Intra-abdominal anaerobic infections. Diagnostics and therapy

Elisabeth Nagy MD. PhD. DSc.

Institute of Clinical Microbiology, Faculty of Medicine,
University of Szeged

4th ESCMID School, Szeged, Hungary (2005)

Intra-abdominal infection ≠ peritonitis

Peritonitis = inflammation of the peritoneum independent from the aetiology

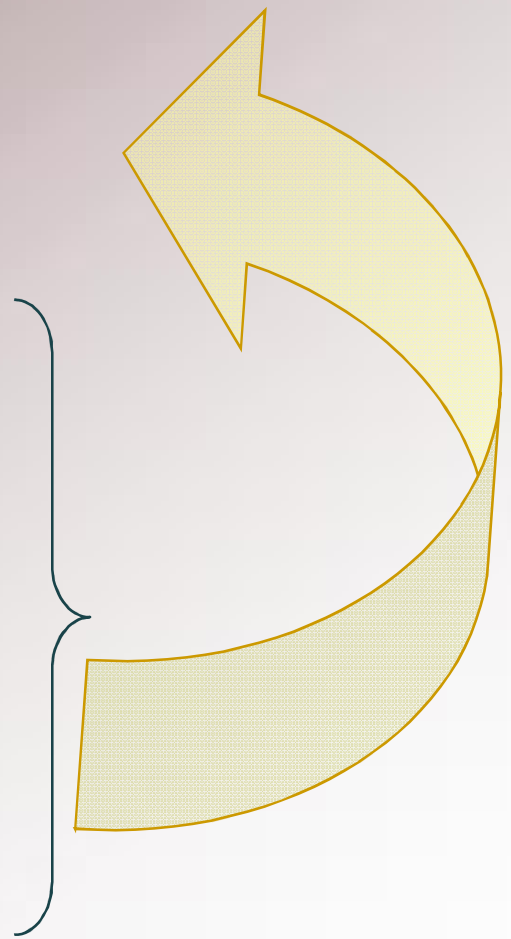
"In the literature the terms secondary peritonitis and intra-abdominal infection are, with very few exceptions, used almost synonymously".

"Secondary bacterial peritonitis describes peritoneal infections secondary to abdominal lesions".

Infection 1998; 26: 329-334.

Classical scheme of intra-abdominal infections (Mandell et al: Principeles and Practice of Infectious Diseases 2005)

- Different forms of peritonitis
- Intra-peritoneal abscesses
- Infections of the biliary system
- Liver abscesses
  (with different aetiology)
- Pancreatic infections
- Splenic abscess
- Appendicitis
- Diverticulitis; typhlitis



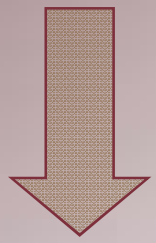
New concept of intra-abdominal infections (IAIs)

The main question is where the patient acquired the IAI

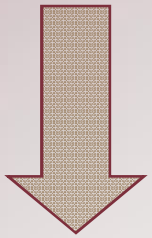
- Community-acquired IAIs:
  - primary peritonitis,
  - secondary peritonitis (spontaneous, post-traumatic)
- Nosocomial IAIs:
  - CAPD,
  - secondary peritonitis (postoperative)
  - "tertiary" peritonitis

Typhlitis (neutropenic enterocolitis)

Neutropenia, mucosal ulceration, ischaemia of the bowel wall



The bowel flora invades the bowel wall, local destruction, elaboration of exotoxins



Differential diagnostic problems to distinguish from other inflammatory bowel diseases

Typhlitis (neutropenic enterocolitis)

- Microbiology tests needed:
  - *C. difficile* toxin test
  - Blood cultures (bacteraemia, or fungaemia can be found in 14-44% of the patients)
  - Most common pathogens:
    - *P. aeruginosa*
    - *Enterobacteriaceae*
    - *B. fragilis*
    - Viridans streptococci
    - Enterococci
    - *Candida*
    - *C. septicum* - more fulminant, lethal course. Malignancy !!

Diverticulitis

- Inflammation, infection of the bowel wall associated with diverticula
- Interestingly in Europe the sites most commonly affected are the sigmoid and the descending colon, whereas in Asia it is the ascending part of the colon.
- Perforation, development of micro- or macro-abscesses, spreading peritonitis

Diverticulitis

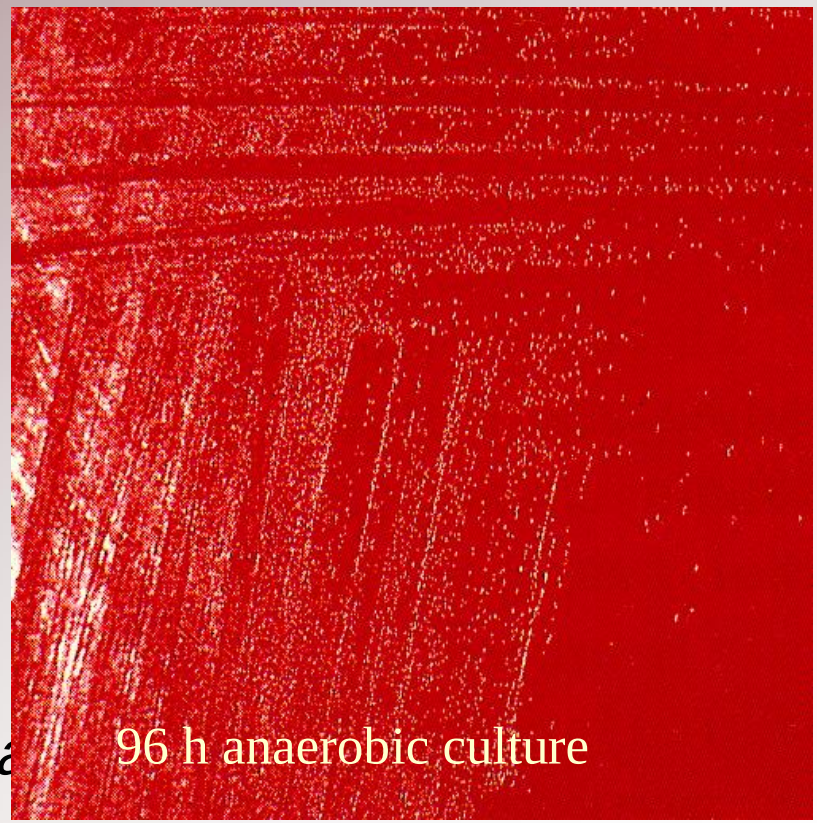
- Microbiology tests needed:
  - Culturing of samples taken during surgery for aerobes and anaerobes
  - Most common pathogens:
    - *Bacteroides* spp
    - *Peptostreptococcus* spp
    - *Enterobacteriaceae*
    - Viridans streptococci
    - Enterococci

Appendicitis

- Acute (*E. coli, B. fragilis*)
- Perforated (10-14 different aerobic and anaerobic bacteria)
- Obstructive (tumours, foreign bodies, strictures, different parasites: *Enterobius vermicularis* *Ascaris lumbricoides,* *Strongyloides stercoralis)*
- Differential diagnostic problems:
  - ileocaecitis, mesenteric adenitis (*Y. enterocolitica, Y. pseudotuberculosis, Campylobacter, Salmonella* sp)

Appendicitis (gangrenous)

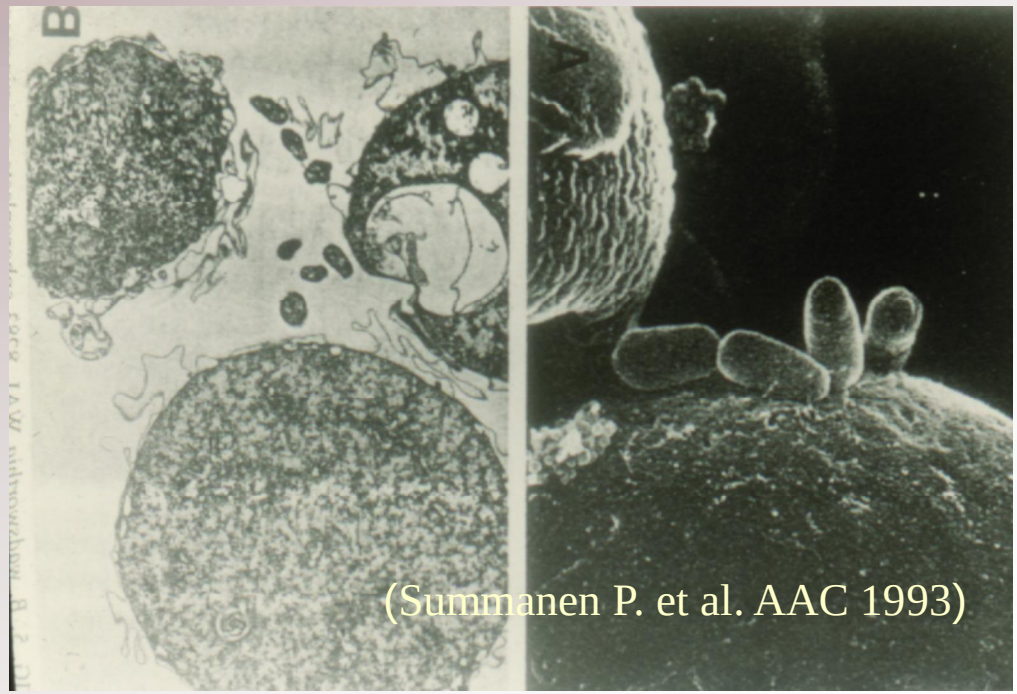
- Dominant flora
  - *E. coli*
  - *B. fragilis* group
  - *Bilophila wadsworthia*
  - Pigmented *Prevotella* spp
  - *Peptostreptococcus* spp
  - *Enterobacteriaceae*
  - Viridans streptococci (*S. a*



The role of *Bilophila wadsworthia* in gangrenous appendicitis

- Member of the normal flora (faeces, saliva, vaginal fluid)
- 1989, first description (present in >80% of the cases)
- Increased (virtual) resistance

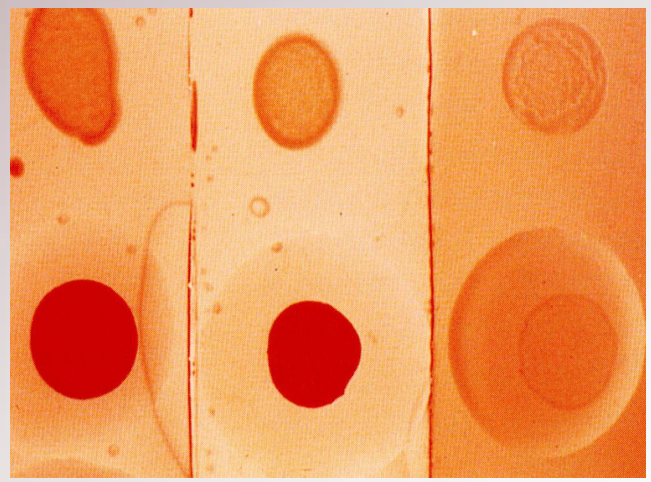
Effect of imipenem (64 µg/ml) on *B. wadsworthia* (transmission and scanning EM)



Problems with determination of the endpoint of growth of *Bilophyia wadsworthia* (agar dilution method)

imipenem

1 µg/ml 2 µg/ml 4 µg/ml



Triphenyltetrazolium chloride →

Viable organisms produce a red colour

IMP MIC 4 µg/ml

Wadsworth manual 6th ed.

Abscesses

- Splenic (infective endocarditis, UTI, *Salmonella* enteritis – haematogenic spread, HIV)
  - *Streptococcus*
  - *Staphylococcus aureus*
  - *E. coli*
  - *Salmonella*
- Pancreatic (after acute pancreatitis, or post-traumatic)
  - *E. coli* (35%)
  - *K. pneumoniae* (24%)
  - *Enterococcus* (24%)
  - *Staphylococcus* (14%)
  - *Pseudomonas* (11%)
  - *Candida* spp
  - (anaerobes)

(based on 1100 cases)

Abscesses

- Liver abscess
  - Amoebic (*E. hystolitica*, *E. dispar* – the latter only in HIV patients) - diagnostic problems in the lab.
  - Pyogenic (40-50% originate from the biliary tree, 5-15% through haemtogenic spread, 5-10% direct extension, 0-5% trauma, and 20-40% of unknown origin)
    - Blood culture 50% positive
    - Culturing result on the aspirate: *E. coli*, *Klebsiella* spp, *Str. anginosus*, *Enterococcus*, *Bacteroides spp* } >10%

Acute cholecystitis

In 95%, inflammation caused by gall stone

In 5%, acalculous inflammation

In 60%, secondary bacterial inflammation

30% monobacterial

70% polymicrobial

Taking samples for bacteriological investigation

- Sample taken through duodenal bougie
  - Fraction A
  - Fraction B*
  - Fraction C*
- Sample taken during endoscopic retrograde cholangio-pancreatography (ERCP) *
- Bile and/or gallbladder wall sample taken during surgery*
- Blood cultures are positive in 30-40% of patients

*in chronic infections, anaerobic culture should be carried out routinely

Bacteriology of the biliary system

- In healthy persons — sterile
- Retrograde contamination from the duodenum (contaminated small bowel syndrome) — bile-tolerant bacteria
- Systemic infection through the bloodstream or lymphatic system — any bacteria
- Classical acute cholecystitis — *E. coli, Klebsiella, Proteus* spp
  other *Enterobacteriacae*
  Enterococcus spp
  non-haemolytic *Str.*, anaerobes

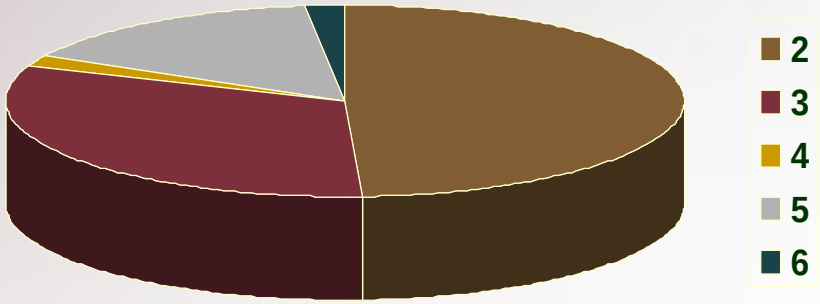
Culture results on bile, taken by ERCP January-October 2004

82 samples were positive

39 (47%) monobacterial

- *Clostridium spp*
- *Enterococcus spp*
- Other *Enterobacteriacae*
- *Candida spp*
- *Pseudomonas spp*
- *E. coli*
- *Streptococcus alfa-haem.*
- *Bilophila wadsworthia*

43 (53%) polymicrobial aerobe / anaerobe

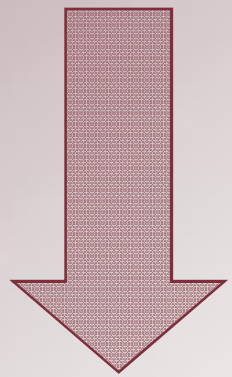


Peritonitis

- Primary:
  - Spontaneous bacterial peritonitis in children
    - *Str. pneumoniae,* or *Str.* beta-haemolyticus
  - Spontaneous peritonitis in adults
    - *E. coli, Klebsiella*, > Gram-positive cocci > anaerobes
  - Peritonitis in CAPD patients
    - Coag-neg. *Staphylococcus*, *S. aureus* (MRSA)
    - *Enterobacteriacae* are rear; they mostly occur in recurrences
  - (Peritonitis due to TBC)

Peritonitis

- Secondary
  - Peritonitis after acute perforation
  - Postoperative peritonitis
  - Posttraumatic peritonitis (CAPD complication)



Mixed faecal flora (aerobes / anaerobes) !!

Peritonitis

- "Tertiary"
  - Peritonitis caused by fungi (*Candida* spp)
  - Peritonitis caused by bacteria with low pathogenicity
  - An autoaggressive process after antibiotic treatment of secondary peritonitis

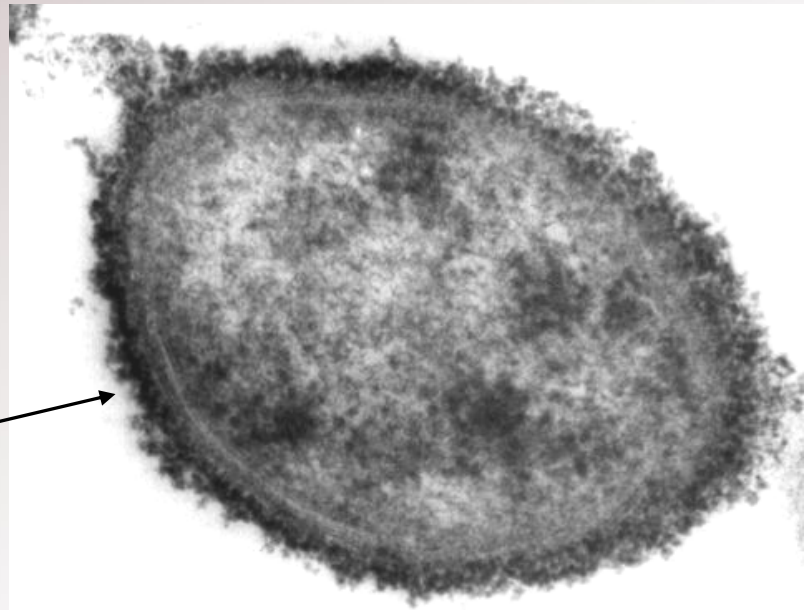
Intra-abdominal abscesses

- Can follow primary peritonitis

- Can follow secondary peritonitis

Anaerobic bacteria (*Bacteroides fragilis* group strains)
predominating the process

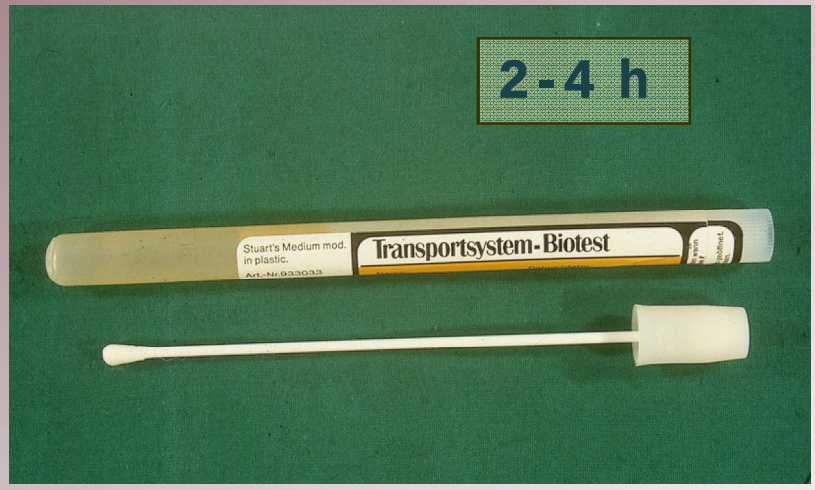
The capsule responsible for the abscess formation (EM)

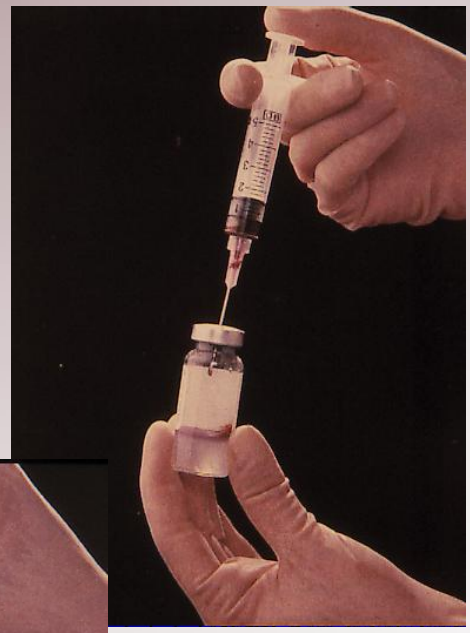


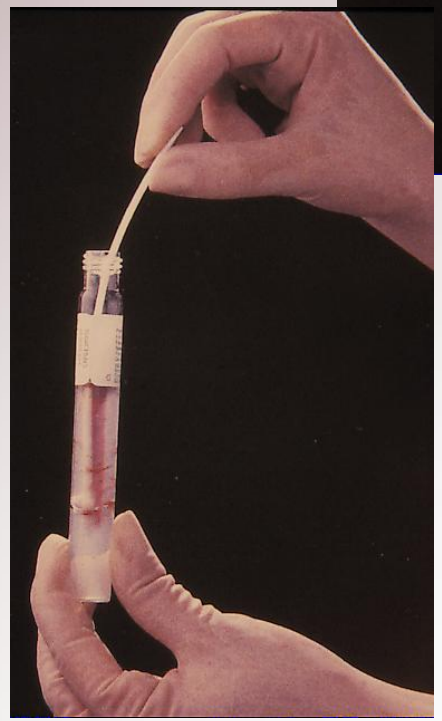
Sample-taking in intra-abdominal infection cases

- Samples taken intraoperatively or by puncture *versus* samples taken form drainage after surgery
- More than one abscess – more than one sample
- Sample taken by swab *versus* sample taken by syringe.
- Samples should be suitable for aerobic and anaerobic culture
- Transport : normally in transport medium in a plastic tube; if >2 h requiered for transport, than in a glass tube

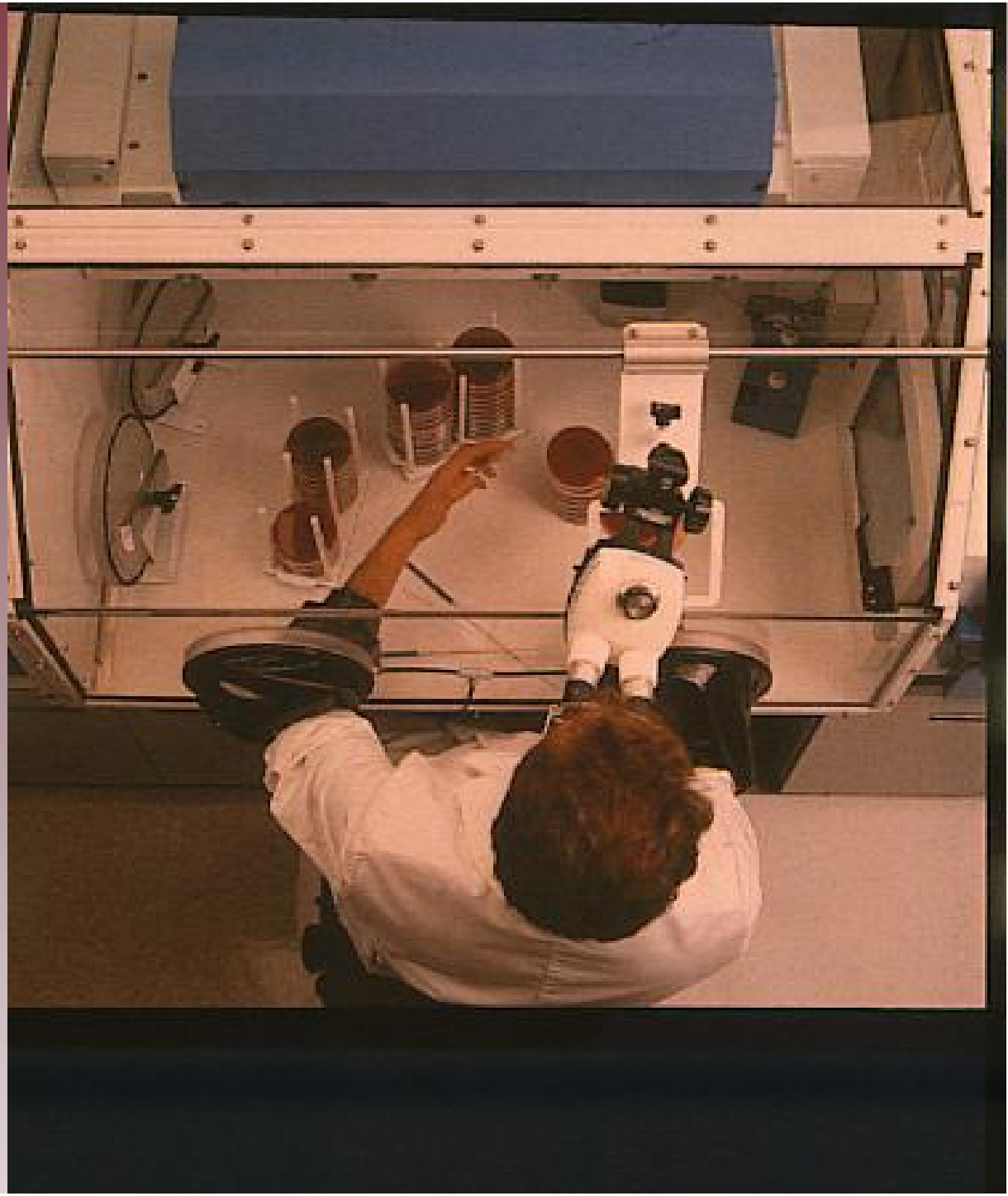
How to take and send samples to the laboratory



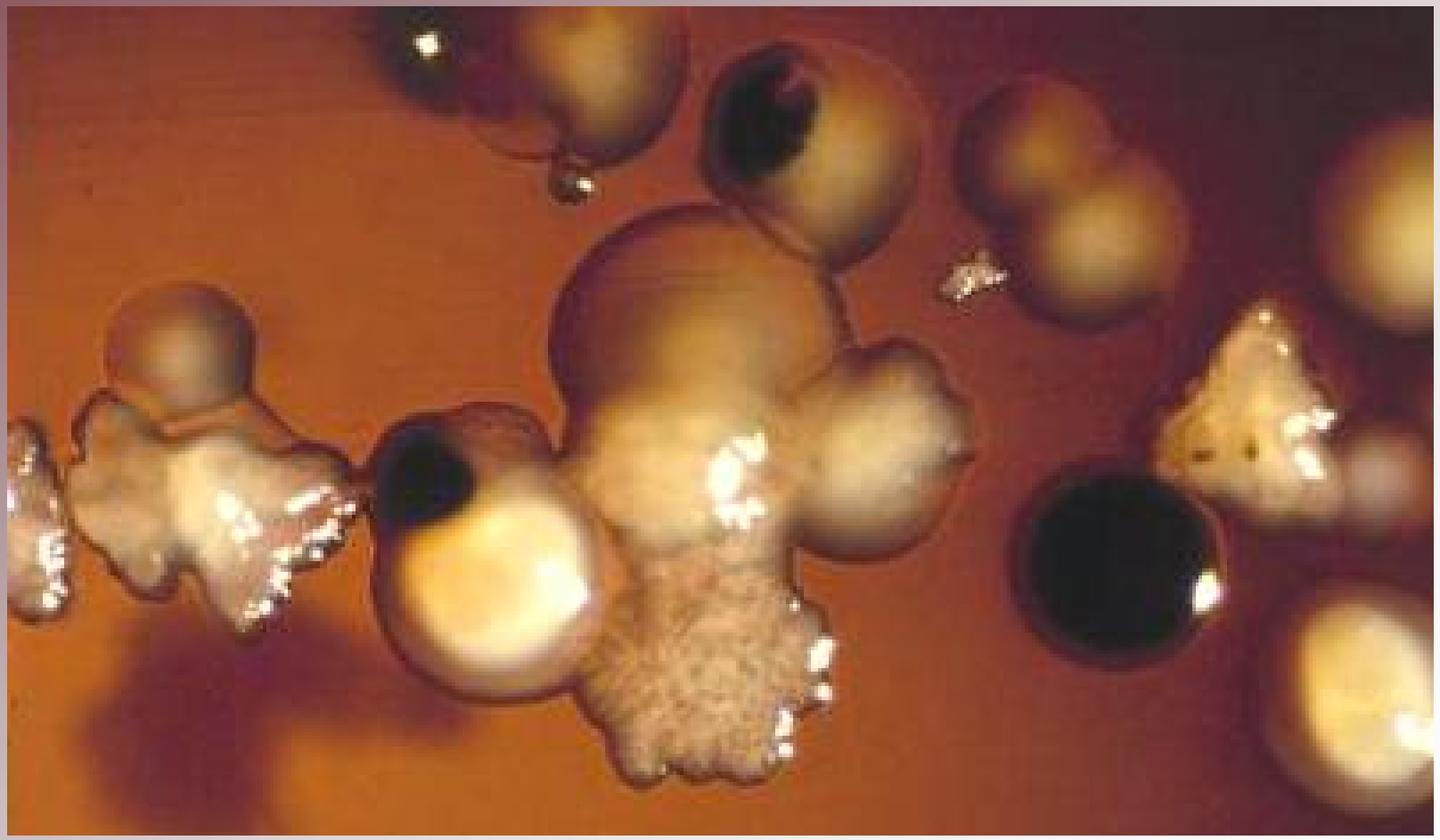




>4 h



Typical picture of anaerobic primary culture plate (after 72 h of incubation in an anaerobic environment) of a sample from an intra-abdominal infection



Processing of the specimen

- Direct examination: Gram stainig (or native) - preliminary diagnosis
- Direct GLC examination – preliminary examination
- Aerobic and CO_2 primary culture result (24-48 h)
- Anaerobic primary culture result (48-96 h)
- (Aerobic/anaerobic liquid cultures)
- Isolation from mixed cultures
- Species and resistance determination – final diagnosis

Do we need this time and work-consuming process?

Guidelines on antibiotic therapy for intra-abdominal infections (The Surgical Infection Society 2002)

Main questions concerning IAIs:

- Which patients require therapeutic administration of antimicrobials because of IAIs? How do we distinguish patients with contamination, requiring only prophylactic antibiotics, from those with established IAIs?
- How long should antimicrobial agents be administered to patients with IAIs?

Guidelines on antibiotic therapy for intra-abdominal infections (The Surgical Infection Society 2002)

- What antimicrobial regimens are recommended for the treatment of patients with IAIs?
- What risk factors can be used to identify patients likely to fail initial antimicrobial therapy? Should the antimicrobial regimen be intensified in such patients to decrease the risk of failure?

Conditions for which therapeutic antimicrobials (>24 h) are not recommended

- Traumatic and iatrogenic enteric perforations (operated on within 12 h)
- Gastroduodenal perforations (operated on within 24 h)
- Acute or gangrenous appendicitis without perforation
- Acute or gangrenous cholecystitis without perforation
- Transmural bowel necrosis from occlusion without perforation /established peritonitis /abscess formation

Bacteria involved in CA-IAI versus NA-IAI (AAC *44:* 2028-2033, 2000)

Bacteria	CA infections		HA infections
E. coli	93 (33%)	⟷	62 (24%)
Proteus spp.	11 (4%)		8 (3%)
Klebsiella spp.	16 (6%)		12 (5%)
Enterobacter spp.	10 (4%)	⟷	22 (8%)
Pseudomona spp.	5 (2%)		12 (5%)
Enterococcus spp.	30 (11%)	⟷	54 (21%)
Staphylococcus spp.	6 (2%)		10 (4%)
Streptococcus spp.	30 (11%)		11 (4%)
Other aerobes	19 (7%)		16 (6%)
Bacteroides spp	24 (9%)		18 (7%)
Clostridium spp.	7 (3%)		4 (2%)
Other anaerobes	13 (5%)		14 (5%)
Candida spp	12 (4%)		15 (6%)

Microbiology of postoperative peritonitis

(Roehrborn A. et al.: Clin.Infect.Dis. 33:1513-9, 2001)

Study period: 1994 September - 2000 June

Patient groups:

- 93 HA- IAI (postoperative peritonitis) patients
  (67 culture-positive, 27 colonized)
- 114 CA-IAI (peritonitis) patients
  (68 culture-positive)

Mortality: 26 (39 %) *vs* 6 (9 %)

APACHE II. score : 14 vs 10

There were patients with mixed infections

Microbiology of postoperative peritonitis

(Roehrborn A. et al.: Clin.Infect.Dis. 33:1513-9, 2001)

Strains	HA- peritonitis (n=111)	CA-peritonitis (n=118)	P
Enterococci	23 (21%)	6 (5%)	.001
E. coli	21 (19%)	42 (36%)	.005
Enterobacter spp.	13 (12%)	4 (3%)	<.05
Bacteroides spp.	8 (7%)	12 (10%)	
Klebsiella spp.	9 (7%)	8 (7%)	
S. aureus MRSA?	7 (6%)	1 (1%)	<.05

Microbiology of postoperative peritonitis

(Roehrborn A. et al.: Clin.Infect.Dis. 33:1513-9, 2001)

Strains	HA-peritonitis (n=111)	CA-peritonitis (n=118)	P
CNS	6 (5%)	1 (1%)	.05
Candida spp.	4 (4%)	8 (7%)	
Pseudomonas spp.	7 (6 %)	2 (2%)	
Streptococci	4 (4 %)	17 (14%)	.005
Beta-haemolytic streptococci		4 (3%)	
Others	10 (9 %)	13 (11%)	

What is the role of enterococci in IAIs?

- It is not yet decided whether the empirical antibiotic therapy should contain a drug against enterococci
  - Often-used combination: cefotaxime + metronidazole
  - Is it correct in life-threatening condition?
  - In immune suppression?
- If the therapy is introduced according to the culture results
  - but the patient is not improving on a therapy not containing an anti-enterococcal drug,
  - the patient has an *Enterococcus*-positive blood culture
  - or the patient is in a life-threatening condition and enterococci are also present in the mixed flora
  - or VRE can often be found in the ward? (Linezolid,Synercid)

What is the role of *Pseudomonas aeruginosa* in IAIs?

- In CA-IAIs which are recognized late or have already been treated by antibiotics. Should the empirical antibiotic treatment contain an anti-pseudomas drug?
  - After 24 h the possibility increase, by 5-20%

- In HA-IAIs with long-term antibiotic therapy, we should consider the presence of multi-drug resistant *Pseudomonas /Acinetobacter*. The empirical therapy had to contain an anti-pseudomas drug.

Empirical antibiotic therapy of IAIs ???

- Changing pattern of aerobes involved
  - Pseudomonas (multi/pan-resistant)
  - Enterococci (VRE??)
- Increasing resistance problems among aerobic bacteria
  - ESBL producing *Klebsiella,* other Gram-negatives
  - Multi-resistant *Enterobacter* spp
  - Carbapenem resistance

Empirical antibiotic therapy of IAIs ???

- Increasing resistance problems concerning anaerobes (Bacteroides strains)

Metronidazole	spreading of *nim* gene (present breakpoints???)
Imipenem (carbapenems)	~1% (*cfiA* gene > 5%) (expression depends on IS elements)
Clindamycin	3-30%
Tetracyclin	10-45%
Amoxicillin/clavulanate	3-10%
4th gen. quinolones	????

Summary of therapy, I

- To treat IAI successfully, you need:
  - Cooperation of surgeons, infectious disease specialists, specialists in intensive care, microbiologists and radiologists
  - The selected antibiotic (antibiotic combination) should cover aerobes and anaerobes !!
  - The outcome is highly influenced by risk factors (the time of the operation, APACHE II score, presence of enterococci and *P. aeruginosa*, activity of antibiotics)

Summary of therapy, II

- There are many questions concerning the treatment of IAIs:
  - Is there any "first choice"?
  - Is it necessary to start with an antibiotic active against enterococci?
  - Should penicillins or cephalosporins be the selected beta-lactams?
  - What is the place of the aminoglycosides today in the treatment of IAIs?