Update on the Management of Complicated Intra-abdominal Infection

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Objectives

- Discuss complicated intra-abdominal infection (cIAI)
- Present the evidence for current practice
- Review the role of tigecycline in cIAI
The Clinical Impact of Intra-abdominal Infection (IAI)

IAI is a major cause of morbidity and mortality

- Intra-abdominal infections are among the most common infections in general surgery\textsuperscript{1,2}
- The keys to appropriate management are\textsuperscript{1,2}:
  - Early diagnosis
  - Appropriate surgical intervention
  - Adequate antimicrobial therapy
- In a retrospective study of 604 consecutive patients who underwent emergency surgery for unequivocal IAIs, morbidity rates of 59\% and mortality rates of 21\% were reported\textsuperscript{3}

Definition of a Complicated Intra-Abdominal Infection (cIAI)

Abscess Formation¹

- Complicated intra-abdominal infections:
  - Extend beyond the hollow viscus of origin into the peritoneal space, and are associated with either abscess formation or peritonitis³
  - Require either surgery or percutaneous drainage for source control, as well as antimicrobial therapy³

Peritonitis²

² Printed with permission from Custom Medical Stock Photo, Inc.
Risk Factors for Treatment Failure

- Patient factors
  - Age, comorbidity, malnutrition\(^1\)
  - Prolonged prestudy hospital length of stay\(^2\)
  - Antimicrobial resistance\(^1\)
    - Prior antibiotic exposure
  - Severity of illness\(^1\)
- Surgical factors
  - Inadequate source control\(^1\)
  - Ineffective antibiotic therapy\(^3\)

Consequences of Treatment Failure of Initial Therapy in cSSSI

- Nearly 4 times more likely to die in hospital
- Odds ratio for in-hospital mortality 2.91 in multivariate analysis (95% CI, 2.34-3.62) (P<0.01)
- Received a mean of 5 additional days of IV antibiotic therapy (10 vs. 4 days)
- Spent a mean of 5 additional days in hospital
- Accrued $5,285 more in total inpatient charges
- Highest rate of treatment failure was associated with fluoroquinolones not active against MRSA

Microbiology of Peritonitis: Community-Acquired versus Nosocomial

CNS = Coagulase-negative staphylococci.

*P<0.05
Management Principles in cIAI

- Rapid diagnosis
- Identification of high-risk patients
- Fluid resuscitation
- Empiric broad-spectrum antimicrobial therapy
- Source control
  - Percutaneous drainage of abscess
  - Surgical intervention

SIS/IDSA Guidelines: Empiric Antimicrobial Therapy for Community-Acquired cIAI

- Select therapy with activity against
  - Enteric Gram-negative aerobic and facultative bacilli
  - Enteric Gram-positive streptococci
- Coverage for obligate anaerobic bacilli for certain infections
- Routine culture/susceptibility testing if significant resistance of a common community isolate to a widely used local regimen

# SIS/IDSA Guidelines: Agents for Extra-Biliary cIAI

## Community-Acquired Infections in Adults

<table>
<thead>
<tr>
<th></th>
<th>Mild-to-Moderate*</th>
<th>Severe</th>
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</thead>
<tbody>
<tr>
<td><strong>Single agent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefoxitin</td>
<td></td>
<td>Imipenem/cilastatin</td>
</tr>
<tr>
<td>Ertapenem</td>
<td></td>
<td>Meropenem</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td></td>
<td>Doripenem</td>
</tr>
<tr>
<td>Ticarcillin/clavulanic acid</td>
<td></td>
<td>Piperacillin/tazobactam</td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td></td>
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<tr>
<td><strong>Combination regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin†, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole</td>
<td>Cefepime, ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole</td>
<td></td>
</tr>
</tbody>
</table>

*These regimens are preferable to regimens with substantial antipseudomonal activity.

†Caution: Local antibiograms should direct use of this agent.

Severity of Illness and Risk of Failure
(from a study of cefepime/metronidazole vs. imipenem/cilastatin)

APACHE II Score (no. of patients)

<table>
<thead>
<tr>
<th>APACHE II Score</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>(n=55)</td>
</tr>
<tr>
<td>5-9</td>
<td>(n=88)</td>
</tr>
<tr>
<td>10-14</td>
<td>(n=44)</td>
</tr>
<tr>
<td>15-19</td>
<td>(n=16)</td>
</tr>
<tr>
<td>≥20</td>
<td>(n=14)</td>
</tr>
</tbody>
</table>

% Failure

APACHE = Acute Physiology and Chronic Health Evaluation
Does Antibiotic Choice Matter in High-Risk Patients?

<table>
<thead>
<tr>
<th></th>
<th>Adequate Therapy (n = 46)</th>
<th>Inadequate Therapy (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>12 (26%)</td>
<td>27 (50%)*</td>
</tr>
<tr>
<td>Re-operations</td>
<td>45 (39%)</td>
<td>103 (57%)*</td>
</tr>
</tbody>
</table>

- Mortality: 39%
- Inadequate empiric therapy is associated with mortality and re-operation

*P<0.05

Does Initial Antibiotic Choice Matter?

- 175 cases of secondary cIAI
- Risk of clinical failure was 17.1%
- Inappropriate initial antibiotic treatment increased the risk of clinical failure 3.4-fold (95% CI, 1.3-9.1) and was the only independent predictor for clinical failure
- Length of hospital stay and costs of hospitalization were significantly increased for patients with clinical failure

Study Design: Two double-blind, randomized, multicenter studies

Randomization

Tigecycline 100 mg IV then 50 mg IV q12h

or

Imipenem-cilastatin 500 mg IV q6h*

5-14 days

Clinical and microbiological outcomes

*Imipenem-cilastatin dosage was dependent on body weight and creatinine clearance.


Cure Rate† (%)

Microbiologically Evaluable Population

Tigecycline Imipenem-cilastatin

N = 512 513

Cure = the course of tigecycline or imipenem-cilastatin and initial intervention (operative and/or radiographically controlled drainage procedures) resolved the intra-abdominal infectious process.
Cure Rates by Diagnosis in the ME Population in cIAI Studies

S. anginosus group includes S. anginosus, S. intermedius, and S. constellatus.
Tigecycline Efficacy in cIAI: An Open-Label Comparison with CTX/Met

**Study Design:** Multicenter, open-label, randomized study

Randomization:
- Tigecycline 100 mg IV then 50 mg IV q12h
- Ceftriaxone 2 g/d + Metronidazole 1-2 g/d

4-14 days

Clinical and microbiological outcomes

Microbiologically Evaluable Population

- **Tigecycline**
  - Cure Rate: 66%
  - N = 138

- **Ceftriaxone + Metronidazole**
  - Cure Rate: 70%
  - N = 137

†Cure = the course of tigecycline or ceftriaxone + metronidazole and initial intervention (operative and/or radiographically controlled drainage procedures) resolved the intra-abdominal infectious process.

# Common Treatment-Emergent Adverse Events: Tigecycline versus CTX/Met

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Tigecycline (n=236)</th>
<th>Ceftriaxone-Metronidazole (n=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>38.6</td>
<td>27.7</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>8.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>3.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Oral moniliasis</td>
<td>3.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>0.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Generalized edema</td>
<td>0.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>0.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*P < 0.05 for all above values*

Tigecycline for Severe Infection

- Prospective, multicenter, non-interventional study investigated the efficacy and safety of tigecycline in severely ill patients with cIAI and complicated skin and soft tissue infections.

- 656 patients enrolled:
  - 41% cIAI (13% multiple infection sites)
  - 51% monotherapy
  - Mean APACHE II score = 19.1
  - 55% failed prior antibiotics
  - Drug-related adverse events = 6.7%

- Clinical cure/improvement = 75% for cIAI

Eckmann C et al. Chemotherapy 2011;57:275-284
Case of Intra-abdominal Infection

- The patient was a 19 YO presenting to the hospital to have her first child
- Because of poor fetal heart tones she underwent a Cesarean delivery
  - Healthy baby
  - Mother develops fever at 24 hours
  - Initial infection work-up negative
- Begun on ampicillin, gentamicin, and clindamycin
Case of Intra-Abdominal Infection

- Fevers continue
  - Lower end of surgical incision indurated at 48 hours and then opened and wound packed
  - Initial CT scan negative for abscess
- Infectious Disease consult requested (day 7)
- On interview
  - She had no complaints – tearful over infection
  - 5-7cm area of intense tenderness and thick induration on one edge of her surgical incision
  - WBC = 25,000; pulse >100 beats/minute
WBC Count
Questions – What to do?

To treat this infection, what would you switch to?

1. Piperacillin-tazobactam and Linezolid
2. Ertapenem plus Vancomycin
3. Ciprofloxacin plus Metronidazole
4. Tigecycline
Case of Intra-abdominal Infection

- Antibiotics changed to tigecycline alone
- Repeat CT 2 days later showed 3 cm abscess as a deep organ space infection
  - Small amount of fluid aspirated
  - 2+ wbc and no bacteria (grew coag-neg staph; anaerobe culture not performed)
- Improved over 72 hours
  - Discharged on oral amoxicillin/clavulanate
Conclusions: cIAI

- Epidemiology and microbiology of cIAI are changing
  - Increasingly resistant pathogens
- Source control remains paramount
- Adequate empiric antibiotic therapy correlates with clinical success
- Tigecycline monotherapy has demonstrated efficacy in cIAI
- Tigecycline has a broad spectrum of in vitro activity, including activity against many resistant pathogens