OBJECTIVE
To compare whether administration of antibiotic therapy for 4 days after source control would lead to equivalent outcomes and a shorter duration of therapy as compared with the traditional strategy of administration of antibiotics until 2 days after resolution of SIRS

BACKGROUND OF THE STUDY

- **Intra-abdominal Infection (IAI)** is broadly defined as peritoneal inflammation in response to microorganisms, resulting in purulence in the peritoneal cavity (Wittmann, 1996).
- Average incidence of 3.5 million cases per year, with mortality rate as high as 60% among those with well-established infection complicated by multisystem organ failure.

**Pathophysiology**
- Intra-abdominal infections usually arise after a breach in the normal mucosal defense barrier that allows normal bowel flora to inoculate the abdominal cavity
- Perforation, and the bacterial inoculation that ensues, causes an inflammatory response that acts locally to contain the infection but in the setting of overwhelming contamination, it can cause systemic inflammation
- Common pathogens in IAI’s are coliforms (E. coli, Klebsiella, Proteus, Enterobacter), anaerobes (Bacteroides), Streptococci, and Enterococci

- It can be classified into:
  - Uncomplicated- inflammation of the gastrointestinal tract without anatomic disruption
  - Complicated- extend beyond the source organ into peritoneal space and causes peritoneal inflammation or abscess formation

**Community Acquired IAI**
- Mild to Moderate - perforated/ abscessed appendicitis
- High-Risk or Severe- severe physiological disturbance, advanced age, immunocompromised

**Healthcare Associated IAI**- relatively new term pertaining to patients who have close association to acute care hospital or reside in chronic care settings
- Community Onset – at least (1) risk factor:
  - Presence of invasive device at time of admission
  - History of MRSA
  - History of surgery, hospitalization, dialysis, LTCF residence within 12 months preceding culture date
- Hospital Onset – positive culture results from a normally sterile site obtained > 48h after hospital admission

**Diagnosis:**
- Radiographic Imaging
- Cultures- high risk patients, health care associated, community acquired if high resistance area
- Physical Exam
  - Abdominal pain, Anorexia, Nausea, Vomiting, Bloating, Obstipation
  - Fever, tachycardia, tachypnea
  - For patients with unreliable physical examination (eg obtunded mental status, immunosuppressed), suspect IAI if presenting with infection from undetermined source
- Laboratory Findings – increased WBC, lactate*

**Management:**
- Fluid Resuscitation
- Source Control Procedure- procedures that eliminate infectious foci, control factors that promote ongoing infection, and correct or control anatomical derangements to restore normal physiological factor
- Antimicrobials
  - Biliary Infection (Community Acquired)
    - Anaerobic coverage only if (+) biliary-enteric anastomosis
    - Enterococcus coverage not needed unless immunosuppressed (eg liver transplant)
      - Mild to Moderate Community acquired Biliary Infection
        - Enteric gram (-) bacilli and enteric gram (+) streptococci
        - Resistance: Ampi-Sul (CA- E. coli); Cefotetan and Clindamycin (Bacteroides)
  - Extrabiliary Infection (Community Acquired)
    - Anaerobic coverage for distal small bowel, appendix, colon-derived infection; and for proximal GI perforations in case of ileus or obstruction
    - Empiric coverage of Enterococcus not necessary
  - Severe/ High-risk (Community-Acquired)
    - APACHE II Score > 15 and/or predicting factors for failure of source control
    - Additional coverage: Enterococci; Antifungal (Fluconazole, Echinocandin) if Candida is growing
    - Resistance: Quinolone*
  - Healthcare associated Infections
    - Extended spectrum coverage for gram (-) bacilli
- Additional coverage: *Enterococci*; Antifungal (Fluconazole, Echinocandin) if *Candida* is growing
- VRE coverage if immunosuppressed (e.g. liver transplant donor with hepatobiliary infection)
- MRSA coverage: patients known to be colonized, prior treatment failure

**Duration of therapy:**
- Should be limited to 4-7 days, unless adequate source control is achieved
- For acute stomach and proximal jejunal perforations
  - Source control within 24 hrs = coverage for GPC for 24 hours
  - Delayed source control = coverage for mixed flora
- < or = 24 hour antibiotic coverage
  - Acute appendicitis/cholecystitis (no perforation, abscess or local peritonitis)
  - Acute Stomach and proximal jejunal perforation (in the absence of malignancy or acid-reducing therapy) repaired within 24 hours
  - Bowel Injuries 2/2 trauma repaired within 12 hours

### METHODS

**Funding**
National Institute of Health, Study to Optimize Peritoneal Infection Therapy (STOP-IT trial)

**Study Design**
- Open Label, Multi-Center trial
- August 2008 to August 2013 in 23 sites in USA and Canada

**Inclusion Criteria**
- Age ≥ 16
- Presented with complicated IAI with either fever (>38 C), Leukocytosis (>11 K WBC), or gastrointestinal dysfunction secondary to peritonitis precluding intake of more than half their normal diet
- Undergone source control procedure

**Exclusion Criteria**
- Patients who did not receive adequate source control

**Baseline Characteristics**
- Age 16-88 (Mean: 52 years)
- Mostly male
- APACHE II Score 0-29 (Mean: 10)
- Most common origin of infection is rectum or colon
- Similar composition between racial groups

**Interventions**
- 518 patients went into randomization by independent contract research organization (Merge Healthcare)
- One patient withdrew consent after randomization
- Patients were followed to assess their clinical course and adherence to protocol
- Adherence to protocol is defined as:
  - Experimental Group (n= 257): Receiving effective antimicrobial agents 4 +/- 1 days after index source-control procedure
  - Control Group (n= 260): Receiving effective antimicrobial agents until 2 +/- 1 days after the first day of resolution (Temp <38C for 24 hours, Normalization of WBC to <11 K, patient's ability to consume more than half his/her regular diet without adverse effects; Up to a maximum of 10 days of therapy was allowed for IAI treatment
- Patients were followed for 30 days after the initial source control procedure and assessed for infectious complications, use of antimicrobial therapy, and death

**Study Limitations**
- The specific choice of antimicrobial agents not dictated by the protocol but was considered acceptable if consistent with IDSA guidelines
- Targeted enrollment levels is not achieved
- Exclusion of patients with inadequate source control
- Rate of nonadherence to protocol is moderately high, about 18% in experimental group

**Outcomes**
- Primary Outcomes:
  - Development of surgical site infection or recurrent IAI
  - Death within 30 days after the source control procedure
- Secondary Outcomes:
  - Duration of antimicrobial therapy
  - Adherence to protocol

**Statistical Analysis**
- Primary Outcome- chi square test, t-test, Wilcoxon signed rank test
- Secondary Outcome- Multivariate logistic regression

**Results and Discussion**
- Traditionally, physicians continue antimicrobial therapy for IAI until clinical and laboratory evidence suggests that the infection has resolved, reasoning that ongoing SIRS is indicative of continuing replication of pathogen.
- Observational studies state that currently, the average duration of antibiotic therapy for IAI is 10-14 days (Riccio, 2014).
- More recent experiments suggest that prolonged SIRS may be more a reflection of host immune activity than an indication of the presence of viable microorganisms (Sursal, 2013).
- That being said, new studies are being made to shorten the duration of antimicrobial therapy despite the presence of ongoing markers of SIRS
Results and Discussion

- No significant between-group differences for the primary endpoint
  - Development of surgical site infection (absolute difference, -2.2 percentage points; 95% CI, -2.4 to 7.0; P= 0.43)
  - Recurrent IAI (absolute difference, 1.8 percentage points; 95% CI, -4.5 to 7.8; P= 0.67)
  - Death (absolute difference, 0.4 percentage points; 95% CI, -1.7 to 2.7; P= 0.99)
- Median duration of antimicrobial treatment is 4 days in experimental group compared to 8 days in control group (absolute difference, -4.0 days; 95% CI, -4.7 to -3.3; P <0.001)
  - There were significantly fewer median antimicrobial-free days at 30 days in control group than with experimental group
- Adherence to Protocol: 211 of 258 patients in the experimental group (81%) VS 189 of 260 patients in control group (72.7%)

Conclusion

- Provided that adequate source control is achieved, a fixed, 4-day duration of antimicrobial regimen for IAI appear to have similar outcomes in patients who receive antimicrobial therapy until after clinical resolution is achieved.
- Considering outcomes are similar, a shorter duration of antimicrobial regimen is preferable due to less adverse effects, lower costs, and preventing development of antimicrobial resistance.

References