administered having not been shown to improve post-operative outcomes (5).

More recently there have been limited studies investigating the relative efficacy of established antibiotic prophylaxis regimes. Although one study comparing ertapenem to cefotetan showed ertapenem to be more effective, this was probably due to the limited anaerobic activity provided by cefotetan (6). A more recent study comparing ceftriaxone and metronidazole to ertapenem, with no difference in SSI rates, supports a conclusion that ertapenem is not a more effective antibiotic for prophylaxis than standard regimes with effective anaerobic cover (7).

Enterobacteriaceae and SSIs

The family Enterobacteriaceae includes a number of clinically relevant species including E. coli, Klebsiella spp, Enterobacter spp, Serrati spp and Proteus spp. The antimicrobial treatment of infections caused by Enterobacteriaceae is often similar, but this does not mean these bacteria should be considered equal with respect to their potential to cause SSIs. Most human Enterobacteriaceae infections, including SSIs, are caused by E. coli. This reflects that E. coli is different to other Enterobacteriaceae with respect to their interaction with mammals and the environment. E. coli is it seems adapted to the intestine of mammals, in preference to the environment. Whereas, other Enterobacteriaceae e.g. Klebsiella spp, are reportedly adapted to the non human environment as well (8). It seems likely that, even when colonised with non-E. coli Enterobacteriaceae, E. coli will still be the predominant coliform in the

gastrointestinal tract. An exception to this may be in the presence of antibiotic selection pressure. The clinical importance of antibiotic resistance in the different species of Enterobacteriaceae is therefore likely to vary between species with regard their risk of SSIs.

Enterobacteriaceae antibiotic resistance mechanisms and SSI risk

There are many resistance mechanisms described in Enterobacteriaceae which may impact on the treatment of infections. An example of the range of resistance mechanisms can be seen within resistance to co-amoxiclav, which is commonly used for surgical prophylaxis. Co-amoxiclav may be ineffective against Enterobacteriaceae due to mechanisms including hyper production of class A beta-lactamases (e.g. TEM1), AmpC beta-lactamases, TEM inhibitor resistant bet-lactamases, OXA beta lactamases and extended spectrum beta-lactamases (ESBL). In addition, combinations of these mechanisms are possible (9). Whilst most described mechanisms of resistance result in a reduced susceptibility to an antibiotic, some do so only when the bacteria is repeatedly exposed to an antibiotic e.g. inducible AmpC resistance in Enterobacter spp. Therefore, not all mechanisms of resistance relevant to treatment of infections are likely to be relevant to surgical prophylaxis which is normally prescribed as a single dose.

It will clearly never be possible to relate all resistance mechanisms individually to SSI risk. So research which attempts to understand how resistance affects SSI risk will either determine risks associated with Minimum Inhibitory Concentrations (MICs), or resistance mechanisms will need to be arbitrarily considered equally able to impact on the efficacy of surgical prophylaxis.

Antibiotic treatment breakpoints in relation to SSI risk

Antimicrobial resistance is defined when the MIC of an antibiotic for a bacteria is above what is referred to as breakpoint concentration. A breakpoint concentration is an antibiotic concentration (MIC value) above/below which clinical cure is considered less likely/more likely to occur. Setting breakpoints to predict the efficacy of a treatment requires knowledge of the relationship between antibiotic concentrations and their effect on outcomes, so called exposure-response relationships. An example of a treatment exposure-response relationship is fT>MIC (the time free (unbound) drug in serum is above the MIC value) (10). Whilst research has investigated exposure-response relationships to predict the efficacy of the treatment of infection, the nature of these relationships for prophylaxis has not been

determined. Even if the relationship between drug concentration and outcome is the same in treatment and prophylaxis, e.g. fT>MIC is a relevant outcome measure, this target may need to be achieved for a much shorter time period for surgical procedures which normally last less than 3 hours, compared to the 8-12 hours dosing interval commonly used for antibiotic treatment dosing. On this basis antibiotic prophylaxis may be more resilient to increases in MICs than antibiotic treatment of an infection. For these reasons breakpoints determined for the treatment of infection cannot be directly applied to the antibiotic prophylaxis setting.

Phamakokinetic/Pharmakodynamic (PK/PD) modelling to predict the efficacy of antibiotic prophylaxis

In 2013, a Monte Carlo modelling study of antibiotic prophylaxis efficacy, using fT>MIC as the target, was carried out by Moine et al (11). It showed that only a few antibiotics, cefuroxime, cefazolin and ertapenem, achieved fT>MIC targets over a 4 hour time period when the MICs of E. coli reported by EUCAST (European Committee on Antimicrobial Susceptibility Testing) were considered. Given there is clinical data which demonstrates equal efficacy between ertapenem, supported by Moine's modelling, and ceftriaxone, which was predicted to be less effective, caution is needed before widely applying these findings (11). Another caution to the use of the results produced by Moine is that they used EUCAST MIC data which may include studies with high proportions of resistant isolates. The necessity for Moine to use this data is because there is a near absence of MIC data for Enterobacteriaceae colonising patients before their operation. Given EUCAST data may not be representative of local epidemiological data in colonising Enterobacteriaceae isolates, local data is required before considering applying Monte Carlo modelling results to local antibiotic prophylaxis selection. Also, it is unclear if fT>MIC is an appropriate exposure-response to target. There is some evidence to support this from Burke and Zelenitsky as they show that drug concentrations at the start and end of surgery seem to be related to the exposure-response (2, 12). Burke identified SSI rates were associated with drug concentrations at the time of incision-closure (incision and closure occurred within five minutes), and Zelenitsky reported that low gentamicin serum levels at the end, not beginning, of colorectal surgery were associated with an increase in SSIs. Interestingly, this discounts therapeutic exposure-response targets for gentamicin which are based on the peak concentration, which would be assumed to relate to incision concentrations.

Testing for antibiotic resistant Enterobacteriaceae colonisation

Determining the antibiotic resistance of colonising Enterobacteriaceae is required if an epidemiological study is planned, if individualised antibiotic prophylaxis is planned, or if research into correlations between resistance and SSI is planned. A number of issues require consideration before undertaking tests to determine resistance. The sample type requires selection, but based on most published studies this seems to have been accepted as rectal swabs (Table I). Further considerations include choosing molecular detection or culture based detection of resistance, and also, within culture based detection, if the majority coloniser (the colonising strain that is present in the highest concentration) should be prioritised over selection for the most resistant coloniser. Molecular detection has the advantage that it can offer rapid results, even point of care tests. A European funded study investigating the clinical utility of a test and treat strategy using a molecular based test for resistance is underway (R-GNOSIS). However, molecular detection of resistance may not be as discriminatory as a culture based method from which an MIC can be obtained. MICs have been reported to be much better correlated with treatment outcomes than the presence of resistance mechanisms(13). Molecular detection also may not identify which species of Enterobacteriaceae has the resistance mechanism, and if this species is within the majority strain. This may be relevant as it is not clear if different species have different potential to cause SSIs. Some species may be innately more able to cause SSIs than other species, but it may also be that some species are present at higher concentrations in the bowel than other species i.e. E. coli is likely to be the majority coliform in most people.

In Leeds Teaching Hospitals we completed a feasibility study (RESIST study) of a culture based approach. Co-amoxiclav resistance was detected in colorectal surgery patients prior to administration of co-amoxiclav prophylaxis using a method to select co-amoxiclav resistant isolates, according to treatment based criteria. Samples tested were pre-operative rectal swabs. Clinical outcomes were assessed at 30 days and identified an SSI rate in patients with co-amoxiclav sensitive Enterobacteriaceae of 16% (5/31) and 33% (2/6) in patients with resistant Enterobacteriaceae. Within E. coli, 2 of 3 resistant isolates were associated with an SSI, compared to 0/3 non E. coli resistant Enterobacteriaceae. These are, due to the limited numbers, only an indication that the species and/or the quantity of bacteria present are related to SSI risk.

Clinical studies into antibiotic resistance and surgical prophylaxis

The impact of antibiotic resistance on SSI rates has not been widely investigated. A few studies have related resistance, using treatment resistance breakpoints; to post-operative infection (14-19). The main area this has been investigated is liver transplantation, it is assumed this relates to the potentially high mortality rate associated with post-operative infections. The most informative study, by Bert et al, showed that pre-operative colonisation with ESBL Enterobacteriaceae increased the rate of post operative ESBL infections, although the overall infection rate was not reported (14). Within surgical biopsies of the prostate, another situation where prophylaxis is used, colonisation with ciprofloxacin resistant Enterobacteriaceae has been shown to indicate a higher risk of post-operative infection, 7.1% vs. 1.1%, in those not colonised (17). In non-surgical settings e.g. neutropenia, colonisation with resistant Enterobacteriaceae has been reported as both increasing and not increasing the risk of an ESBL infection (18-20). A selection of studies relating antibiotic resistance to outcomes are summarised in Table I.

Clinical practice recommendations

The first priority in this time of increasing antibiotic resistance is to ensure that antibiotic resistance is reduced. So any clinician concerned about the efficacy of prophylaxis should first focus on limiting antibiotic use e.g. single dose antibiotic prophylaxis, and reducing the transmission of resistant bacteria e.g. optimising hand hygiene. Then modifiable risk factors should be modified as much as possible e.g. limit pre-operative smoking, increase rates of laparoscopic surgery, use alcoholic chlorhexidine for surgical skin preparation and implement the Enhanced Recovery after Surgery (ERAS) pathway.

A decision about modifying antibiotic prophylaxis should only be made after a survey of the resistance profile of E. coli isolates colonising the rectum in a local population of patients pre-operatively. And the most reasonable method of applying this data would seem to be in conjunction with the fT>MIC exposure-response relationship for the duration of the operation. A reasoned decision, taking account of the E. coli MIC distribution and fT>MIC with consideration to antibiotic pharmacokinetics, could then be made over the choice, dose, and frequency of an antibiotic regime for prophylaxis.

Research recommendations

There is a near absence of evidence within the field of predicting the efficacy of antibiotic prophylaxis. Research is therefore needed to derive a fundamental evidence base with which to guide the selection of antibiotic prophylaxis regimes. Research recommendations are to:

- Determine exposure-response relationships relevant to antibiotic prophylaxis of SSIs
- Determine MIC breakpoints predictive of SSI risk
- Determine a colonic bacterial concentration threshold relevant to SSIs
- Determine species specific SSI potential.
- Determine the best test for predicting risk of antibiotic prophylaxis failure e.g. molecular or culture based.
- Investigate the use of oral antibiotics in reducing SSI rates.
- Determine if oral antibiotics, achieving high colonic concentrations, are clinically useful, particularly in patients colonised with resistant Enterobacteriaceae.

Conclusions

In conclusion, antibiotic resistance, as defined by MICs for the treatment of infections, does appear to be impacting on post-operative infection rates in some specific patient groups (liver transplant/prostate biopsy), though evidence of impact outside these areas and on SSI rates including in colorectal surgery is essentially absent. Research is needed to understand the exposure-response relationships as well as determinants of resistance relevant to surgical prophylaxis, and this data should facilitate research to optimise antibiotic prophylaxis for all surgical patients.

References

1. Poth EJ. Historical development of intestinal antisepsis. World journal of surgery. 1982;6(2):153-9.
2. Burke JF. Preoperative antibiotics. The Surgical clinics of North America. 1963;43:665-76.
3. Nelson RL, Gladman E, Barbateskovic M. Antimicrobial prophylaxis for colorectal surgery. The Cochrane database of systematic reviews. 2014;5:CD001181.
4. Morita S, Nishisho I, Nomura T, Fukushima Y, Morimoto T, Hiraoka N, et al. The significance of the intraoperative repeated dosing of antimicrobials for preventing surgical wound infection in colorectal surgery. Surgery today. 2005;35(9):732-8.
5. Contant CM, Hop WC, van't Sant HP, Oostvogel HJ, Smeets HJ, Stassen LP, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. Lancet. 2007;370(9605):2112-7.
6. Goldstein EJ, Citron DM, Merriam CV, Abramson MA. Infection after elective colorectal surgery: bacteriological analysis of failures in a randomized trial of cefotetan vs. ertapenem prophylaxis. Surgical infections. 2009;10(2):111-8.
7. Leng XS, Zhao YJ, Qiu HZ, Cao YK, Zhu WH, Shen JF, et al. Ertapenem prophylaxis of surgical site infections in elective colorectal surgery in China: a multicentre, randomized, double-blind, active-controlled study. The Journal of antimicrobial chemotherapy. 2014.
8. Podschun R, Ullmann U. Klebsiella spp. as nosocomial pathogens: epidemiology, taxonomy, typing methods, and pathogenicity factors. Clinical microbiology reviews. 1998;11(4):589-603.
9. Ortega A, Oteo J, Aranzamendi-Zaldumbide M, Bartolome RM, Bou G, Cercenado E, et al. Spanish multicenter study of the epidemiology and mechanisms of amoxicillin-clavulanate resistance in Escherichia coli. Antimicrobial agents and chemotherapy. 2012;56(7):3576-81.
10. Ambrose PG, Bhavnani SM, Rubino CM, Louie A, Gumbo T, Forrest A, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2007;44(1):79-86.
11. Moine P, Fish DN. Pharmacodynamic modelling of intravenous antibiotic prophylaxis in elective colorectal surgery. International journal of antimicrobial agents. 2013;41(2):167-73.
12. Zelenitsky SA, Ariano RE, Harding GK, Silverman RE. Antibiotic pharmacodynamics in surgical prophylaxis: an association between intraoperative antibiotic concentrations and efficacy. Antimicrobial agents and chemotherapy. 2002;46(9):3026-30.
13. Andes D, Craig WA. Treatment of infections with ESBL-producing organisms: pharmacokinetic and pharmacodynamic considerations. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2005;11 Suppl 6:10-7.
14. Bert F, Larroque B, Paugam-Burtz C, Dondero F, Durand F, Marcon E, et al. Pretransplant fecal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae and infection after liver transplant, France. Emerging infectious diseases. 2012;18(6):908-16.
15. Giannella M, Trecarichi EM, De Rosa FG, Del Bono V, Bassetti M, Lewis RE, et al. Risk factors for carbapenem-resistant Klebsiella pneumoniae bloodstream infection among rectal carriers: a prospective observational multicentre study. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2014.
16. Lubbert C, Becker-Rux D, Rodloff AC, Laudi S, Busch T, Bartels M, et al. Colonization of liver transplant recipients with KPC-producing Klebsiella pneumoniae is associated with high infection rates and excess mortality: a case-control analysis. Infection. 2014;42(2):309-16.
17. Roberts MJ, Williamson DA, Hadway P, Doi SA, Gardiner RA, Paterson DL. Baseline prevalence of antimicrobial resistance and subsequent infection following prostate biopsy using empirical or altered prophylaxis: A bias-adjusted meta-analysis. International journal of antimicrobial agents. 2014;43(4):301-9.

18. Arnan M, Gudiol C, Calatayud L, Linares J, Dominguez MA, Batlle M, et al. Risk factors for, and clinical relevance of, faecal extended-spectrum beta-lactamase producing Escherichia coli (ESBL-EC) carriage in neutropenic patients with haematological malignancies. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2011;30(3):355-60.
19. Ben-Ami R, Schwaber MJ, Navon-Venezia S, Schwartz D, Giladi M, Chmelnitsky I, et al. Influx of extended-spectrum beta-lactamase-producing enterobacteriaceae into the hospital. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2006;42(7):925-34.
20. Reddy P, Malczynski M, Obias A, Reiner S, Jin N, Huang J, et al. Screening for extended-spectrum beta-lactamase-producing Enterobacteriaceae among high-risk patients and rates of subsequent bacteremia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2007;45(7):846-52.