Medscape
EDUCATION

Treatment of Complicated Intra-abdominal Infections

Moderator

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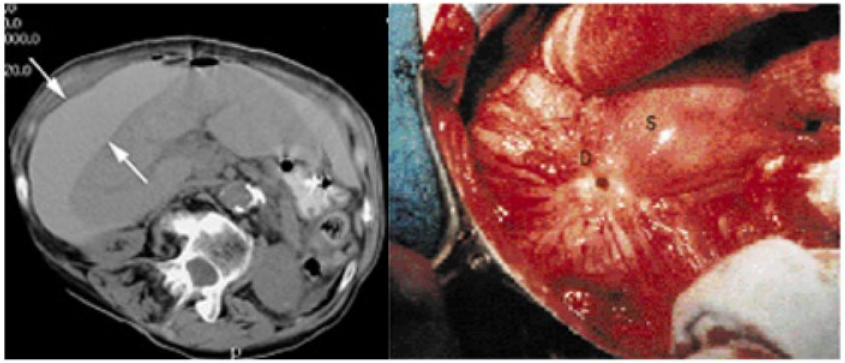
This program will include a discussion of off-label treatment options, and it will include a discussion of investigational agents not approved by the FDA for use in the United States.

What Makes a cIAI Complicated?

- Complicated intra-abdominal infection originates from a leak in the GI tract and extends beyond the hollow viscus of origin into the peritoneal space
  - Associated with either abscess formation, or localized or diffuse peritonitis
    - Not necessarily complex
    - Not necessarily difficult to treat

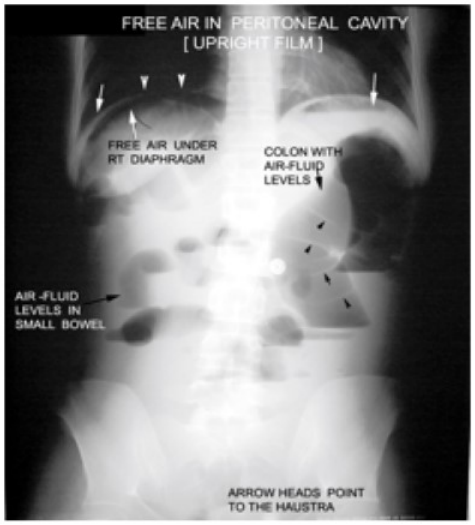


Perforated Gastroduodenal Ulcer

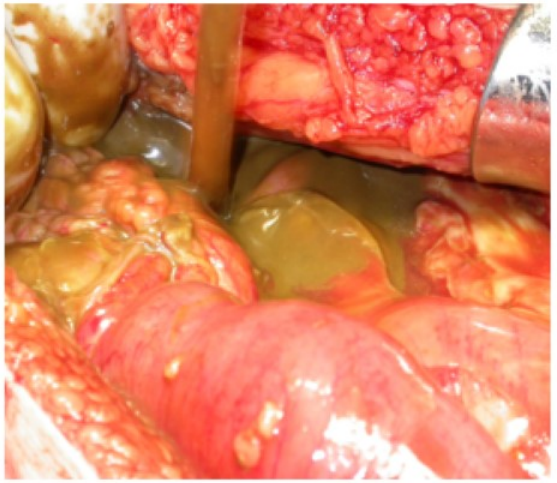
Solomkin JS, et al. *Clin Infect Dis*. 2010;50:133-163.

Case: 72-Year-Old Woman Presented to Emergency Department Severely Ill

- Pain
- Septic shock
  - Hypotension
  - Tachycardia
  - Tachypnea
  - Fever
  - Elevated WBC count
- Free air in the abdomen on abdominal x-ray

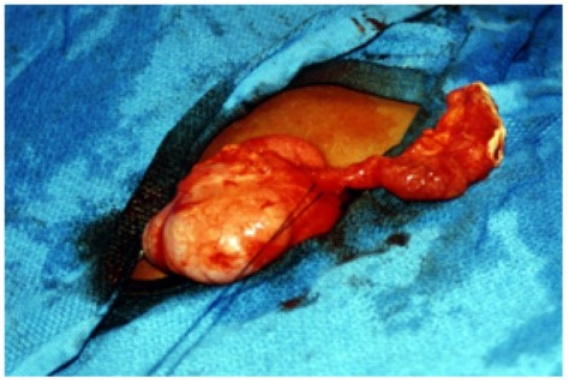


Perforated Colon



Burden of cIAIs on the Healthcare System

- ~300,000 cases/year of appendicitis
  - Up to 70,000 are perforated
- 1 million hospital days
- Serious cIAIs (eg, perforated colon) are the second most common cause of infection-related mortality in the ICU



Acute Appendicitis

Epidemiology of cIAIs

Community-acquired vs Hospital-associated

- Community-acquired IAIs are occur outside of a healthcare setting
- Hospital-associated IAIs are acquired by patients in acute care hospitals and chronic care settings
  - Increased risk for MDR organisms
  - Increased risk for treatment failure
  - Increased risk for complications and mortality

Common Pathogens in Community-acquired cIAIs*

Facultative and Aerobic Gram-negative Organisms	%
Escherichia coli	71.3
Klebsiella spp	14.3
Pseudomonas aeruginosa	14.1
Proteus spp	5.2
Enterobacter spp	5.1
Others	12.3

*Mostly community-acquired IAIs, including some hospital-associated IAIs.

Solomkin JS, et al. *Ann Surg*. 2003;237:235-245.
Solomkin JS, et al. *Ann Surg*. 2001;233:79-87.
Solomkin JS, et al. *Ann Surg*. 1996;223:303-315.

Common Pathogens in Community-acquired cIAIs (cont)

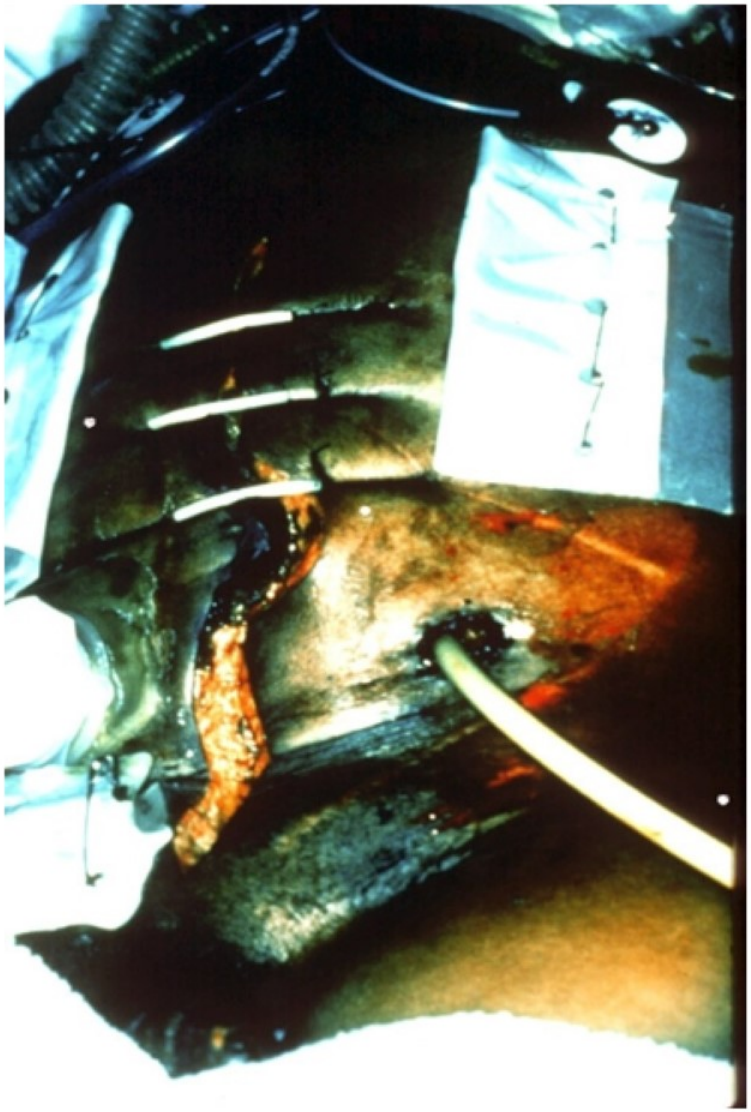
Gram-positive Organisms	%
Streptocossus spp	38
Enterococcus faecalis	11.6
Enterococcus faecium	3.4
Enterococcus spp	7.8
Staphylococcus aureus	3.5
Anaerobic Organisms	
Bacteroides fragilis	34.5
Other *Bacteroides*	71.0
Clostridium spp	29.2
Prevotella spp	12.0
Peptostreptococcus spp	16.7
Fusobacterium spp	8.6
Eubacterium spp	16.5
Others	19.4

*Mostly community-acquired IAIs, some hospital-associated IAIs included.

Solomkin JS, et al. *Ann Surg*. 2003;237:235-245.; Solomkin JS, et al. *Ann Surg*. 2001;233:79-87.
Solomkin JS, et al. *Ann Surg*. 1996;223:303-315.

cIAIs
Polymicrobial

- *E coli*, *Bacteroides fragilis*, and sometimes *Streptococcus*
- Microbial synergy
  - Organisms may work together even at low densities to produce more serious infections than either would alone
  - May be due to the production of factors by 1 organism that enhances the growth (or toxin production) of the other
  - Predisposes to local necrosis and thrombosis spreading along facial and subfacial planes, and invasive infection



cIAIs
Initial Evaluation and Management

- Fluid resuscitation
  - Protocolized, per Surviving Sepsis Campaign[a]
  - For diffuse peritonitis, resuscitation may not be possible until source-control procedure is performed
- Timely source-control procedure
- Microbiologic evaluation[b]
  - Blood culture: depends on patient's clinical presentation, but is rarely useful
  - Source cultures: fluid or tissue

a. Dellinger RP, et al. *Crit Care Med*. 2013:41:550-637.
b. Solomkin JS, et al. *Clin Infect Dis*. 2010;50:133-164.

cIAIs
Initial Evaluation and Management (cont)

- Failure to achieve adequate source control and administration of inappropriate antibiotics were independent predictors of mortality in patients with a bloodstream infection of intra-abdominal origin
- Damage-control laparotomy
  - Abbreviated procedure (minimal time in OR) to decrease innocula at the source
  - Abdomen is not closed
  - When more stable, patient returns to OR for source control

Tellor B, et al. *Surg Infect* (Larchmt). 2015 Aug 10. [Epub ahead of print]
Solomkin JS, et al. *Clin Infect Dis*. 2010;50:133-164.
Solomkin JS, et al. *Surg Infect*. (Larchmt) 2010;11:79-109.

cIAIs
Initial Evaluation and Management (cont)

- Empiric antibiotic therapy
  - Begin as soon as an infection is suspected
  - Within 4 hours in patients not in septic shock
  - Verify whether redosing of antibiotics is needed within 60 minutes of incision and continue as clinically indicated to decrease the risk for SSI
    - The primary reason for treatment failure is SSI, superficial (incisional) or complex (fasciitis or abscess)
  - Early therapy decreases the risk for progression

Solomkin JS, et al. *Clin Infect Dis*. 2010;50:133-164.
Solomkin JS, et al. *Surg Infect*. (Larchmt) 2010;11:79-109.

Empiric Antibiotic Therapy for cIAIs

- How do you determine which antibiotics to use?
  - Origin/site of infection
  - Severity of infection
  - Risk factors for resistance
    - Antibiotic history
- Should you change antibiotics when culture susceptibility data are available?
  - Depends on clinical response to empiric therapy
  - Patient is getting better → no
  - Patient remains quite ill → yes

STOP IT
Appropriate Duration of Antibiotic Therapy?

- Method: RCT comparing outcomes in patients with IAI treated with antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, vs a fixed-course regimen for 4 ±1 days (n = 257)
  - All patients had adequate source control*
- Composite end point: SSI, recurrent IAI, or death within 30 days after the index source-control procedure

Outcome	Longer Course (n = 260) (days; median, 8.0)	Shorter Course (n = 257) (days; median, 4.0)	*P*
SSI	8.8	6.6	0.40
Recurrent IAI	13.8	15.6	0.45
Death	0.8	1.2	0.68
Composite of above	21.8	22.3	0.83

*Study specifically excluded patients that had a damage control laparotomy and an open abdomen.

Sawyer RG, et al. *N Engl J Med*. 2015;372:1996-2005.

STOP IT

Benefit of Antibiotics Limited to First Few Days After Intervention

- Conclusion: no significant between-group differences in recurrent IAI or death: 21.8% in the experimental group vs 22.3% in the control group (CI, −7.0 to 8.0; *P*=.92)
  - Adequate source control is the key to shorter antibiotic therapy in patients with cIAI

Empiric Antibiotic Therapy for cIAI

*Severity-based Selection**

Antibiotics	Severity of Infection: Mild to Moderate	Severity of Infection: High
Single agents	Cefoxitin Ertapenem Moxifloxacin Tigecycline	Doripenem Meropenem Imipenem/cilastatin Piperacillin/tazobactam
Combination Regimens	Cefazolin Cefuroxime Ceftriaxone Cefotaxime ~~Ciprofloxacin~~ ~~Levofloxacin~~	Cefepime ~~Ciprofloxacin~~ ~~levofloxacin~~

*In many areas, the acquired resistance rate of *E coli to* fluoroquinolones is >20% ; in such cases, use of these agents is not recommended.

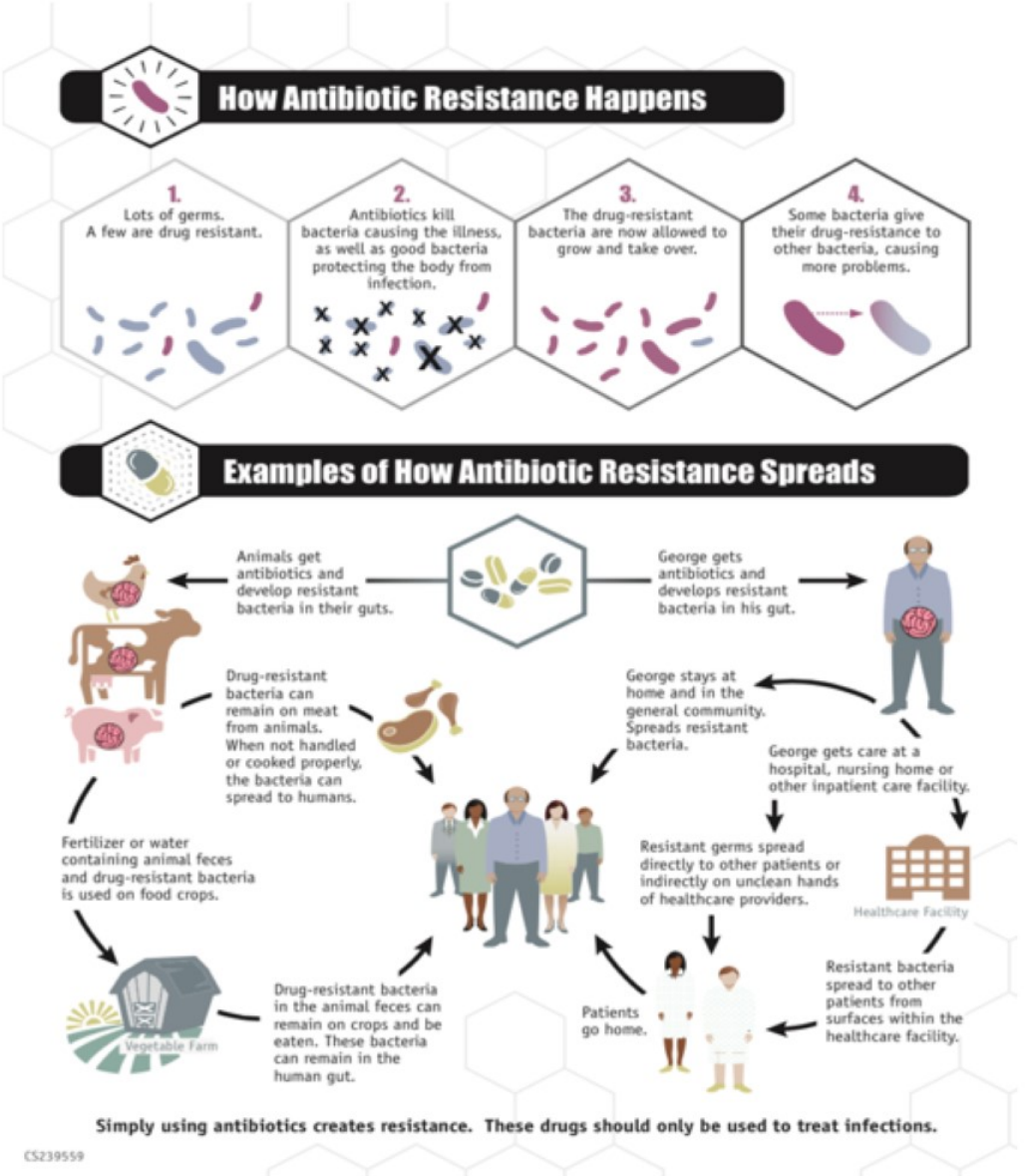
Solomkin JS, et al. *Clin Infect Dis*. 2010;50:133-164.
Solomkin JS, et al. *Surg Infect*. (Larchmt) 2010;11:79-109.

ESBLs

- Increasing degree of antibiotic resistance among gram-negative pathogens, the most common mechanisms being the production of ESBLs
  - Enzymes that mediate resistance to extended-spectrum (third-generation) cephalosporins (eg, ceftazidime, cefotaxime, and ceftriaxone) and monobactams (eg, aztreonam), but do not affect cephamycins (eg, cefoxitin and cefotetan) or carbapenems (eg, meropenem or imipenem)

Antibiotic Resistance

- The widespread use of antibiotics is selecting for a variety of resistance mechanisms that seriously challenge our ability to treat bacterial infections
- Antibiotic resistance has emerged as a very significant health care problem due to the extensive use and misuse of antibiotics in human and veterinary medicine and in agriculture



Novel Cephalosporins Coupled With a Beta-lactamase Inhibitor

- Ceftazidime/avibactam (CAZ/AVI)
  - Avibactam (non-β-lactam β-lactamase inhibitor): restores in vitro activity of ceftazidime against class A, class C and some class D β-lactamase-producing pathogens, including those commonly associated with cIAIs
  - In vitro activity against Ambler classes A and C β-lactamases, including KPC and some class D enzymes
  - Combined with ceftazidime, restores in vitro activity against ESBL-producing *Enterobacteriaceae* and MDR *Pseudomonas aeruginosa*
- Ceftolozane/tazobactam (CEF/TAZO)
  - Tazobactam: (non-β-lactam β-lactamase inhibitor), especially against those belonging to the SHV-1 and TEM-1 groups
  - Combined with ceftolozane, is active against MDR *Pseudomonas aeruginosa* and ESBL-producing *Enterobacteriaceae*

RECLAIM-1 and RECLAIM-2

Phase 3 Trial Results of the Single-pooled Dataset

- **Method:** compared the efficacy and safety of CAV-AZI in combination with MTZ vs meropenem
  - CAZ-AVI as a 2-h IV infusion (2000 mg/500 mg) every 8 h + MTZ 500 mg as a 1-h IV infusion every 8 h, compared with meropenem 1 g as a 30-min IV infusion every 8 h, in hospitalized adult patients with presumed or definite diagnosis of cIAI
- **End point:** clinical cure rate at 28 to 35 days after randomization
- **Findings:** CAV-AZI met statistical noninferiority compared with meropenem
  - AE and SAE rates were similar for CAZ-AVI + metronidazole and meropenem (45.9% vs 42.9% and 7.9% and 7.6%)
- **Conclusion:** CAZ-AVI in combination with MTZ was effective in the treatment of cIAI, including ceftazidime-resistant bacterial infections

Mazuski JE, et al. ECCMID. Copenhagen, Denmark; April 25-28, 2015. Abstract O191.

ASPECT-cIAI

A Randomized, Double-blind, Phase 3 Trial of Hospitalized Patients With cIAI

- **Method**: CEF/TAZO 1.5 g plus metronidazole (500 mg) every 8 h vs meropenem 1 g every 8 h IV for 4-14 days
  - Patients were severely ill: 20% were aged ≥65 years, 33% had renal impairment, >80% had peritonitis, the most frequent site of infection was the appendix, and the rate of ESBL-positive isolates was high (7.2%)
- **Prespecified noninferiority end point**: clinical cure rates at the test-of-cure visit (24-32 d from start of therapy) in the microbiological intent-to-treat (1°) and microbiologically evaluable (2°) populations
- **Findings**: CEF/TAZO plus metronidazole was noninferior to meropenem
  - Primary (83.0% [323/389] vs 87.3% [364/417]; weighted difference, −4.2%; 95% confidence interval [CI], −8.91 to 0.54)
  - Secondary (94.2% [259/275] vs 94.7% [304/321]; weighted difference, −1.0%; 95% CI, −4.52 to 2.59) end points
- **Conclusion**: CEF/TAZO plus metronidazole had high clinical cure rates in adults with cIAI, including common infections and those caused by MDR organisms

Solomkin J, et al. *Clin Infect Dis*. 2015;60:1462-1471.

Novel Cephalosporins Coupled With a Beta-lactamase Inhibitor

Main Targets of Therapy

CEF/TAZO

- MDR and extensively resistant *Pseudomonas* in critically-ill patients
- ESBL-carrying organisms

CAV/AVI

- Carbapenemase producers and carbapenem-resistant enterobacteriaceae (*E coli*, *Klebsiella*, and *Enterobacter)*

These are carbapenem-sparing agents for ESBL-producing bacteria and with augmented activity against MDR *Pseudomonas* (CEF/TAZO) and carbapenemase-producing *Enterobacteriacea* in patients with hospital-acquired IAIs in most geographic areas.

Treatment Failure

- Short-term
  - Clinical deterioration within 24-48 hours of operation for source control and initiation of empiric antibiotic therapy
- Longer-term
  - Patient improves, but remains fairly ill with fever and elevated WBC count at postoperative day 4 to 6
- Risk factors
  - Inadequate source control
  - Inadequate antimicrobial agent
  - SSI: degree of peritoneal contamination, surgical technique
  - Factors that adversely impact tissue healing
  - Underlying physiological status
  - Pre-existing medical disorders
  - Severity of illness

Abbreviations

ASPECT-cIAI = Assessment of the Safety Profile of Ceftolozane/Tazobactam in Complicated Intra-abdominal Infections trial

AVI = avibactam

CAI = community acquired infection

CAZ = ceftazidime

CAZ/AVI = ceftazidime + avibactam

CEF/TAZO = ceftolozane + avibactam

cIAI= complicated intra-abdominal infection

ESBL = extended-spectrum beta-lactamase

ICU = intensive care unit

OR = operating room

IAI = intra-abdominal infection

RECLAIM = phase III program of ceftazidime-avibactam in patients with complicated intra-abdominal infections

SMART = Study for Monitoring Antimicrobial Resistance Trends

STOP IT = Trial of short-course antimicrobial therapy for intraabdominal infection

TAZO = tazobactam