



**ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ**  
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**ΙΑΤΡΙΚΗ ΣΧΟΛΗ**  
**ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ «ΛΟΙΜΩΞΙΟΛΟΓΙΑ»**  
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## **Ενδο-κοιλιακές λοιμώξεις : Συντηρητική Αντιμετώπιση**

**Καρόλινα Ακινόσογλου**

**Παθολόγος – Λοιμωξιολογος**

**Επικουρη Καθηγητρια Παθολογιας**

**Πανεπιστημίου Πατρών**

# Intra-abdominal infection

- Inflammation or disruption of the gastrointestinal tract
- Gynaecologic or urinary tract
- Usually polymicrobial and result in  
→ intra-abdominal abscess or secondary peritonitis, which may be → generalized or localized (phlegmon).

**Table 3** Source of infection in 4553 patients from 132 hospitals worldwide (15 October 2014–2015 February 2015) [1]

Source of infection	Number (%)
Appendicitis	1553 (34.2)
Cholecystitis	837 (18.5)
Post-operative	387 (8.5)
Colonic non-diverticular perforation	269 (5.9)
Gastro-duodenal perforations	498 (11)
Diverticulitis	234 (5.2)
Small bowel perforation	243 (5.4)
Others	348 (7.7)
PID	50 (1.1)
Post traumatic perforation	114 (2.5)
Total	4553 (100)

# Ταξινόμηση ενδοκοιλιακών λοιμώξεων (I)

## I. Λοιμώξεις κοινότητας

## II. Λοιμώξεις σχετιζόμενες με χώρους παροχής υπηρεσιών υγείας (Health care associated infections)

### α. ενεργείς νοσοκομειακές λοιμώξεις

- έναρξη μετά από 48h νοσηλείας
- επανεισαγωγή με λοίμωξη σε λιγότερο από 48 h από εξιτήριο
- λοίμωξη χειρουργικού πεδίου εντός μηνός από επέμβαση
- λοίμωξη χειρουργικού πεδίου εντός 3 μηνών αν φέρει πρόθεση

### β. σχετιζόμενες με χώρους παροχής υπηρεσιών υγείας

- Νοσηλεία τους τελευταίους 3 μήνες για >48 h.
- Διαμονή σε οίκο ευγηρίας
- Αιμοκαθαιρόμενοι
- Ευρέος φάσματος αντιβιοτικά για > 2 ημέρες τους τελευταίους 3 μήνες

# IAI: Classification (II)

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## **α. Uncomplicated IAI**

- Generally involve transmural inflammation of a portion of the GI tract or its appendages.**
  - No extension of the infection beyond the hollow viscus.**
  - Microorganisms cannot be cultured from peritoneal or other surrounding fluid**
- If untreated, there is a substantial probability of these infections progressing to a complicated intra-abdominal infection.**

# IAI: Classification (II)

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## **β. Complicated IAI**

- **Growth of pathogenic microorganisms in a normally sterile region of the abdominal cavity**
- **Usually refers to secondary or tertiary peritonitis or an intra- abdominal abscess arising from a perforated viscus (eg appendix, colon or small bowel, Stomach or duodenum, gallbladder, postoperative).**

# Περιτονίτιδα

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- **Πρωτοπαθής**
  - Αυτόματη εμφάνιση χωρίς εμφανή εστία μικροβίων
- **Δευτεροπαθής**
  - Προκαλείται από τη λύση της συνεχείας σε κάποιο σημείο του γαστρεντερικού σωλήνα, όπως διάτρηση ή δευτερογενώς από λοίμωξη ενός ενδοκοιλιακού οργάνου
- **Δευτεροπαθής μετεγχειρητική**
  - Σε νοσηλευόμενους ως επιπλοκή χειρουργικής επέμβασης όπως διαφυγή αναστόμωσης και ισχαιμία εντέρου
- **Τριτογενής**
  - Σχετίζεται με επανειλημμένες υποτροπιάζουσες δευτερογενείς περιτονίτιδες
  - Θεωρείται ως έκπτωση οργάνου (του περιτοναίου)

# Microbiology

Μικροβιολογικό φάσμα  
εξαρτάται από την ακριβή

πηγή (π.χ λεπτό vs παχύ έντερο –  
διατήρηση πεπτικού ελκους → αερόβια και  
αναερόβια gram+ βακτηρια)

Εντόπιση	Αποικίες	χλωρίδες
στόμαχος	1000 CFU/ml	Προαιρετικά αναερόβια (Facultative) gram θετικά του στόματος
Εγγύς λεπτό έντερο	λιγοστές	ομοίως
Λεπτό έντερο	1-100 εκ. CFU/ml	Enterobacteriaceae, enterococcus, αυστηρώς αναερόβια
Παχύ έντερο	10-100 δισεκ. CFU/ml	Αυστηρώς αναερόβια, enterobacteriaceae, enterococcus, streptococci



## Κυριότερα παθογόνα σε 2 μελέτες ενδοκοιλιακών λοιμώξεων της κοινότητας

Παθογόνα	Cattan (n=317)	Sendt (n=313)
Gram Positive Cocci		
<i>Streptococcus</i> spp.	12%	7%
<i>Enterococcus</i> spp.	7%	6%
Gram Negative Bacilli		
<i>Escherichia coli</i>	40%	47%
<i>Klebsiella</i> spp.	3%	7%
<i>Enterobacter</i> spp.	1%	4%
<i>Pseudomonas aeruginosa</i>	4%	4%
<i>Bacteroides fragilis</i>	9%	2%
Other <i>Bacteroides</i> spp.	6%	6%



REVIEW

Open Access

## The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections



Massimo Sartelli<sup>1\*</sup>, Alain Chichom-Mefire<sup>2</sup>, Francesco M. Labricciosa<sup>3</sup>, Timothy Hardcastle<sup>4</sup>, Fikri M. Abu-Zidan<sup>5</sup>,

## The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection

John E. Mazuski<sup>1</sup>, Jeffrey M. Tessier<sup>2</sup>, Addison K. May<sup>3</sup>, Robert G. Sawyer<sup>4</sup>, Evan P. Nadler<sup>5</sup>

## **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.**

Solomkin JS<sup>1</sup>, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O'Neill PJ, Chow AW, Dellinger EP, Eachempati SR, Gorbach S, Hilfiker M, May AK, Nathens AB, Sawyer RG, Bartlett JG.

## General principles

- Regimens against enteric streptococci, coliforms, and anaerobes
- Evaluate need for **broader empiric coverage / risk stratification**
- Type of infection (e.g gram-negative anaerobes are generally not critical pathogens in infections arising from the upper gastrointestinal tract)
- Plan for surgical intervention
- Local rates of antibiotic-resistant Enterobacteriaceae
- Expected patient tolerance
- Antibiotic stewardship

## Antimicrobial regimen and indications for broader antimicrobial coverage depends on

- Community-acquired vs health care-associated.
- Risk factors for resistant bacteria
- High risk for adverse outcomes.

[advanced age (>70 years), delay in initial intervention >24 hours, inability to achieve adequate debridement or control of infection with drainage, other comorbidity (eg, renal or liver disease, malignancy), immunocompromising condition (eg, poorly controlled diabetes mellitus, chronic high-dose corticosteroid use, use of other immunosuppressive agents, neutropenia, advanced HIV infection, B or T lymphocyte defects), organ dysfunction, severe peritoneal involvement or diffuse peritonitis, low albumin level, and poor nutritional status]

# General principles

## RISK ASSESSMENT

- Use phenotypic and physiologic factors, including signs of sepsis or septic shock, extremes of age, and patient co-morbidities; the extent of abdominal infection and adequacy of initial source control; and the presence or persistence of resistant or opportunistic pathogens in assessing risk for treatment failure and mortality in patients with IAI (Grade 1-B).
- Characterize patients as being at either lower or higher risk for treatment failure or death, and as having either a community-acquired IAI (CA-IAI) or a healthcare or hospital-associated IAI (HA-IAI), including a postoperative infection, for purposes of planning source control and empiric antimicrobial therapy (Grade 2-C).

# General principles

## RISK ASSESSMENT

- Patients meeting Surviving Sepsis Campaign criteria for sepsis or septic shock and those with APACHE II >10 → **higher-risk patients** (Grade 1-B).
- If at least two physiologic/phenotypic risk factors for an adverse outcome, those having diffuse peritonitis, and those having delayed or inadequate source control → **higher-risk patients** (Grade 2-B).
- Patients hospitalized >48 hours during the previous 90 days; residing in a skilled nursing or long-term care facility during the previous 30 days; received IV infusion therapy, wound care, or renal replacement therapy within the preceding 30 days; those who have received several days of broad-spectrum antimicrobial therapy within the previous 90 days; those who have postoperative infections; known to have been colonized or infected previously with a resistant pathogen as having **HA-IAI and at potential risk for infection because of resistant or opportunistic organisms** (Grade 2-B).

# Microbiologic evaluation

Microbiologic evaluation may be useful in selected patients, **but is not necessary in most**

- Do not routinely obtain peritoneal fluid cultures in lower-risk patients with CA-IAI for purposes of guiding antimicrobial therapy (1-B).
- Obtain cultures of peritoneal fluid or infected tissue in higher-risk patients with CA-IAI and in patients with HA-IAI to identify potential resistant or opportunistic pathogens (1-C).

## Mild to moderate community-acquired intra-abdominal infections

*(eg, perforated appendix or appendiceal abscess) who have no risk factors for antibiotic resistance or treatment failure, coverage of streptococci, non-resistant Enterobacteriaceae, and (in most cases) anaerobes is generally sufficient(1A)*

- Single-agent regimens – Ertapenem or piperacillin-tazobactam.
- Combination regimens – Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole (although for most uncomplicated biliary infections of mild to moderate severity, the addition of metronidazole is not necessary)(1A-2B))
- An oral regimen (for example, a fluoroquinolone plus metronidazole) is a reasonable choice

**For these community-acquired infections, an empiric antimicrobial regimen does not have to include specific activity against enterococci (1A) or antifungal (2B)**



## TIPS for mild to moderate community-acquired infections

- Cefotetan and clindamycin are not recommended for use because of increasing prevalence of resistance to these agents among the *Bacteroides fragilis* group (B-II).
- Because of the availability of less toxic agents demonstrated to be at least equally effective, aminoglycosides are not recommended for routine use in adults with community acquired intra-abdominal infection (B-II).

# High risk **community-acquired** intra-abdominal infections

*(severe or in patients at high risk for adverse outcomes or resistance)*

- agent with gram-negative activity (cover *P. aeruginosa* and Enterobacteriaceae resistant to non-pseudomonal cephalosporins) + coverage against enteric streptococci and (in most cases) anaerobes
  - Empiric antifungal therapy → not warranted, but reasonable for critically ill patients with an upper GI (1B-2B)
  - MRSA is generally NOT warranted, even if known to be MRSA-colonized.
- IF local resistance <10%
- Single-agent regimens – Imipenem-cilastatin, [meropenem](#), [doripenem](#), or [piperacillin-tazobactam](#) (2A).
  - Combination regimens – [Cefepime](#) or [ceftazidime](#), each administered with [metronidazole](#).(2B)

## TIPS for high risk community-acquired infections

- If risk for ESBL (eg, known colonization or prior infection with ESBL) → a carbapenem (imipenem-cilastatin, [meropenem](#)) should be chosen.
- Adding [vancomycin](#) or [ampicillin](#) for regimens other than imipenem-cilastatin or [piperacillin-tazobactam](#) to provide enterococcal coverage, (but not routinely for community-acquired infections).
- If allergy on beta-lactams or carbapenems → [vancomycin](#) plus [aztreonam](#) plus [metronidazole](#)
- For critically ill patients who warrant empiric antifungal therapy → an echinocandin (eg, [anidulafungin](#), [caspofungin](#), [micafungin](#))
- When beta-lactams or carbapenems chosen → prolonged infusion dosing strategy

# Healthcare-associated infections

- Possibility of drug resistance is high
- **Streptococci and anaerobes + gram-negative bacilli** (including *P. aeruginosa* & Enterobacteriaceae resistant to non-pseudomonal third-generation cephalosporins & fluoroquinolones) (2B)
- **Anti-enterococcal activity for those with** postoperative infection, previously received cephalosporins or other antimicrobial agents selecting for *Enterococcus* species, immunocompromised patients, valvular heart disease or prosthetic intravascular materials (2B)
- For **highly resistant gram-negative bacteria**, + an aminoglycoside, polymyxin, or novel beta-lactam combination ([ceftolozane-tazobactam](#) or [ceftazidime-avibactam](#)) to an empiric regimen + metronidazole (2B)
- **Empiric VRE coverage not** recommended, except for liver transplant recipients and patients known to be colonized (+ [linezolid](#) or [daptomycin](#)) – If known to be colonized with ampicillin-sensitive VRE, [ampicillin](#), [piperacillin-tazobactam](#), or [imipenem](#) (2B)

## Empiric antibiotic regimens for health care-associated intra-abdominal infections in adults

### Single-agent regimen

Imipenem-cilastatin	500 mg IV q4h
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Meropenem	1 g IV q8h
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Doripenem	500 mg IV q8h
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Piperacillin-tazobactam	4.5 g IV q6h
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### Combination regimen

ONE of the following:

Cefepime	2 g IV q8h
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OR

Ceftazidime	2 g IV q8h
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PLUS:

Metronidazole	500 mg IV or PO q8h
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PLUS ONE of the following (in some cases\*):

Ampicillin	2 g IV q4h
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OR

Vancomycin	15 to 20 mg/kg IV q8-12h
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## Healthcare-associated infections

**\*Coverage against MRSA :** in those known to be colonized, those with prior treatment failure, and those with significant prior antibiotic exposure

**\* Empiric antifungal coverage appropriate :** pts at risk for *Candida* spp, : upper GI perforations, recurrent bowel perforations, surgically treated pancreatitis, heavy colonization with *Candida* spp, and/or yeast identified on Gram stain of samples from infected peritoneal fluid or tissue) – preferably echinocandin (fluco if sensitive *Candida* isolated).

# Targeted Antimicrobial Therapy - General principles of regimen selection

- Culture of specimen asap before or after antibiotic initiation – BUT do not delay treatment
- Avoid collecting from drains / fistulas
- Target therapy based on the results of culture and susceptibility testing from appropriate specimens BUT do not change if empiric successful and low risk (1B)
- De-escalate asap (1B)
- Assume anaerobic coverage
- Transition to an oral regimen if clinical condition and susceptibility allows

# Antimicrobial Therapy – When and for How long ?

- Start ASAP (within an hour) (2B)
- If adequate source control : 4-5 days (1A) & 7 days if secondary bacteraemia (2B)
- If uncertain longer course 7-10 days (2C)
- In abscesses longer courses based on clinical judgement, inflammatory markers, imaging
- Do not use antibiotic agents to prevent infection in patients with severe or necrotizing pancreatitis (1-B).
- Consider deferral of antibiotic therapy in lower-risk patients with uncomplicated acute colonic diverticulitis (2-B)
- Inadequate evidence for immunosuppressed





# Antimicrobial Therapy – When and for How long ?

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- For acute stomach and proximal jejunum perforations, in the absence of acid-reducing therapy or malignancy and when source control is achieved within 24 h, **prophylactic antiinfective therapy directed at aerobic gram-positive cocci for 24 h is adequate (B-II)**.
- In the presence of delayed operation for acute stomach and proximal jejunum perforations, the presence of gastric malignancy or the presence of therapy reducing gastric acidity, antimicrobial therapy to cover mixed flora (eg, as seen in complicated colonic infection) should be provided (B-III).

# REMEMBER SOURCE CONTROL



# Source control

- Routinely use a source control procedure to remove infected fluid and tissue - **except for** those with clinical problems for which there is clear evidence that a non-interventional approach is associated with a good clinical outcome (1-A)
- Undertake source control within 24 hours of the diagnosis of IAI, **except for** clinical evidence indicates a non-interventional or delayed approach is appropriate (2-B) (more urgent in sepsis or septic shock (2-C))
- If no improvement within 48-72h undertake further source control (2C) and obtain cultures (1C)
- Use the least invasive approach (1-B) except for.....failure....

## **Table 1. Clinical Factors Predicting Failure of Source Control for Intra-abdominal Infection**

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Delay in the initial intervention (>24 h)

High severity of illness (APACHE II score  $\geq 15$ )

Advanced age

Comorbidity and degree of organ dysfunction

Low albumin level

Poor nutritional status

Degree of peritoneal involvement or diffuse peritonitis

Inability to achieve adequate debridement or control of drainage

Presence of malignancy

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**NOTE.** APACHE, Acute Physiology and Chronic Health Evaluation.

## Treatment failure

- Do not routinely change antimicrobial therapy when early treatment failure and undergo repeat source control within 48 hours of the initial source control intervention (Grade 2-C). Consider altering antimicrobial therapy, using an alternative antibiotic class if feasible, in patients who have late treatment failure (Grade 2-C).
- Consider discontinuation of antimicrobial therapy in patients with clinical evidence of treatment failure but negative results of imaging studies for recurrent or persistent IAI (Grade 2-B).

# Treatment failure

- Consider a trial of further antimicrobial therapy in patients with clinical evidence of treatment failure and imaging studies showing ongoing intra-abdominal inflammation; if there is no clinical response to this antimicrobial trial within a few days, discontinue antimicrobial therapy and reinstate only if there is evidence of clinical deterioration (Grade 2-C).
- Consider continuation of antimicrobial therapy in patients with clinical evidence of treatment failure and imaging studies showing recurrent or persistent IAI, in whom further source control cannot be achieved
- Extra-abdominal sources of infection and noninfectious inflammatory conditions should also be investigated if the patient is not experiencing a satisfactory clinical response to a microbiologically adequate initial empiric antimicrobial regimen (A-II).



**A couple of every day  
life stories....**





# 1. Οξεία σκωληκοειδίτιδα – αντιμετώπιση

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- **Appendectomy** remains the treatment of choice for acute appendicitis.
- Antibiotic therapy is a safe means of primary treatment for patients with uncomplicated acute appendicitis, but this conservative approach is less effective in the long-term due to significant recurrence rates. (1A)

## 2. Οξεία εκκολπωματίτιδα

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- Patients with uncomplicated acute diverticulitis should be treated with antibiotic therapy to address gram-negative and anaerobic pathogens (2C)
- Systemic antibiotic treatment alone is usually the most appropriate treatment for patients with small (< 4 cm in diameter) diverticular abscesses; Image guided (ultrasound- or CT-guided) percutaneous drainage is suggested for patients with large diverticular abscesses (> 4 cm in diameter) (2B).

# 3. Ηπατικό απόστημα – τοπογραφία & μικροβιολογία

75% Δεξιό λοβό ( → αυξημένη αιμάτωση)

20% Αριστερό λοβό

5% κερκοφόρο

Ασυνήθης η προσβολή και των δύο λοβών με  
πολλαπλά αποστήματα

Αποστήματα:

μονήρη ή πολλαπλά,

μονόχωρα ή πολύχωρα

μεγέθους mm- cm,

- Gram-negative

*Escherichia coli, Klebsiella, Proteus vulgaris*

- Gram-positive

*Streptococcus milleri, Strept. anginosus group (incl.S. constellatus & S. intermedius), Staph. aureus and Strept. pyogenes (endocarditis and infected catheters)*

- Αναεροβιοι μικροοργανισμοι : *Bacteroides fragilis*

- Μύκητες : *Candida spp.* (ουδετεροπενικούς, IVDU)

- Σπάνια: *Pseudomonas, Proteus, Enterobacter, Citrobacter, Serratia, β-hemolytic streptococci, microaerophilic streptococci, Fusobacterium, and Clostridium species.*

### 3. Ηπατικό απόστημα - αντιμετώπιση

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**Drainage of liver abscess, either surgically (either open or laparoscopic), percutaneously, or via endoscopic retrograde cholangiopancreatography, is standard**

- For patients with a single unilocular abscess, we suggest percutaneous drainage ([Grade 2B](#)):
  - single abscesses  $\leq 5$  cm : needle aspiration only or through placement of a drainage catheter.
  - For drainage of single abscesses  $>5$  cm in diameter, : percutaneous catheter drainage rather than needle aspiration ([Grade 2B](#)). Drainage catheters should remain in place until drainage ceases (usually up to seven days).
- For patients with multiple or multiloculated abscesses, the drainage approach depends on the number, size, and accessibility of the abscess(es), the experience of the surgeons and radiologists, and the underlying condition and comorbidities of the patient.
- Surgical drainage is appropriate when there is an underlying disease that requires primary surgical management, when there is an inadequate response to catheter drainage, or if the abscess has viscous contents that preclude successful percutaneous drainage.

### 3. Ηπατικό απόστημα - αντιμετώπιση

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- Empiric broad-spectrum parenteral antibiotics should be administered pending aspiration of the abscess and microbiologic analysis of the abscess contents.
- empiric regimen that covers streptococci, gram-negative bacilli, and anaerobes ([Grade 2C](#)). For patients in whom the possibility of *E. histolytica* cannot be reasonably excluded:  
+ [metronidazole](#) ([Grade 2C](#)).
- Once culture and susceptibility results (from blood and drainage specimens) are available, the antibiotic regimen can be tailored to them. Antibiotics are generally continued for 4-6 weeks total, depending on the clinical response to therapy (6-8 if multiple --- 2iv + 4-6 po)
- Follow up imaging ??? Only if not response

## 4. Cholecystitis and Cholangitis

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- ❑ Αερόβια Gram(-) εντερικά βακτήρια
  - E. Coli (27-66%)
  - Klebsiella (4-21%)
  
- ❑ Αερόβια Gram(+)
  - Streptococcus spp.
  - Staphylococcus spp.
  - Enterococcus spp?? (in cholangitis 10%)
  
- ❑ Αναερόβια
  - Clostridium spp.
  - Bacteroides spp.
  
- ❑ Αερόβια πολυμικροβιακή αιτιολογία (17-50%)
  
- ❑ Μικτή (αερόβια-αναερόβια) αιτιολογία (ως 40%)

# 4. Cholecystitis and Cholangitis

**Table 3** Antibiotic regimens

a. Antimicrobial therapy for community-acquired cholecystitis

Choice	Antibiotic class (Best choice from 1 to 5)	Antibiotic choice
1	Beta-lactam/beta-lactamase inhibitor combinations based regimens	Amoxicillin/Clavulanate (in stable patients) Ticarcillin/Clavulanate (in stable patients) Piperacillin/Tazobactam (in unstable patients)
2	Cephalosporins-based regimens	Ceftriazone + Metranidazole (in stable patients) Cefepime + Metranidazole (in unstable patients)
3	Carbapenem-based regimens	Ertapenem (in stable patients if risk factors for ESBLs)
4	Fluoroquinolone-based regimens (in case of allergy to beta-lactams)	Ciprofloxacin + Metronidazole (only in stable patients) Levofloxacin + Metronidazole (only in stable patients) Moxifloxacin (only in stable patients)
5	Glycylcycline-based regimen	Tigecycline (in stable patients if risk factors for ESBLs)

b. Antimicrobial therapy for health care-associated

Clinical patient's condition	Antibiotic choice
Stable	Tigecycline + Piperacillin/Tazobactam
Unstable	Imipenem/Cilastatin ± Teicoplanin
	Meropenem ± Teicoplanin
	Doripenem ± Teicoplanin

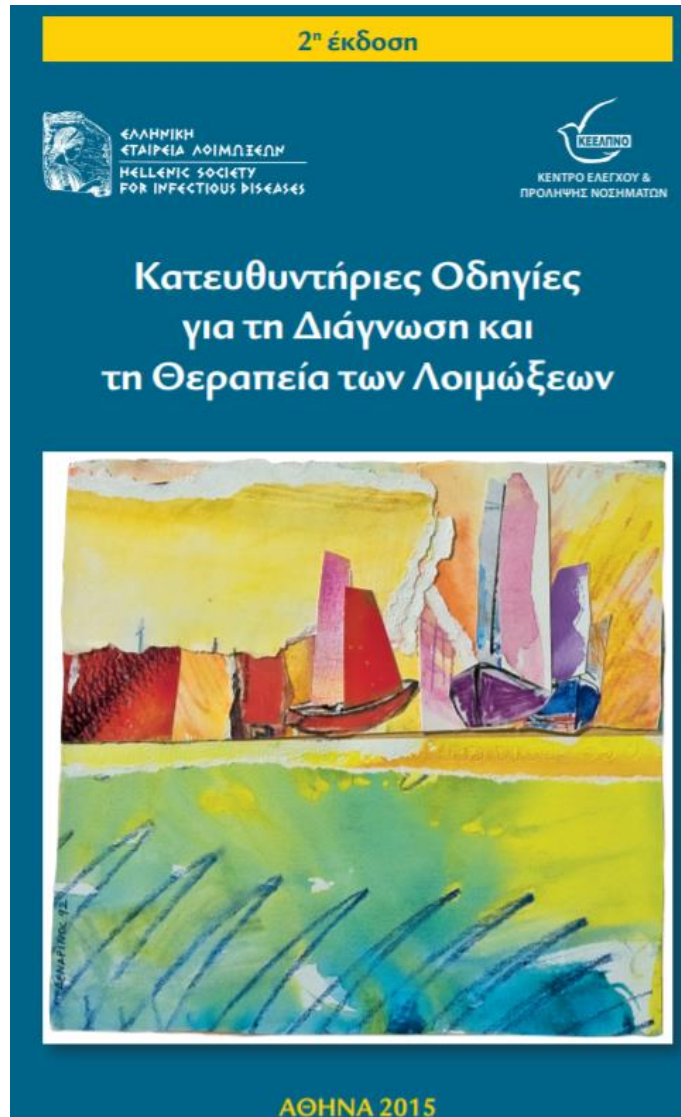
- For community-acquired biliary infection, antimicrobial activity against enterococci is not required, because the pathogenicity of enterococci has not been demonstrated.
- For selected immunosuppressed patients, particularly those with hepatic transplantation, enterococcal infection may be significant and require treatment (B-III).



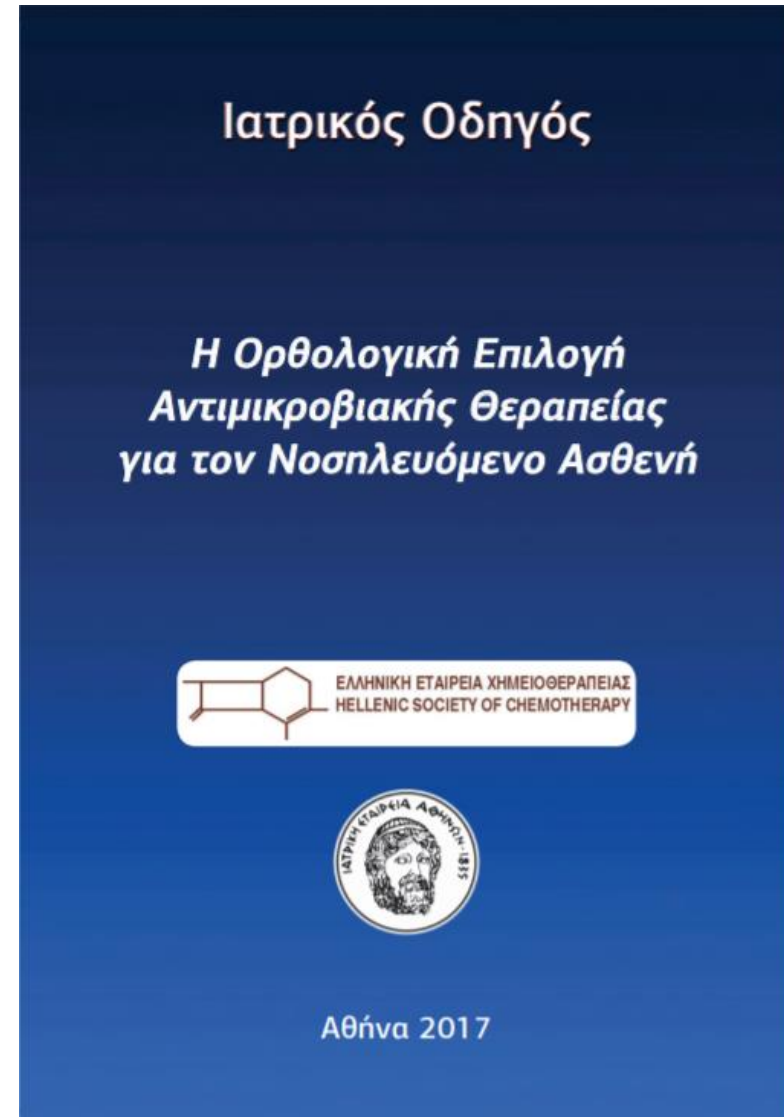
## 5. Acute pancreatitis

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- Prophylactic antibiotics in patients with acute pancreatitis are not associated with a significant decrease in mortality or morbidity. Thus, routine prophylactic antibiotics are no longer recommended for all patients with acute pancreatitis (1A)
- Antibiotics are always recommended to treat **infected** severe acute pancreatitis (2A)
- A CT-guided fine-needle aspiration (FNA) for Gram stain and culture can confirm an infected severe acute pancreatitis and drive antibiotic therapy but is no longer in routine use (1B)



Κεφαλαίο 16



Κεφαλαίο 4 & 5

**R**

**right drug  
right time  
right dose  
Right duration**

**Thank you for your patience !**