ESS 2012 ISTANBUL
Askeri Museum / November 22-24, 2012

# Severe Abdominal Sepsis
# Antimicrobial treatment

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ANADOLU
In Affiliation with
JOHNS HOPKINS MEDICINE

# Outline

- Definitions
- Pathohenesis of cIAI
  - Community acquired
  - Health care associated
  - Mild to moderate vs severe
- Treatment
- Guidelines
  - IDSA 2010
  - others

# clAI

1


www.akademikcerrahi.com
Acute app

3


www.akademikcerrahi.com
Late onset nazocomial clAI

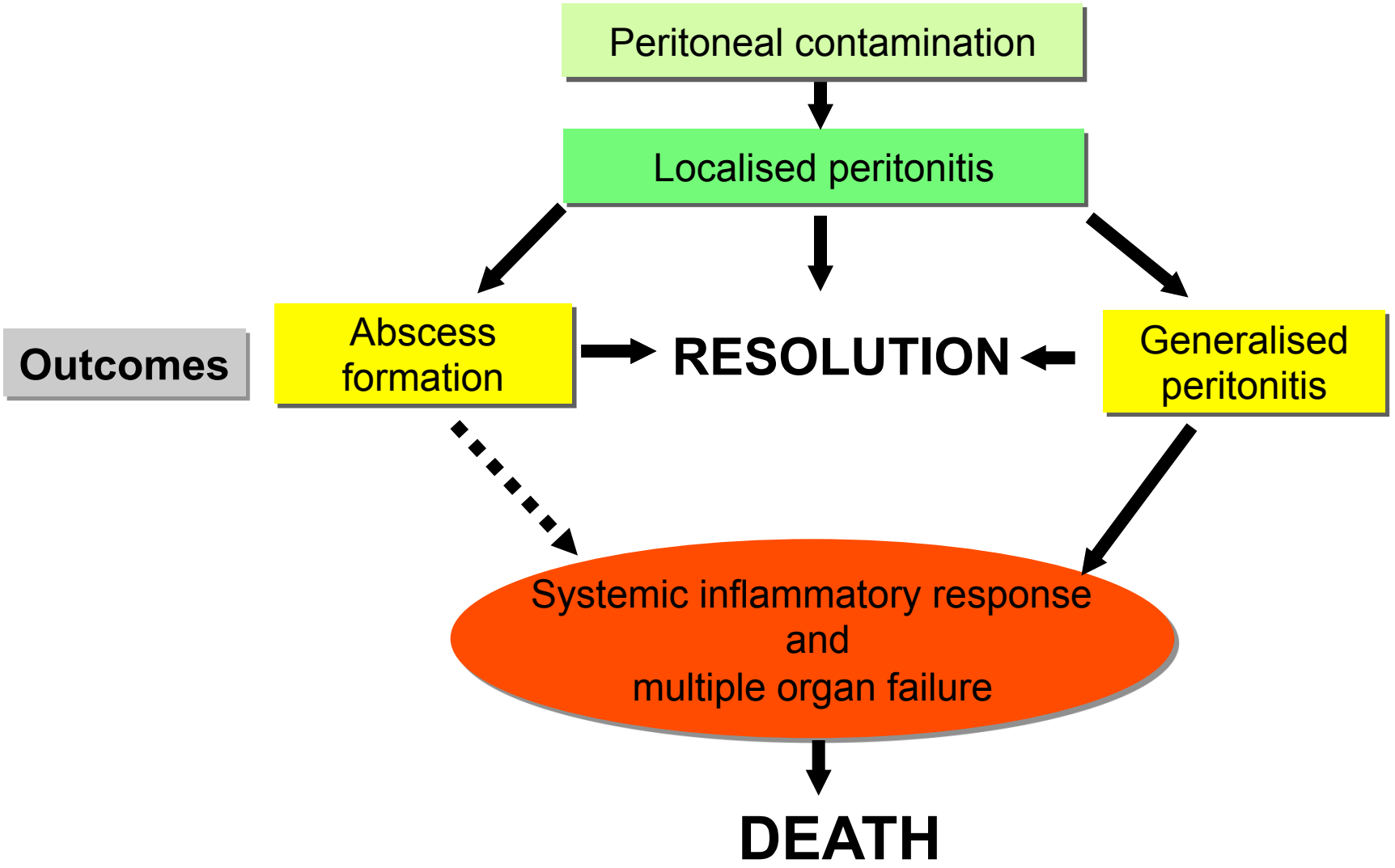
2


MVO
02/01/2005

4

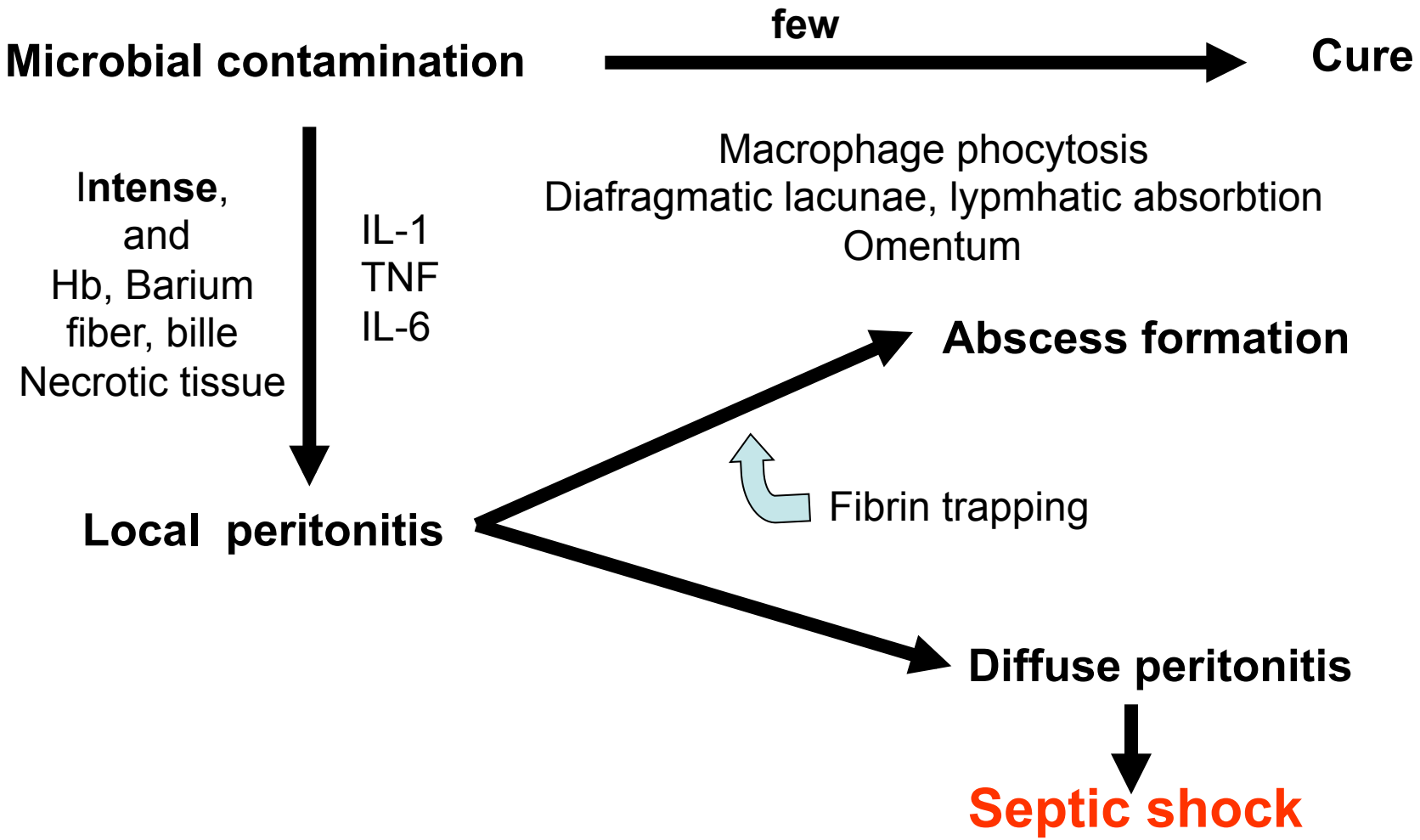

www.akademikcerrahi.com
Aeroenteric fistula, tertiary peritonitis

# Pathogenesis of peritoneal contamination




Adapted from Fig. 2 Cheadle WG *et al*. *Am J Surg*. 2003; **186** (5A): 15–22S

# IAI Pathogenesis




Cerrahi infeksiyonlar ve konak faktörü. Agalar F, Çakmakçı M. in: **İntraabdominal İnfeksiyonlar kitabı.** Eds: Arman D, Agalar F. Bilimsel tıp Yayınevi, Ankara, 2009

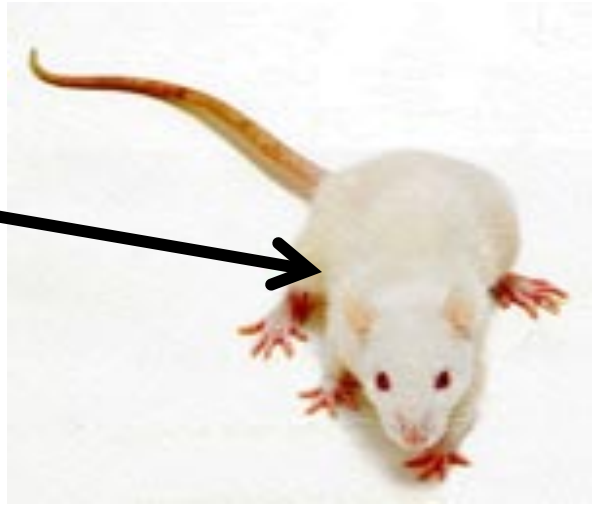
# Abscess

- E coli + B Fragilis,
- Pepto streptoccus
- Adjuvant materials
  - Hemoglobin,
  - Fiber,
  - Barium,
  - Bile
- Fibrin

# Peritonitis: Bimodal disease

Onderdonk. Infect Immun. 1974

Clonic content



No antibiotic therapy

***Duration***

72 hour

mortality

1. week

Abscess formation %100

# antibitoics must be effective to both aerobic and anaerobic bacteria

Onderdonk. J Infect Dis. 1976

Colonic content

| | Mortality | Abscess |
|---|---|---|
| Gentamicin : | %4 | %98 |
| Clindamicin : | %35 | %5 |
| Clin + Genta: | %9 | %6 |

**B Fragilis**

**E Coli**

# High risk patients

- Poor nutritional status
- Significant cardiovascular disease
- Inadequate control of infection source
- Immunosuppression (cancer, transplant, steroids, diabetes, etc)
- Pre-operative antibiotics (not prophylaxis)
- High APACHE II score
- Chronic inflammatory disease
- Elderly
- Renal failure
- Severe obesity
- Nosocomial infection
- Resistant pathogens

**CONSIDER USING 'BIG GUNS'**

Mazuski JE, *Surg Infect* 2002; **3**:161–73

# Intra-abdominal infections: one name, many distinct conditions

- Primary peritonitis
  - Spontaneous bacterial peritonitis
- Secondary peritonitis 
- Tertiary peritonitis
  - Recurrent/persistent peritonitis

# Secondary peritonitis

- Perforated gastroduodenal ulcers
- Biliary tract infections
- Small bowel perforations
- Complicated appendicitis (with abscess or perforation)
- Complicated diverticulitis (with abscess or perforation)

# Tertiary peritonitis

It is a serios disease with a high mortality rate due to inadequate or unproper treatment of low virulent but highly resistant microoraganisms.

It can be defined as secondary peritonitis that persists after 48 hours of appropriate therapy or as patients who require >1 operation for infection source control

Treatment decisions should be considered according to the hospital resistance profiles.

- Coagulse - Staphylococcus
- Enterococcus
- MDR Gr - Bacillus
- Fungi

# FDA definition of intra-abdominal infections

## Uncomplicated[1]

- May be treated with antimicrobial therapy without operative or percutaneous intervention
- Examples:
  - Acute cholecystitis
  - Uncomplicated diverticulitis
  - Acute appendicitis ?

## Complicated[2]

- Extends beyond the hollow viscus of origin into the peritoneal space causing:
  - Peritonitis
  - Abscess
- Requires operative intervention or percutaneous drainage

[1]Solomkin JS *et al*. *Clin Infect Dis*. 1992; **15 Suppl 1**: S33-42; [2]Solomkin JS *et al*. IDSA Guidelines. *Clin Infect Dis*. 2003; **37**: 997–1005

# Stratification of intra-abdominal infections

- Mild-to-moderate vs severe infection according to risk factors
- Community- vs healthcare-associated
- Etiologic causes at site of origin

# IDSA guideline classification: *complicated* intra-abdominal infections

Community-acquired

- Gangrene, necrosis or perforation of the stomach, duodenum and bowel
- Biliary tract infections
- Complicated appendicitis (with abscess or perforation)

Healthcare-associated

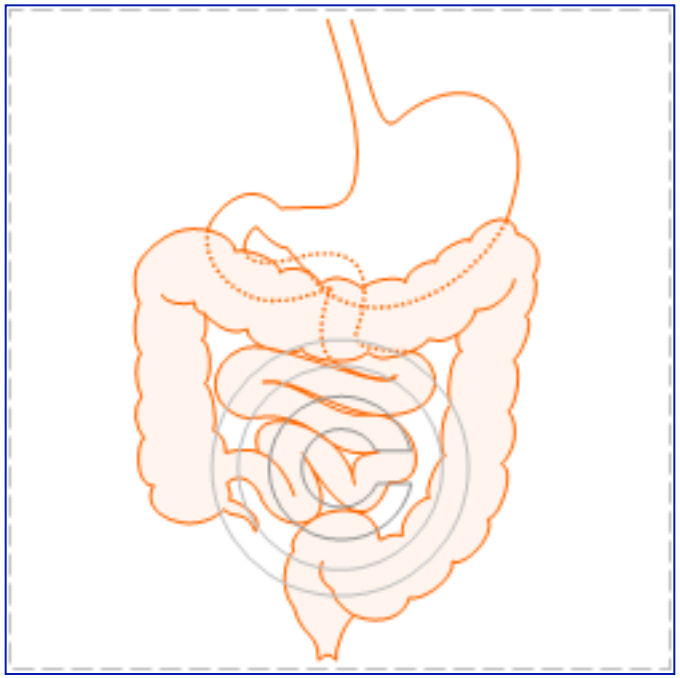
- Complications of previous elective or emergent intra-abdominal operations associated with nosocomial isolates

80% of all intra-abdominal infections are community-acquired[2]

[1]Solomkin JS *et al*. *Clin Infect Dis*. 1992; **15 Suppl 1**: S33-42; [2]Solomkin JS *et al*. IDSA Guidelines. *Clin Infect Dis*. 2003; **37**: 997–1005

# Community-acquired infections: location of GI perforation defines infecting flora

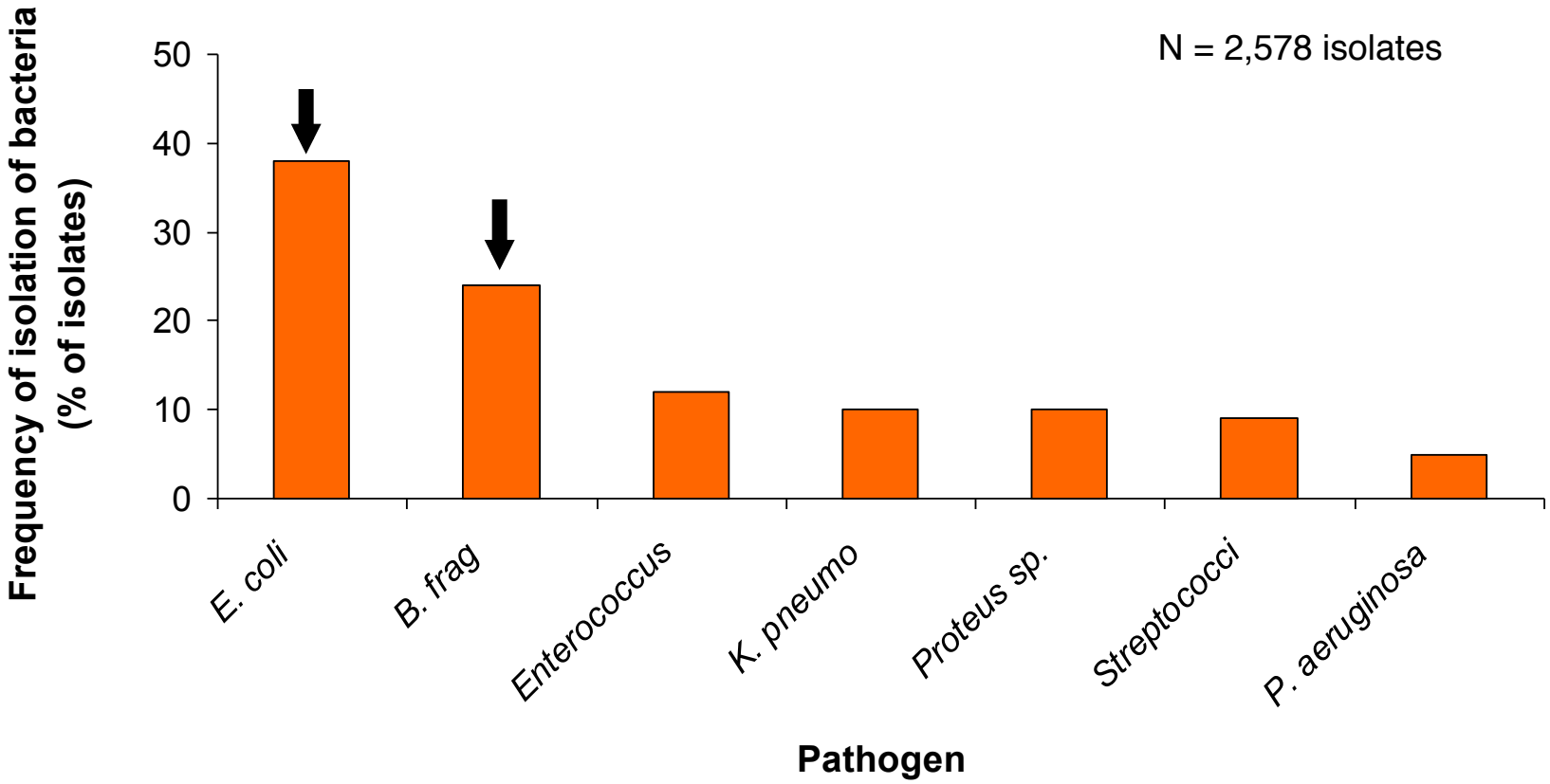
- Stomach, duodenum, biliary tract, proximal small bowel:
  - Gram-positive or Gram-negative aerobes and facultative organisms
- Distal small bowel:
  - Perforation – Gram-negative aerobes and facultative organisms
  - Abscess – anaerobes (e.g. *B. fragilis*)
- Colon:
  - Obligate anaerobes and facultative organisms
  - Gram-positive aerobes (e.g. enterococci)
  - Gram-negative facultative organisms (e.g. *E. coli*)



**Increasing complexity distally**

Solomkin JS *et al*. IDSA Guidelines. *Clin Infect Dis*. 2003; **37**: 997–1005

# Major pathogens in community-acquired intra-abdominal infections




Wittmann DH, in *Infectious Diseases*, Gorbach SL *et al*. (eds.); W.B. Saunders, Toronto 2004. pp714–23

# Changing polymicrobial flora in post-operative peritonitis

| Strain | Community-acquired (% isolates)† | Postoperative (% isolates)‡ |
|---|---|---|
| ***E. coli*** | 36 | 19 |
| **Enterococci** | 5 | 21 |
| ***Enterobacter* spp.** | 3 | 12 |
| **Streptococci** | 14 | 4 |
| ***Bacteroides* spp.** | 10 | 7 |
| ***S. aureus*** | 1 | 6 |
| **Coagulase-neg. staphylococci** | 1 | 5 |
| ***Pseudomonas* spp.** | 2 | 6 |
| ***Candida* spp.** | 7 | 4 |
| ***Klebsiella* spp.** | 7 | 7 |

†68 patients, 118 isolates; ‡67 patients, 111 isolates

Adapted from Roehrborn A *et al*. *Clin Infect Dis*. 2001; **33**: 1513–1519

# Bacteriologic findings at relaparotomy in non-survivors of postoperative peritonitis

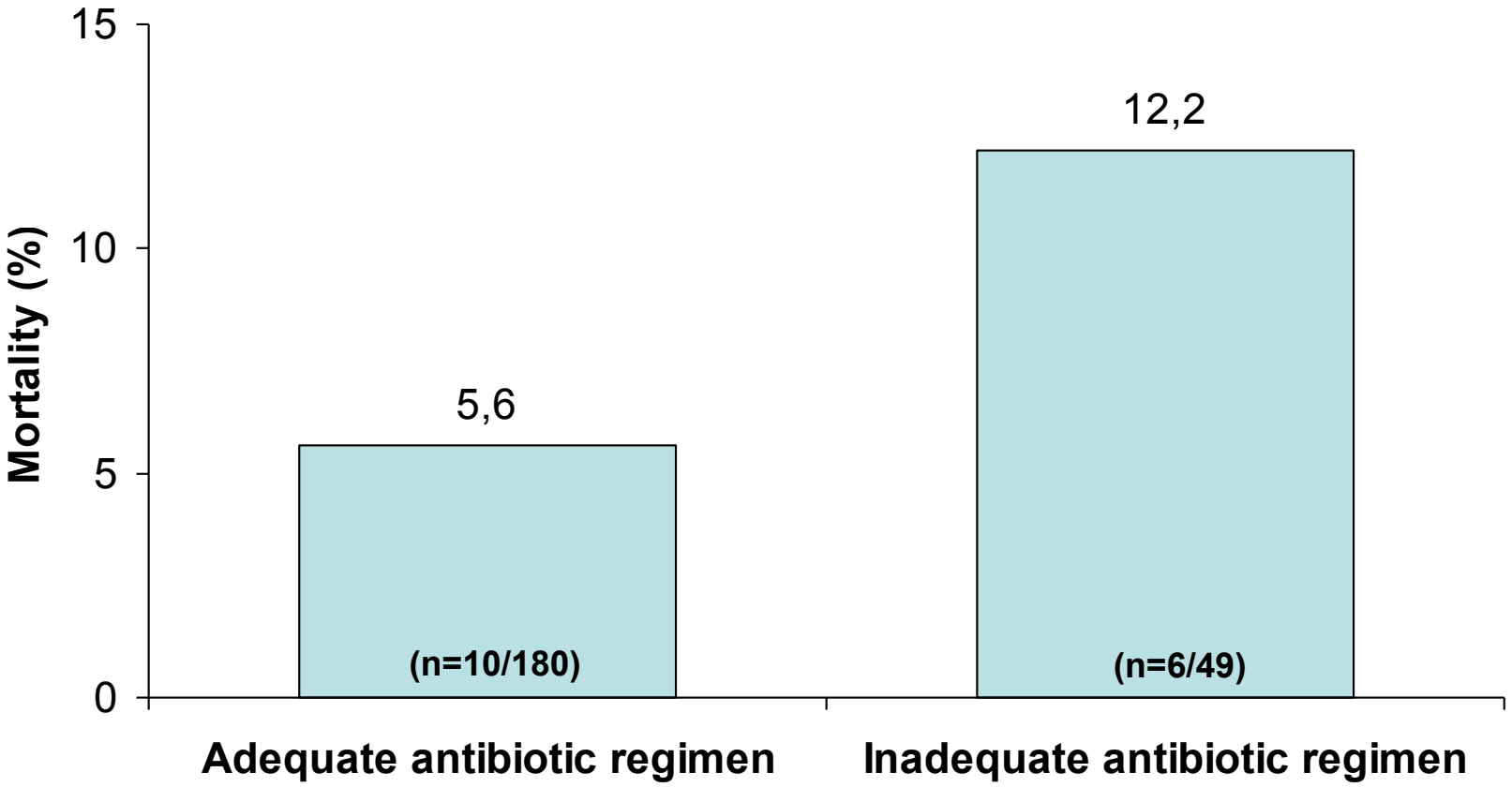
| Strain | Isolates recovered from 26 non-survivors (n[%]) |
|---|---|
| ***Total*** | **53** |
| ***Enterococci*** | 13 (25) |
| ***Enterobacter* spp.** | 10 (19) |
| ***E. coli*** | 5 (9) |
| ***Bacteroides* spp.** | 4 (8) |
| ***Klebsiella* spp.** | 4 (8) |
| ***S. aureus*** | 4 (8) |
| ***Candida* spp.** | 3 (6) |
| **Coag.-neg. staphylococci** | 2 (4) |
| **Streptococci** | 3 (6) |
| ***Pseudomonas* spp.** | 1 (2) |
| **Other** | 4 (8) |

Adapted from Roehrborn A *et al*. *Clin Infect Dis*. 2001; **33**: 1513–1519

# Summary

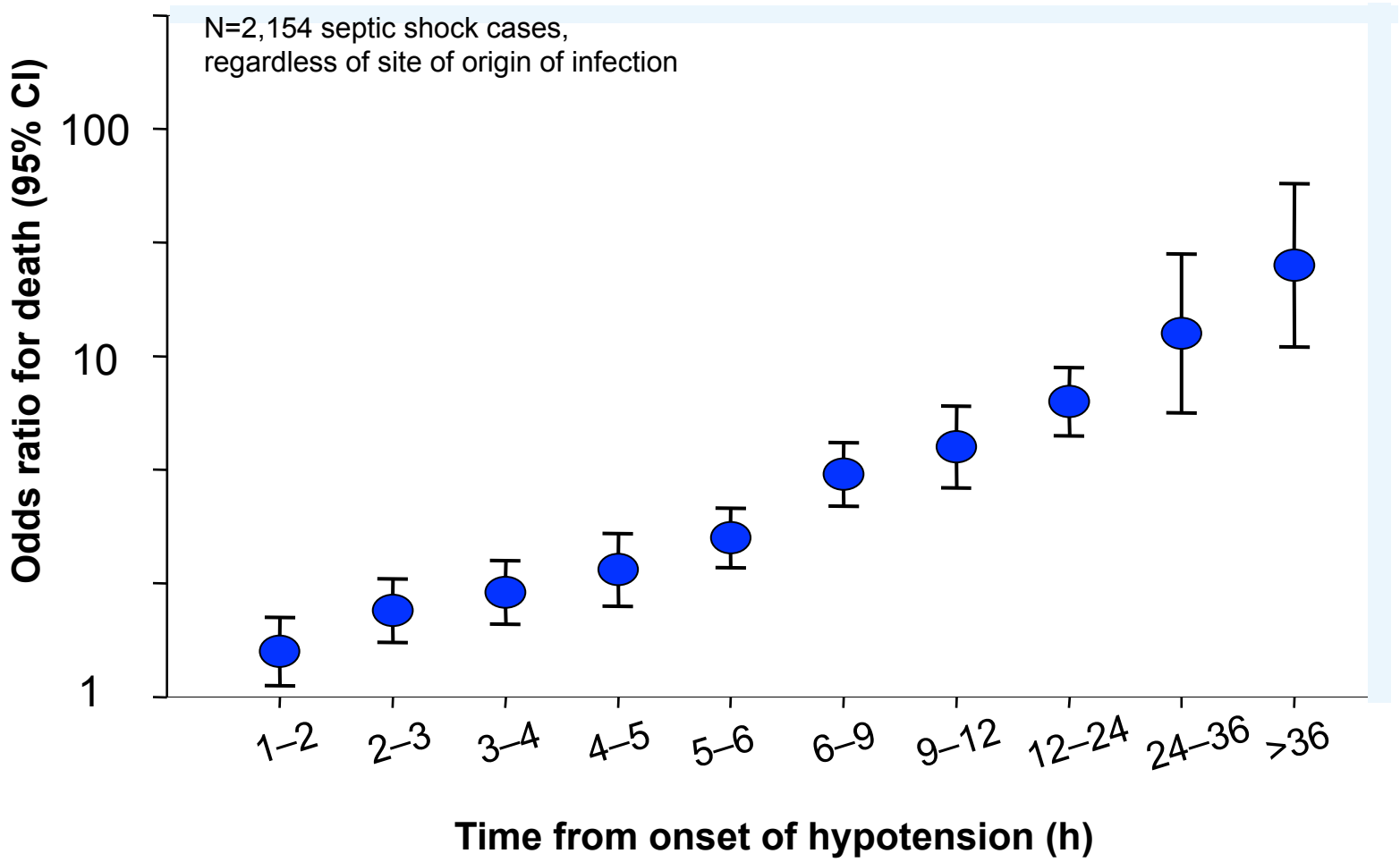
- **Community-acquired infections**
  - Location of the GI perforation defines the infecting flora and severity
  - Empiric treatment should cover *Bacteroides spp*. and *E. coli*, the most common pathogens
- **Health care-associated infections**
  - Caused by more resistant flora in post-operative patients
  - Consider local susceptibility patterns when selecting empiric antimicrobial therapy

# Effect of appropriate vs inappropriate therapy on mortality in IAI



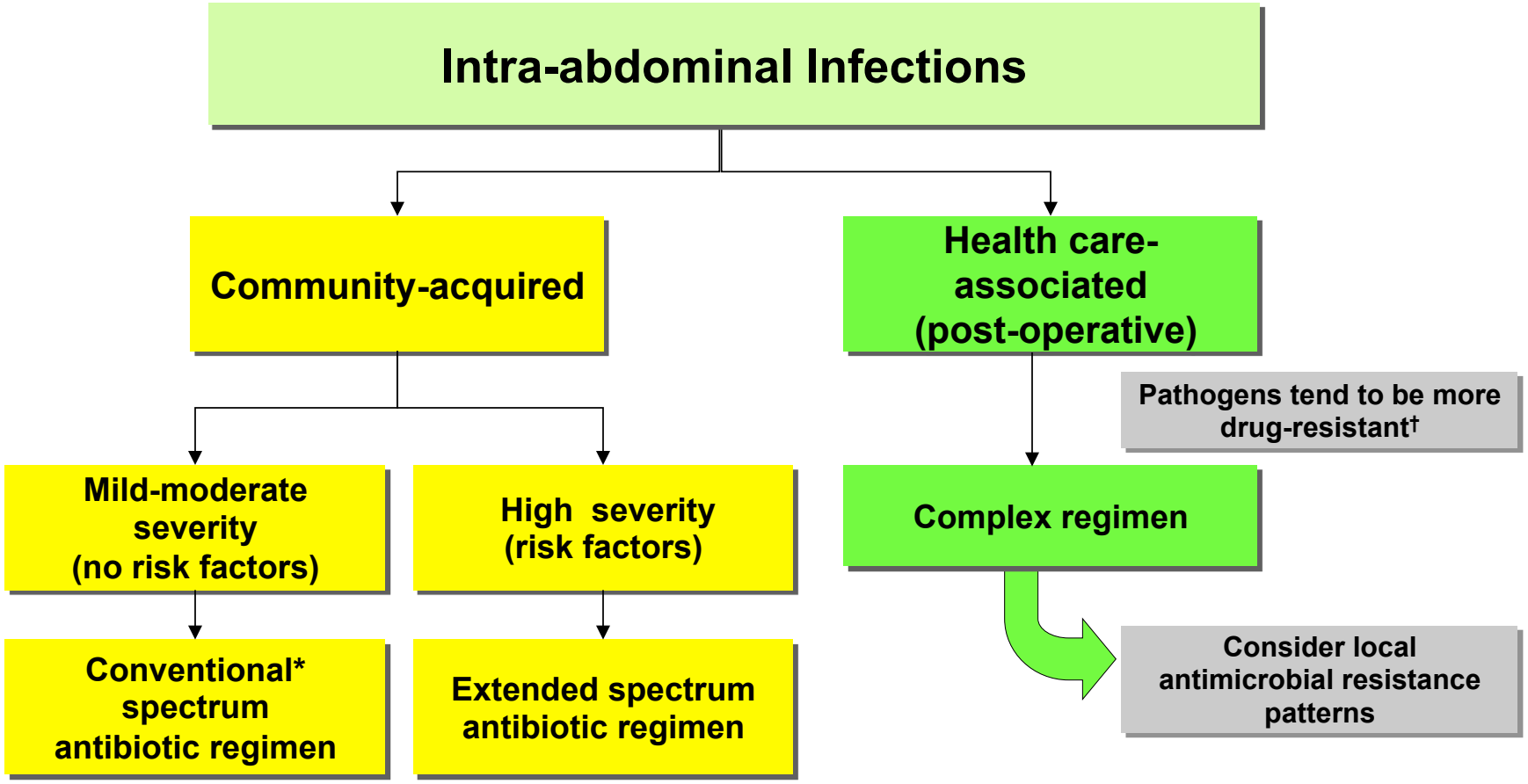

Mosdell *et al. Ann Surg* 1991; **214** (5): 543–52

# Impact of delayed antibiotic therapy on clinical outcome




Kumar A *et al*. *Crit Care Med 2006;* **34**: 1589

# Antimicrobial treatment of intra-abdominal infections




*** Coverage for *B. fragilis* and *E. coli***

Adapted from Solomkin JS *et al*. IDSA Guidelines. *Clin Infect Dis*. 2003; **37**: 997–1005

# Bu xsıraya antibiyotikler girmeli

# Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America

**Joseph S. Solomkin,[1] John E. Mazuski,[2] John S. Bradley,[3] Keith A. Rodvold,[7,8] Ellie J. C. Goldstein,[5] Ellen J. Baron,[6] Patrick J. O'Neill,[9] Anthony W. Chow,[16] E. Patchen Dellinger,[10] Soumitra R. Eachempati,[11] Sherwood Gorbach,[12] Mary Hilfiker,[4] Addison K. May,[13] Avery B. Nathens,[17] Robert G. Sawyer,[14] and John G. Bartlett[15]**

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**Evidence-based guidelines for managing patients with intra-abdominal infection were prepared by an Expert Panel of the Surgical Infection Society and the Infectious Diseases Society of America. These updated guidelines replace those previously published in 2002 and 2003. The guidelines are intended for treating patients who either have these infections or may be at risk for them. New information, based on publications from the period 2003–2008, is incorporated into this guideline document. The panel has also added recommendations for managing intra-abdominal infection in children, particularly where such management differs from that of adults; for appendicitis in patients of all ages; and for necrotizing enterocolitis in neonates.**

# IDSA

- The newest, comprehensive and valid
- Replaced the previous versions of IDSA and SIS-NA guidelines
  - Peritonitis, intra-abdominal infection + biliary infection, apandicitids, and pediatric cIAI
  - 16 key questions
  - 111 recommendations
    - 15 Level 1 (A-I)
- Doripenem ,Tigesiklin and Moxiflokcacin included
- Sefoksitin came back

# cIAI Treatment: Candida

**2003**

Indicated if,

- the patient receives on an immunosuppressive therapy
- or the patient has had a recurrent IAI (B-2).

**2010**

- Indicated in serious cIAI or the patient has had a HCA IAI and abdominal fluid cultures revealed candida (B-II).
- More serious patients may probably require ecinoquandin (B-III).

# Key questions addressed by the guideline

1. When should antimicrobial therapy initiated for patients suspected or confirmed intra-andominal infection?
2. When and how microbial specimens be obtained and processed?
3. Which are appropriate antimicrobial regimens for patients with community acquired intra-abdominal infection, particularly with regard to candida, enterococcus and MRSA

# Key questions addressed by the guideline

4. How should antimicrobilogical results be used to adjust antimicrobial therapy?
5. What is the appropriate duration of therapy for patients with complicated intra-abdominal infection?
6. How should suspected treatment failure be managed?

# IDSA Guideline Recommendations for Community Acquired cIAIs (2010)

**Table 2. Agents and Regimens that May Be Used for the Initial Empiric Treatment of Extra-biliary Complicated Intra-abdominal Infection**

| Regimen | Community-acquired infection in pediatric patients | Community-acquired infection in adults | |
|---|---|---|---|
| | | Mild-to-moderate severity: perforated or abscessed appendicitis and other infections of mild-to-moderate severity | High risk or severity: severe physiologic disturbance, advanced age, or immunocompromised state |
| Single agent | Ertapenem, meropenem, imipenem-cilastatin, ticarcillin-clavulanate, and piperacillin-tazobactam | Cefoxitin, ertapenem, moxifloxacin, tigecycline, and ticarcillin-clavulanic acid | Imipenem-cilastatin, meropenem, doripenem, and piperacillin-tazobactam |
| Combination | Ceftriaxone, cefotaxime, cefepime, or ceftazidime, each in combination with metronidazole; gentamicin or tobramycin, each in combination with metronidazole or clindamycin, and with or without ampicillin | Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole[a] | Cefepime, ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole[a] |

[a] Because of increasing resistance of *Escherichia coli* to fluoroquinolones, local population susceptibility profiles and, if available, isolate susceptibility should be reviewed.

* Because of increasing resistance of *Escherichia coli to fluoroquinolones, local population susceptibility profiles and, if available, isolate susceptibility should*be reviewed.

# IDSA Guideline Recommendations for Health Care Associated cIAIs (2010)

**Table 3. Recommendations for Empiric Antimicrobial Therapy for Health Care–Associated Complicated Intra-abdominal Infection**

| | Regimen | | | | |
|---|---|---|---|---|---|
| Organisms seen in health care–associated infection at the local institution | Carbapenem[a] | Piperacillin-tazobactam | Ceftazidime or cefepime, each with metronidazole | Aminoglycoside | Vancomycin |
| <20% Resistant *Pseudomonas aeruginosa*, ESBL-producing Enterobacteriaceae, *Acinetobacter*, or other MDR GNB | Recommended | Recommended | Recommended | Not recommended | Not recommended |
| ESBL-producing Enterobacteriaceae | Recommended | Recommended | Not recommended | Recommended | Not recommended |
| *P. aeruginosa* >20% resistant to ceftazidime | Recommended | Recommended | Not recommended | Recommended | Not recommended |
| MRSA | Not recommended | Not recommended | Not recommended | Not recommended | Recommended |

**NOTE.** ESBL, extended-spectrum β-lactamase; GNB, gram-negative bacilli; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*. "Recommended" indicates that the listed agent or class is recommended for empiric use, before culture and susceptibility data are available, at institutions that encounter these isolates from other health care–associated infections. These may be unit- or hospital-specific.

[a] Imipenem-cilastatin, meropenem, or doripenem

# Agents and Regimens that May Be Used for the Initial Empiric Treatment of Biliary Infection in Adults IDSA (2010)

**Table 4. Agents and Regimens that May Be Used for the Initial Empiric Treatment of Biliary Infection in Adults**

| Infection | Regimen |
|---|---|
| Community-acquired acute cholecystitis of mild-to-moderate severity | Cefazolin, cefuroxime, or ceftriaxone |
| Community-acquired acute cholecystitis of severe physiologic disturbance, advanced age, or immunocompromised state | Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, or cefepime, each in combination with metronidazole[a] |
| Acute cholangitis following bilio-enteric anastamosis of any severity | Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, or cefepime, each in combination with metronidazole[a] |
| Health care–associated biliary infection of any severity | Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, or cefepime, each in combination with metronidazole, vancomycin added to each regimen[a] |

[a] Because of increasing resistance of *Escherichia coli* to fluoroquinolones, local population susceptibility profiles and, if available, isolate susceptibility should be reviewed.

# Routine coverage of enterococci and fungi not necessary if it is mild disease

## Enterococci

- **Not necessary** in community-acquired infections
- Treat empirically if healthcare-associated infection
- Consult local susceptibility patterns

## Fungi

- **Not necessary** unless patient has risk factors or postoperative infection
- If *Candida albicans* found – fluconazole
- For fluconazole resistant *Candida* species – amphotericin B, caspofungin, or voriconazole

Adapted from Solomkin JS *et al*. IDSA Guidelines. *Clin Infect Dis*. 2003; **37**: 997–1005

# Enterococcus

- It is role in early mortality is unkown
- Enterococcus bacteremia is the most important parameter of treatment failure.
- Older age, high APACHE II, longer ICU stay are the risk factors for enterecoccus septicemia

Burnett et al. Surg 1995

# Multidrug-resistant pathogens

- The threat of antimicrobial resistance has been identified as one of the major challenges in the management of complicated intra-abdominal infections.
- Over the past few decades, an increase of infections caused by antibiotic-resistant pathogens, including methicillin-resistant Staphylococcus aureus, vancomycin resistant Enterococcus species, carbapenem-resistant
- Pseudomonas aeruginosa, extended-spectrum beta-lactamase- producing Escherichia coli and Klebsiella spp., and multidrug-resistant Acinetobacter spp., has been observed, also in intra-abdominal infections.

# Initial Intravenous Adult Dosages of Antibiotics for Empiric Treatment of Complicated Intra-abdominal Infection IDSA (2010)

**Table 6. Initial Intravenous Adult Dosages of Antibiotics for Empiric Treatment of Complicated Intra-abdominal Infection**

| Antibiotic | Adult dosage[a] |
|---|---|
| β-lactam/β-lactamase inhibitor combination | |
| Piperacillin-tazobactam | 3.375 g every 6 h[b] |
| Ticarcillin-clavulanic acid | 3.1 g every 6 h; FDA labeling indicates 200 mg/kg/day in divided doses every 6 h for moderate infection and 300 mg/kg/day in divided doses every 4 h for severe infection |
| Carbapenems | |
| Doripenem | 500 mg every 8 h |
| Ertapenem | 1 g every 24 h |
| Imipenem/cilistatin | 500 mg every 6 h or 1 g every 8 h |
| Meropenem | 1 g every 8 h |
| Cephalosporins | |
| Cefazolin | 1–2 g every 8 h |
| Cefepime | 2 g every 8–12 h |
| Cefotaxime | 1–2 g every 6–8 h |
| Cefoxitin | 2 g every 6 h |
| Ceftazidime | 2 g every 8 h |
| Ceftriaxone | 1–2 g every 12–24 h |
| Cefuroxime | 1.5 g every 8 h |
| Tigecycline | 100 mg initial dose, then 50 mg every 12 h |
| Fluoroquinolones | |
| Ciprofloxacin | 400 mg every 12 h |
| Levofloxacin | 750 mg every 24 h |
| Moxifloxacin | 400 mg every 24 h |
| Metronidazole | 500 mg every 8–12 h or 1500 mg every 24 h |
| Aminoglycosides | |
| Gentamicin or tobramycin | 5–7 mg/kg[c] every 24 h[d] |
| Amikacin | 15–20 mg/kg[c] every 24 h[d] |
| Aztreonam | 1–2 g every 6–8 h |
| Vancomycin | 15–20 mg/kg[e] every 8–12 h[d] |

**NOTE. FDA, United States Food and Drug Administration.**

a Dosages are based on normal renal and hepatic function.

b For *Pseudomonas aeruginosa infection, dosage may be increased to 3.375 g every 4 h or 4.5 g every 6 h.*

c Initial dosage regimens for aminoglycosides should be based on adjusted body weight.

d Serum drug-concentration monitoring should be considered for dosage individualization.

e Initial dosage regimens for vancomycin should be based on total body weight.

# Organisms Identified in 3 Randomized Prospective Trials of Investigational Antibiotics for Complicated Intra-abdominal Infection, including 1237 Microbiologically Confirmed InfectionsOrganisms Identified in 3 Randomized Prospective Trials of Investigational Antibiotics for Complicated Intra-abdominal Infection, including 1237 Microbiologically Confirmed Infections

**Table 8. Organisms Identified in 3 Randomized Prospective Trials of Investigational Antibiotics for Complicated Intra-abdominal Infection, including 1237 Microbiologically Confirmed Infections**

| Organism | Patients, % ($n$ = 1237) |
|---|---|
| Facultative and aerobic gram-negative | |
| *Escherichia coli* | 71 |
| *Klebsiella* species | 14 |
| *Pseudomonas aeruginosa* | 14 |
| *Proteus mirabilis* | 5 |
| *Enterobacter* species | 5 |
| Anaerobic | |
| *Bacteroides fragilis* | 35 |
| Other *Bacteroides* species | 71 |
| *Clostridium* species | 29 |
| *Prevotella* species | 12 |
| *Peptostreptococcus* species | 17 |
| *Fusobacterium* species | 9 |
| *Eubacterium* species | 17 |
| Gram-positive aerobic cocci | |
| *Streptococcus* species | 38 |
| *Enterococcus faecalis* | 12 |
| *Enterococcus faecium* | 3 |
| *Enterococcus* species | 8 |
| *Staphylococcus aureus* | 4 |

**NOTE.** Adapted from [77, 165, 189]. The frequency of specific *Bacteroides* species and other anaerobes is provided elsewhere [59].

IDSA 2010

# Duration of therapy

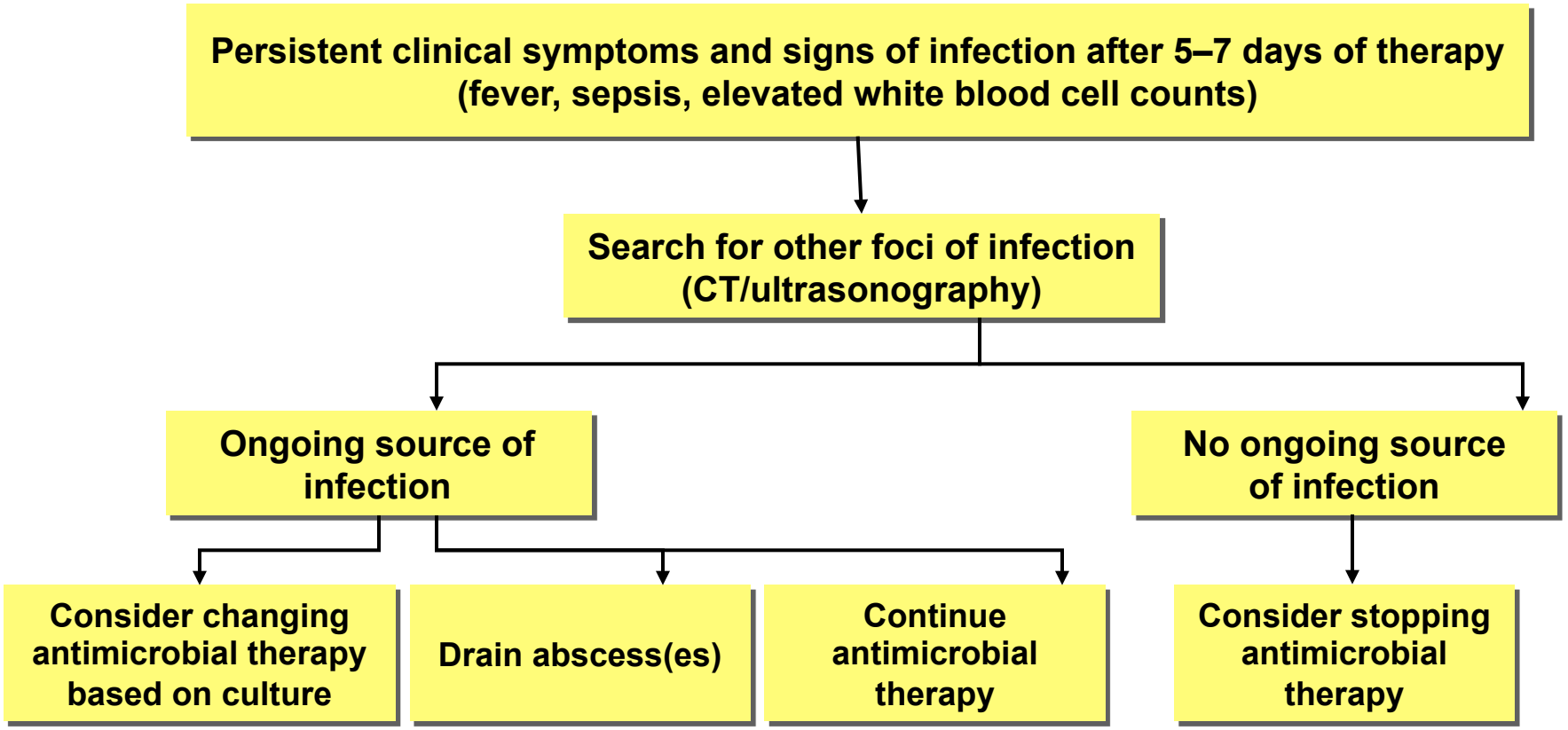
- Continue therapy until clinical symptoms are resolving
  - Afebrile
  - Normalising WBC count

- Step-down therapy is acceptable for patients who are able to tolerate an oral diet
  - Fluoroquinolone + metronidazole
  - Moxifloxacin
  - Oral amoxicillin/clavulanic acid

**Consequence:** if clinical resolution not achieved by 5–7 days, appropriate diagnostic investigation should be undertaken

Solomkin JS *et al*. IDSA Guidelines. *Clin Infect Dis*. 2003; **37**: 997–1005; Malangoni MA *et al*. *Ann Surg*. 2006; **244**(2): 204–211

# Treatment of persistent or recurrent infection following antimicrobial treatment




Solomkin JS *et al*. IDSA Guidelines. *Clin Infect Dis*. 2003; **37**: 997–1005

# Conclusion

- The most important component of peritonitis treatment is to control of septic source
- In severe cIAI emprirical entibiotic treament should cover both anaerobic, aerobic bacteria.
- Agents against fungi and enterococ should also be considered.
- Hospital resistance perofiles are noteworthy in determining the antimicrobial treatment.

***Thanks for your attention***

- To predict the main pathogens involved and the related resistance patterns, infections are to be classed as community or hospital acquired.
- During the past 2 decades the incidence of hospital acquired infection caused by resistant microorganisms has significantly risen, probably in relationship with high level of antibiotic exposure and increasing rate of patients with one or more predisposing conditions such as recent exposure to antibiotics, high severity of illness, advanced age, co-morbidity, degree of organ dysfunction, low albumin level, poor nutritional status, immunodepression and presence of malignancy.

- The major pathogens involved in community-acquired intra-abdominal infection are Enterobacteriaceae, Streptococcus spp and anaerobes (especially B. fragilis).
- Within the healthcare-associated infections, the spectrum of microorganism involved is broader, encompassing not only Enterobacteriaceae, Streptococcus spp. And anaerobes, but also Enterococcus spp and Candida spp.

- The threat of antimicrobial resistance has been identified as one of the major challenges in the management of intra-abdominal infections. The emergence of multidrug- resistant bacteria and the scanty pipeline of new antibiotics to fight them are, as of today, a concern especially for gram negative microorganisms, as highlighted in a recent report from the European Antimicrobial Resistance Surveillance System [39].
- Hospital-acquired IAIs are commonly caused by more resistant bacteria, although the level of resistance is significant also in the community acquired infections.
- The Study for Monitoring Antimicrobial Resistance Trends (SMART) program has been monitoring the activity of antibiotics against aerobic Gram-negative intra-abdominal infections. Hawser and coll. [40] reported susceptibility levels of key intra-abdominal pathogens in Europe for 2008, and showed that the options for effective empirical therapy of intraabdominal infection have significantly reduced

- Coque and coll. highlighted the growing threat posed by increasing prevalence of extended-spectrum beta lactamase (ESBL) producing Enterobacteriaceae all over Europe, even in countries traditionally showing low prevalence rates of resistance [41]. Increase of this resistance pattern has led to a progressive expansion of carbapenems use, because this class of antibiotics was traditionally considered the last resort for managing ESBL producers Enterobacteriaceae.

The inevitably increased carbapenem consumption has been associated to increasing carbapenemase production among Enterobacteriaceae. The recent rapid spread of serine carbapenemase in Klebsiella pneumoniae (KPC) is now an additional major threat for antimicrobial therapy in hospitals worldwide, and stresses the concept that the use of carbapenems must be mandatorily optimized in terms of indication and exposure [42].

Also Acinetobacter spp have worldwide shown similar alarming rates of increasing resistance to antibiotics. Today, Carbapenem-resistant A. baumannii-producing oxacillinases retaining susceptibility to only colistin and tigecycline is an ominous reality in hospitals worldwide and compounding this problem is the paucity of new antibiotics under development to address it [43].

In hospital acquired IAIs also P. aeruginosa plays an important - although less critical than in other settings - role.

The high intrinsic antibiotic resistance of this pathogen, together with its extraordinary capacity for acquiring additional resistances through chromosomal mutations, should be always taken into consideration.

- Among multidrug resistant Gram positive bacteria, Enterococci remain a challenge despite the availability of large number of antimicrobial agents theoretically active against this species.
- The clinical management of enterococcal infection remains challenging, mainly because no single agent could be anticipated to exert strong bactericidal activity against them.

Enterococci are frequently responsible for hospital acquired IAIs. During the past 2 decades the incidence of hospital-acquired enterococcal infection has significantly risen, probably in relationship with high level of antibiotic exposure and increasing number of patients with variable levels of immunosuppresion. In the aforementioned French survey, the prevalence of enterococcal isolation was significantly higher in the nosocomial cases of peritonitis and a significant increased incidence of fatal cases of peritonitis with positive cultures for enterococci was reported (20% versus 9% - $p < 0.003$) [35].

# At which time

Recent international guidelines for the management of severe sepsis and septic shock (Surviving Sepsis Campaign) [6] recommend intravenous antibiotics within the first hour after severe sepsis and septic shock are recognized, use of broad-spectrum agents with good penetration into the presumed site of infection, and reassessment of the antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity and minimize costs [6].

- For example, in critically ill patients, higher-than-standard loading doses of b-lactams, aminoglycosides or glycopeptides should be administered to ensure optimal exposure at the infection site independently of the patient’s renal function [47-49].

For lipophilic antibiotics such as fluoroquinolones and tetracyclines, the ‘dilution effect’ in the extracellular fluids during severe sepsis may be mitigated by the rapid redistribution of the drug from the intracellular compartment to the interstitium. In contrast to what happens with hydrophilic antimicrobials, standard dosages of lipophilic antimicrobials may frequently ensure adequate loading even in patients with severe sepsis or septic shock [47].

# Burada kaldım

Once appropriate initial loading is achieved, daily reassessment of the antimicrobial regimen is warranted, because the pathophysiological changes that may occur could significantly affect drug disposition in the critically ill patients.

- Conversely, it is less evident that higher than standard dosages of renally excreted drugs may be needed for optimal exposure in patients with glomerular hyperfiltration [47].

- Therefore, selecting higher dosages and/or alternative dosing regimens focused on maximizing the pharmacodynamics of antimicrobials might be worthwhile, with the intent being to increase clinical cure rates among critically ill patients.

- Sartelli et al. World Journal of Emergency Surgery 2011, 6:2 http://www.wjes.org/content/6/1/2 Page 7
- Two patterns of of bactericidal activity have been identified: time-dependent activity (where the time that the plasma concentration persists above the MIC of the etiological agent is considered the major determinant for efficacy) and concentration- dependent activity (where the efficacy is mainly related to the plasma peak concentration in relation to the MIC of the microorganism). In addition, these agents show an associated concentration-dependent post-antibiotic effect, and bactericidal action continues for a period of time after the antibiotic level falls below the MIC [50]

Beta-lactams, glycopeptides, oxazolidinones, and azoles exhibit time-dependent activity: the shorter the drug elimination half-life, the more frequent the daily dose fractioning must be.

For these drugs the employ of intravenous continuous infusion, which ensures the highest steady-state concentration under the same total daily dosage, may be the most effective way of maximizing pharmacodynamic exposure [51-54].

On the other hand, quinolones, daptomycin, tigecycline, aminoglycosides, polienes and echionocandins exhibit **concentration-dependent activity;** therefore the entire daily dose should be administered in a once daily way (or with the lowest possible number of daily administrations) with the intent of achieving the highest peak plasma level. The use of extended-interval aminoglycoside dosing strategies for the treatment of moderate-to severe infections encountered in critically ill surgical patients [55,56].

- The major pathogens involved in community-acquired IAIs are Enterobacteriaceae, streptococci and anaerobes.
- The main resistance problem is represented by ESBL producers Enterobacteriaceae, even today frequently found in community acquired infections.

- Many factors can raise the risk of selection of ESBL but prior exposition to antibiotics (mainly third generation cephalosporins) and comorbidities that make frequent the exposure of patients to multiple antibiotic treatments, are the most significant [1,176,177].

- Therefore in a stable and low risk patient simpler antibiotic choice, not including ESBL in the spectrum of activity is correct, while in critical and high risk patients any antibiotic regimen must take into account the risk of ESBL

The available therapeutic options for the treatment of ESBL-associated infections are limited by drug resistance conferred by the ESBLs. The frequently observed co-resistances include various antibiotic classes (fluoroquinolones, aminoglycosides, tetracyclines, and trimethoprim/ sulfamethoxazole).

Carbapenems, stable against hydrolyzing activity of ESBLs, are considered as the drug of choice for the treatment of these infections.

Tigecycline and polymyxins have a strong in vitro antimicrobial activity against ESBL-producing bacteria, and the first should be considered a reasonable alternative. This is particularly true from an epidemiological point of view; in fact today any large hospital should implement carbapenems-sparing stewardship programs to control the spread of carbapenemase producing gram negative bacteria.

- Although in the prospective French survey by Montravers and coll, a higher percentage of isolation of Enterococcus faecalis in non surviving patients was reported (23% versus 9%) [35], empirical treatment against Enterococci and has not been generally recommended for patients with community-acquired IAI. In fact in several clinical trials comparing different therapeutic options inclusion/exclusion of agents with enterococcal coverage provides no impact in outcomes for patients with community-acquired infections [178,179].

# Comm acq cIAI

Beta-lactam/beta-lactamase inhibitor combinations have an in vitro activity against gram-positive, gram negative and anaerobe organisms [181,182] and are still reliable option for the empiric treatment of IAIs [183]. However, the increasing resistance of Enterobacteriaceae reported in the last decade also among community acquired infections restricts their empirical use to patients without risk factor for resistances [184].

In the past Cephalosporins have been often used in the treatment of intra-abdominal infections. Among third generation cephalosporins both subgroups with poor activity against Pseudomonas aeruginosa and with activity against Pseudomonas aeruginosa (cefepime and ceftazidime) have been used in the treatment of IAIs in association with metronidazole. Both cephalosporins have acquired resistance in enterobacteriaceae and intrinsic resistance in Enterococci [185-188]. In light of the emerging concern of ESBL producing enterobacteriaceae species due to selection pressure by increase use of cephalosporins, the routinely use of all cephalosporins should be discouraged.

- Carbapenems have a spectrum of antimicrobial activity that includes Gram-positives (except MDR resistant gram positive cocci) and Gram-negative aerobic and anaerobic pathogens. They are the preferred antimicrobial agents for ESBL and AmpC-producing organisms; however, their widespread use in outbreaks and endemic regions of these organisms has led to increased rates of carbapenem-resistant P. aeruginosa and Acinetobacter sp. İn addition to those such as Stenotrophomonas maltophilia and vancomycinresistant Enterococcus faecium can be seen [189]

- Group 1 carbapenems includes ertapenem, a once a day carbapenem that shares the activity of imipenem and meropenem against most species, including extended-spectrum beta-lactamase (ESBL) – producing pathogens, but is not active against Pseudomonas spp. and Enterococcus [190,191].

- Group 2 includes imipenem/cilastatin, meropenem and doripenem, that share activity against non-fermentative gram-negative bacilli. Slightly higher in-vitro activity against some strains of Pseudomonas sp. has been reported with doripenem in registrative trials [192].

- Also fluoroquinolones have been widely used in the last years for the treatment of IAIs, because of their excellent activity against aerobic Gram-negative bacteria and tissue penetration.
- In addition all the fluoroquinolones are rapidly and almost completely absorbed from the gastrointestinal tract [193,194].
- The combination of ciprofloxacin/metronidazole has been one of the most commonly used regimens for the treatment of patients with complicated IAIs in the last years.

The last quinolone developed, Moxifloxacin, has shown activity against a wide range of aerobic Gram-positive and Gram-negative [195]. Compared with ciprofloxacin, moxifloxacin has enhanced activity against Gram-positive bacteria with a decrease in activity against Gram-negative bacteria [196].

Among quinolones moxifloxacin seems to be effective also against Bacterioides fragilis, suggesting that it may be effective without antianaerobic agents [197-199].

Aminoglycosides are particularly active against aerobic Gram-negative bacteria and act synergistically against certain Gram-positive organisms. They are effective against Pseudomonas aeruginosa but not effective against anaerobic bacteria. The aminoglycosides may not be optimal for-the treatment of abscesses o intraabdominal infections due to their low penetration in acidic environments [200].

Therefore they are not recommended for the routine empiric treatment of community-acquired IAIs and may be reserved for patients with allergies to b-lactam agents [1].

Tigecycline is a parenteral glycylcycline antibiotic derived from minocycline. It is the first representative of the glycylcycline class of antibacterial agents to be marketed for clinical use [201,202].

Tigecycline has **no activity** in vitro against P. aeruginosa and P. mirabilis but represents a significant treatment option for complicated **IAIs due to its favorable in vitro activity against anaerobic organisms, Enterococci, several ESBL-producing Enterobacteriaceae and carbapenemase-producing Enterobacteriaceae, Acinetobacter sp. and Stenotrophomonas maltophilia** [203-206].

The use of tigecycline in the abdominal infections is particularly attractive in view of its pharmacokinetics/ pharmacodynamics properties. In fact the drug is eliminated by active biliary secretion, able to determinate very high biliary and fecal concentrations [207].

More over a PD analysis based on the data of microbiological surveys, performed by the Montecarlo simulation, demonstrated a predicted cumulative response (PCR) fraction for Tigeciclyne in peritonitis over 95% for E. coli and Enterococcus and over 75% for Klebsiella spp, Enterobacter spp and A. baumannii [209]. Tigecycline (TGC) has demonstrated non-inferiority in terms of clinical efficacy and safety versus imipenem/ cilastatin and combination regimen of Ceftriaxone/ metronidazole in Phase 3 clinical trials for complicated intra-abdominal infection [210,211].

But the greater significance of the use of tigecycline in empirical antibiotic regimens for IAIs is related to the possibility of saving carbapenems prescriptions. From an epidemiological point of view tigecycline should be a qualified therapeutic option in a carbapenems-sparing stewardship programs, as extended-spectrum  lactamases become widely disseminated among the endogenous gut Enterobacteriaceae

# Hospital acquired ia infections

- Hospital-acquired intra-abdominal infections are infections not present on admission that become evident 48 hours or more after admission in patients hospitalized for a reason other than intra-abdominal infection [247

**Both post-operative and non post-operative nosocomial intra-abdominal infections are associated with increased mortality due to underlying patient health status and increased likelihood of infection caused by MDR organisms [248-255].**

The main clinical differences between the patients with community-acquired intra-abdominal infections and patients with nosocomial intra-abdominal infectionsare [35]:

**higher proportion of underlying disease**

**severity criteria at the time of diagnosis for nosocomial cases**

The most common cause of postoperative peritonitis is anastomotic failure/leak.

In few instances of postoperative peritonitis, the anastomosis may be intact; however, the patient may remain sick because of residual peritonitis.

Among them is the inadequate drainage of the initial septic focus, in which the surgeon failed to drain completely, or more commonly, the peritoneum does not have the sufficient defense capacity to control the problem.

Hospital acquired, non-postoperative IAIs, which arise in patients hospitalized for reasons unrelated to abdominal pathology, portend a particularly poor prognosis.

- Diagnosis is often delayed due to both a low index of suspicion, poor underlying health status, and altered sensorium.
- Non-postoperative nosocomial intra-abdominal infections are frequently characterized as severe infections diagnosed lately in fragile patients [254].

Prospective analysis of patients operated for secondary non-postoperative nosocomial intra-abdominal infections collected in 176 French study centers was published 2004 [254]. When compared with CAI patients, Non-Postop NAI patients presented:

- increased interval between admission to the surgical ward and operation
- increased proportions of underlying diseases

# Antimicrobial treatment of hospital-acquired intraabdominal infections

- Hospital-acquired IAIs are among the most difficult infections to diagnose early and treat effectively.
- A successful outcome depends on early diagnosis, rapid and appropriate surgical intervention, and the selection of effective antimicrobial regimens.

- Hospital acquired infections are commonly caused by larger and more resistant flora, and for these infections, complex multidrug regimens are always recommended (Recommendation 1 B).

In order to describe the differences in microbiological and resistance patterns between community-acquired and nosocomial intra-abdominal infections a prospective, observational multicentric study (EBIIA) was completed in French [35]. From January to July 2005, patients undergoing surgery/interventional drainage for IAIs with a positive microbiological culture were included by 25 French centers. A total of 829 microorganisms were cultured.

# EBIIA

- In this study the number of peritoneal microorganisms per sample was ≥3 in 34% and 54% of cases, respectively, for community-acquired and nosocomial infections ($P < 0.001$).

# EBIIA

The distribution of the microorganisms differed according to the nosocomial or community origin of the infection but not according to their location.

In nosocomial patients, increased proportions of Enterococcus faecalis (33% versus 19% in community acquired patients; $P < 0.05$) and Pseudomonas aeruginosa strains (13% versus 5% in community-acquired patients; $P < 0.01$)

# EBIIA

Conversely, in nosocomial patients, decreased proportions of Escherichia coli (52% versus 72% in community-acquired patients, $P < 0.001$) and streptococci strains were reported (31% versus 50% in community-acquired patients, $P < 0.01$).

# EBIIA

Therefore the inclusion of anti-enterococcal drugs in any empirical antibiotic regimens in severe nosocomial IAIs and/or in patients with well known risk factors, seems appropriate, mainly if directed against E. faecalis

- Empiric therapy directed against vancomycin-resistant Enterococcus faecium is not recommended unless the patient is at very high risk for an infection due to this organism, such as a liver transplant recipient with an intra-abdominal infection originating in the hepatobiliary tree or a patient known to be colonized with vancomycin- resistant E. faecium.
- Enterococcus infections are difficult to treat because of both intrinsic and acquired resistance to many antibiotics.

Enterococci are intrinsically resistant to many penicillins, and all cephalosporins with the possible exception of ceftobiprole and ceftaroline, currently undergoing clinical evaluation. Besides Enterococci have acquired resistance to many other classes of antibiotics, to which the organisms are not intrinsically resistant, including fluoroquinolones, aminoglycosides, and penicillins.

Many strains of E. faecalis are susceptible to certain penicillins and glycopeptides; however, some strains of E. faecium may be resistant to these agents [272].

Vancomycin-resistant Enterococcus (VRE) infections have been associated with increased morbidity and mortality [273,274].

# Many factors can increase the risk of colonization with VRE

Many factors can increase the risk of colonization with VRE.

These include previous antibiotic therapy (the number and duration of antibiotics received) prolonged hospitalization, hospitalization in an intensive care unit severity of illness, invasive procedures and devices, gastrointestinal surgery, transplantation, proximity to another VRE-positive patient [275].

# Candida

In the survey of Montravers and coworkers no differences in frequency of isolation of Candida spp were dentified in community or hospital acquired IAIs, and the overall prevalence was under 5%, in contrast with other observations, especially those related to patients with recurrent gastrointestinal perforation/anastomotic leakage [276,277].

# Candida

Although the epidemiological role of Candida spp in nosocomial peritonitis is not yet defined, the clinical role is significant, because Candidal isolation is normally associated to a poor prognosis.

The same study group on 2006 published an elegant retrospective, case-control study conducted in critically ill patients admitted to 17 French ICUs where the yielding of Candida spp from peritoneal specimen **was a variable independently associated to mortality in the setting of nosocomial peritonitis [37].**

More recently Montravers and coll. reported a mortality rate of 38% in a prospective cohort of 93 patients admitted to ICU with candidal peritonitis [38].

Therefore, like for Enterococci, the inclusion of an anticandidal drug in the empiric regimen of severe nosocomial acquired IAIs, seems appropriate as confirmed by IDSA guidelines [1].

# Flucanozole vs echinocandins

The recently published IDSA guidelines for the treatment of invasive candidiasis [278] don’t comprise a chapter specifically dedicated to candidal peritonitis. However the expert panels generically favor the use o echinocandins as first line empirical therapy in severely ill patients, recommending fluconazole for less severe conditions.

## Conclusions

The timing and adequacy of source control is the most important issue in the management of intra-abdominal sepsis, because an inadequate and late operation may have a negative effect on the outcome. Concomitant adequate empiric antimicrobial therapy further influences patients' morbidity and mortality. Inappropriate antibiotic therapy of intra-abdominal infections may result in poor patient outcome and the selection of an appropriate agent is a real challenge because of the emerging resistance of target organisms to commonly prescribed antibiotics. It is demonstrated that a strategy of early goal-directed therapy decreases the in-hospital mortality of patients who are taken to the emergency department in septic shock. An organized approach to the haemodynamic support to sepsis includes use of fluid resuscitation, vasopressor therapy and inotropic therapy. A multidisciplinary approach to the management of critically ill patients may be an important factor in the quality of care.

**Mazuski 2007**

# Mazuski 2007, Expert opinion in Pharmacotherapy

**Box 1. Microbiology of intra-abdominal infections.**

**Gram-negative bacilli**

*Escherichia coli*

*Klebsiella* sp.

*Pseudomonas aeruginosa*[*]

*Enterobacter* sp.[*]

**Gram-positive cocci**

Streptococci

*Enterococcus* sp.[*]

*Staphylococcus aureus*[*]

Coagulase-negative staphylococci[*]

**Anaerobic bacteria**

*Bacteroides fragilis*

Other *Bacteroides fragilis* group

**Fungi**

*Candida albicans*[*]

[*]Incidence increased in patients with nosocomial intra-abdominal infections.

In the past, the Gram-negative bacilli isolated from patients with community-acquired, intra-abdominal infections were usually susceptible to most commonly-used antibiotics. **However, there have been some disturbing trends in the susceptibility profiles of community-acquired isolates of *E. coli* .** *In a recent study, > 40% of worldwide isolates of E. coli were resistant to ampicillin/ sulbactam, even among* isolates obtained from patients hospitalized < 48 h, who presumably had community-acquired infections. Although not as widespread, there was also a trend toward increasing resistance of *E. coli to ciprofloxacin as well; this was most* apparent in isolates obtained from the Asia/Pacific region and Latin America, and less so among isolates from Europe and the US [13] .

With postoperative or other intra-abdominal infections acquired in the healthcare setting, there is an increased incidence of Gram-negative organisms such a *Enterobacter sp.* and *Pseudomonas aeruginosa , and a corresponding decreased* incidence of *E. coli [7] . As would be expected, the* organisms isolated from patients with these nosocomial infections exhibit increased resistance to a number of antibiotics. This is likely due in part to prior exposure to antimicrobial agents.

Gram-positive cocci are isolated from the cultures of many patients with intra-abdominal infections. The most common isolates are streptococcal organisms, predominately of the viridans type [2,12] . Enterococci are isolated much less frequently than streptococci. These organisms are reported in 10 – 20% of patients with community-acquired, intra-abdominal infections [2,12,14] . However, the incidenceof enterococcal infections increases in patients who have received prior therapy, likely related to selective anti microbial pressure.

- In one study, *Enterococcus sp. was isolated in only* 11% of patients with community-acquired, intra-abdominal infections, but in 50% of patients with postoperative, intra-abdominal infections and in 23% of patients with intra-abdominal abscesses [15]

Most enterococcal isolates are *E. faecalis , but the incidence of E. faecium increases in* patients with postoperative, nosocomially-acquired infections.

Resistance of enterococci, especially *E. faecium is an* increasing problem. Although most strains of *E. Faecalis* remain sensitive to penicillin or ampicillin, isolates of *E. faecium are generally resistant [16] . There is also an* increasing prevalence of vancomycin-resistant *E faecium [17]* in hospitals, although intra-abdominal infections with this resistant pathogen are still uncommon, occurring primarily in patients with tertiary peritonitis

Staphylococcal organisms are uncommon isolates from patients with intra-abdominal infections and are primarily found with tertiary peritonitis [18,19] . Methicillin resistance is common when staphylococci are isolated in patients with intra-abdominal infections.

Fungal organisms, primarily yeast, are infrequently isolated from patients with community-acquired, intraabdominal infections. Isolation of *Candida is more common* in patients with nosocomial intra-abdominal infections and this organism is frequently found in patients with tertiary peritonitis [18,19] . *C. albicans is the most common species* recovered in cultures. However, non- *C. albicans species are* increasingly encountered in patients with candidemia, which could conceivably apply to patients with intra-abdominal nfections as well [22,23] .

# SAM, cAIA

sets of guidelines, its usefulness has also come under increased scrutiny. The IDSA guidelines indicated this agent should not be used in areas where there was substantial resistance of *E. coli to the drug. However, such resistance* appears to be widespread worldwide, even among community-acquired stains of *E. coli [13] . Therefore, it is* questionable as to whether or not ampicillin/sulbactam should be used at all for initial empiric treatment of patients with intra-abdominal infections.

After the SIS guidelines were completed, a follow-up meta-analysis found that aminoglycoside-based regimens were inferior to most other comparator regimens for treatment of these infections [29] . These data argue against using aminoglycoside-based regimens as primary therapy for complicated intra-abdominal infections, particularly when one also considers the potential toxicities of aminoglycosides. If these agents are used, alternative aminoglycoside dosing schedules may be needed for critically-ill patients with altered volumes of distribution and kinetics of elimination [30] .

# Mazuski, 2007

**Box 4. Independent risk factors for mortality or treatment failure.**

| *Mortality (five studies)* | *Treatment failure (two studies)* |
|---|---|
| APACHE II Score* | APACHE II Score* |
| Age* | Age |
| Hypoalbuminemia* | Hypoalbuminemia |
| Hypocholesterolemia | Prolonged prestudy length of hospitalization |
| Malnutrition | |
| Pre-operative organ impairment | |
| NYHA functional class | |
| Liver disease | |
| Malignant disease | |
| Renal disease | |
| Corticosteroid therapy | |
| Mannheim peritonitis index | |
| Unsuccessful operation | |

*Identified in multiple studies.
Adapted from [28].
NYHA: New York Heart Association.

Several single agents are effective against most strains of *E. faecalis , including piperacillin/tazobactam,* imipenem/cilastatin and meropenem; these agents do not generally require supplementation with additional anti microbial agents to provide enterococcal coverage. However, if higher-risk patients are treated with combination regimens based on third- or fourth-generation cephalosporins, aztreonam or ciprofloxacin, an antienterococcal agent should be added, as these regimens have little or no anti-enterococcal activity. Vancomycin is the common antimicrobial agent added to provide enterococcal coverage. Vancomycin can also be used when penicillinresistant strains of *Enterococcus spp., primarily E. faecium ,* are present or considered likely because of prior antimicrobial exposure. The rare intra-abd

# VRE

- The rare intra-abdominal infections caused by vancomycin-resistant strains of *E. faecium present a* therapeutic dilemma. When infection with one of these strains is documented, treatment with daptomycin, quinupristin–dalfopristin, linezolid or possibly tigecycline can be considered, as these agents appear to have activity against this pathogen [46,47] .
- Empiric use of these agents has not been studied and could only be justified for patients known to be at very high risk for infections due to vancomycin-resistant *Enterococcus spp.*

# Staphylococci

Staphylococci are uncommon isolates in patients with complicated intra-abdominal infections. They are occasionally recovered from patients with postoperative infections, pancreatic infections and tertiary peritonitis [18,19,37,48] . Both coagulase-negative and -positive staphylococci may contribute to nosocomial intra-abdominal infections, although there is debate with regard to the pathogenic role of the former organism [49] . There is very little data available with regard to antimicrobial selection in patients with intra-abdominal infections secondary to staphylococci. In general, recommendations are similar to those for treatment of other staphylococcal infections [47,50] . In patients with infections due to methicillin-sensitive strains of *Staphylococcus aureus ,* treatment with an antistaphy lo coccal penicillin is recommended.

# MSSA

- As many of the agents used to treat intra-abdominal infections, such as piperacillin/tazobactam, carbapenems and some of the third- and fourth-generation cephalosporins have reasonable activity against methicillinsensitive *S. aureus , these agents may suffice as long as the* patient does not have an associated bacteremia.

- For patients with methicillin-resistant *S. aureus or with coagulase-negative* staphylococci, vancomycin is generally considered the first-line agent. Quinupristin/ dalfopristin, linezolid, daptomycin and tigecycline also have activity against methicillin-resistant staphylococci [51-53] , but experience with these antimicro bials in the treatment of patients with intra-abdominal infections is limited

# Mazuski, 2007

**Box 5. Personal recommendations for antimicrobial agents to treat patients with intra-abdominal infections.**

***For lower-risk patients with community-acquired, intra-abdominal infections:***

Initiate therapy with cefoxitin 1 – 2 g i.v. every 6 h, ticarcillin/clavulanate 3.1 g i.v. every 4 – 6 h, ertapenem 1 g i.v. every 24 h, moxifloxacin 400 mg i.v. every 24 h, tigecycline 100 mg i.v. followed by 50 mg i.v. every 12 h, or a combination of cefazolin 1 – 2 g i.v. every 8 h or cefuroxime 1.5 g i.v. every 8 h plus metronidazole 500 mg i.v. every 8 h

***For higher-risk patients, including those with more severe infections, postoperative infections or recent exposure to antimicrobial therapy:***

Initiate therapy with piperacillin/tazobactam 3.375 – 4.5 g i.v. every 6 h or a combination of cefotaxime 1 – 2 g i.v. every 8 h, ceftriaxone 1 – 2 g i.v. every 24 h, ceftazidime 1 – 2 g i.v. every 8 h, cefepime 2 g i.v. every 12 h, aztreonam 1 – 2 g i.v. every 8 – 12 h, or ciprofloxacin 400 mg i.v. every 12 h plus metronidazole

Add ampicillin 1 – 2 g i.v. every 4 – 6 h or vancomycin 15 mg/kg i.v. every 12 h for enterococcal coverage to cephalosporin-, aztreonam- or ciprofloxacin-based regimens

Use fluconazole 400 mg i.v. once daily in selected patients considered at high risk for *Candida* spp. peritonitis

De-escalate antimicrobial regimen when definitive culture results are available

***For patients with tertiary peritonitis or those who have had extensive prior antimicrobial therapy:***

Initiate therapy with piperacillin/tazobactam, imipenem/cilastatin 500 mg – 1 g i.v. every 6 – 8 h, meropenem 1 g every 8 h or a combination of ceftazidime, cefepime or aztreonam plus metronidazole

Consider addition of another agent, such as an aminoglycoside, ciprofloxacin, tigecycline or colistin for additional coverage of resistant Gram-negative pathogens, depending on local resistance patterns

Add vancomycin for treatment of resistant Gram-positive organisms

Add fluconazole for pre-emptive antifungal therapy. For patients with confirmed *Candida* spp. peritonitis, initiate therapy with caspofungin 70 mg i.v. followed by 50 mg i.v. every 24 h or anidulafungin 200 mg i.v., followed by 100 mg i.v. every 24 h

De-escalate antimicrobial regimen when definitive culture results are available

The patient who has tertiary peritonitis is much more difficult to treat. Highly-resistant bacteria are the rule rather than the exception. Local resistance patterns and the patient's history of prior antimicrobial exposure should be used to select specific antimicrobial agents. Imipenem/cilastatin and meropenem are reasonable choices for these patients, as are other antibiotics with good pseudomonal coverage, such as piperacillin/tazobactam, ceftazidime, cefepime or aztreonam, if the patient has not already been exposed to them. Metronidazole should be used in combination with the latter three antibiotics. If the patient is at high risk for multiple-resistant, Gram-negative pathogens and local susceptibility patterns suggest that certain agents may be effective, a second Gram-negative agent, such as an aminoglycoside, ciprofloxacin, tigecycline or even colistin could also be started empirically.

- Gram-negative coverage should
- **Box 5 . Personal recommendations for antimicrobial agents to treat patients with intra-abdominal infections.**
- ***For lower-risk patients with community-acquired, intra-abdominal infections:***
- Initiate therapy with cefoxitin 1 – 2 g i.v. every 6 h, ticarcillin/clavulanate 3.1 g i.v. every 4 – 6 h, ertapenem 1 g i.v.
- every 24 h, moxifl oxacin 400 mg i.v. every

AntIMIcRobIAl tREAtMEnt of „coMPlIcAtEd“ IntRA-AbdoMInAl InfEctIons And tHE nEw IdsA GuIdElInEs – A coMMEntARy And An AltERnAtIvE EuRoPEAn APPRoAcH AccoRdInG to clInIcAl dEfInItIons

c. Eckmann1, M. dryden2, P. Montravers3, R. Kozlov4, G. Sganga5

European Journal of medical Research, 2011

- It is inappropriate to restrict treatment recommendations for MRsA in cIAI to vancomycin and for Esbl-producing Enterobacteriaceae to carbapenems and pipera cillin/tazobactam [

due to the substantially increasing, but geographically varying prevalence of resistant Gram-positive and Gram-negative pathogens there have been numerous efforts to encourage research in the development of new antimicrobials with efficacy and safety in this field [5]. As a result, new antibiotics with efficacy against resistant bacteria (linezolid against MRsA and vRE, daptomycin against MRsA and vRE, tigecycline against MRsA, vRE, Esbl-producing Enterobacteriaceae, carbapenem-resistant bacteria) have shown activity in vitro and in vivo [6, 7, 8]. unfortunately, the new IdsA guidelines for the treatment of resistant bacteria summarized in a table about treatment of „health-care associated complicated intra-abdominal infection“ fail to mention any of these drugs [1], although clinical data for the treatment of „complicated IAI“ exist for linezolid and tigecycline which is approved for „cIAI“ [8- 10, 11*, 12* (*=published after the IdsA guidelines have been published)].

# Choosing Antibiotics for Intra-Abdominal Infections:

# What Do We Mean by "High Risk"?*

Brian [illegible]:ger,1
Traci L[illegible]arney,1
Rc[illegible],1
Kimbe[illegible]Pruett,

TABLE 2. ODDS RATIOS OF ISOLATION OF COMMON BACTERIA FROM HEALTH-CARE ASSOCIATED VS. COMMUNITY-ACQUIRED INTRA-ABDOMINAL INFECTIONS, EXCLUDING PATIENTS WITH SOLID ORGAN ALLOGRAFTS

| *Pathogen* | *Health-care associated* N = 619 (%) | *Community acquired* N = 351 (%) | *Odds ratio* | *95% CI* |
|---|---|---|---|---|
| Gram-negative bacteria | 260 (42.0) | 142 (40.5) | 1.07 | 0.82, 1.39 |
| *Escherichia coli* | 84 (13.6) | 62 (17.7) | 0.73 | 0.51, 1.05 |
| *Klebsiella pneumoniae* | 42 (6.8) | 31 (8.8) | 0.75 | 0.46, 1.22 |
| *K. oxytoca* | 7 (1.1) | 9 (3.1) | 0.43 | 0.16, 1.18 |
| *Enterobacter cloacae* | 27 (4.4) | 4 (1.1) | 3.96 | 1.37, 11.40 |
| *E. aerogenes* | 12 (1.9) | 2 (0.57) | 6.82 | 1.51, 30.71 |
| *Pseudomonas aeruginosa* | 32 (5.2) | 7 (2.0) | 2.68 | 1.17, 6.14 |
| *Citrobacter* spp. | 10 (1.6) | 7 (2.0) | 0.81 | 0.31, 2.15 |
| *Serratia* spp. | 7 (1.1) | 0 | — | — |
| *Proteus mirabilis* | 11 (1.8) | 4 (1.1) | 1.57 | 0.50, 4.97 |
| *Stenotrophomonas maltophilia* | 10 (1.6) | 2 (0.57) | 2.87 | 0.62, 13.15 |
| *Acinetobacter* spp. | 3 (0.48) | 0 | — | — |
| Gram-positive bacteria | 322 (52.0) | 165 (47.0) | 1.11 | 0.85, 1.44 |
| *Staphylococcus aureus* | 57 (9.2) | 29 (8.3) | 0.88 | 0.56, 1.42 |
| MRSA | 38 (6.1) | 9 (2.6) | 2.53 | 1.21, 5.29 |
| *S. epidermidis*/CNS | 36 (5.8) | 13 (3.7) | 1.63 | 0.85, 3.12 |
| All enterococci | 168 (27.1) | 30 (8.5) | 4.00 | 2.63, 6.03 |
| *Enterococcus faecalis* | 91 (14.7) | 23 (6.5) | 2.46 | 1.52, 3.96 |
| *E. faecium* | 73 (11.8) | 5 (1.4) | 9.25 | 3.70, 23.12 |
| VRE | 36 (5.8) | 4 (1.1) | 5.36 | 1.89, 15.18 |
| *Streptococcus* spp. | 46 (7.4) | 77 (21.9) | 0.30 | 0.20, 0.44 |
| Anaerobic bacteria | 135 (21.8) | 94 (26.8) | 0.63 | 0.47, 0.85 |
| *Bacteroides fragilis* | 43 (6.9) | 20 (5.7) | 1.23 | 0.73, 2.19 |
| Other *Bacteroides* | 14 (2.3) | 4 (1.1) | 2.01 | 0.66, 6.15 |
| *Prevotella* spp. | 6 (1.0) | 2 (0.57) | 1.71 | 0.34, 8.51 |
| Unspeciated | 72 (11.6) | 68 (19.4) | 0.55 | 0.38, 0.79 |
| Fungi | 226 (36.5) | 63 (17.9) | 2.63 | 1.91, 3.61 |
| All *Candida* | 184 (29.7) | 52 (14.8) | 2.43 | 1.73, 3.42 |
| *C. albicans* | 114 (18.4) | 38 (10.8) | 1.86 | 1.25, 2.76 |
| *C. glabrata* | 45 (7.3) | 9 (2.6) | 2.98 | 1.44, 6.17 |
| Other *Candida* spp. | 25 (4.0) | 5 (1.4) | 2.91 | 1.10, 7.68 |
| Unspeciated yeast | 42 (6.8) | 11 (3.1) | 2.29 | 1.16, 4.51 |

MRSA = methicillin-resistant *S. aureus*; CNS = coagulase-negative staphylococci; VRE = vancomycin-resistant enterococci (all were *E. faecium*).

# Choosing Antibiotics for Intra-Abdominal Infections:
# What Do We Mean by "High Risk"?*

Brian R. Swenson,1 Rosemarie Metzger,1 Traci L. Hedrick,1 Shannon T. McElearney,1 Heather L. Evans,1 Robert L. Smith,1 Tae W. Chong,1 Kimberley A. Popovsky,1 Timothy L. Pruett,1,2 and Robert G. Sawyer1,3

- **Abstract**
- ***Background: The definition of "high risk" in intra-abdominal infection remains vague. The purpose of this*** study was to investigate patient characteristics associated with a high risk of isolation of resistant pathogens from an intra-abdominal source.
- ***Methods: All complicated intra-abdominal and abdominal organ/spac surgical site infections treated over a*** ten-year period in a single hospital were analyzed. Infections were categorized by pathogen(s). Organisms designated "resistant" were those that had a reasonable probability of being resistant to the broad-spectrum agents imipenem/cilastatin and piperacillin/tazobactam, and included non-fermenting gram-negative bacilli (e.g., *Pseudomonas aeruginosa), resistant gram-positive pathogens, vancomycin-resistant enterococci, and fungi. Patient* characteristics were analyzed to define associations with the risk of isolation of "resistant" pathogens.
- ***Results: A total of 2,049 intra-abdominal infections were treated during the period of study, of which 1,182 had*** valid microbiological data. The two genera of pathogens isolated from more than 25% of health care-associated infections and more commonly than from community-acquire infections were *Enterococcus spp. (29%) and*

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TABLE 4. PATIENT CHARACTERISTICS AND OUTCOMES, RESISTANT VS. NON-RESISTANT PATHOGENS FOR ALL INTRA-ABDOMINAL INFECTIONS AMONG PATIENTS WITH SOLID ORGAN ALLOGRAFTS

| | Resistant pathogens[2] (N = 371) | | Non-resistant pathogens (N = 384) | | Odds ratio | 95% CI or p value |
|---|---|---|---|---|---|---|
| Demographics | | | | | | |
| Male (%) | 275 | (51.5) | 319 | (53.3) | 0.93 | 0.72, 1.21 |
| Age (years) | 53.7 | ± 0.6 | 54.1 | ± 0.68 | | 0.73 |
| APACHE II score | 14.3 | ± 0.4 | 12.2 | ± 0.3 | | <0.0001 |
| Healthcare-associated (%) | 290 | (78.2) | 329 | (54.9) | 2.94 | 2.19, 3.94 |
| In intensive care unit (%) | 77 | (20.8) | 50 | (8.3) | 2.88 | 1.96, 4.22 |
| Days from admission to treatment | 9.9 | ± 1.1 | 2.1 | ± 0.4 | | <0.0001 |
| Maximum temperature, °C | 37.9 | ± 0.1 | 37.9 | ± 0.1 | | 0.99 |
| Maximum white blood cell count (1,000/mm³) | 16.0 | ± 0.4 | 16.6 | ± 0.3 | | 0.23 |
| Medical conditions (%) | | | | | | |
| Current corticosteroid use | 58 | (14.8) | 43 | (7.2) | 2.1 | 1.38, 3.24 |
| Diabetes mellitus | 79 | (21.3) | 126 | (21.0) | 1.02 | 0.74, 1.40 |
| Cardiac disease | 63 | (17.0) | 103 | (17.2) | 0.99 | 0.70, 1.39 |
| Malignant disease | 52 | (14.0) | 96 | (16.0) | 0.85 | 0.59, 1.23 |
| Chronic pulmonary disease | 36 | (9.7) | 58 | (9.7) | 1.69 | 1.09, 2.41 |
| Ventilator dependence | 36 | (9.7) | 41 | (6.8) | 1.48 | 0.93, 2.30 |
| Liver disease | 20 | (5.4) | 19 | (3.2) | 1.74 | 0.92, 3.30 |
| Dialysis dependence | 30 | (8.1) | 20 | (5.0) | 1.67 | 0.99, 2.82 |
| Crohn's disease/UC | 28 | (8.1) | 43 | (7.2) | 1.14 | 0.70, 1.85 |
| Source of infection | | | | | | |
| Stomach | 28 | (7.5) | 21 | (3.5) | 2.25 | 1.25, 4.02 |
| Duodenum | 34 | (9.2) | 15 | (2.5) | 3.91 | 2.11, 7.32 |
| Pancreas | 26 | (7.0) | 40 | (6.7) | 1.05 | 0.63, 1.76 |
| Liver/biliary | 53 | (14.3) | 95 | (15.9) | 0.88 | 0.61, 1.27 |
| Small bowel | 83 | (22.4) | 111 | (18.5) | 1.27 | 0.92, 1.74 |
| Appendix | 8 | (2.2) | 60 | (10.0) | 0.20 | 0.09, 0.42 |
| Colorectal | 113 | (30.5) | 194 | (32.4) | 0.91 | 0.69, 1.21 |
| Other/unknown | 26 | (7.0) | 62 | (10.4) | 0.65 | 0.40, 1.05 |
| Outcomes | | | | | | |
| Duration of antibiotic therapy (days) | 16.4 | ± 0.6 | 13.2 | ± 0.44 | | <0.0001 |
| Length of stay[4] | 25.1 | ± 1.6 | 14.9 | ± 0.8 | | <0.0001 |
| In-hospital death (%) | 53 | (14.3) | 50 | (8.3) | 1.82 | 1.21, 2.75 |

[1]Includes *P. aeruginosa*, *S. maltophilia*, *Acinetobacter* spp., methicillin-resistant *S. aureus*, coagulase-negative staphylococci, vancomycin-resistant enterococci, or any fungi.
[2]Resistant pathogens/non-resistant pathogens; odds ratios with 95% confidence intervals for categorical variables; p value by Student *t*-test for continuous variables.
[3]At time of diagnosis of intra-abdominal infection.
[4]From initiation of treatment for intra-abdominal infection.
APACHE = Acute Physiology and Chronic Health Evaluation; UC = ulcerative colitis.

# Essentials for Selecting Antimicrobial Therapy for Intra-Abdominal Infections Stijn Blot, Jan J. De Waele and Dirk Vogelaers, Drugs, 2012

Frequently isolated pathogens in complicated intra-abdominal infections

| Micro-organism | Clinically relevant resistance problem |
|---|---|
| Gram-negative bacteria | |
| *Enterobacteriaceae* (*Escherichia coli, Enterobacter* spp., *Klebsiella* spp., *Proteus* spp., etc. ) | ESBL-producing strains likely in healthcare-associated infection. In *E. coli* fluoroquinolone-resistance may be up to 20% in some geographic areas |
| Non-fermenting Gram-negative bacteria (*Pseudomonas aeruginosa, Acinetobacter baumannii*, etc.) | Multidrug resistance most likely in healthcare-associated infection |
| Gram-positive bacteria | |
| Streptococci | No clinically relevant resistance problem. |
| Enterococci | Problems of resistance likely in healthcare-associated infections, especially when caused by *Enterococcus faecium*.[13] Ampicillin-resistance and associated production of β-lactamases is a concern in some geographic areas, as is glycopeptide resistance |
| Coagulase-negative Staphylococci | Methicillin resistance most likely in healthcare-associated infection. Clinical pathogenecity uncertain |
| *Staphylococcus aureus* | Methicillin resistance possible in healthcare-associated infection |
| Anaerobic bacteria (*Bacteroides fragilis*, *Clostridium* spp., etc) | Important resistance against clindamycin and cefoxitin in certain geographic areas. Resistance against metronidazole is rare[14] |
| *Candida* spp. | Selection towards non-*albicans Candida* spp. with reduced susceptibility to fluconazole in patients with prior exposure to this agent in hospitalized patients |

**ESBL** = extended-spectrum β-lactamase.

# 2005

**Antibiotic regimens for secondary peritonitis of gastrointestinal origin in adults (Review)**

Wong PF, Gilliam AD, Kumar S, Shenfine J, O'Dair GN, Leaper DJ

THE COCHRANE COLLABORATION®

- **Selection criteria**

Randomised and quasi-randomised controlled trials comparing different antibiotic regimens in the treatment of secondary peritonitis in adults were selected. Trials reporting gynaecological or traumatic peritonitis were excluded from this review. Ambiguity regarding suitability of trials were discussed among the review team.

- **Data collection and analysis**

Six reviewers independently assessed trial quality and extracted data. Data collectio as standardised using data collection form to ensure uniformity among reviewers. Statistical analyses were performed using the random effects model and the results expressed as odds ratio for dichotomous outcomes, or weight mean difference for continuous data with 95% confidence intervals. **Main results** Fourty studies with 5094 patients met the inclusion criteria. Sixteen different comparative antibiotic regimens were reported. All antibiotics showed equivocal comparability in terms of clinical success. Mortality did not differ between the regimens. Despite the potential high toxicity profile of regimens using aminoglycosides, this was not demonstrated in this review. The reason for this could be the inherent bias within clinical trials in the form of patient selection and stringency in monitoring drug levels.

- **Authors' conclusions**

No specific recommendations can be made for the first line treatment of secondar peritonitis in adults with antibiotics, as all regimens showed equivocal efficacy. Other

# Prospective Randomized Trials Affect the Outcomes of Intraabdominal Infection

James I. Merlino, MD, Mark A. Malangoni, MD, Carolyn M. Smith, RN, and Ruth L. Lange, RN. Aqnn surgery, 2001

**Objective**

To compare the characteristics and outcomes of patients with intraabdominal infections enrolled in prospective randomized trials (PRTs) with those of a cohort of patients not enrolled in a trial.

**Summary Background Data**

Prospective randomized trials are the gold standard for the evaluation of new treatments. Patients are screened using rigorous eligibility criteria and sometimes are excluded from PRTs because of associated medical conditions or more severe illness. However, the effect that the exclusion of these patients has on the applicability of clinical trial outcomes has not been defined.

- **Methods**

One hundred sixty-eight adults with intraabdominal infection were treated at a single institution during 7 years. Fifty-three patients were enrolled in four PRTs comparing various antibiotic regimens for treatment; 115 were not enrolled. Patient characteristics and outcomes of these two groups were compared.

- **Results**
- Patients with infections from appendicitis (n 5 68) had a low severity of illness and similar outcomes in both groups. These patients and those for whom a concurrent PRT was unavailable were excluded from subsequent analysis. Eighty-eight patients (42 PRT, 46 not enrolled) with serious infection remained for analysis. Patients enrolled in PRTs were younger, had less severe illness, had a decreased length of stay, a lower incidence of antibiotic resistance, and less frequent extraabdominal infections than those not enrolled in a trial. Patients enrolled in PRTs were more likely to be cured and were less likely to die. Logistic regression analysis demonstrated that cure was associated with a lower initial severity of illness, absence of antibiotic resistance, and participation in a PRT. **Conclusions**

# Prospective Randomized Trials Affect the Outcomes of Intraabdominal Infection James I. Merlino, MD, Mark A. Malangoni, MD, Carolyn M. Smith, RN, and Ruth L. Lange, RN, Aqnn surgery, 2001

**Table 5. COMPARISON OF PATIENTS ENROLLED AND NOT ENROLLED IN CLINICAL TRIAL OF INTRAABDOMINAL INFECTION**

| | Enrolled (n = 42) (%) | Not Enrolled (n = 46) (%) | *P* Value |
|---|---|---|---|
| Age (yr) | 48.6 ± 15.5 | 57.7 ± 18.0 | <.02 |
| Gender | | | |
| Male | 21 (50.0%) | 24 (52.2%) | .627 |
| Female | 21 (50.0%) | 22 (47.8%) | |
| Race | | | |
| White | 28 (66.7%) | 31 (67.4%) | |
| African American | 10 (23.8%) | 9 (19.6%) | .913 |
| Other | 4 (9.5%) | 6 (13.0%) | |
| Admission APACHE II score (mean) | 8.2 ± 5.1 | 12.2 ± 6.9 | <.02 |
| Overall LOS (days) | 14.1 ± 9.2 | 27.1 ± 18.8 | <.02 |
| Antibiotic days* | 8.1 ± 3.3 | 14.2 ± 9.1 | <.02 |

Patients with appendiceal sources of infection have been excluded. LOS, length of stay.

# Prospective Randomized Trials Affect the Outcomes of Intraabdominal Infection

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**Table 6. OUTCOMES BASED ON ENROLLMENT STATUS**

| Outcome | Enrolled in PRT (%) | Not Enrolled in PRT (%) |
|---|---|---|
| Cure | 33 (78.6%) | 19 (41.3%) |
| Failure | 9 (21.4%) | 27 (58.7%) |
| Reoperation | 3 (7.1%) | 9 (19.6%) |
| Resistance | 2 (4.8%) | 3 (6.5%) |
| Death | 4 (9.5%) | 15 (32.6%) |

PRT, prospective randomized trial.