ANTIBIOTIC THERAPY IN THE INFECTIONS IN COLO-RECTAL SURGERY. CLINICAL AND MICROBIOLOGICAL APPROACHES.

An analytical review.

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ABSTRACT

Infections encountered in the surgery of colon and rectum are serious and often require a multi-disciplinary team. A typical feature is the participation of mixed aerobic + anaerobic flora, poly-microbial in number, and synergistically acting in two phases: during the first 4 – 5 days – development of diffuse peritonitis and bacteraemia, governed by aerobic organisms, and > 5 days: organization of infection in abscess with the main participation of anaerobes. The commonest pathogens among anaerobes are *B. fragilis*, possessing capsular polysaccharide, adherence potential, piliation and toxin production, following by *B. fragilis* group. Clostridia may participate in the synergistic poly-microbial aerobic-anaerobic infections, or to cause the typical clostridial myonecrosis. Appropriate specimens from the site of infection include fluid/pus/aspirate, collected by syringe and/or aseptically cut small tissue piece. A set of two blood-cultures should be obtained. Successful treatment and management of secondary peritonitis and intra-abdominal abscesses depends first on the effective surgical intervention: to debride gross fibrinous debris, drainage of pus and gross contamination from the peritoneal cavity; resection or repair of the pathology (perforation, tumour etc). Antibiotic therapy contributes to lower both morbidity and mortality. It should be large-spectrum, bactericidal, prescribed in sufficient dosage regimen for enough time. Secondary peritonitis, incl. the post-operative in elderly and debilitated patients may cause particular challenge, especially in presence of resistant organisms.

Keywords: intra-abdominal, polymicrobial-, anaerobe- infection, clinical presentation, microbiology investigation, antibiotic therapy

RISK OF INFECTION IN THE SURGERY OF COLON AND RECTUM

Infections encountered in the surgery of colon and rectum are serious and often require a multi-disciplinary team (1). They are community- or hospital- acquired; may be established before the operation, or to develop after the operative procedure (2-6). Median increase in hospital stay (LOS) because of development of surgical site infection (SSI) in colon surgery is 6 days and the median increase in cost/patient in USD is 2671 (7). Recto-sigmoid colon is known to contain the highest number of bacteria in the body: $10^{10} – 10^{12}$ CFU/g stool. Wound even in elective intestinal resection, e.g. sigmoid colectomy, as an example of clean-contaminated procedures, would be contaminated at least by *B. fragilis* and *E. coli* and would necessitate prophylactic antibiotic to prevent infection, which arises in rates 4 – 10 %. In

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contaminated procedures: e.g. elective with high intestinal spillage or emergency laparatomy for stab/gunshot injury, rate of SSI is > 10 %. Dirty procedures take place when active infection (pus) is already present: acute intra-abdominal peritonitis and abscesses. Modern surgery evaluates further the risk for infection. The simplified NNIS (National nosocomial infection system, USA) risk index is characterized by points from 0 to 3: 1 point is given for contaminated or dirty operation, another point, if the patient has ASA score of 3, 4 or 5, and 1 more point, if the operation exceeds the 75th percentile of the standard developed from the NNIS database (8, 9). As a result, the colon surgery is characterized by the highest risk category among all surgical procedures (7):

T point (hrs) Risk Category	0	1	2	3
	3.2	8.5	6.0	22.0

Another comprehensive system, SIGN (Scottish intercollegiate guideline network) (10), states the antibiotic prophylaxis in colo-rectal surgery as highly recommended, because of preventing both from infection and mortality with Odds ratio of 0.37 and 0.38; NNT (number needed to threat) 5 and 17 respectively, evidence level Ia.

MICROORGANISMS INVOLVED IN THE INFECTION IN COLO-RECTAL SURGERY

Infection in colo-proctology most often is due to organisms from the normal bowel flora (Table 1).

pH, low oxydo-reduction potential present real obstacles for both antibiotic penetration and activity (17).

As it can be seen from the Table 1, the most frequent participating aerobe organisms are *E. coli* and other *Enterobacteriaceae*, which typical factors of virulence are: their endotoxins (lipopolisaccharides), flagellae and pilli.

Table 1. Microbial flora isolated from peritonitis, abscess and other infections related to the surgery of colon and rectum

	Anaerobe bacteria	Aerobe bacteria	Comments	References
Secondary peritonitis	Bacteroides spp, Peptostreptococcus, Clostridium spp	Enterococcus, Enterobacteriaceae, Pseudomonas, B haem Streptococcus, S. aureus, Yeast		PHLS, UK, 2002; (11)
Post-operative wound infection	Bacteroides spp, Clostridium spp	S. aureus, Eterobacteriaceae, Pseudomonas, B haem Streptococcus, Enterococcus		PHLS, UK, 2002; (11)
Perirectal abscess	Different anaerobes	Enterobacteriaceae, Streptococci, S. aureus	Rectal surgery, cancer, ulcer. colitis, malignancy, immunodeficiency	PHLS, UK, 2002; (11)
Psoas abscess	Bacteroides spp	Enterobacteriaceae, S. aureus, Streptococci, Mycobacterium spp	Secondary to: diverticulitis, appendicitis, osteomyelitis, bactaeremia	PHLS, UK, 2002; (11)
Intra-abdominal infection	%:B. fragilis - 32, other Bacteroides - 44, Peptostreptococcus - 12, Fusobacterium spp - 8	%: E. coli 64, Enterobacter/ Klebsiella - 33, Proteus - 15,P. aeruginosa - 18, Staphylococcus - 16, Enterococcus - 15	Intra-operative culture	Barie PS, (12) 1999, J Chemother,11
Abdominal abscess	n: B. fragilis-47, BFGBS -14, CSCP - 19, Prevotella - 9, 24 -Peptostreptococcus	E. coli - 57	Abdominal abscess n =83	Brook I, 2002, JAC, 50; (13)
Retroperitoneal abscess	B. fragilis - 34, BFGBS-44, CSCP - 23, Prevotella - 19, Fusobacterium -14, Peptostreptococcus-95	E. coli- 60, S. aureus -11, Enterococcus - 19	Retroperitoneal abscess n = 161	Brook I, 2002, JAC, 50; (13)
Perirectal abscess	B. fragilis-58, BFGBS-44, CSCP-15, Prevotella-50, Fusobacterium -21, Peptostreptococcus - 72	E. coli-19, S.aureus-34, Enterococcus -9	Perirectal abscess n = 144	Brook I, 2002, JAC, 50; (13)
Diverticulitis	B. fragilis-14, BFGBS-8, Prevotella-10, Peptostreptococcus-6	E. coli-15, S.aureus-1, Enterococcus-3	Diverticulitis& n = 22	Brook I, 2002, JAC, 50; (13)

Legend: BFGBS – Bacteroides fragilis group + Bacteroides spp; CSCP – Clostridium spp + C. perfringens

A typical feature is the participation of mixed aerobic + anaerobic flora, poly-microbial in number, and synergistically acting in two phases: during the first 4 – 5 days – development of diffuse peritonitis and bacteraemia, governed by aerobic organisms, and > 5 days: organization of infection in abscess with the main participation of anaerobes (3, 13-16). Abscess wall, density of bacterial populations, acid

Enterococci and nonhaemolytic streptococci are not especially virulent, but *S. aureus* and beta-haemolytic streptococci elaborate variety of toxins and enzymes that destroy tissues aggressively, and specific toxins may cause shock.

ANAEROBES: PATHOGENICITY, RISK FACTORS, CLUES TO

RECOGNITION OF ANAEROBIC INFECTION

The commonest pathogen amongst anaerobes is *B. fragilis*. Its factors of virulence include (1,14): capsular polysaccharide, adherence potential, piliation and toxin production. *B. fragilis* blood-culture isolates are more likely to carry an enterotoxin gene and to be more resistant to antibiotics. Virulent pathogens of the *B. fragilis* group include also: *B. thetaiotaomicron, B. distasonis, B. vulgatus, B. ovatus, B. uniformis.* The rate of isolation of *B. fragilis* is ~ 19 %, but it rises to 46 % in bacteraemia intra-abdominal isolates. *B. fragilis* group accounts for ~ 35 % of all anaerobe isolates. Anaerobic bacteraemia is not frequent: 1 – 4 % of all bacteraemias; the most frequent isolates are *B. fragilis* and *Clostridium* spp, almost always from bowel origin. It is established, that among surgery patients ~ 25 % of bacteraemias emanate from the large bowel, 5 % - from the small bowel, 9 % - from appendix, 9 % - fro exploratory laparatomy (13-16).

Clostridia may participate in the synergistic poly-microbial aerobic-anaerobic infections, or to cause the typical clostridial myonecrosis, "gas gangrene", where ~ 80 % of isolates are *C. perfringens* – the fastest growing anaerobe (15,18,19). Collagenases and proteases produced by

the typical appearance and crepitations are installed, the patient may be near the death. Early debridement, hyperbaric oxygenation and Penicillin 24 million units are the present treatment approach.

Risk factors for the development of anaerobic infections are: trauma, foreign body, malignancy, surgery, oedema, shock, colitis, vascular disease; they low the oxidation-reduction potential (7,20,21).

There are several clues to clinical diagnosis of anaerobic infection (20). The presence of putrid smell and gas formation in tissues are caused by metabolic end products: organic acids. Other signs may be: infection adjacent to a mucosal surface, classic presentation (necrotic gangrenous tissue, gas gangrene, abscess); bacteraemia without growth from aerobic culture; infection related to tumours, septic trombo-embolitis; infection after an antibiotic course with ceftazidime, older quinolones, aminoglycosides, co-trimoxazole. Anaerobes are fastidious and difficult for isolation, they are often overlooked. Isolation of these organisms is important to direct antibiotic therapy and requires special/appropriate methods of collection, transportation and cultivation of specimens (1,14,17,20-22).

Table 2 presents contemporary information about susceptibility patterns of anaerobic bacteria (adapted from ref. 23 and 24).

As it concerns *Clostridium* spp, Penicillin G 24 mill U/24 h

Table 2. Antibiotic resistance in % in selected anaerobe bacteria. (Adapted from Ref. 23 and 24)

	Bacteroides fragilis	**B. fragilis group**	**Prevotella**	**Fusobacterium**	**Peptostreptococcus**
Cefotaxime	30-50	> 50	5	5-15	
Cefotetan	5-15	30-50		5-15	
Cefoxitin	5	5-15	5	5	5
Ceftriaxone	16-30	> 50	5-15	5	5
Chloramphenicol	5	5	5	5	5
Clindamycin	5-15	16-30	5	5-30	10-15
Imipenem	5	5	5	5	5
Meropenem	5	5	5	5	5
Metronidazole	5	5	5	5	5
Penicillin G	> 50	> 50	> 50	5-30	5
Augmentin	5	5-15	5	5-15	5
Piperacillin	5	5-15	5	5-15	5

clostridia destroy the tissues, whereas the alpha-toxin (letal & necrotic) contributes to the high mortality rate ~ 60 %. Sudden onset of pain at the site of the surgical wound or trauma, rapidly increasing in severity and extending beyond the original borders is typical. Skin is characterized by pale appearance, then by oedematous/ hemorrhagic bullae and foul-smelling discharge. Gram stains from discharge and tissue sample show large Gram-positive rods. When

is still considered the treatment of choice, although cases of penicillin-resistance have been reported in *C. perfringens* (25). It is interesting that new data showed in a mouse model of *C. perfringens* infection (gas gangrene) better outcome after treatment with clindamycin or metronidazole, or rifampicin, or chloramphenicol, or tetracycline alone, as well as of the combination clindamycin + penicillin than penicillin G alone (25). In the same model the combination

metronidazole + penicillin showed antagonistic effect. The conclusion drawn from these findings is that it is better to combine clindamycin with penicillin, but not metronidazole in proved/suspected clostridial infection.

CLINICAL PRESENTATION AND DIAGNOSIS OF INTRA-ABDOMINAL INFECTION

Patient with suspected intra-abdominal infection complains of abdominal pain (but immuno-suppressed or critically ill patients in ICU may not complain (12). It is important to clarify the onset, evolution, localisation and character of the pain. Patient will try to lie (even slight motion of the peritoneum causes discomfort). Other symptoms as nausea, vomiting, diarrhoea may be present or not. Profuse diarrhoea is typical for gastro-enteritis, while the bloody – for ischemic enteritis. Surgeon should ask where patient feels the point of the most severe pain. Inspection, percussion, palpation, auscultation, imaging study (the best is computed tomography) will contribute to the clinical diagnosis.

The minimum laboratory tests include complete blood count, amylases, urinanalysis.

Critically ill patients may need resuscitation (fluid resuscitation to restore oxygen delivery to hypoperfused ischemic tissues).

CLINICAL MICROBIOLOGY INVESTIGATION

Clinical microbiology investigation is a highly desired procedure when dealing with infection in colo-proctology (7,12-19, 23, 25, 26):

1. Definition of SSI (CDC) necessitates microbiology confirmation of the infection as one of the possible considerations (superficial – organ/space infection) (27).
2. The need to know the particular pathogens involved and their antibiotic susceptibility patterns – in order to guide antibiotic therapy
3. Infections in colo-proctology are typically severe and even life-threatening: the hazard in their therapy should be replaced by evidence-based clinical decisions
4. Antibiotic resistance nowadays is not rare, but typical, especially in the hospital setting event, with different mechanisms, epidemiologic spread and social consequences.

Appropriate specimens from the site of infection include fluid/pus/aspirate, collected by syringe and/or aseptically cut small tissue piece. These specimens should be obtained by the surgeon and disposed onto the surface of transport medium (e.g. Stuart) in a tube. Then the specimen should be pushed to the bottom of the tube (anaerobic conditions) with a sterile swab, by one punch through the medium, without making air bubbles. The tube should be sent to Microbiology laboratory, but this specimen may wait for 24

hour at room temperature until be proceeded. Another possible way is the pus/fluid, collected in the syringe, without air, to be closed and immediately sent to the laboratory (when the laboratory is in the same hospital); this way require urgent activities (receiving in 15' – 30') and is more-dependent on the higher volume of specimen for recovering of anaerobes.

Another appropriate specimen is blood-culture: two sets of blood-cultures –in aerobic and anaerobic bottles each, should be obtained by the nurse at 20' – 30' apart.

Fastidious anaerobes require much more time than usual to recover: antibiotic therapy should not wait the microbiologic result, but should be tailored when the result becomes available. Sometimes Gram stain (urgent diagnosis) may show the presence of important organisms, e.g. clostridia, staphylococci.

MANAGEMENT OF INFECTIONS ENCOUNTERED IN COLO-RECTAL SURGERY

The first key to successful treatment and management of secondary peritonitis and intra-abdominal abscesses is the effective surgical intervention: to debride gross fibrinous debris (lavage), drainage of pus and gross contamination from the peritoneal cavity; resection or repair of the pathology (perforation, tumour etc (21). Some patients require intensive care therapy because of sepsis, hypovolemia and hypoxia. What is the role of antibiotic treatment? Among all infections of the colon and rectum and their consequences, only non-complicated diverticulitis (sigmoiditis and recto-colitis) could be treated by antibiotics without surgery (17). In all other cases antibiotics play important role in prevention and treatment of infection, and even in prevention of mortality – they are of paramount significance for saving life, but there activity can be exerted in the condition of good surgical work (21). The statistical data shows that mortality of intra-abdominal infection in 1900 has been $\sim 90\%$, in $1980 - 1990 \sim 25\% (20 - 50\%)$, nowadays the prognosis is improved with the larger antibiotic choice, asepsis, improved diagnosis and care for patients. However, we should underline the adequacy of "surgical source control" – adequacy of operative procedure for the underlying cause of peritonitis. Poorly chosen, improperly performed operation will cause antibiotic effect to fail (CFU $> 10^8$ bacteria/ml). Small abdominal abscess (d< 2 cm) sometimes may responds to antibiotic therapy alone, but if the d > 4 cm, will not respond without drainage.

In brief, successful management of serious intra-abdominal infections will rely first on timely and appropriate surgical investigations that resolve the primary problem. Supportive care and antibiotic treatment are necessary adjunct which may also have life-saving effect.

PRINCIPLES OF ANTIBIOTIC THERAPY

1. Antibiotic should be appropriately chosen

They should be broad-spectrum to cover the most frequent aerobic and anaerobic pathogens. They should be quickly acting and bactericidal. Antibiotics should be appropriate for the concrete type of infection – e.g. community – or hospital- acquired (Roehborn et al (28) have noticed recently higher rates of *Enterococcus* and *Enterobacter* in nosocomial peritonitis). Antibiotics should be the best for the particular patient: e.g. not beta-lactams if penicillin allergy, but e.g. aztreonam instead; not aminoglycosides, if renal insufficiency, but ciprofloxacin etc. Antibiotics should be given urgent in severe cases.

2. What dose, route, dosage interval?

The dose should be higher, to obtain sufficient tissue concentrations for enough time at the site of infection. The IV route provides quick and high tissue level. Dosage regimen should be optimal to maintain high antibiotic concentrations (29).

3. Antibiotic resistance should be considered (30)

The antibiotic chosen should be active on the involved/supposed pathogens. Local Microbiology laboratory and na-

Table 3. Recommendations for antibiotic therapy of intra-abdominal infections

Monotherapy	Combined therapy	Comments	References
Augmentin	Beta-lactam + AG + nitro-imidazole (Europe)/ + clinda (USA)	Diverticulitis, sigmoiditis, recto-colitis	Beytout J, 1986, Mal Infect; (17)
Augmentin	Beta-lactam + AG + nitro-imidazole Cephalosporin + nitro-imidazole Clinda + AMP or AG	Peritonitis, abscess	Beytout J, 1986, Mal Infect; (17)
Cefoxitin or cefotetan or Ampicillin/sulbactam or Piperacillin/tazobactam	AG + clinda or metro or IMP&ATM or FEP or CAZ or CIP + metro or clinda	Enterococcus - AMP or PIP; PEN allergy, MRSA - vancomycin; Pseudomonas - AG + ATM or FEP or CAZ or CIP or PTZ, or IMP;Candida - Fluconazole	Barie PS, 1999, J Chemother; (12)
Anti-pseudomonas activity -CAZ or FEP or PTZ or IMP	Triple combination that covers Enterococcus, and Pseudomonas	AG - renal toxicity; do not achieve sufficient tissue concentrations	Fry DE, 2001, Surg Infect; (21)
FOX, or CTA, or PTZ, or ETP, or IMP, or MER	AG or CFX or CEF3 or ATM or CIP + clinda or metro	Elderly patients-diverticulitis	Podnos YD, 2002, CID; (15)
PTZ or IMP or MER	AG + clinda or metro	Colon Ca, perforation, mesenteric ischemia, sigmoid volvulus-elderly	Podnos YD, 2002, CID; (15)
SAM or PTZ or FOX or CTA or IMP or MER	clinda or metro + another appropriate; sufficient dose	Documented R to traditional anti-anaerobes	Edmiston CE, 2002, CID; (16)
Beta-lactam/inhibitor (A)	Clinda or metro + AG + PEN (B)	(B): immuno-suppression, late surgery, non-resectable Ca or necrotic tissue, sepsis	Sganga G, 2002 Hosp Infect; (36)
PEN/inh; or CPZ/S; or ETP	AG + CAZ or FEP or CPZ/S or PTZ or PEN/inh or AMP+ metro or clinda	Post-operative peritonitis: penem; or FEP or AG + metro; or PTZ or CPZ/S	Gelfand BP, (32) 2002, Moskow
SAM or CTA or FOX or ETP or IMP or MER or PTZ	AG + metro or clinda; ATM + clinda; CFX or CIP+ metro; FEP or CAZ or CTX or CRO + metro or clinda		Goldstein E, 2004, JAC; (14)
PTZ or SAM or ETP&IMP or MER - ICU	AMP + metro + CIP or LVX; AMP + AG-AP	VAN for MRSA	Gilbert DN, 2004 Sanford Guide (33)

Legend: PEN/inh – penicillin/inhibitor; PIP –piperacillin; PTZ-piperacillin/tzobactam; SAM, ampicillin-sulbactam; CPZ/S-cefoperazone/sulbactam; AUG, augmentin; FOX, cefoxitin, CTA, cefotetan; CFX, cefuroxime; CAZ-ceftazidime; CTX – cefotaxime; CRO – ceftriaxone; FEP, cefepime, ATM – aztreonam;ETP; ertapenem; IMP – imipenem; MER –meropenem; VAN – vancomycin; CIP – ciprofloxacin; LVX – levofloxacin; CEF3 – cephalosporins 3rd generation; AG – aminoglycosides

tional antibiotic susceptibility data should be consulted (www.bam_bg.net). A common approach is the de-escalation therapy: first the empiric therapy is broad-spectrum and powerful to guarantee broad-coverage. Once the patient is going better and microbiologic result becomes available, the therapy is usually adapted by using more-narrow-spectrum antibiotic. If the patient condition is stable, the antibiotic may be switched on (e.g. to apply PO ciprofloxacin (same bioavailability as IV) (31).

Antibiotics that do not select for antibiotic resistance should be preferred. In the upper case of hospital-acquired peritonitis (28) it was shown that cephalosporins usage had been selected for enterococci and *Enterobacter*. Cephalosporins uncontrolled usage selects also *P. aeruginosa* because of natural resistance.

The other situation – when the pathogens in cause are antibiotic-resistant, is much more difficult to overcome and may be reason the therapy to fail. As a rule, nosocomial bacteria are more resistant. Important resistant bacteria of surgery interest are MRSA, which require therapy with vancomycin; ESBL-producing *Enterobacteriaceae* and multiple resistant *P. aeruginosa*, which require therapy with carbapenems (32,33).

4. How long?

Contemporary guidelines suggest that antibiotic prophylaxis in surgery should not exceed 24, maximum 48 hours, and therapy in contaminated elective/urgent procedure – 5 days (34-40). However, therapy of established serious infection: bacterial secondary peritonitis, abdominal abscess, may require 3-4 weeks until full regression of symptoms (13,32,33).

Table 3 shows some examples of contemporary antibiotic therapy for intra-abdominal infections.

CONCLUSIONS

Successful management of infections in the surgery of colon and rectum requires knowledge, scientific attitudes, analysis, skills and financial resources in both surgery and antibiotic therapy. Multidisciplinary approach should be used for better care of patients.

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