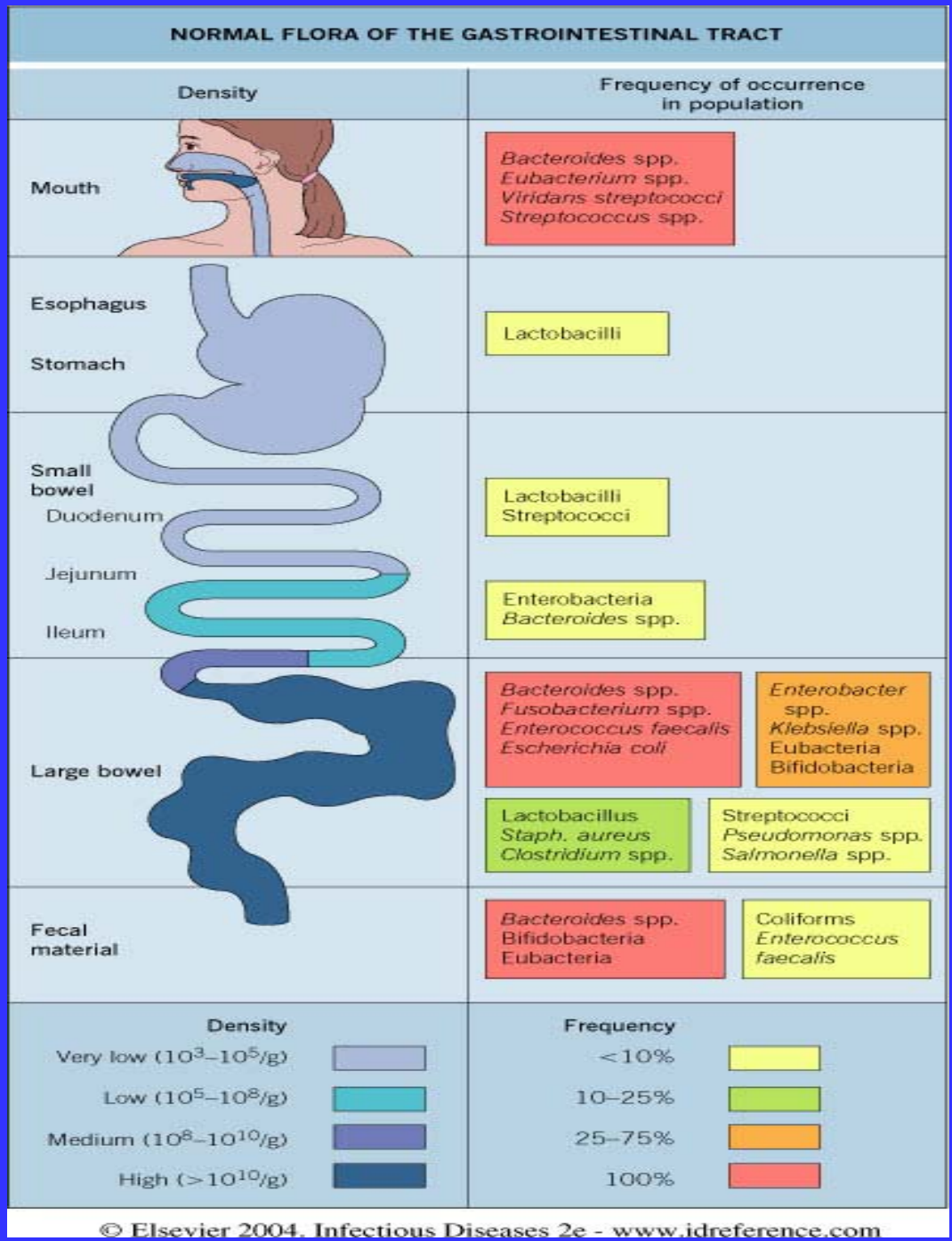
Secondary peritonitis

- Caused by spillage of gastrointestinal micro-organisms into the peritoneal cavity secondary to loss of the integrity of the mucosal barriers
- Etiology:
  - perforation of peptic ulcer
  - traumatic perforation of stomach, small or large bowel
  - spontaneous perforation (typhoid, tuberculosis, strongyloides…)
  - Appendicitis, diverticulitis, intestinal neoplasms
  - Operative contamination of the peritoneum
  - …


NORMAL FLORA OF THE GASTROINTESTINAL TRACT
Density
Frequency of occurrence in population
Mouth
Bacteroides spp.
Eubacterium spp.
Viridans streptococci
Streptococcus spp.
Esophagus
Stomach
Lactobacilli
Small bowel
Duodenum
Jejunum
Ileum
Lactobacilli
Streptococci
Enterobacteria
Bacteroides spp.
Large bowel
Bacteroides spp.
Fusobacterium spp.
Enterococcus faecalis
Escherichia coli
Enterobacter spp.
Klebsiella spp.
Eubacteria
Bifidobacteria
Lactobacillus
Staph. aureus
Clostridium spp.
Streptococci
Pseudomonas spp.
Salmonella spp.
Fecal material
Bacteroides spp.
Bifidobacteria
Eubacteria
Coliforms
Enterococcus faecalis
Density
Very low (10^3–10^5/g)
Low (10^5–10^8/g)
Medium (10^8–10^10/g)
High (>10^10/g)
Frequency
<10%
10–25%
25–75%
100%
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Microbiologic characteristics of secondary peritonitis

- Mostly endogenous in origin by large number and variety of micro-organisms

Stomach and upper small intestine:

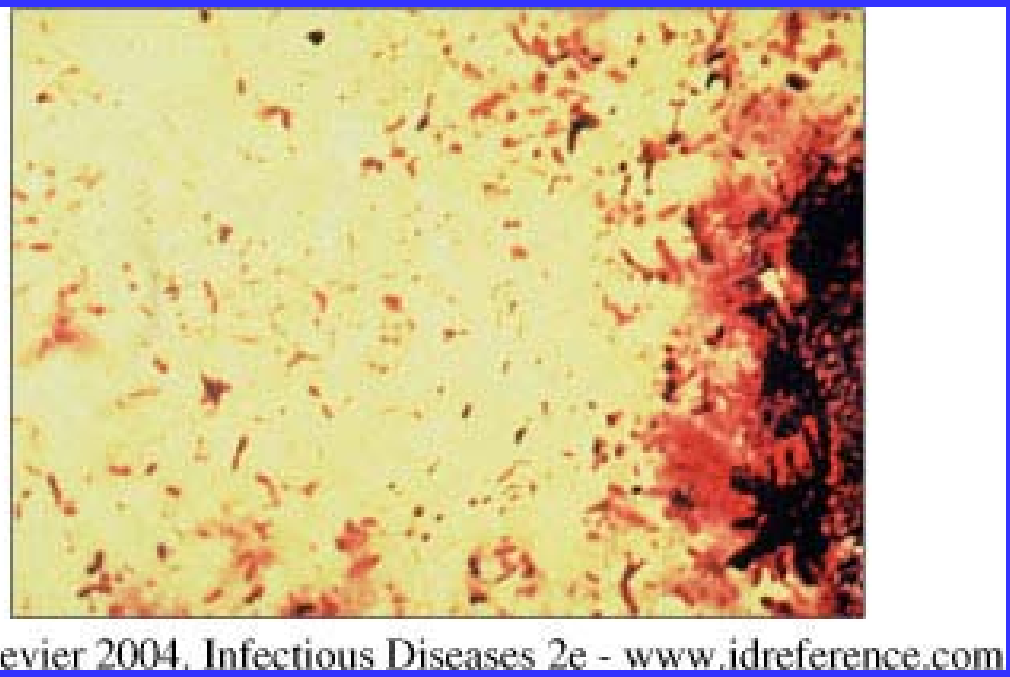
- 10^3 CFU/mL salivary micro-organisms (streptococci, lactobacilli, Candida)
- Disturbance if there is achlorhydria, blood in stomach

Ileum:

- E.coli, enterococci and equal number of anaerobes (e.g. Bacteroides fragilis)

Colon:

- $>10^{11}$ CFU/mL
  predominantly anaerobes: Bacteroides, Bifidobacterium Eubacterium, Clostridium
  facultative = E.coli, enterococci, Klebsiella, Proteus, Enterobacter, viridans streptococci
- Relatively stable (exception = antibiotic therapy)



Impact of antibiotics on the gastrointestinal microflora (colon)

agent	Dose mg/d	Days of adm	Impact on			Emergence of resistance			Over growth
			aerG+ cocci	Enterob	anaerob	Entero-cocci	Enterob.	Bacte-roides	Candi-da
Amoxicilline-clav	875/125	7	↑	↑	..	..	..	..	..
Piperacillin-tazob	400/500 x3	4-8	..	↓	↓	..	+	..	..
Ceftriaxone	1000 mg	10	↑	↓↓	↓	..	..	..	+
Cefepime	1000 mg x2	8	..	↓	..	..	..	..	..
Meropenem	500 mg x3	7	↑	↓	↓	..	..	..	..
Clindamycin	150 x4	7	↑	↑	↓↓	+	+	..	..
Vancomycin	125 x4	10	↓	..	↓	+	+	..	..
Linezolid	600 x2	7	↓	↑	↓↓	..	..	+	..

↓↓> 4 log 10 CFU/g, ↓ 2-4 log 10 CFU/g, ↑ increase +: mayor impact, ..: no significant change

Lancet Infect Dis 2001, 1:101

Intestinal disorders and related changes in intestinal microflora

Crohn's disease	- Colonization of duodenum by E. coli and streptococci - decrease in enterococci
Chronic diarrhea	-decrease in total anaerobes
Colon cancer	-Increase in anaerobes, -decrease in facultatives
Achlorhydria	-E. coli and E. faecalis in duodenum and jejunum

Salminen S et al, Chemotherapy 1995: 41 (suppl 1): 5-15

Microbiological characteristics of secondary peritonitis

Model of Onderdonck

- Intraperitoneally implantation of faecal contents into rats
  - Initially (3-5 days) E.coli predominated, frequently associated with bacteraemia and high mortality rate (prevention with gentamicin)
  - Later on (after 1 week) development of intra-abdominal abscesses with B. fragilis (prevention with clindamycin)

Infect. Immun. 1974, 10:1256-1259

Death rate and abdominal abscesses in the rat

Microorganism	Inoculum (log10)	Death rate % (bacteraemia)	Intra-abdominal abscesses %
E. coli	7.8	100	-
	7.4	65	0
	7.1	35	0
	6.8	0	0
E. coli + E. faecalis	7.1 + 7.4	25	0
E. coli + B. fragilis	7.1 + 7.4	37	100
B. fragilis + F. varium	7.4 + 7.4	0	5
E. faecalis + B. fragilis	7.4 + 7.4	0	95

Onderdonck AB et al., Infect. Immun. 1974, 10: 1256-1259

Microbiologic characteristics of secondary peritonitis

- Perforation of the colon
  - Initially more than 10^{11} CFU/mL of hundreds of different species spills into peritoneal cavity
  - Evolution to peritoneal infection with simplification of the microflora to about five species: three anaerobic (relative oxygen tolerant, virulence factors) and two aerobic species. Most common isolates = E. coli and B. fragilis.

Microbiologic characteristics of secondary peritonitis

- Bacteroides fragilis
  - Minor component among Bacteroides (10^8-10^9 CFU/mL)
  - Virulence factors
    - Oxygen tolerant = "superoxide dismutase" ➔detoxification of oxygen radicals
    - Catalase ($2H_2O_2$➔$2H_2O + O_2$)
    - Polysaccharide capsule = inhibition of phagocytosis, attachment to mesothelial cells
    - Periplasmic enzymes = lipases, proteases, neuraminidases

Microbiologic characteristics of secondary peritonitis

- Pathogenesis = which species become dominant?
  1. Granulocytic killing = first line of defense
     →encapsulated bacteria survive
  2. Peritoneal cavity is well oxygenated
     →killing of oxygen-sensitive anaerobes
  3. Proliferation of facultative bacteria (e.g. E.coli)
     - Consumption of oxygen
     - Tissue necrosis (gas production)
     - Generation of substances essential for growth of anaerobes (e.g. vit K)
  4. Proliferation of oxygen-tolerant anaerobes

Bacteriology of postoperative versus community acquired peritonitis

strain	N° of isolates of		
	Postoperative perit. (n = 111)	Community acquired perit. (n = 118)	p.
Enterococci	**23**	6	.001
E.coli	21	**42**	.005
Enterobacter spp	**13**	4	.004
Bacteroides spp	8	12	
Klebsiella spp	8	8	
Staphylococcus aureus	**7**	1	.008
CNS	6	1	.05
Candida spp	4	8	
Pseudomonas spp	**7**	2	
Streptococci	4	17	.005
other	10	17	

Roehrborn A et al., Clin Infect Dis 2001; 33:1513

Need for intraoperative cultures

- Not necessary in patients with perforated appendicitis
  - Study by Kokoska ER et al. (J. Pediatr. Surg. 1999, 34: 749)

    Modified antibiotics

    ~higher incidence of infectious complications

    ~longer fever duration

    ~increase length of hospitalization
  - Study Blik R et al. (Am. J. Surg. 1998; 175: 267)

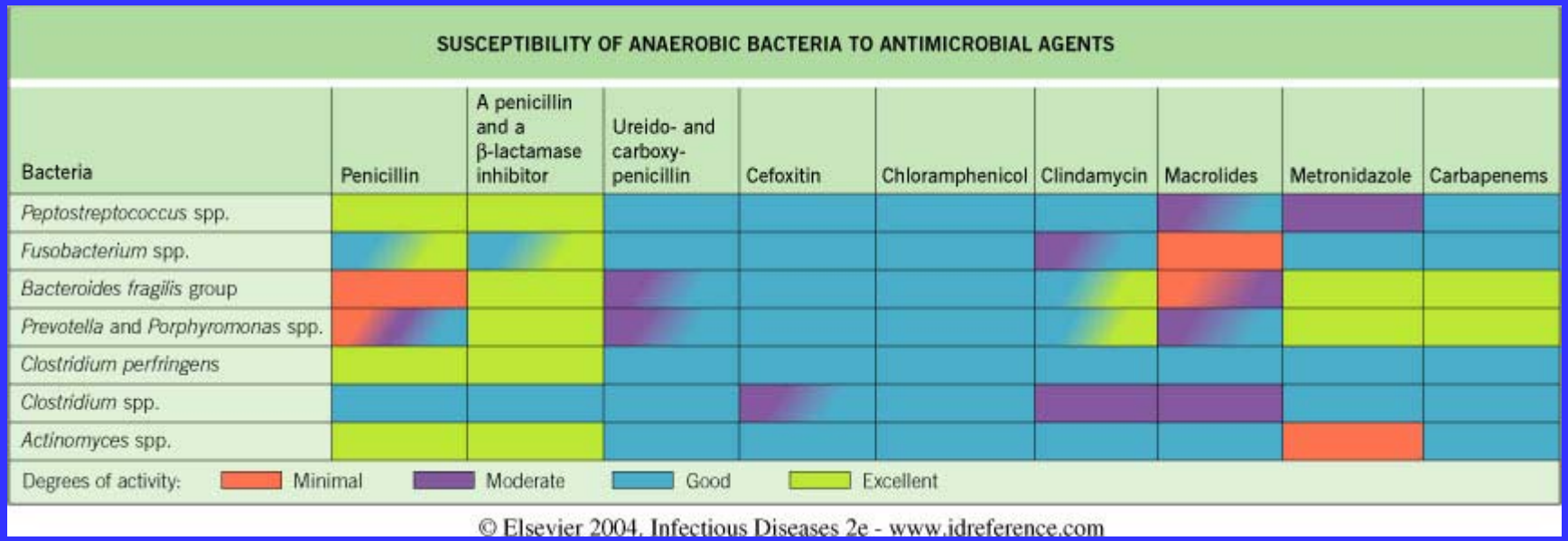
    "…traditional intraabdominal cavity culture can be abandoned. Colonic flora can be predicted and antibiotic therapy begin without culture results. This approach will save money and reduce laboratory work without affecting the patient's morbidity…".

Need for intraoperative cultures

- Controversial for many indications
- Always necessary
  - Nosocomial acquired
  - Recent antimicrobial therapy
  - Severe immunosuppression

Antimicrobial therapy of intra-abdominal infections

- Often combination of surgical drainage and antimicrobial therapy
- Role of antibiotics
  - Reduction of mortality
  - Reduction of suppurative complications
  - Prevention of local spread of existing infection
- Start of antibiotics = immediately after bloodcultures are obtained



SUSCEPTIBILITY OF ANAEROBIC BACTERIA TO ANTIMICROBIAL AGENTS

Bacteria	Penicillin	A penicillin and a β-lactamase inhibitor	Ureido- and carboxy-penicillin	Cefoxitin	Chloramphenicol	Clindamycin	Macrolides	Metronidazole	Carbapenems
Peptostreptococcus spp.	Excellent	Excellent	Good	Good	Good	Good	Moderate	Moderate	Good
Fusobacterium spp.	Good	Good	Good	Good	Good	Moderate	Minimal	Good	Good
Bacteroides fragilis group	Minimal	Excellent	Moderate	Good	Good	Excellent	Minimal	Excellent	Excellent
Prevotella and *Porphyromonas* spp.	Minimal	Excellent	Moderate	Good	Good	Excellent	Moderate	Excellent	Excellent
Clostridium perfringens	Excellent	Excellent	Good	Good	Good	Good	Good	Good	Good
Clostridium spp.	Good	Good	Good	Moderate	Good	Moderate	Moderate	Good	Good
Actinomyces spp.	Excellent	Excellent	Good	Good	Good	Good	Good	Minimal	Good

Degrees of activity: Minimal, Moderate, Good, Excellent

Initial antibiotic therapy for secondary peritonitis

- Need for broad spectrum initial parenteral therapy against the “usual” enteric flora
  - Appropriate therapy = all identified bacteria sensitive to at least one drug
  - Inappropriate therapy =
    - Twofold increases in repeat operation and death
    - Significant increase in postoperative infection
    - Need for second-line parenteral antibiotic therapy
    - Longer length of stay (13.9d vs 19.8d)

Krobot K et al., Eur J Clin Microb Infect Dis 2004; 23:682

Selection of antibiotics

- Results of antimicrobial trials

  Difficult interpretation of the results

  - Inadequate study design
  - Differences in
    - patient populations
    - types and severity of underlying illnesses
    - community vs hospital acquired

- Recommended regimens with activity against
  - E. coli and other common Enterobacteriaceae
  - Bacteroides fragilis

Selection of antimicrobial trials in secondary peritonitis

Antimicrobial therapy	Reference
Ampicillin / sulbactam vs clindamycin+ gentamicin	Pourriat et al. Lettre de l'infect. 1995 (1); 30-35
Piperacillin / tazobactam vs imipenem	Niinikoski J et al. Surg. Gynaec. Obstet. 1993: 176: 255
Cefotaxime + metronidazole vs ciprofloxacine + metronidazole	Hoogkamp - Korstange. Infection 1995; 23: 278
Cefepime + metronidazole vs imipenem	Barie et al. Arch. Surg. 1997; 132: 1294
Imipenem vs ciprofloxacine + metronidazole	Solomkin et al. Ann. Surg. 1996; 223: 303
Cefotaxime + metronidazole vs meropenem	Kempf et al. Infection 1996; 24: 473

Antimicrobial therapy of intra-abdominal infections

- Choice of antibiotics
  - Good penetration to infection site → sufficient concentration to overcome:
    - High bacterial density (↔β-lactams)
    - metabolic inactivity of bacteria (↔β-lactams, fluoroquinolones)
    - Low pH (↔ aminoglycosides, clindamycin)
    - Low redox potential, necrotic tissue (↔ amino-glycosides)

Antimicrobials effective for treatment of intra-abdominal infections

- Single agents:
  - amoxicillin-clavulanic acid
  - piperacillin- tazobactam
  - imipenem- cilastatin
  - Meropenem
  - (Ertapenem)
- Combination regimens:
  - Third / (fourth) generation cephalosporin plus metronidazole
  - Fluoroquinolone plus metronidazole

Treatment options for secondary peritonitis in UH Leuven

Community acquired:

- Amoxicillin-clavulanate (4x 1g IV) plus :
  - Levofloxacine 1x 500 mg IV

  or
  - Gentamicin IV
- Levofloxacine 1x 500 mg IV + ornidazol 1x 1g IV

Nosocomial acquired:

- Piperacilline/tazobactam 3x 4g/500 mg IV

  or
- Meropenem 3x 1g IV

% susceptible aerobic and facultative Gram-negatives (UH Leuven, 2004)

	E. coli	P. mirabilis	Klebsiella spp.	M. morganii	S. marces-cens	Enterobac-ter spp.	P. aeruginosa
Amoxicillin-clavulanate	**84.6**	89.3	86.3	0.5	0	0.4	0
Piperacillin - tazobactam	97.6	99	89.4	95.3	**82.1**	**71.9**	89.6
Cefotaxime	94.4	98.9	94.2	88	94.9	84.3	< 50%
Cefepime	94.5	99.8	94.4	100	100	99.6	81.2
Meropenem	100	100	99.9	99.5	100	99.6	83.6
Levofloxacine	**84**	78.5	92.2	82.3	**79.5**	**64.9**	60.7
Gentamicine	94.1	90.9	95.2	89.6	93.6	97.1	76.3
Amikacine	99.9	99.8	98.7	99	91	99	88.5

Treatment options for secondary peritonitis in UH Leuven

Monotherapy excluded

- Amoxicilline – clavulanate
  - 15% R in E. coli
  - no activity against some β-lactamases = chromosomal inducible and plasmid ESBL
- Fluoroquinolones
  - 15% R in E.coli
  - No activity against B. fragilis and other anaerobes

Are there patients with secondary peritonitis who require emperic therapy for Enterococcus?

- The role of Enterococci as primary pathogens in polymicrobial peritonitis is still controversial
- Recent studies have suggested that enterococci increase:
  - the infectious postoperative complication rate
  - the risk of death (21% vs 4%, $p<0.001$ Sitges-Serra et al., Brit J Surg 2002, 89: 361)

Harbarth S. et al., Eur J Clin Microb Infect Dis 2004; 23: 73

Are there patients with secondary peritonitis who require empiric therapy for Enterococcus?

- Evidence for coverage:
  - Immunocompromised patients with nosocomial peritonitis
  - Patients with severe sepsis who have previously received cephalosporins and /or fluoroquinolones selecting for Enterococcus spp.
  - Patients with valvular heart disease or prosthetic intravascular material (risk of endocarditis)

Harbarth S. et al., Eur J Clin Microb Infect Dis 2004; 23: 73

Aminoglycosides in the treatment of secondary peritonitis?

- Ideal therapy with piperacillin/tazobactam or meropenem in patients with bacteraemia or septic shock (3 days)
  - Excellent activity against Enterobacteriaceae and P. aeruginosa
  - Bactericidal activity