IDSA GUIDELINES

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]

[1]Department of Surgery, the University of Cincinnati College of Medicine, Cincinnati, Ohio; [2]Department of Surgery, Washington University School of Medicine, Saint Louis, Missouri; Departments of [3]Pediatric Infectious Diseases and [4]Surgery, Rady Children's Hospital of San Diego, San Diego, [5]R. M. Alden Research Laboratory, David Geffen School of Medicine at UCLA, Los Angeles, [6]Department of Pathology, Stanford University School of Medicine, Palo Alto, California; Departments of [7]Pharmacy Practice and [8]Medicine, University of Illinois at Chicago, Chicago; [9]Department of Surgery, The Trauma Center at Maricopa Medical Center, Phoenix, Arizona; [10]Department of Surgery, University of Washington, Seattle; [11]Department of Surgery, Cornell Medical Center, New York, New York; [12]Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts; [13]Department of Surgery, Vanderbilt University Medical Center, Nashville, Tennessee; [14]Department of Surgery, University of Virginia, Charlottesville; [15]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; and [16]Department of Medicine, University of British Columbia, Vancouver, British Columbia, and [17]St Michael's Hospital, Toronto, Ontario, Canada

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.

EXECUTIVE SUMMARY

The 2009 update of the guidelines contains evidence-based recommendations for the initial diagnosis and subsequent management of adult and pediatric patients with complicated and uncomplicated intra-abdominal infection. The multifaceted nature of these infections has led to collaboration and endorsement of these recommendations by the following organizations: American Society for Microbiology, American Society of Health-System Pharmacists, Pediatric Infectious Diseases Society, and Society of Infectious Diseases Pharmacists.

These guidelines make therapeutic recommendations on the basis of the severity of infection, which is defined for these guidelines as a composite of patient age, physiologic derangements, and background medical conditions. These values are captured by severity scoring systems, but for the individual patient, clinical judgment is at least as accurate as a numerical score [1–4]. "High risk" is intended to describe patients with a range

Received 7 October 2009; accepted 9 October 2009; electronically published 23 December 2009.

Reprints or correspondence: Dr Joseph S. Solomkin, Dept of Surgery, University of Cincinnati College of Medicine, 231 Albert B. Sabin Way, Cincinnati OH 45267-0558 (joseph.solomkin@uc.edu).

Clinical Infectious Diseases 2010; 50:133–64

1058-4838/2010/5002-0001$15.00
DOI: 10.1086/649554

This guideline might be updated periodically. To be sure you have the most recent version, check the Web site of the journal (http://www.journals.uchicago.edu/page/cid/IDSAguidelines.html).

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

of reasons for increased rates of treatment failure in addition to a higher severity of infection, particularly patients with an anatomically unfavorable infection or a health care–associated infection [5] (Table 1).

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

Delay in the initial intervention (>24 h)
High severity of illness (APACHE II score ⩾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

NOTE. APACHE, Acute Physiology and Chronic Health Evaluation.

Initial Diagnostic Evaluation

1. Routine history, physical examination, and laboratory studies will identify most patients with suspected intra-abdominal infection for whom further evaluation and management is warranted (A-II).
2. For selected patients with unreliable physical examination findings, such as those with an obtunded mental status or spinal cord injury or those immunosuppressed by disease or therapy, intra-abdominal infection should be considered if the patient presents with evidence of infection from an undetermined source (B-III).
3. Further diagnostic imaging is unnecessary in patients with obvious signs of diffuse peritonitis and in whom immediate surgical intervention is to be performed (B-III).
4. In adult patients not undergoing immediate laparotomy, computed tomography (CT) scan is the imaging modality of choice to determine the presence of an intra-abdominal infection and its source (A-II).

Fluid Resuscitation

5. Patients should undergo rapid restoration of intravascular volume and additional measures as needed to promote physiological stability (A-II).
6. For patients with septic shock, such resuscitation should begin immediately when hypotension is identified (A-II).
7. For patients without evidence of volume depletion, intravenous fluid therapy should begin when the diagnosis of intra-abdominal infection is first suspected (B-III).

Timing of Initiation of Antimicrobial Therapy

8. Antimicrobial therapy should be initiated once a patient receives a diagnosis of an intra-abdominal infection or once such an infection is considered likely. For patients with septic shock, antibiotics should be administered as soon as possible (A-III).
9. For patients without septic shock, antimicrobial therapy should be started in the emergency department (B-III).
10. Satisfactory antimicrobial drug levels should be maintained during a source control intervention, which may necessitate additional administration of antimicrobials just before initiation of the procedure (A-I).

Elements of Appropriate Intervention

11. An appropriate source control procedure to drain infected foci, control ongoing peritoneal contamination by diversion or resection, and restore anatomic and physiological function to the extent feasible is recommended for nearly all patients with intra-abdominal infection (B-II).
12. Patients with diffuse peritonitis should undergo an emergency surgical procedure as soon as is possible, even if ongoing measures to restore physiologic stability need to be continued during the procedure (B-II).
13. Where feasible, percutaneous drainage of abscesses and other well-localized fluid collections is preferable to surgical drainage (B-II).
14. For hemodynamically stable patients without evidence of acute organ failure, an urgent approach should be taken. Intervention may be delayed for as long as 24 h if appropriate antimicrobial therapy is given and careful clinical monitoring is provided (B-II).
15. In patients with severe peritonitis, mandatory or scheduled relaparotomy is not recommended in the absence of intestinal discontinuity, abdominal fascial loss that prevents abdominal wall closure, or intra-abdominal hypertension (A-II).
16. Highly selected patients with minimal physiological derangement and a well-circumscribed focus of infection, such as a periappendiceal or pericolonic phlegmon, may be treated with antimicrobial therapy alone without a source control procedure, provided that very close clinical follow-up is possible (B-II).

Microbiologic Evaluation

17. Blood cultures do not provide additional clinically relevant information for patients with community-acquired intra-abdominal infection and are therefore not routinely recommended for such patients (B-III).
18. If a patient appears clinically toxic or is immunocompromised, knowledge of bacteremia may be helpful in determining duration of antimicrobial therapy (B-III).
19. For community-acquired infections, there is no proven value in obtaining a routine Gram stain of the infected material (C-III).

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.

20. For health care–associated infections, Gram stains may help define the presence of yeast (C-III).

21. Routine aerobic and anaerobic cultures from lower-risk patients with community-acquired infection are considered optional in the individual patient but may be of value in detecting epidemiological changes in the resistance patterns of pathogens associated with community-acquired intra-abdominal infection and in guiding follow-up oral therapy (B-II).

22. If there is significant resistance (ie, resistance in 10%–20% of isolates) of a common community isolate (eg, *Escherichia coli)* to an antimicrobial regimen in widespread local use, routine culture and susceptibility studies should be obtained for perforated appendicitis and other community-acquired intra-abdominal infections (B-III).

23. Anaerobic cultures are not necessary for patients with community-acquired intra-abdominal infection if empiric antimicrobial therapy active against common anaerobic pathogens is provided (B-III).

24. For higher-risk patients, cultures from the site of infection should be routinely obtained, particularly in patients with prior antibiotic exposure, who are more likely than other patients to harbor resistant pathogens (A-II).

25. The specimen collected from the intra-abdominal focus of infection should be representative of the material associated with the clinical infection (B-III).

26. Cultures should be performed from 1 specimen, provided it is of sufficient volume (at least 1 mL of fluid or tissue, preferably more) and is transported to the laboratory in an appropriate transport system. For optimal recovery of aerobic bacteria, 1–10 mL of fluid should be inoculated directly into an aerobic blood culture bottle. In addition, 0.5 mL of fluid should be sent to the laboratory for Gram stain and, if indicated, fungal cultures. If anaerobic cultures are requested, at least 0.5 mL of fluid or 0.5 g of tissue should be transported in an anaerobic transport tube. Alternately, for recovery of anaerobic bacteria, 1–10 mL of fluid can be inoculated directly into an anaerobic blood culture bottle (A-I).

27. Susceptibility testing for *Pseudomonas, Proteus, Acinetobacter, Staphylococcus aureus,* and predominant Enterobacteriaceae, as determined by moderate-to-heavy growth, should be performed, because these species are more likely than others to yield resistant organisms (A-III).

RECOMMENDED ANTIMICROBIAL REGIMENS

The antimicrobials and combinations of antimicrobials detailed in Tables 2–4 are considered adequate for empiric treatment of community- and health care–associated intra-abdominal infection as indicated.

Community-Acquired Infection of Mild-to-Moderate Severity in Adults

28. Antibiotics used for empiric treatment of community-acquired intra-abdominal infection should be active against enteric gram-negative aerobic and facultative bacilli and enteric gram-positive streptococci (A-I).

29. Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus (A-I).

30. For adult patients with mild-to-moderate community-acquired infection, the use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity (Table 2) (A-I).

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

Organisms seen in health care–associated infection at the local institution	Regimen				
	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

31. Ampicillin-sulbactam is not recommended for use because of high rates of resistance to this agent among community-acquired *E. coli* (B-II).

32. Cefotetan and clindamycin are not recommended for use because of increasing prevalence of resistance to these agents among the *Bacteroides fragilis* group (B-II).

33. 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).

34. Empiric coverage of *Enterococcus* is not necessary in patients with community-acquired intra-abdominal infection (A-I).

35. Empiric antifungal therapy for *Candida* is not recommended for adult and pediatric patients with community-acquired intra-abdominal infection (B-II).

36. The use of agents listed as appropriate for higher-severity community-acquired infection and health care–associated infection is not recommended for patients with mild-to-moderate community-acquired infection, because such regimens may carry a greater risk of toxicity and facilitate acquisition of more-resistant organisms (B-II).

37. For those patients with intra-abdominal infection of mild-to-moderate severity, including acute diverticulitis and various forms of appendicitis, who will not undergo a source control procedure, regimens listed for treatment of mild-to-moderate–severity infection are recommended, with a possibility of early oral therapy (B-III).

High-Risk Community-Acquired Infection in Adults

38. The empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended for patients with high-severity community-acquired intra-abdominal infection, as defined by APACHE II scores >15 or other variables listed in Table 1 (Table 2) (A-I).

39. Quinolone-resistant *E. coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones (A-II).

40. Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended (B-III).

41. In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy (A-I).

42. Empiric use of agents effective against enterococci is recommended (B-II).

43. Use of agents effective against methicillin-resistant *S. aureus* (MRSA) or yeast is not recommended in the absence of evidence of infection due to such organisms (B-III).

44. In these high-risk patients, antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated in culture (A-III).

Health Care–Associated Infection in Adults

45. Empiric antibiotic therapy for health care–associated intra-abdominal infection should be driven by local microbiologic results (A-II).

46. To achieve empiric coverage of likely pathogens, multidrug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime

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.

or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required (Table 3) (B-III).

47. Broad-spectrum antimicrobial therapy should be tailored when culture and susceptibility reports become available, to reduce the number and spectra of administered agents (B-III).

Antifungal Therapy

48. Antifungal therapy for patients with severe community-acquired or health care–associated infection is recommended if *Candida* is grown from intra-abdominal cultures (B-II).

49. Fluconazole is an appropriate choice for treatment if *Candida albicans* is isolated (B-II).

50. For fluconazole-resistant *Candida* species, therapy with an echinocandin (caspofungin, micafungin, or anidulafungin) is appropriate (B-III).

51. For the critically ill patient, initial therapy with an echinocandin instead of a triazole is recommended (B-III).

52. Because of toxicity, amphotericin B is not recommended as initial therapy (B-II).

53. In neonates, empiric antifungal therapy should be started if *Candida* is suspected. If *C. albicans* is isolated, fluconazole is an appropriate choice (B-II).

Anti-enterococcal Therapy

54. Antimicrobial therapy for enterococci should be given when enterococci are recovered from patients with health care–associated infection (B-III).

55. Empiric anti-enterococcal therapy is recommended for patients with health care–associated intra-abdominal infection, particularly those with postoperative infection, those who have previously received cephalosporins or other antimicrobial agents selecting for *Enterococcus* species, immunocompromised patients, and those with valvular heart disease or prosthetic intravascular materials (B-II).

56. Initial empiric anti-enterococcal therapy should be directed against *Enterococcus faecalis*. Antibiotics that can potentially be used against this organism, on the basis of susceptibility testing of the individual isolate, include ampicillin, piperacillin-tazobactam, and vancomycin (B-III).

57. 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* (B-III).

Anti-MRSA Therapy

58. Empiric antimicrobial coverage directed against MRSA should be provided to patients with health care–associated intra-abdominal infection who are known to be colonized with the organism or who are at risk of having an infection due to this organism because of prior treatment failure and significant antibiotic exposure (B-II).

59. Vancomycin is recommended for treatment of suspected or proven intra-abdominal infection due to MRSA (A-III).

Cholecystitis and Cholangitis in Adults

60. Ultrasonography is the first imaging technique used for suspected acute cholecystitis or cholangitis (A-I).

61. Patients with suspected infection and either acute cholecystitis or cholangitis should receive antimicrobial therapy, as recommended in Table 4, although anaerobic therapy is not indicated unless a biliary-enteric anastamosis is present (B-II).

62. Patients undergoing cholecystectomy for acute cholecystitis should have antimicrobial therapy discontinued within 24 h unless there is evidence of infection outside the wall of the gallbladder (B-II).

63. 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 he-

Table 5. Initial Intravenous Pediatric Dosages of Antibiotics for Treatment of Complicated Intra-abdominal Infection

Antibiotic, age range	Dosage[a]	Frequency of dosing
Amikacin[b]	15–22.5 mg/kg/day	Every 8–24 h
Ampicillin sodium[c]	200 mg/kg/day	Every 6 h
Ampicillin-sulbactam[c]	200 mg/kg/day of ampicillin component	Every 6 h
Aztreonam[c]	90–120 mg/kg/day	Every 6–8 h
Cefepime[c]	100 mg/kg/day	Every 12 h
Cefotaxime[c]	150–200 mg/kg/day	Every 6–8 h
Cefotetan[c]	40–80 mg/kg/day	Every 12 h
Cefoxitin[c]	160 mg/kg/day	Every 4–6 h
Ceftazidime[c]	150 mg/kg/day	Every 8 h
Ceftriaxone[c]	50–75 mg/kg/day	Every 12–24 h
Cefuroxime[c]	150 mg/kg/day	Every 6–8 h
Ciprofloxacin	20-30 mg/kg/day	Every 12 h
Clindamycin	20–40 mg/kg/day	Every 6–8 h
Ertapenem		
3 months to 12 years	15 mg/kg twice daily (not to exceed 1 g/day)	Every 12 h
⩾13 years	1 g/day	Every 24 h
Gentamicin[b]	3–7.5 mg/kg/day	Every 2–4 h
Imipenem-cilastatin[c]	60–100 mg/kg/day	Every 6 h
Meropenem[c]	60 mg/kg/day	Every 8 h
Metronidazole	30–40 mg/kg/day	Every 8 h
Piperacillin-tazobactam[c]	200–300 mg/kg/day of piperacillin component	Every 6–8 h
Ticarcillin-clavulanate[c]	200–300 mg/kg/day of ticarcillin component	Every 4–6 h
Tobramycin[b]	3.0–7.5 mg/kg/day	Every 8–24 h
Vancomycin[b]	40 mg/kg/day as 1 h infusion	Every 6–8 h

[a] Dosages are based on normal renal and hepatic function. Dose in mg/kg should be based on total body weight. Further information on pediatric dosing can be obtained elsewhere [186–188].
[b] Antibiotic serum concentrations and renal function should be monitored.
[c] β-Lactam antibiotic dosages should be maximized if undrained intra-abdominal abscesses may be present.

patic transplantation, enterococcal infection may be significant and require treatment (B-III).

Pediatric Infection

64. Routine use of broad-spectrum agents is not indicated for all children with fever and abdominal pain for whom there is a low suspicion of complicated appendicitis or other acute intra-abdominal infection (B-III).

65. Selection of specific antimicrobial therapy for pediatric patients with complicated intra-abdominal infection should be based on considerations of the origin of infection (community vs health care), severity of illness, and safety of the antimicrobial agents in specific pediatric age groups (A-II).

66. Acceptable broad-spectrum antimicrobial regimens for pediatric patients with complicated intra-abdominal infection include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase–inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole (Tables 2 and 5) (B-II).

67. For children with severe reactions to β-lactam antibiotics, ciprofloxacin plus metronidazole or an aminoglycoside-based regimen are recommended (B-III).

68. Necrotizing enterocolitis in neonates is managed with fluid resuscitation, intravenous broad-spectrum antibiotics (potentially including antifungal agents), and bowel decompression. Urgent or emergent operative intervention, consisting of either laparotomy or percutaneous drainage, should be performed when there is evidence of bowel perforation. Intraoperative Gram stains and cultures should be obtained (B-III).

69. Broad-spectrum antibiotics that may be useful in neonates with this condition include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected MRSA or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the Gram stain or cultures of specimens obtained at operation are consistent with a fungal infection (B-II).

Pharmacokinetic Considerations

70. Empiric therapy of patients with complicated intra-abdominal infection requires the use of antibiotics at optimal

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.

doses to ensure maximum efficacy and minimal toxicity and to reduce antimicrobial resistance (Tables 5 and 6) (B-II).

71. Individualized daily administration of aminoglycosides according to lean body mass and estimated extracellular fluid volume is preferred for patients receiving these agents for intra-abdominal infection (B-III).

Use of Microbiology Results to Guide Antimicrobial Therapy

72. Lower-risk patients with community-acquired intra-abdominal infection do not require alteration of therapy if a satisfactory clinical response to source control and initial therapy occurs, even if unsuspected and untreated pathogens are later reported (B-III).

73. If resistant bacteria were identified at the time of initial intervention and there are persistent signs of infection, pathogen-directed therapy is recommended for patients with lower severity disease (B-III).

74. Use of culture and susceptibility results to determine antimicrobial therapy in high-severity community-acquired or health care–associated infection should be based on pathogenic potential and density of identified organisms (B-III).

75. Microbes recovered from blood cultures should be assumed to be significant if they have established pathogenic potential or are present in ⩾2 blood cultures (A-I) or if they are recovered in moderate or heavy concentrations from samples obtained from drainage (B-II).

Duration of Therapy for Complicated Intra-abdominal Infections in Adults

76. Antimicrobial therapy of established infection should be limited to 4–7 days, unless it is difficult to achieve adequate source control. Longer durations of therapy have not been associated with improved outcome (B-III).

77. 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).

78. 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).

79. Bowel injuries attributable to penetrating, blunt, or iatrogenic trauma that are repaired within 12 h and any other intraoperative contamination of the operative field by enteric contents should be treated with antibiotics for ⩽24 h (A-I).

80. Acute appendicitis without evidence of perforation, abscess, or local peritonitis requires only prophylactic administration of narrow spectrum regimens active against aerobic and facultative and obligate anaerobes; treatment should be discontinued within 24 h (A-I).

81. The administration of prophylactic antibiotics to patients with severe necrotizing pancreatitis prior to the diagnosis of infection is not recommended (A-I).

Use of Oral or Outpatient Intravenous Antimicrobial Therapy

82. For children and adults whose signs and symptoms of infection are resolved, no further antibiotic therapy is required (B-III).

83. For adults recovering from intra-abdominal infection, completion of the antimicrobial course with oral forms of moxifloxacin, ciprofloxacin plus metronidazole, levofloxacin plus metronidazole, an oral cephalosporin with metronidazole, or amoxicillin-clavulanic acid (B-II) is acceptable in patients able to tolerate an oral diet and in patients in whom susceptibility studies do not demonstrate resistance (B-II).

84. If culture and susceptibility testing identify organisms that are only susceptible to intravenous therapy, such therapy may be administered outside of the hospital (B-III).

85. For children, outpatient parenteral antibiotic management may be considered when subsequent drainage procedures are not likely to be required but symptoms of ongoing intra-abdominal inflammation persist in the context of decreasing fever, controlled pain, ability to tolerate oral fluids, and ability to ambulate (B-II).

86. For oral step-down therapy in children, intra-abdominal cultures at the time of the drainage procedure are recommended to allow for the use of the narrowest-spectrum, best-tolerated, and safest oral therapy. A second- or third-generation cephalosporin in combination with metronidazole, or amoxicillin-clavulanate, may be options if the isolated organisms are susceptible to these agents. Fluoroquinolones, such as ciprofloxacin or levofloxacin, may be used to treat susceptible *Pseudomonas, Enterobacter, Serratia,* and *Citrobacter* species (B-III). If ciprofloxacin or levofloxacin is used, metronidazole should be added.

87. Drug susceptibility results of isolated gram-negative aerobic and facultative organisms, if available, should be used as a guide to agent selection in children and adults (B-III).

88. Because many of the patients who are managed without a primary source control procedure may be treated in the outpatient setting, the oral regimens recommended (see recommendations 83 and 86) can also be used as either primary therapy or step-down therapy following initial intravenous antimicrobial therapy (B-III).

Suspected Treatment Failure

89. In patients who have persistent or recurrent clinical evidence of intra-abdominal infection after 4–7 days of therapy, appropriate diagnostic investigation should be undertaken. This should include CT or ultrasound imaging. Antimicrobial therapy effective against the organisms initially identified should be continued (A-III).

90. 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).

91. For patients who do not respond initially and for whom a focus of infection remains, both aerobic and anaerobic cultures should be performed from 1 specimen, provided it is of sufficient volume (at least 1.0 mL of fluid or tissue) and is transported to the laboratory in an anaerobic transport system (C-III). Inoculation of 1–10 mL of fluid directly into an anaerobic blood culture broth bottle may improve yield.

Pathways for the Diagnosis and Management of Patients with Suspected Acute Appendicitis

92. Local hospitals should establish clinical pathways to standardize diagnosis, in-hospital management, discharge, and outpatient management (B-II).

93. Pathways should be designed by collaborating clinicians involved in the care of these patients, including but not limited to surgeons, infectious diseases specialists, primary care practitioners, emergency medicine physicians, radiologists, nursing providers, and pharmacists, and should reflect local resources and local standards of care (B-II).

94. Although no clinical findings are unequivocal in identifying patients with appendicitis, a constellation of findings, including characteristic abdominal pain, localized abdominal tenderness, and laboratory evidence of acute inflammation, will generally identify most patients with suspected appendicitis (A-II).

95. Helical CT of the abdomen and pelvis with intravenous, but not oral or rectal, contrast is the recommended imaging procedure for patients with suspected appendicitis (B-II).

Table 7. Strength of Recommendation and Quality of Evidence

Assessment	Type of evidence
Strength of recommendation	
Grade A	Good evidence to support a recommendation for use
Grade B	Moderate evidence to support a recommendation for use
Grade C	Poor evidence to support a recommendation
Quality of evidence	
Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from the Canadian Task Force on the Periodic Health Examination [11].

96. All female patients should undergo diagnostic imaging. Those of child-bearing potential should undergo pregnancy testing prior to imaging and, if in the first trimester of pregnancy, should undergo ultrasound or magnetic resonance instead of imaging ionizing radiation (B-II). If these studies do not define the pathology present, laparoscopy or limited CT scanning may be considered (B-III).

97. Imaging should be performed for all children, particularly those aged <3 years, when the diagnosis of appendicitis is not certain. CT imaging is preferred, although to avoid use of ionizing radiation in children, ultrasound is a reasonable alternative (B-III).

98. For patients with imaging study findings negative for suspected appendicitis, follow-up at 24 h is recommended to ensure resolution of signs and symptoms, because of the low but measurable risk of false-negative results (B-III).

99. For patients with suspected appendicitis that can neither be confirmed nor excluded by diagnostic imaging, careful follow-up is recommended (A-III).

100. Patients may be hospitalized if the index of suspicion is high (A-III).

101. Antimicrobial therapy should be administered to all patients who receive a diagnosis of appendicitis (A-II).

102. Appropriate antimicrobial therapy includes agents effective against facultative and aerobic gram-negative organisms and anaerobic organisms, as detailed in Table 2 for the treatment of patients with community-acquired intra-abdominal infection (A-I).

103. For patients with suspected appendicitis whose diagnostic imaging studies are equivocal, antimicrobial therapy should be initiated along with appropriate pain medication and antipyretics, if indicated. For adults, antimicrobial therapy should be provided for a minimum of 3 days, until clinical symptoms and signs of infection resolve or a definitive diagnosis is made (B-III).

104. Operative intervention for acute, nonperforated appendicitis may be performed as soon as is reasonably feasible. Surgery may be deferred for a short period of time as appropriate according to individual institutional circumstances (B-II).

105. Both laparoscopic and open appendectomy are acceptable procedures, and use of either approach should be dictated by the surgeon's expertise in performing that particular procedure (A-I).

106. Nonoperative management of selected patients with acute, nonperforated appendicitis can be considered if there is a marked improvement in the patient's condition prior to operation (B-II).

107. Nonoperative management may also be considered as part of a specific approach for male patients, provided that the patient is admitted to the hospital for 48 h and shows sustained improvement in clinical symptoms and signs within 24 h while receiving antimicrobial therapy (A-II).

108. Patients with perforated appendicitis should undergo urgent intervention to provide adequate source control (B-III).

109. Patients with a well-circumscribed periappendiceal abscess can be managed with percutaneous drainage or operative drainage when necessary. Appendectomy is generally deferred in such patients (A-II).

110. Selected patients who present several days after development of an inflammatory process and have a periappendiceal phlegmon or a small abscess not amenable to percutaneous drainage may delay or avoid a source control procedure to avert a potentially more morbid procedure than simple appendectomy. Such patients are treated with antimicrobial ther-

apy and careful inpatient follow-up, in a manner analogous to patients with acute diverticulitis (B-II).

111. The use of interval appendectomy after percutaneous drainage or nonoperative management of perforated appendicitis is controversial and may not be necessary (A-II).

INTRODUCTION

Complicated intra-abdominal infection extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis. These guidelines do not include management of nonperforated primary enteritis and/or colitis or perforations due to diseases that are rare in North America. This term is not meant to describe the infection's severity or anatomy. Uncomplicated infection involves intramural inflammation of the gastrointestinal tract and has a substantial probability of progressing to complicated infection if not adequately treated.

Complicated intra-abdominal infection is a common problem, with appendicitis alone affecting ~300,000 patients/year and consuming >1 million hospital days [6]. Intra-abdominal infection is the second most common cause of infectious mortality in the intensive care unit [7]. Nonetheless, this disease classification encompasses a variety of processes that affect several different organs. The requirement for intervention in most cases and the controversies surrounding the choice and nature of the procedure performed add another layer of complexity to the management of these patients.

Appropriate management of these infections has evolved considerably, because of advances in supportive intensive care, diagnostic imaging, minimally invasive intervention, and antimicrobial therapy. These guidelines are intended to provide a framework involving these various care measures. Given the frequency of acute appendicitis, the information in this document is suitable for developing local management guidelines for pediatric and adult patients with suspected acute appendicitis.

The following clinical questions will be addressed in this guideline:

I. What Are the Appropriate Procedures for Initial Evaluation of Patients with Suspected Intra-abdominal Infection?

II. When Should Fluid Resuscitation Be Started for Patients with Suspected Intra-abdominal Infection?

III. When Should Antimicrobial Therapy Be Initiated for Patients with Suspected or Confirmed Intra-abdominal Infection?

IV. What Are the Proper Procedures for Obtaining Adequate Source Control?

V. When and How Should Microbiological Specimens Be Obtained and Processed?

VI. What Are Appropriate Antimicrobial Regimens for Patients with Community-Acquired Intra-abdominal Infection of Mild-to-Moderate Severity?

VII. What Are Appropriate Antimicrobial Regimens for Patients with Community-Acquired Intra-abdominal Infection of High Severity?

VIII. What Antimicrobial Regimens Should Be Used in Patients with Health Care–Associated Intra-abdominal Infection, Particularly with Regard to *Candida, Enterococcus,* and MRSA?

IX. What Are Appropriate Diagnostic and Antimicrobial Therapeutic Strategies for Acute Cholecystitis and Cholangitis?

X. What Are Appropriate Antimicrobial Regimens for Pediatric Patients with Community-Acquired Intra-abdominal Infection?

XI. What Constitutes Appropriate Antibiotic Dosing?

XII. How Should Microbiological Culture Results Be Used to Adjust Antimicrobial Therapy?

XIII. What Is the Appropriate Duration of Therapy for Patients with Complicated Intra-abdominal Infection?

XIV. What Patients Should Be Considered for Oral or Outpatient Antimicrobial Therapy and What Regimens Should Be Used?

XV. How Should Suspected Treatment Failure Be Managed?

XVI. What Are the Key Elements that Should Be Considered in Developing a Local Appendicitis Pathway?

PRACTICE GUIDELINES

"Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances" [8, p 8]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [8].

Update Methodology

Panel composition. A panel of experts in infectious diseases, surgery, pharmacology and microbiology was assembled by the Infectious Diseases Society of America (IDSA) and the Surgical Infection Society (SIS) to prepare these guidelines. The panelists had both clinical and laboratory experience.

Literature review and analysis. The Panel reviewed studies on the site of origin of intra-abdominal infections, their microbiology, the laboratory approach to diagnosis of infection, the selection and duration of antibiotic therapy, and use of ancillary therapeutic aids. The Panel further reviewed the initial diagnostic work-ups, resuscitations, timings of intervention, and source control elements for infection. Previous guidelines detail recommendations made in 2002 and 2003 [9, 10].

These guidelines are based on randomized clinical trials using

antimicrobials for treatment of intra-abdominal infection published from 2002 through December 2008. The 2002 cut-off was used because relevant literature available through 2002 was used for the previous guidelines. The Medline database was searched using multiple strategies in which the names of specific antimicrobials or more general descriptors (ie, cephalosporins) were paired with words and phrases indicating an intra-abdominal infection (ie, peritonitis or appendicitis). Articles were also retrieved for review by searches for resuscitation, septic shock, CT scan, imaging, appendicitis, diverticulitis, source control, wound closure, and drainage. The Panel members contributed reference lists in these areas. This search included studies that were in the Medline database as of December 2008. The Cochrane database was also searched for relevant trials.

Process overview. In evaluating the information regarding the management of intra-abdominal infection, the Panel followed a process used to develop other IDSA guidelines [11]. The published studies were first categorized according to study design and quality, and in turn, the recommendations developed from these studies were graded according to the strength of evidence behind them. The level of evidence and the strength of the recommendation for a particular point were defined as described elsewhere [11] (Table 7).

Consensus development on the basis of evidence. The Panel met on 4 occasions, 3 times via teleconference and once in person, to complete the guideline. The meetings were held to discuss the questions to be addressed, to make writing assignments, and to discuss recommendations. There was a large volume of e-mail comments, because drafts were regularly circulated electronically. All panel members participated in the preparation and review of the draft guideline. Feedback from external peer reviewers was obtained. The guideline was reviewed and endorsed by the Pediatric Infectious Diseases Society, the American Society for Microbiology, the American Society of Health-System Pharmacists, and the Society of Infectious Disease Pharmacists. The guideline was also reviewed and approved by the IDSA Standards and Practice Guidelines Committee, the IDSA Board of Directors, the SIS Therapeutics and Guidelines Committee, and the SIS Executive Council prior to dissemination.

Guidelines and conflict of interest. All members of the Expert Panel complied with the IDSA policy regarding conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided a conflict of interest disclosure statement from the IDSA and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

Revision dates. At annual intervals, the Panel Chair, the IDSA, and SIS will determine the need for revisions to the guideline on the basis of an examination of current literature. If necessary, the entire Panel will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revision of the guideline for approval by the IDSA and SIS.

RECOMMENDATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF COMPLICATED INTRA-ABDOMINAL INFECTION IN ADULTS AND CHILDREN

I. WHAT ARE THE APPROPRIATE PROCEDURES FOR INITIAL EVALUATION OF PATIENTS WITH SUSPECTED INTRA-ABDOMINAL INFECTION?

Recommendations

1. Routine history, physical examination, and laboratory studies will identify most patients with suspected intra-abdominal infection for whom further evaluation and management is warranted (A-II).
2. For selected patients with unreliable physical examination findings, such as those with an obtunded mental status or spinal cord injury or those immunosuppressed by disease or therapy, intra-abdominal infection should be considered if the patient presents with evidence of infection from an undetermined source (B-III).
3. Further diagnostic imaging is unnecessary in patients with obvious signs of diffuse peritonitis and in whom immediate surgical intervention is to be performed (B-III).
4. In adult patients not undergoing immediate laparotomy, CT scan is the imaging modality of choice to determine the presence of an intra-abdominal infection and its source (A-II).

Evidence Summary

Patients with intra-abdominal infection typically present with rapid-onset abdominal pain and symptoms of gastrointestinal dysfunction (loss of appetite, nausea, vomiting, bloating, and/or obstipation), with or without signs of inflammation (pain, tenderness, fever, tachycardia, and/or tachypnea). Often, a careful history and physical examination will provide a limited differential diagnosis and a clear assessment of the degree of the patient's physiologic disturbance. This assessment, in turn, allows for immediate decisions regarding the need for and intensity of resuscitation/rehydration, appropriate diagnostic test-

ing, the need for and timing of initiation of antimicrobial therapy, and whether emergent intervention is required. On the basis of these findings, the timing and nature of operative or percutaneous intervention can be determined. The clinician must be alert to the fact that signs of sepsis may be minimal in elderly patients and in patients receiving corticosteroids or other immunosuppressive therapy.

The value of a range of symptoms, signs, and physical findings in the diagnostic work-up for intra-abdominal infection has been most fully studied in relation to acute appendicitis [12–14]. The findings of several analyses involving both children and adults are that no scoring system provides greater diagnostic sensitivity or specificity than clinical impression, although the analyses used to generate and then verify these systems have identified independent variables and their positive and negative predictive values, which may help focus the attention of treating clinicians [13, 15].

In general, CT is the preferred imaging modality [16]; helical scanning is preferred [17]. A recent meta-analysis found that pooled sensitivity and specificity for diagnosis of appendicitis in children were 88% and 94%, respectively, for ultrasound studies and 94% and 95%, respectively, for CT studies. Pooled sensitivity and specificity for diagnosis in adults were 83% and 93%, respectively, for ultrasound studies and 94% and 94%, respectively, for CT studies [18]. No such studies have been performed on other intra-abdominal processes.

II. WHEN SHOULD FLUID RESUSCITATION BE STARTED FOR PATIENTS WITH SUSPECTED INTRA-ABDOMINAL INFECTION?

Recommendations

5. Patients should undergo rapid restoration of intravascular volume and additional measures as needed to promote physiological stability (A-II).

6. For patients with septic shock, such resuscitation should begin immediately when hypotension is identified (A-II).

7. For patients without evidence of volume depletion, intravenous fluid therapy should begin when the diagnosis of intra-abdominal infection is first suspected (B-III).

Evidence Summary

Volume depletion is common in febrile patients and is worsened by poor fluid intake because of nausea and/or vomiting and in the presence of ileus induced by intra-abdominal inflammation. Much of the fluid loss is attributable to tachypnea. Commonly, patients experience a panting response through which tidal volume is minimized and breathing frequency is maximized [19, 20]. Blood-gas tensions and pH are maintained during this hyperventilation, and the associated heat loss by evaporation helps regulate body temperature. A second pattern of breathing adopted in hyperthermia, thermal hyperpnea, results in increased tidal volume as well as increased breathing frequency, resulting in a respiratory alkalosis and further evaporative water loss. There is compelling historically controlled data that patients with perforated or abscessed appendicitis benefit from administration of fluids even absent septic shock [21].

For patients with septic shock or organ failure, more-aggressive fluid therapy should be provided. We recommend following The Surviving Sepsis Campaign guidelines for managing septic shock [22]. Key recommendations include early goal-directed resuscitation during the first 6 h after recognition (administration of either crystalloid or colloid fluid resuscitation, fluid challenge to restore mean circulating filling pressure, reduction in rate of fluid administration with increasing filling pressures and no improvement in tissue perfusion, vasopressor preference for norepinephrine or dopamine to maintain an initial target of mean arterial pressure $\geqslant$65 mm Hg, dobutamine inotropic therapy when cardiac output remains low despite fluid resuscitation and combined inotropic/vasopressor therapy, and stress-dose steroid therapy given only in septic shock after blood pressure is identified to be poorly responsive to fluid and vasopressor therapy).

III. WHEN SHOULD ANTIMICROBIAL THERAPY BE INITIATED FOR PATIENTS WITH SUSPECTED OR CONFIRMED INTRA-ABDOMINAL INFECTION?

Recommendations

8. Antimicrobial therapy should be initiated once a patient receives a diagnosis of an intra-abdominal infection or once such an infection is considered likely. For patients with septic shock, antibiotics should be administered as soon as possible (A-III).

9. For patients without septic shock, antimicrobial therapy should be started in the emergency department (B-III).

10. Satisfactory antimicrobial drug levels should be maintained during a source control intervention, which may necessitate additional administration of antimicrobials just before initiation of the procedure (A-I).

Evidence Summary

Delaying antimicrobial therapy has been associated with poorer outcomes in patients with septic shock, including those with intra-abdominal infection [23]; however, the study [23] was of low quality, as judged by the methodologic quality score system presented by van Nieuwenhoven et al [24]. On the basis of this study [24], sepsis guidelines have recommended that antibiotics be administered within 1 h of recognition of septic shock [22]. In patients without hemodynamic or organ compromises, the Expert Panel members agreed that antibacterials should be administered within 8 h after presentation.

In patients undergoing a source control procedure, antimicrobial therapy provides for surgical wound prophylaxis and treatment of pathogens that are potentially disseminated during the procedure, in addition to providing ongoing therapy for the infection. Antimicrobial therapy is, therefore, also considered to be wound prophylaxis for all patients undergoing intervention. The rules for prophylaxis in elective surgical procedures include use of agents that are likely to be effective against the contaminating organisms and administration within 1 h before the operation [25, 26].

IV. WHAT ARE THE PROPER PROCEDURES FOR OBTAINING ADEQUATE SOURCE CONTROL?

Recommendations

11. An appropriate source control procedure to drain infected foci, control ongoing peritoneal contamination by diversion or resection, and restore anatomic and physiological function to the extent feasible is recommended for nearly all patients with intra-abdominal infection (B-II).

12. Patients with diffuse peritonitis should undergo an emergency surgical procedure as soon as is possible, even if ongoing measures to restore physiologic stability need to be continued during the procedure (B-II).

13. Where feasible, percutaneous drainage of abscesses and other well-localized fluid collections is preferable to surgical drainage (B-II).

14. For hemodynamically stable patients without evidence of acute organ failure, an urgent approach should be taken. Intervention may be delayed for as long as 24 h if appropriate antimicrobial therapy is given and careful clinical monitoring is provided (B-II).

15. In patients with severe peritonitis, mandatory or scheduled relaparotomy is not recommended in the absence of intestinal discontinuity, abdominal fascial loss that prevents abdominal wall closure, or intra-abdominal hypertension (A-II).

16. Highly selected patients with minimal physiological derangement and a well-circumscribed focus of infection, such as a periappendiceal or pericolonic phlegmon, may be treated with antimicrobial therapy alone without a source control procedure, provided that very close clinical follow-up is possible (B-II).

Evidence Summary

Source control is defined as any single procedure or series of procedures that eliminate infectious foci, control factors that promote ongoing infection, and correct or control anatomic derangements to restore normal physiologic function [27]. The timing of intervention is a key decision, particularly in the presence of diffuse peritonitis. Patients with diffuse peritonitis from a perforated viscus cannot be fully resuscitated until ongoing soiling has been controlled. In such patients, resuscitation should be continued intraoperatively. For hemodynamically stable patients without peritonitis, delay of up to 1 day may be appropriate. The Expert Panel notes that this decision is a complex calculation based on a variety of patient-, institution-, and surgeon-specific factors, and a greater or lesser delay may be appropriate, with most patients benefiting from a more urgent approach.

Source control failure is more likely to occur in patients with delayed (>24 h) procedural intervention, higher severity of illness (APACHE II score $\geqslant$15), advanced age (>70 years), preexisting chronic medical conditions, poor nutritional status, and a higher degree of peritoneal involvement and is heralded by persistent or recurrent intra-abdominal infection, anastomotic failure, or fistula formation [28–32].

Well-localized fluid collections of appropriate density may be drained percutaneously with acceptable morbidity and mortality [47, 33–35]. Percutaneous drainage of appropriately selected infectious sources may result in significantly less physiologic alterations in patients and may eliminate or reduce the need for open techniques. Open surgical techniques are likely required for poorly localized, loculated, complex, or diffuse fluid collections and necrotic tissue, high density fluid, or percutaneously inaccessible collections. The majority of patients respond to a single intervention without significant complication.

Given the range of diseases and the various risk factors for poor outcome in nonappendiceal disease, clinical practice has been driven by uncontrolled case series [36–42]. Percutaneous techniques have continued to evolve, and many abscesses that were previously considered to be best approached by laparotomy are now often approached by interventional radiography [43].

It is important to discuss radiographic findings with the surgeon to avoid inappropriate abscess drainage in the presence of free hollow-organ perforation and acute peritonitis. Acute peritonitis is best treated surgically rather than with percutaneous drainage.

There are some patients in whom drainage catheter placement is not appropriate, and laparotomy is the procedure of choice. If clinical evaluation suggests peritonitis, the patient should proceed to surgery even if imaging demonstrates drainable collections, except in extreme circumstances in which a patient is deemed unfit for surgical intervention. Extraluminal air and fluid in a "contained" distribution immediately adjacent to underlying diseased bowel (eg, in diverticulitis or appendicitis) can be drained. However, a patient with a similar abscess but with extensive and massive free air or fluid remote from the perforation site should usually undergo surgery for such an "uncontained" perforation. There is only a limited role for catheter placement in some pancreatitis-related collections.

When laparotomy is undertaken for nonappendiceal intra-

abdominal infection, a range of factors will determine the extent (if any) of bowel resection, whether an anastamosis or ostomy is created, what tissue is debrided, what type of drainage (if any) is necessary, and what wound management technique is used. These questions have not been addressed in controlled trials, and specific guidelines cannot be provided.

Three general strategies should be considered for critically ill patients who are either physiologically unstable or at high risk of experiencing failed source control. These include (1) laparostomy or the "open abdomen," (2) planned re-laparotomy, and (3) on-demand re-laparotomy [44].

Generally accepted indications for laparostomy in which neither the fascia nor skin are closed include severe physiologic derangements intraoperatively that preclude completion of the planned procedure, intra-abdominal hypertension, and loss of abdominal soft-tissue preventing immediate fascial closure. Generally accepted indications for either laparostomy or planned re-laparotomy include settings in which adequate source control cannot be obtained at the index procedure, control or re-establishment of hollow viscus continuity cannot be safely performed, and possible ongoing intestinal ischemia requiring a second-look operation to ensure enteric viability [45]. Unless clear indications for re-laparotomy exist, re-laparotomy on demand has been shown to reduce use of health care services, costs, and laparotomies with similar outcomes.

V. WHEN AND HOW SHOULD MICROBIOLOGICAL SPECIMENS BE OBTAINED AND PROCESSED?

Gram Stain and Blood Cultures

Recommendations

17. Blood cultures do not provide additional clinically relevant information for patients with community-acquired intra-abdominal infection and are therefore not routinely recommended for such patients (B-III).

18. If a patient appears clinically toxic or is immunocompromised, knowledge of bacteremia may be helpful in determining duration of antimicrobial therapy (B-III).

19. For community-acquired infections, there is no proven value in obtaining a routine Gram stain of the infected material (C-III).

20. For health care–associated infections, Gram stains may help define the presence of yeast (C-III).

21. Routine aerobic and anaerobic cultures from lower-risk patients with community-acquired infection are considered optional in the individual patient but may be of value in detecting epidemiological changes in the resistance patterns of pathogens associated with community-acquired intra-abdominal infection and in guiding follow-up oral therapy (B-II).

22. If there is significant resistance (ie, resistance in 10%–20% of isolates) of a common community isolate (eg, *E. coli)* to an antimicrobial regimen in widespread local use, routine culture and susceptibility studies should be obtained for perforated appendicitis and other community-acquired intra-abdominal infections (B-III).

23. Anaerobic cultures are not necessary for patients with community-acquired intra-abdominal infection if empiric antimicrobial therapy active against common anaerobic pathogens is provided (B-III).

24. For higher-risk patients, cultures from the site of infection should be routinely obtained, particularly in patients with prior antibiotic exposure, who are more likely than other patients to harbor resistant pathogens (A-II).

25. The specimen collected from the intra-abdominal focus of infection should be representative of the material associated with the clinical infection (B-III).

26. Cultures should be performed from 1 specimen, provided it is of sufficient volume (at least 1 mL of fluid or tissue, preferably more) and is transported to the laboratory in an appropriate transport system. For optimal recovery of aerobic bacteria, 1–10 mL of fluid should be inoculated directly into an aerobic blood culture bottle. In addition, 0.5 mL of fluid should be sent to the laboratory for Gram stain and, if indicated, fungal cultures. If anaerobic cultures are requested, at least 0.5 mL of fluid or 0.5 g of tissue should be transported in an anaerobic transport tube. Alternately, for recovery of anaerobic bacteria, 1–10 mL of fluid can be inoculated directly into an anaerobic blood culture bottle (A-I).

27. Susceptibility testing for *Pseudomonas, Proteus, Acinetobacter, Staphylococcus aureus,* and predominant Enterobacteriaceae, as determined by moderate-to-heavy growth, should be performed, because these species are more likely than others to yield resistant organisms (A-III).

Evidence Summary

Blood cultures are seldom useful adjuncts for diagnosing intra-abdominal infection, even in health care–associated or complicated cases. Published rates of bacteremia related to the organisms present in the infected abdominal site range from 0% in a large appendicitis series [46] to 5% in a percutaneous drainage series [47]. Bacteremia appears to be more common in patients in the intensive care unit and is associated with increased mortality [48].

The organisms isolated in bacteremia that accompanied community-acquired complicated intra-abdominal infection have low potential for forming endocarditis on normal valves or metastatic abscesses. Positive blood cultures for the organisms that may do so, including *S. aureus, Candida* species, and *Streptococcus milleri* [49], are so rarely reported prior to therapy for these infections that blood cultures are not recommended.

There are few data indicating that Gram stain, culture, and susceptibility data provide information likely to alter outcome in patients with a community-acquired complicated intra-abdominal infection. For patients with perforated or gangrenous appendicitis, many surgeons do not obtain cultures [50, 51]. For patients with health care–associated infection, antimicrobial therapy that fails to cover eventual pathogens has been associated with higher rates of treatment failure and mortality [52]. Thus, Gram stains may be of value in detecting gram-positive cocci or yeast that would lead to additional empiric antimicrobial therapy before definitive culture results are available.

Local susceptibility patterns for *S. aureus* and for enterococci might warrant addition of an MRSA-active agent until results of cultures and susceptibility testing are available [52]. For enterococci, local susceptibilities should be monitored for penicillin and vancomycin resistance. If yeasts are identified on a Gram stain, additional therapy for *Candida* species may be considered.

The major pathogens in community-acquired intra-abdominal infection are coliforms (Enterobacteriaceae, especially *E. coli*) and anaerobes (especially *B. fragilis*) (Table 8). Pathogens are nearly always present in concentrations $\geqslant 1 \times 10^5$ organisms/g of tissue or 1×10^5 organisms/mL of exudate. This would correspond to moderate or heavy growth on the primary isolation plates. The primary focus should, therefore, be on the predominant organisms isolated from these cultures.

Most intra-abdominal infections involve anaerobic bacteria, but laboratories show great variation in reliably performing in vitro susceptibility tests. Sentinel studies of *B. fragilis,* the major pathogen, show uniform susceptibility to metronidazole, carbapenems, and some β-lactam/β-lactamase inhibitors [53–57]. Studies of the activity of quinolones against *B. fragilis* isolates have yielded conflicting data, in part because of the use of abdominal abscess versus bacteremic isolates [58–61]. Susceptibility testing of individual anaerobic isolates should be considered when there is persistent isolation of the organism, bacteremia, or when prolonged therapy is needed because of immunosuppression or prosthetic infection. Laboratories can purify and hold isolates for additional testing if requested by the clinician [62].

In many locations, there is increasing resistance to selected antibiotics among community-acquired strains of gram-negative organisms. These include the widespread prevalence of ampicillin/sulbactam-resistant *E. coli* worldwide, the high penetration of fluoroquinolone-resistant *E. coli* in Latin America and East Asia, and locations with a high prevalence of extended-spectrum β-lactamase–producing strains of *Klebsiella* species and *E. coli* [63]. In some populations and communities, a relatively high prevalence of more-resistant nonenteric gram-negative organisms, such as *Pseudomonas aeruginosa,* will impact the selection of appropriate empiric antibiotic therapy [64–66]. Routine cultures from patients with community-acquired intra-abdominal infection may facilitate recognition of local changes in resistance and, thereby, optimal selection of antimicrobial agents for both definitive treatment and oral step-down therapy. There are marked differences in susceptibility patterns within and between different communities and institutions. These epidemiologic data are of considerable value in defining the most suitable antimicrobial therapy for intra-abdominal infection. The failure to provide adequate antimicrobial therapy in such patients has been repeatedly associated with an increased incidence of therapeutic failure and, in some cases, increased mortality [52, 67].

Certain communities and age groups have an inexplicably high incidence of *P. aeruginosa* infection associated with community-acquired appendicitis [64–66, 68]. Even if therapy with a broader spectrum is used empirically, culture results may allow the clinician to narrow the spectrum of therapy considerably for more-prolonged, definitive therapy.

Complete inoculation of all appropriate media (8 agar plates, a Gram stain, and a broth enrichment tube) for aerobic and anaerobic bacterial cultures alone calls for 0.05 mL of tissue or

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].

fluid per medium or slide, requiring a minimum of 1.0 mL or 1.0 g of specimen. Fungal or acid-fast cultures will necessitate additional sample volume.

VI. WHAT ARE APPROPRIATE ANTIMICROBIAL REGIMENS FOR PATIENTS WITH COMMUNITY-ACQUIRED INTRA-ABDOMINAL INFECTION OF MILD-TO-MODERATE SEVERITY?

Recommendations

28. Antibiotics used for empiric treatment of community-acquired intra-abdominal infection should be active against enteric gram-negative aerobic and facultative bacilli and enteric gram-positive streptococci (A-I).

29. Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus (A-I).

30. For adult patients with mild-to-moderate community-acquired infection, the use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity (Table 2) (A-I).

31. Ampicillin-sulbactam is not recommended for use because of high rates of resistance to this agent among community-acquired *E. coli* (B-II).

32. Cefotetan and clindamycin are not recommended for use because of increasing prevalence of resistance to these agents among the *Bacteroides fragilis* group (B-II).

33. 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).

34. Empiric coverage of *Enterococcus* is not necessary in patients with community-acquired intra-abdominal infection (A-I).

35. Empiric antifungal therapy for *Candida* is not recommended for adult and pediatric patients with community-acquired intra-abdominal infection (B-II).

36. The use of agents listed as appropriate for higher-severity community-acquired infection and health care–associated infection is not recommended for patients with mild-to-moderate community-acquired infection, because such regimens may carry a greater risk of toxicity and facilitate acquisition of more-resistant organisms (B-II).

37. For those patients with intra-abdominal infection of mild-to-moderate severity, including acute diverticulitis and various forms of appendicitis, who will not undergo a source control procedure, regimens listed for treatment of mild-to-moderate–severity infection are recommended, with a possibility of early oral therapy (B-III).

Evidence Summary

Infections derived from the stomach, duodenum, biliary system, and proximal small bowel contain gram-positive and gram-negative aerobic and facultative organisms. Infections derived from distal small bowel perforations contain gram-negative facultative and aerobic organisms with variable density. Perforations of this type often evolve into localized abscesses, with peritonitis developing only after rupture of the abscess. Anaerobes, such as *B. fragilis,* are commonly present. Colon-derived intra-abdominal infections harbor facultative and obligate anaerobic organisms. Streptococci, particularly the *S. milleri* group, and enterococci are also commonly present. By far the most commonly detected gram-negative facultative organism is *E. coli.*

The efficacy and cost advantages of generic agents are noted elsewhere [69–72]. Single agents approved for use include ticarcillin-clavulanate, cefoxitin, moxifloxacin, ertapenem, and tigecycline [73–78]. Given the very broad spectrum of tigecycline, including activity against MRSA and a wide variety of other gram-positive and gram-negative organisms not commonly seen in appendix-derived infection, there is concern for its use in mild-to-moderate complicated intra-abdominal infection. The Expert Panel is also concerned that broad use of ertapenem may hasten the appearance of carbapenem-resistant *Enterobacteriacae, Pseudomonas,* and *Acinetobacter* species. Quinolone-resistant *E. coli* has become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolone.

The occurrence of organisms in the community that have resistance to commonly prescribed agents is becoming a reality. If resistance to a given antibiotic is present in 10%–20% or more of isolates of a common intra-abdominal pathogen in the community, use of that agent should be avoided. Because of widespread resistance of *E. coli* to ampicillin-sulbactam, that antibiotic is no longer recommended for routine empiric therapy of complicated intra-abdominal infection [63].

Increasing antimicrobial resistance among *B. fragilis* isolates is similarly of concern, and there are data indicating higher failure rates if these organisms are treated with an inactive agent [79, 80]. Given that no outcome differences have been identified in randomized controlled trials, antimicrobial selection should be based on local microbiologic data, cost advantage, allergies, and formulary availability. Use of moxifloxacin for the treatment of patients who are likely to harbor *B. fragilis* should be avoided if patients have received quinolone therapy within 3 months, because organisms from such patients are likely to be quinolone resistant [81, 82].

The expanded gram-negative spectrum against which some agents have been shown to be effective in clinical trials is not advantageous for patients with community-acquired infection, and their unnecessary use may contribute to the emergence of

antimicrobial resistance [35, 43]. Hospitals should review local microbiologic findings, because use of broader-spectrum regimens may be required.

Numerous prospective blinded and randomized trials have compared regimens active against routine isolates of *Enterococcus* for treatment of community-acquired infection. In at least 6 of these studies, the comparator regimen did not provide similar coverage [64, 83–87]. None of these trials demonstrated an advantage for treatment of enterococci.

Patients with intra-abdominal infection, including acute diverticulitis and certain forms of acute appendicitis, may be managed nonoperatively. The microbiology of patients managed nonoperatively is likely similar to that of patients managed operatively, and regimens recommended for patients with complicated intra-abdominal infection are recommended [88].

VII. WHAT ARE APPROPRIATE ANTIMICROBIAL REGIMENS FOR PATIENTS WITH COMMUNITY-ACQUIRED INTRA-ABDOMINAL INFECTION OF HIGH SEVERITY?

Recommendations

38. The empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended for patients with high-severity community-acquired intra-abdominal infection, as defined by APACHE II scores >15 or other variables listed in Table 1 (Table 2) (A-I).

39. Quinolone-resistant *E. coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E. coli* to quinolones (A-II).

40. Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended (B-III).

41. In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy (A-I).

42. Empiric use of agents effective against enterococci is recommended (B-II).

43. Use of agents effective against MRSA or yeast is not recommended in the absence of evidence of infection due to such organisms (B-III).

44. In these high-risk patients, antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated in culture (A-III).

Evidence Summary

Several attempts have been made to identify clinical features that increase the risk of adverse outcomes in patients with complicated intra-abdominal infection. These analyses have identified parameters that are predictive of mortality rather than of the risk of recurrent infection. These risk factors include higher APACHE II scores, poor nutritional status, significant cardiovascular disease, and an inability to achieve adequate source control [89–94]. Similarly, patients who are immunosuppressed by medical therapy for transplantation, cancer, or inflammatory disease are at higher risk of an adverse outcome. Prolonged hospital length of stay before the operation ($\geqslant$5 days) and prolonged ($\geqslant$2 days) preoperative antimicrobial therapy are significant predictors of failure from recurrent infection. Patients with other acute and chronic diseases may also be immunosuppressed, although this is difficult to define. Intraoperative cultures, including cultures from percutaneous drainage procedures, are central to the prescribing of definitive therapeutic regimens for these patients and may allow de-escalation to less broad–spectrum therapy.

In patients with higher-severity infection, the consequences of treatment failure may be more significant than they are in patients with infection of mild-to-moderate severity. The use of initial empiric antimicrobial regimens that are subsequently identified to lack in vitro activity against the organisms isolated from the intra-abdominal infection has been associated with an increased need for additional source control procedures and more-aggressive antimicrobial therapy, increased hospital lengths of stay and costs, and increased mortality [67]. Therefore, use of broader-spectrum agents providing activity against some gram-negative facultative and aerobic organisms that are occasionally isolated from such patients has the potential to improve outcomes, although this hypothesis has not been rigorously examined in clinical trials.

In these cases, cultures and susceptibility tests are particularly important. The rationale for the widening of coverage to less common organisms is that the risk of treatment failure in such patients is higher and the consequences potentially greater.

Aminoglycosides have relatively narrow therapeutic ranges and associated problems of ototoxicity and nephrotoxicity [95, 96]. These agents should be reserved for patients with allergies to β-lactam agents and, even then, are second choices to quinolone-based regimens. Aminoglycosides may be reasonable choices for empiric or definitive treatment of selected patients with health care–associated intra-abdominal infection, depending on local susceptibility patterns of nosocomial gram-negative bacilli. A meta-analysis of data from prospective, randomized, controlled trials found that aminoglycoside-based regimens ap-

peared to be inferior to many other regimens for the treatment of patients with intra-abdominal infection [95].

There is no evidence that routine use of agents effective against enterococci improves outcome, but infection due to this organism has been associated with a poorer outcome. Nearly all enterococci isolated from community-acquired infection are *E. faecalis* and are generally susceptible to ampicillin, piperacillin, and vancomycin. If the regimen selected lacks such coverage, selective addition of an agent providing such coverage can be considered. Isolation of staphylococci and yeast are quite uncommon in patients with community-acquired intra-abdominal infection, and use of agents effective against MRSA and yeast is not recommended in the absence of evidence that such organisms are involved in the infection.

VIII. WHAT ANTIMICROBIAL REGIMENS SHOULD BE USED IN PATIENTS WITH HEALTH CARE–ASSOCIATED INTRA-ABDOMINAL INFECTION, PARTICULARLY WITH REGARD TO *CANDIDA, ENTEROCOCCUS,* AND MRSA?

Recommendations

45. Empiric antibiotic therapy for health care–associated intra-abdominal infection should be driven by local microbiologic results (A-II).

46. To achieve empiric coverage of likely pathogens, multidrug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required (Table 3) (B-III).

47. Broad-spectrum antimicrobial therapy should be tailored when culture and susceptibility reports become available, to reduce the number and spectra of administered agents (B-III).

Antifungal Therapy

Recommendations

48. Antifungal therapy for patients with severe community-acquired or health care–associated infection is recommended if *Candida* is grown from intra-abdominal cultures (B-II).

49. Fluconazole is an appropriate choice for treatment if *C. albicans* is isolated (B-II).

50. For fluconazole-resistant *Candida* species, therapy with an echinocandin (caspofungin, micafungin, or anidulafungin) is appropriate (B-III).

51. For the critically ill patient, initial therapy with an echinocandin instead of a triazole is recommended (B-III).

52. Because of toxicity, amphotericin B is not recommended as initial therapy (B-II).

53. In neonates, empiric antifungal therapy should be started if *Candida* is suspected. If *C. albicans* is isolated, fluconazole is an appropriate choice (B-II).

Anti-Enterococcal Therapy

Recommendations

54. Antimicrobial therapy for enterococci should be given when enterococci are recovered from patients with health care–associated infection (B-III).

55. Empiric anti-enterococcal therapy is recommended for patients with health care–associated intra-abdominal infection, particularly those with postoperative infection, those who have previously received cephalosporins or other antimicrobial agents selecting for *Enterococcus* species, immunocompromised patients, and those with valvular heart disease or prosthetic intravascular materials (B-II).

56. Initial empiric anti-enterococcal therapy should be directed against *Enterococcus faecalis.* Antibiotics that can potentially be used against this organism, on the basis of susceptibility testing of the individual isolate, include ampicillin, piperacillin-tazobactam, and vancomycin (B-III).

57. 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* (B-III).

Anti-MRSA Therapy

Recommendations

58. Empiric antimicrobial coverage directed against MRSA should be provided to patients with health care–associated intra-abdominal infection who are known to be colonized with the organism or who are at risk of having an infection due to this organism because of prior treatment failure and significant antibiotic exposure (B-II).

59. Vancomycin is recommended for treatment of suspected or proven intra-abdominal infection due to MRSA (A-III).

Evidence Summary

Health care–associated infection is a relatively new term that includes a spectrum of adult patients who have close association with acute care hospitals or reside in chronic care settings [97]. These factors increase their risk of infection due to multidrug-resistant bacteria. The definitions for health care–associated infections provided by Klevens et al [97] are used in this guideline. "Health care–associated infection" includes "community-onset" and "hospital-onset." Community-onset health care–associated infection includes cases involving patients with at least 1 of the following health care risk factors: (1) presence of an invasive device at time of admission; (2) history of MRSA infection or colonization; or (3) history of surgery, hospitali-

zation, dialysis, or residence in a long-term care facility in the 12 months preceding the culture date. Hospital-onset infection includes cases involving patients with positive culture results from a normally sterile site obtained >48 h after hospital admission. These patients might also have ⩾1 of the community-onset risk factors.

Health care–associated infection is commonly caused by a more resistant flora, which may include the nonfermenting gram-negative *P. aeruginosa* and *Acinetobacter* species, extended spectrum β-lactamase–producing *Klebsiella* and *E. coli*, *Enterobacter* species, *Proteus* species, MRSA, enterococci, and *Candida* species [52, 98–100]. For these infections, complex multidrug regimens are recommended, because adequate empiric therapy appears to be important in determining postoperative complications and mortality [52]. Failure to adequately treat resistant organisms has, in similar health care–associated infections, been associated with increased death [101–103]. Local resistance patterns of nosocomial isolates observed in the specific hospital should dictate empiric treatment, and treatment should be altered on the basis of a thorough microbiologic work-up of infected fluid.

In infection occurring after elective or emergent operation, a more resistant flora is routinely encountered [52]. The organisms observed are similar to those seen in other nosocomial infections, and anaerobes are not frequently important sources of resistant organisms. The selection of antibiotics would be tailored according to the known nosocomial flora present at the institution where the patient developed the infection.

Candida infection has been the subject of recent guidelines from the IDSA [104]. *C. albicans* or other fungi are cultured from ~20% of patients with acute perforations of the gastrointestinal tract. Even when fungi are recovered, antifungal agents are unnecessary in adults unless the patient has recently received immunosuppressive therapy for neoplasm or has a perforation of a gastric ulcer on acid suppression or malignancy, transplantation, or inflammatory disease or has postoperative or recurrent intra-abdominal infection [104–106]. In neonates with necrotizing enterocolitis, *Candida* is not uncommon and is more likely to represent a true pathogen in such patients than in previously healthy adults.

In these settings, *Candida* is associated with increased mortality [98]. Patients with health care–associated intra-abdominal infection are at higher risk of *Candida* peritonitis, particularly patients with recurrent gastrointestinal perforations and surgically treated pancreatic infection [104–106]. Preemptive antifungal therapy with fluconazole may decrease the incidence of *Candida* peritonitis in such high-risk patients [107, 108].

There has been an evolution of the species of *Candida* observed in candidemia and *Candida* peritonitis [109]. Because of its high susceptibility to fluconazole, *C. albicans* has decreased in prevalence, and *Candida glabrata* and other species have become somewhat more common. This observation, coupled with the common use of fluconazole prophylaxis in the intensive care unit, suggests empiric use of echinocandins (caspofungin, anidulafungin, and micafungin) [110–114].

Certain patient groups at particularly high risk of a poor outcome due to enterococcal infection include (1) immunocompromised patients; (2) patients with health care–associated postoperative peritonitis; (3) patients with severe sepsis of abdominal origin who have previously received cephalosporins and other broad-spectrum antibiotics selecting for *Enterococcus* species; and (4) patients with peritonitis and valvular heart disease or prosthetic intravascular material, which place them at high risk of endocarditis [5, 99, 100, 115].

Isolation of *Enterococcus* is more common among patients with health care–associated intra-abdominal infection, particularly those with postoperative infections, and its isolation is a risk factor for treatment failure and death [116, 117]. Thus, in patients with health care–associated intra-abdominal infection, including those with postoperative infection, a reasonable option would be to include coverage of *Enterococcus* in the empiric regimen until definitive culture results are available. Ampicillin and vancomycin are agents that have activity against this organism and could be added to a regimen lacking anti-enterococcal activity. Specific risk factors for vancomycin-resistant enterococci have been detailed [118–121] and center on transmission from other colonized or infected patients in an epidemic manner.

MRSA isolates are recovered from patients with postoperative infection, pancreatic infection, and tertiary peritonitis [122, 123]. MRSA is not commonly isolated from patients with community-acquired intra-abdominal infection. There are no specific data with regard to antibiotic preferences in treatment of intra-abdominal infections due to MRSA. In general, vancomycin has been used to treat infections due to this organism. Other antibiotics, including quinupristin-dalfopristin, linezolid, daptomycin, and tigecycline, have in vitro activity against MRSA, but there are few published data regarding their efficacy in the treatment of patients with intra-abdominal infection. Thus, vancomycin should remain the first-line agent, with use of the other agents restricted to situations in which vancomycin cannot be used because of severe adverse reactions or when initial therapy with vancomycin is thought to have failed.

IX. WHAT ARE APPROPRIATE DIAGNOSTIC AND ANTIMICROBIAL THERAPEUTIC STRATEGIES FOR ACUTE CHOLECYSTITIS AND CHOLANGITIS?

Recommendations

60. Ultrasonography is the first imaging technique used for suspected acute cholecystitis or cholangitis (A-I).

61. Patients with suspected infection and either acute cholecystitis or cholangitis should receive antimicrobial therapy, as recommended in Table 4, although anaerobic therapy is not indicated unless a biliary-enteric anastamosis is present (B-II).

62. Patients undergoing cholecystectomy for acute cholecystitis should have antimicrobial therapy discontinued within 24 h unless there is evidence of infection outside the wall of the gallbladder (B-II).

63. 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).

Evidence Summary

Recent guidelines have been published for the management of acute cholecystitis and acute cholangitis [124–128]. These guidelines recommend use of abdominal ultrasonography and hepatobiliary scintigraphy. Ultrasonography detects cholelithiasis in ~98% of patients. Acute calculous cholecystitis is diagnosed radiologically by the concomitant presence of thickening of the gallbladder wall (⩾5 mm), pericholecystic fluid, or direct tenderness when the probe is pushed against the gallbladder (ultrasonographic Murphy's sign). In a study involving 497 patients with suspected acute cholecystitis, the positive predictive value of the presence of stones and a positive ultrasonographic Murphy's sign was 92%, and the positive predictive value of stones and thickening of the gallbladder wall was 95% [129]. The negative predictive value of the absence of stones combined with either a normal gallbladder wall or a negative Murphy's sign was 95%. Hepatobiliary scintigraphy involves intravenous injection of technetium-labeled analogues of iminodiacetic acid, which are excreted into bile. The absence of gallbladder filling within 60 min after the administration of tracer indicates obstruction of the cystic duct and has a sensitivity of 80%–90% for acute cholecystitis.

A discussion of the timing of intervention for acute cholecystitis or cholangitis is beyond the scope of these guidelines. The exact timing should, however, depend on acuity and evidence of infection. In any case, there is no evidence supporting improved outcomes from use of antibiotics that are excreted by the liver.

X. WHAT ARE APPROPRIATE ANTIMICROBIAL REGIMENS FOR PEDIATRIC PATIENTS WITH COMMUNITY-ACQUIRED INTRA-ABDOMINAL INFECTION?

Recommendations

64. Routine use of broad-spectrum agents is not indicated for all children with fever and abdominal pain for whom there is a low suspicion of complicated appendicitis or other acute intra-abdominal infection (B-III).

65. Selection of specific antimicrobial therapy for pediatric patients with complicated intra-abdominal infection should be based on considerations of the origin of infection (community vs health care), severity of illness, and safety of the antimicrobial agents in specific pediatric age groups (A-II).

66. Acceptable broad-spectrum antimicrobial regimens for pediatric patients with complicated intra-abdominal infection include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase–inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole (Tables 2 and 5) (B-II).

67. For children with severe reactions to β-lactam antibiotics, ciprofloxacin plus metronidazole or an aminoglycoside-based regimen are recommended (B-III).

68. Necrotizing enterocolitis in neonates is managed with fluid resuscitation, intravenous broad-spectrum antibiotics (potentially including antifungal agents), and bowel decompression. Urgent or emergent operative intervention, consisting of either laparotomy or percutaneous drainage, should be performed when there is evidence of bowel perforation. Intraoperative Gram stains and cultures should be obtained (B-III).

69. Broad-spectrum antibiotics that may be useful in neonates with this condition include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected MRSA or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the Gram stain or cultures of specimens obtained at operation are consistent with a fungal infection (B-II).

Evidence Summary

These guidelines do not deal with biliary infections in children. Although enteric gram-negative bacilli and anaerobes, including *B. fragilis,* are most commonly isolated, an increasing role of *Pseudomonas* has been documented in up to 35% of children from centers in North America, Asia, and Europe [65, 66, 68]. Broad-spectrum empiric therapy for children with clinical or imaging evidence of a perforated appendix with peritonitis is appropriate with carbapenems (imipenem or meropenem), piperacillin-tazobactam, ticarcillin-clavulanate, or an extended-spectrum cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole.

Aminoglycoside-containing regimens have been used successfully for decades to treat complicated intra-abdominal infection in children. The 3-drug regimen of gentamicin, ampicillin, and clindamycin (the latter often replaced with metronidazole) has been the most commonly used regimen [130]. This experience contrasts with that in adults, where dif-

ficulties in achieving therapeutic levels with use of dosing regimens of <5 to 7 mg/kg (administered once daily) and aminoglycoside-induced renal dysfunction have limited enthusiasm for their use [95].

There is, however, an ongoing trend away from the use of aminoglycoside-based regimens for pediatric appendicitis [130]. This is driven largely by the fewer infusions required by other regimens. Retrospective, historical, and case-control single-center reviews have examined multiple clinical and cost-related outcomes of traditional aminoglycoside-based triple antibiotic therapy regimens, compared with non–aminoglycoside-based regimens, and have demonstrated at least equivalent efficacy [131–133]. A large review of data on discharge diagnoses ($n = 8545$) from the Pediatric Health Information database for 32 children's hospitals in the United States was recently completed and found that there was significant and substantial improvement in terms of length of stay, pharmacy charges, and hospital charges, with no increase in hospital readmissions, among children receiving monotherapy, compared with those receiving traditional triple-antibiotic therapy [130].

For children, fever with abdominal pain is a common complaint, and aggressive broad-spectrum antibiotic therapy is not warranted for every child being evaluated for appendicitis. In these situations, less broad–spectrum empiric agents, such as cefoxitin, are appropriate during the period of observation and evaluation. Such therapy is sufficient for definitive treatment of confirmed perforated appendicitis, particularly if all organisms are susceptible [130, 134].

Therapy for pediatric patients with complicated intra-abdominal infection is constrained by safety concerns. Tetracyclines, such as tigecycline, are contraindicated for infections in children aged <8 years [135]. Parenteral fluoroquinolones are not routinely recommended for treatment of infection in situations for which an equally effective alternative exists [136].

Some pediatric centers currently provide outpatient parenteral convalescent therapy for children with complicated appendicitis who, in the opinion of the treating physician, have significant risk for residual infected collections [74]. Oral convalescent therapy is less well described for children but is an option for children who may benefit from and can tolerate ongoing oral antibiotic therapy [137]. An oral second- or third-generation cephalosporin in combination with an anaerobic agent such as metronidazole may be effective [65]. Because of increasing resistance of *B. fragilis* to clindamycin, this agent can no longer be routinely recommended for adults or children. Oral ciprofloxacin may be used for convalescent treatment of children with infection due to *Pseudomonas, Enterobacter, Serratia,* and *Citrobacter* species if these organisms are susceptible, because no other effective oral agents that have been investigated for intra-abdominal infection exist for these pathogens.

Necrotizing enterocolitis primarily affects premature infants and full-term infants with an additional stressful illness [138]. The 3 components necessary for the disease are a substrate for bacterial growth (feedings), an infectious agent (usually bacterial), and an event causing bowel damage, such as decreased blood flow to the bowel or bowel segment (vascular compromise secondary to decreased flow) [139]. This may result in mucosal injury, pneumatosis intestinalis, bacterial overgrowth, and sepsis. More-extensive full thickness bowel injury, as well as bowel perforation, may occur.

The general presentation involves increased episodes of apnea and bradycardia followed by abdominal distension, bloody stools, and bilious emesis [140]. Portal venous gas may also be present. The abdomen may become focally erythematous. Signs of sepsis, such as thrombocytopenia and neutropenia, may also be present; acidosis may also occur if there is bowel ischemia.

In very low birth weight neonates, peritoneal drainage may be used instead of immediate operation when bowel perforation occurs [141]. Some pediatric surgeons advocate this as the only treatment option when combined with antibiotic administration. Other pediatric surgeons use drainage as a temporizing method or not at all. Operation generally involves bowel resection with the creation of stomas or reanastomsis.

The survival rate for necrotizing enterocolitis is close to 95% unless necrotizing enterocolitis involves the entire bowel, which occurs ~25% of the time and is associated with a mortality rate of 40%–90%. Nonoperative management of necrotizing enterocolitis is successful ~70% of the time [142].

XI. WHAT CONSTITUTES APPROPRIATE ANTIBIOTIC DOSING?

Recommendations

70. Empiric therapy of patients with complicated intra-abdominal infection requires the use of antibiotics at optimal doses to ensure maximum efficacy and minimal toxicity and to reduce antimicrobial resistance (Tables 5 and 6) (B-II).

71. Individualized daily administration of aminoglycosides according to lean body mass and estimated extracellular fluid volume is preferred for patients receiving these agents for intra-abdominal infection (B-III).

Evidence Summary

Initial intravenous dosage regimens for adult and pediatric patients with normal renal and hepatic function are shown in Tables 5 and 6, respectively. The recommended regimens are based on dosage ranges that have been shown to be effective in clinical trials and are applicable to patients with mild-to-moderate community-acquired infection, but they have not been well investigated in the treatment of severe and/or nosocomial infection. Product package inserts and/or current published literature should be consulted for dosage adjustments in patients with impaired renal or hepatic function.

Pharmacokinetic-pharmacodynamic properties of specific

antibiotics should be considered in selecting an adequate dosage regimen [143]. The β-lactam antibiotics have time-dependent bactericidal activity and a minimal postantibiotic effect, with the exception of carbapenems against *P. aeruginosa*. The best predictor of microbiological and clinical response to β-lactam antibiotics is the duration during which unbound drug concentrations exceed the minimum inhibitory concentration (MIC) of the microorganism (T > MIC). Optimization of this parameter to treat severe infections or organism with higher MIC values may require dosage strategies that incorporate more-frequent dosing intervals, larger doses, or prolonged (including extended or continuous) intravenous infusion of β-lactams with short elimination half-lives, compared with dosage and interval recommendations from the label [144]. In contrast, agents such as fluoroquinolones, aminoglycosides, and metronidazole have concentration-dependent bactericidal activity and a moderate to prolonged postantibiotic effect. Parameters that incorporate the exposure of unbound drug concentrations, either the ratio of area under the concentration-time curve (AUC) or maximum drug concentration (C_{max}) to MIC of the microorganism (*f*AUC:MIC and *f*C_{max}:MIC), are the best predictors of microbiological and clinical response for these agents [143]. Large intravenous doses administered less frequently (eg, every 24 h) can optimize these parameters and ease administration by decreasing the number infusions required per day.

Antimicrobial dosage considerations are also important in critically ill patients and obese adult patients. Physiological changes can occur in both of these patient populations and may alter the apparent volume of distribution and/or clearance of commonly used antibiotics. In addition, if the estimate of a dosage regimen is dependent on renal function, an accurate estimate of creatinine clearance on the basis of serum creatinine values and body weight may be difficult with commonly used equations, and direct measurement of creatinine clearance may be required. For β-lactams and aminoglycosides, a critically ill patient in the early stages of sepsis may have shifts in body fluid and be in a hypermetabolic state, resulting in an increase in both volume of distribution and clearance and lower serum antibiotic concentrations [145, 146]. Similarly, lower serum concentrations of cephalosporins and carbapenems have been observed in obese patients. Lower tissue concentrations of cephalosporins have also been reported in obese patients following perioperative surgical antibiotic prophylaxis [147, 148]. These studies suggest that higher doses and/or more frequent administration of β-lactams may be needed in selected patients who are obese or critically ill with altered distribution and increased clearance of renally excreted antibiotics. Initial dosage regimens for aminoglycosides and vancomycin should be based on adjusted body weight and total body weight, respectively. Serum drug concentration monitoring is recommended for dosage individualization of aminoglycosides and vancomycin in these patient populations.

There is considerable evidence that less frequent dosing of metronidazole, in particular, is effective. The nitroimidazoles are bactericidal through toxic metabolites that cause DNA strand breakage. Resistance, both clinical and microbiological, has been described only rarely. Liver disease leads to a decreased clearance of metronidazole, and dosage reduction is recommended [149–152].

XII. HOW SHOULD MICROBIOLOGICAL CULTURE RESULTS BE USED TO ADJUST ANTIMICROBIAL THERAPY?

Recommendations

72. Lower-risk patients with community-acquired intra-abdominal infection do not require alteration of therapy if a satisfactory clinical response to source control and initial therapy occurs, even if unsuspected and untreated pathogens are later reported (B-III).

73. If resistant bacteria were identified at the time of initial intervention and there are persistent signs of infection, pathogen-directed therapy is recommended for patients with lower severity disease (B-III).

74. Use of culture and susceptibility results to determine antimicrobial therapy in high-severity community-acquired or health care–associated infection should be based on pathogenic potential and density of identified organisms (B-III).

75. Microbes recovered from blood cultures should be assumed to be significant if they have established pathogenic potential or are present in ⩾2 blood cultures (A-I) or if they are recovered in moderate or heavy concentrations from samples obtained from drainage (B-II).

Evidence Summary

In patients with community-acquired intra-abdominal infection, empiric antimicrobial therapy directed against predominant pathogens is likely to be associated with a successful outcome. However, if the initial antimicrobial regimen does not cover the eventual isolates, it is more likely that the patient will experience a treatment failure. Nonetheless, many patients are still successfully treated with an adequate source control procedure and an empiric regimen directed against coliforms and anaerobes. There are no prospective data indicating that alteration of the regimen on the basis of culture results will improve outcome in patients who have unsuspected pathogens or more-resistant pathogens. However, it would seem prudent to adjust the antimicrobial regimen in higher-risk patients for whom the consequences of treatment failure may be of greater significance and in lower-risk patients who have persistent signs of infection.

XIII. WHAT IS THE APPROPRIATE DURATION OF THERAPY FOR PATIENTS WITH COMPLICATED INTRA-ABDOMINAL INFECTION?

Recommendations

76. Antimicrobial therapy of established infection should be limited to 4–7 days, unless it is difficult to achieve adequate source control. Longer durations of therapy have not been associated with improved outcome (B-III).

77. 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 anti-infective therapy directed at aerobic gram-positive cocci for 24 h is adequate (B-II).

78. 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).

79. Bowel injuries attributable to penetrating, blunt, or iatrogenic trauma that are repaired within 12 h and any other intraoperative contamination of the operative field by enteric contents should be treated with antibiotics for ⩽24 h (A-I).

80. Acute appendicitis without evidence of perforation, abscess, or local peritonitis requires only prophylactic administration of narrow spectrum regimens active against aerobic and facultative and obligate anaerobes; treatment should be discontinued within 24 h (A-I).

81. The administration of prophylactic antibiotics to patients with severe necrotizing pancreatitis prior to the diagnosis of infection is not recommended (A-I).

Evidence Summary

There is a wide range of individual antimicrobial agents and combinations of agents available for use in complicated intra-abdominal infection. There are convincing data that absent or inadequate empiric and definitive antibiotic therapy results in both increased treatment failure rates and increased mortality [64, 67, 153–157]. Conversely, unnecessary and needlessly broad coverage or prolonged therapy carries its own problems, including cost. Patient- and agent-specific toxicities of therapy may occur, including superinfection, *Clostridium difficile* colitis, and organ injury [158]. Acquisition of intrinsically resistant organisms and selective pressure for resistance within the unit, hospital, or community is of increasing concern [28, 159].

Evidence presented in the previous guidelines suggested that a duration of therapy no greater than 1 week was appropriate for most patients with intra-abdominal infection, with the exception of those who had inadequate source control [9, 10, 160]. Within this window, resolution of clinical signs of infection should be used to judge the termination point for antimicrobial therapy. The risk of subsequent treatment failure appears to be quite low in patients who have no clinical evidence of infection at the time of cessation of antimicrobial therapy [161, 162]. This usually implies that the patients are afebrile, have normal white blood cell counts, and are tolerating an oral diet.

The previous guidelines also outlined a number of conditions for which a duration of therapy >24 h was not believed to be necessary. In such patients, the primary goal of therapy is prophylaxis against a surgical site infection, as opposed to treatment of an established infection. These conditions included traumatic or iatrogenic bowel injuries operated on within 12 h, upper gastrointestinal perforations operated on within 24 h, and localized processes, such as nonperforated appendicitis, cholecystitis, bowel obstruction, and bowel infarction, in which the focus of inflammation or infection is completely eliminated by a surgical procedure and there is no extension of infection beyond the organ in question.

Broad-spectrum antibiotic therapy has been used by some clinicians for the treatment of patients with necrotizing pancreatitis, in an effort to prevent an infection in the inflammatory phlegmon and thereby improve patient outcome. In a guideline on the management of severe pancreatitis, however, the authors concluded that this approach was not justified on the basis of available data [4]. A meta-analysis of trials performed in this area have shown that positive results were attributable to poor study design and that well-designed studies did not demonstrate benefit [163]. This practice is not recommended without clinical or culture evidence of an established infection in patients with necrotizing pancreatitis. In those patients with established pancreatic infection, the agents recommended for use with community-acquired infection of higher severity and health care–associated infection (Tables 2 and 3) are the preferred agents. Because of the difficulty of achieving adequate source control in patients with infected pancreatic and peripancreatic phelgma, a longer duration of therapy may be needed.

XIV. WHAT PATIENTS SHOULD BE CONSIDERED FOR ORAL OR OUTPATIENT ANTIMICROBIAL THERAPY AND WHAT REGIMENS SHOULD BE USED?

Recommendations

82. For children and adults whose signs and symptoms of infection are resolved, no further antibiotic therapy is required (B-III).

83. For adults recovering from intra-abdominal infection, completion of the antimicrobial course with oral forms of moxifloxacin, ciprofloxacin plus metronidazole, levofloxacin plus metronidazole, an oral cephalosporin with metronidazole, or

amoxicillin-clavulanic acid (B-II) is acceptable in patients able to tolerate an oral diet and in patients in whom susceptibility studies do not demonstrate resistance (B-II).

84. If culture and susceptibility testing identify organisms that are only susceptible to intravenous therapy, such therapy may be administered outside of the hospital (B-III).

85. For children, outpatient parenteral antibiotic management may be considered when subsequent drainage procedures are not likely to be required but symptoms of ongoing intra-abdominal inflammation persist in the context of decreasing fever, controlled pain, ability to tolerate oral fluids, and ability to ambulate (B-II).

86. For oral step-down therapy in children, intra-abdominal cultures at the time of the drainage procedure are recommended to allow for the use of the narrowest-spectrum, best-tolerated, and safest oral therapy. A second- or third-generation cephalosporin in combination with metronidazole, or amoxicillin-clavulanate, may be options if the isolated organisms are susceptible to these agents. Fluoroquinolones, such as ciprofloxacin or levofloxacin, may be used to treat susceptible *Pseudomonas, Enterobacter, Serratia,* and *Citrobacter* species (B-III). If ciprofloxacin or levofloxacin is used, metronidazole should be added.

87. Drug susceptibility results of isolated gram-negative aerobic and facultative organisms, if available, should be used as a guide to agent selection in children and adults (B-III).

88. Because many of the patients who are managed without a primary source control procedure may be treated in the outpatient setting, the oral regimens recommended (see recommendations 83 and 86) can also be used as either primary therapy or step-down therapy following initial intravenous antimicrobial therapy (B-III).

Evidence Summary

Patients who are convalescing from complicated intra-abdominal infection may be treated with oral antibiotic therapy [164]. Such therapy should be included as part of the brief treatment intervals recommended, which in total should rarely exceed 4–7 days. Providing antimicrobial therapy for patients who are afebrile, with normal peripheral leukocyte counts and with return of bowel function, is rarely indicated. Oral therapy is selected on the basis of susceptibilities of the identified primary isolates or, in the absence of cultures, commonly isolated pathogens that include *E. coli,* streptococci, and *B. fragilis.* Most of those regimens have not been formally studied but provide anticipated activity against the major coliforms and anaerobes encountered in these infections. Increasing resistance of *E. coli* to amoxicillin-clavulanic acid may limit the continued use of this regimen [83, 165].

XV. HOW SHOULD SUSPECTED TREATMENT FAILURE BE MANAGED?

Recommendations

89. In patients who have persistent or recurrent clinical evidence of intra-abdominal infection after 4–7 days of therapy, appropriate diagnostic investigation should be undertaken. This should include CT or ultrasound imaging. Antimicrobial therapy effective against the organisms initially identified should be continued (A-III).

90. 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).

91. For patients who do not respond initially and for whom a focus of infection remains, both aerobic and anaerobic cultures should be performed from 1 specimen, provided it is of sufficient volume (at least 1.0 mL of fluid or tissue) and is transported to the laboratory in an anaerobic transport system (C-III). Inoculation of 1–10 mL of fluid directly into an anaerobic blood culture broth bottle may improve yield.

Evidence Summary

Patients with persistent or recurrent signs of peritoneal irritation, failure of bowel function to return to normal, or continued fever or leukocytosis are at high risk of an intra-abdominal or other infection that may require additional intervention to achieve source control. In general, patients with a persistent or new intra-abdominal infection, an organ-space infection, or a superficial or deep surgical-site infection can be identified through a careful physical examination supplemented by appropriated laboratory and imaging investigations. CT of the abdomen is usually the most accurate method by which to diagnose an ongoing or recurrent intra-abdominal infection. The possibility of an extra-abdominal infection, such as nosocomial pneumonia or urinary tract infection or a noninfectious cause of fever or leukocytosis (ie, venous thrombosis or a pulmonary embolism) and *C. difficile* disease, even without diarrhea, should also be considered. Appropriate antimicrobial therapy should be continued while the investigation proceeds, particularly if the patient manifests signs of sepsis, such as organ dysfunction. Antimicrobial regimens should be adjusted according to the results of the diagnostic investigations. For patients with a confirmed intra-abdominal infection, this may require broadening the regimen to include agents with activity against health care–associated organisms typically isolated with this type of infection. For patients with persistent clinical symptoms and signs but in whom no evidence of a new or persistent infection is uncovered after a careful investigation, termination of antimicrobial therapy is warranted.

XVI. WHAT ARE THE KEY ELEMENTS THAT SHOULD BE CONSIDERED IN DEVELOPING A LOCAL APPENDICITIS PATHWAY?

Recommendations

92. Local hospitals should establish clinical pathways to standardize diagnosis, in-hospital management, discharge, and outpatient management (B-II).

93. Pathways should be designed by collaborating clinicians involved in the care of these patients, including but not limited to surgeons, infectious diseases specialists, primary care practitioners, emergency medicine physicians, radiologists, nursing providers, and pharmacists, and should reflect local resources and local standards of care (B-II).

94. Although no clinical findings are unequivocal in identifying patients with appendicitis, a constellation of findings, including characteristic abdominal pain, localized abdominal tenderness, and laboratory evidence of acute inflammation, will generally identify most patients with suspected appendicitis (A-II).

95. Helical CT of the abdomen and pelvis with intravenous, but not oral or rectal, contrast is the recommended imaging procedure for patients with suspected appendicitis (B-II).

96. All female patients should undergo diagnostic imaging. Those of child-bearing potential should undergo pregnancy testing prior to imaging and, if in the first trimester of pregnancy, should undergo ultrasound or magnetic resonance instead of imaging ionizing radiation (B-II). If these studies do not define the pathology present, laparoscopy or limited CT scanning may be considered (B-III).

97. Imaging should be performed for all children, particularly those aged <3 years, when the diagnosis of appendicitis is not certain. CT imaging is preferred, although to avoid use of ionizing radiation in children, ultrasound is a reasonable alternative (B-III).

98. For patients with imaging study findings negative for suspected appendicitis, follow-up at 24 h is recommended to ensure resolution of signs and symptoms, because of the low but measurable risk of false-negative results (B-III).

99. For patients with suspected appendicitis that can neither be confirmed nor excluded by diagnostic imaging, careful follow-up is recommended (A-III).

100. Patients may be hospitalized if the index of suspicion is high (A-III).

101. Antimicrobial therapy should be administered to all patients who receive a diagnosis of appendicitis (A-II).

102. Appropriate antimicrobial therapy includes agents effective against facultative and aerobic gram-negative organisms and anaerobic organisms, as detailed in Table 2 for the treatment of patients with community-acquired intra-abdominal infection (A-I).

103. For patients with suspected appendicitis whose diagnostic imaging studies are equivocal, antimicrobial therapy should be initiated along with appropriate pain medication and antipyretics, if indicated. For adults, antimicrobial therapy should be provided for a minimum of 3 days, until clinical symptoms and signs of infection resolve or a definitive diagnosis is made (B-III).

104. Operative intervention for acute, nonperforated appendicitis may be performed as soon as is reasonably feasible. Surgery may be deferred for a short period of time as appropriate according to individual institutional circumstances (B-II).

105. Both laparoscopic and open appendectomy are acceptable procedures, and use of either approach should be dictated by the surgeon's expertise in performing that particular procedure (A-I).

106. Nonoperative management of selected patients with acute, nonperforated appendicitis can be considered if there is a marked improvement in the patient's condition prior to operation (B-II).

107. Nonoperative management may also be considered as part of a specific approach for male patients, provided that the patient is admitted to the hospital for 48 h and shows sustained improvement in clinical symptoms and signs within 24 h while receiving antimicrobial therapy (A-II).

108. Patients with perforated appendicitis should undergo urgent intervention to provide adequate source control (B-III).

109. Patients with a well-circumscribed periappendiceal abscess can be managed with percutaneous drainage or operative drainage when necessary. Appendectomy is generally deferred in such patients (A-II).

110. Selected patients who present several days after development of an inflammatory process and have a periappendiceal phlegmon or a small abscess not amenable to percutaneous drainage may delay or avoid a source control procedure to avert a potentially more morbid procedure than simple appendectomy. Such patients are treated with antimicrobial therapy and careful inpatient follow-up, in a manner analogous to patients with acute diverticulitis (B-II).

111. The use of interval appendectomy after percutaneous drainage or nonoperative management of perforated appendicitis is controversial and may not be necessary (A-II).

Evidence Summary

There is now compelling evidence that the use of protocols for patient care management improves both the process of care and patient outcomes. Locally adapted guidelines should be implemented to improve process of care variables and relevant clinical outcomes. The guideline should address a comprehen-

sive set of elements in the process of care rather than a single element in isolation. Benefits accrue through diminished use of limited resources outside of the protocol, reduced demand for hospital beds for observation, standardized documentation of follow-up if no diagnosis is made, less measurable but highly likely decreases in infectious and other postoperative complications, likely decreases in length of stay, and decreases in antibiotic usage.

Locally developed clinical pathways have been established in appendicitis and other disease states to standardize the diagnosis and management of patients with suspicion of a specific disease state [65, 166, 167]. To be effective, these devices should act as a cohesive unit to ensure that all steps of care are reliably delivered and documented. This approach reduces unwarranted clinical variation, prevents avoidable patient morbidity, reduces hospital stays, and improves patient outcomes. In general, pathways that provide for evaluation by clinical judgment, are supported by appropriate laboratory tests and imaging, and are coupled with standardized approaches to management lead to fewer unnecessary operations, less antibiotic use, and shorter hospital stays [168].

This section will identify elements for the construction of local pathways regarding evaluation, antimicrobial treatment, and surgical management of patients with nonperforated appendicitis. These pathways should emphasize comprehensive patient management from the time of first presentation to a health care provider.

The symptoms and signs that suggest appendicitis, as well as their sensitivities and specificities, have been well described [169]. Scoring systems have been developed to aid in decision-making for immediate operation, diagnostic imaging, or observation in or out of the hospital [15]. These systems appear to be useful as documentary devices but should not replace clinical suspicion.

Diagnostic imaging is now the standard for most patients with suspected acute appendicitis. Imaging is recommended for all individuals presenting with acute abdominal pain consistent with appendicitis, except for male patients aged <40 years with classical history and physical findings [16, 170, 171]. Recent guidelines have been published for imaging in women [172].

If appendicitis is excluded by diagnostic imaging and no other diagnosis is confirmed, further management is based on a range of clinical and social factors. When clinical suspicion remains, ongoing observation of the patient in the hospital or emergency department allows for an evaluation of the evolution of symptoms over time. Observation may also be warranted for patients if obtaining further follow-up is likely to be problematic. Patients discharged from the hospital should have follow-up within 24 h, even if the follow-up must be performed by telephone. There remains a measurable false-negative rate with imaging, and other conditions requiring medical intervention may become manifest during this interval. An absence of improvement may require re-examination and possibly re-imaging or consideration of diagnostic laparoscopy.

The evidence supporting the importance of rehydration in appendicitis comes from observational studies anteceding blood-banking [21], in which a 6-fold reduction in mortality attributable to perforated appendicitis was observed following the increased awareness of resuscitation. Other support comes from the Surviving Sepsis Campaign [13, 22].

Clinical trials demonstrating the efficacy of antimicrobial therapy alone in male patients without appendiceal mass but with clinically suspected appendicitis support antimicrobial therapy without intervention for patients with equivocal imaging studies as a possible alternative to operative management and as a means of converting appendectomy from an emergency to an urgent surgical procedure [173]. Further support for a less emergent approach comes from other clinical trials analyzing time to perforation, which indicate this to be an unusual early event [174, 175].

Observation of patients with ultrasound or CT evaluation of appendiceal masses is time honored [174, 176–180]. A recent meta-analysis found that appendiceal abscess or phlegmon was found in 4% of patients with appendicitis. Nonsurgical treatment failed in 7.2% of patients (95% confidence interval [CI], 4.0%–10.5%). Drainage of an abscess occurred early in the course of illness in 20% of patients (95% CI, 11.0%–28.3%) [181]. Immediate surgery was associated with a higher morbidity, compared with nonsurgical treatment (odds ratio, 3.3; 95% CI, 1.9–5.6; $P < .001$). After successful nonsurgical treatment, during follow-up, a malignant disease was detected in 1.2% (95% CI, 0.6%–1.7%) and an important benign disease in 0.7% of patients (95% CI, 0.2%–11.9%). The risk of recurrence was 7.4% (95% CI, 3.7%–11.1%) [182].

It is not apparent whether interval appendectomy is necessary following successful conservative treatment of appendiceal mass. The main debate centers on the recurrence rate, the complication rate of interval appendicectomy, and the potential for underlying malignancy. Two reviews have suggested that interval appendectomy is unnecessary in 75%–90% of cases [183, 184].

PERFORMANCE MEASURES

Given the emphasis placed on development of appendicitis pathways in these guidelines, the Expert Panel recommends that the following performance measures be focused on this disease:

- Determine the time from admission to emergency facility to diagnosis for those patients not undergoing diagnostic imaging.
- Determine the interval from emergency contact to perfor-

mance of diagnostic imaging for patients not receiving a diagnosis of appendicitis on the basis of history and physical examination findings who require operation.

- Determine the interval from diagnosis of appendicitis to administration of antimicrobial therapy.
- Determine the interval from diagnosis to time of intervention.
- Determine the negative appendectomy rate for patients admitted through the emergency department with acute appendicitis.
- For patients with nonperforated appendicitis, determine the duration of prophylactic antimicrobial therapy.
- For patients with perforated or abscessed appendicitis, determine the duration of both intravenous and oral antimicrobial therapy and determine the incidence of surgical-site infection.

ANTIMICROBIAL STEWARDSHIP

The role of antimicrobial stewardship programs in implementing these guidelines is emphasized. If such a program exists within a hospital, specific regimens should be identified for each of the 3 categories of complicated intra-abdominal infections defined in these guidelines: (1) mild-to-moderate–severity community-acquired infections, (2) high-severity community-acquired infections, and (3) health care–associated infections. As a stewardship issue, there is strong evidence that all patients undergoing operation for appendicitis should receive brief antimicrobial therapy [185], and appropriate local regimens should also be identified for this indication. These locally determined regimens should be used preferentially.

AREAS FOR FUTURE RESEARCH

Several areas require further study. The issue of appropriate specimen processing, including the role of routine antimicrobial susceptibility testing, requires close study. This may best be performed by prospective observational studies. This type of study would also generate epidemiological data on community resistance patterns and community-specific microbiologic findings (eg, an unanticipated incidence of multidrug-resistant organisms).

Evaluation of the effects of delaying appendectomy, as recommended in these guidelines, is suggested. Review of data from large multi-hospital databases is one approach to this problem.

There is a pressing need for the study of appropriate duration of antimicrobial therapy. The impact of prolonged therapy, driven by the availability of potent oral regimens, may have a significant impact on the incidence of resistant organisms in the community or in intermediate or chronic-care facilities. However, the duration of therapy is largely dependent on adequate source control. The range of intra-abdominal inoculation varies from none to multiple, widespread intra-abdominal abscesses that may not all be drained well with 1 procedure.

With regard to higher-risk patients, particularly those with health care–associated infection, poor clinical outcomes are still common. Given the infrequency of such patients, prospective comparative randomized trials are unlikely to be performed; therefore, other methodologies, including prospective observational studies, may be useful. The pattern of infecting organisms needs to be confirmed, and the impact of empiric therapy should be examined. The hypothesis that broader-spectrum antimicrobial therapy is beneficial in such patients should be critically examined. Additionally, duration of therapy in postoperative infection is an important variable that requires study.

The pharmacokinetics of antimicrobial therapy in severely ill patients with sepsis syndrome is an urgent need. Few antimicrobials have been studied in severely ill patients, and these studies have suggested that current package insert dosage recommendations may not be sufficient for such patients.

Acknowledgments

We thank Paul Auwaerter, John Bohnen, Ronald V. Maier, and David R. Snydman for their thoughtful reviews of earlier drafts.

Financial support. The Infectious Diseases Society of America and the Surgical Infection Society.

Potential Conflicts of Interest. J.S.S. has received honoraria for lectures in China from Merck; financial support as consultant and principal investigator of a clinical research project in China and honoraria for lectures from Bayer; financial support as consultant, advisory board member, and lecturer from Johnson and Johnson; research support for a project on the interaction of PVL and neutrophils from Pfizer; financial support as consultant, advisory board member, and lecturer from Shering-Plough; and financial support as advisory board member from Optimer. J.E.M. received research support form Artisan Pharmaceuticals, Eli Lilly, Ortho Biotech, Pennisula Pharmaceuticals, Pfizer Pharmaceuticals, and Theravance and has served as a paid consultant, advisory board member, or speaker for Eli Lilly, Merck, Ortho-McNeil Pharmaceuticals, Pfizer Pharmaceuticals, Schering-Plough, and Wyeth Pharmaceuticals. J.G.B. has served on the advisory boards of Abbott Laboratories, Bristol, Pfizer Pharmaceuticals, Tibotec, GlaxoSmithKline and served on the policy board of Johnson & Johnson. J.S.B. has served as a consultant to and received research funding from AstraZeneca, Wyeth Pharmaceuticals, and Johnson & Johnson. A.W.C. served as a speaker for Wyeth Pharmaceuticals and Bayer, is a member of the guideline committee of the Association of Medical Microbiology and Infectious Diseases Canada, and is coauthor of the Canadian Practice Guidelines for Surgical Intra-abdominal Infections. A.B.N. has served as a speaker for Bayer, Schering-Plough, and Wyeth Pharmaceuticals. K.A.R. received research grants and contracts from Sanofi-Aventis and Roche Laboratories; has served as a consultant to Johnson & Johnson, Ortho-McNeil Pharmaceuticals, and GlaxoSmithKline; serves on the speakers bureau or advisory board of Abbott Laboratories, Astellas Pharmaceuticals, AstraZeneca Pharmaceuticals, Daiichi Pharmaceuticals, Ortho-McNeil Pharmaceuticals, Pfizer Pharmaceuticals, Schering-Plough, Targanta, Theravance, and Wyeth Pharmaceuticals; and is a shareholder of Pfizer Pharmaceuticals. R.G.S. has served as a consultant to Pfizer Pharmaceuticals, Merck, Wyeth Pharmaceuticals, and Schering-Plough. E.J.B. has received honoraria or served on advisory panels for Ortho-McNeil, GlaxoSmithKline, Aventis, Cepheid, Becton-Dickinson, bioMérieux, Cubist, Wyeth-Ayerst, Johnson & Johnson, Astra-Zeneca, and Oxonica; received

research support from Roche Molecular Diagnostics; and own shares of Cepheid and Merck. E.J.C.G. has served on advisory boards for Merck, Schering-Plough Pharmaceuticals, Optimer Pharmaceuticals, Theravance, Oculus Innovative Sciences, and Viropharma; has been on speakers bureaus for Ortho-McNiel, Merck, Schering-Plough, Theravance, and Bayer; has received research grants from Merck, Schering-Plough, Cubist, Theravance, Optimer, Replidyne, Oculus Innovative Sciences, Pfizer, Astella, Cerexa, Impex pharmaceuticals, and Optimer Pharmaceuticals. E.P.D. has given lectures for honoraria and/or served on advisory boards for Bayer, Merck, Wyeth-Ayerst, AstraZeneca, Pfizer, Ortho-McNeil, Cubist, Vicuron, InterMune, Peninsula, Johnson & Johnson, Cepheid, Replidyne, Kimberley-Clark, Targanta, Schering-Plough, Enturia, Optimer, and BD-GeneOhm. P.O. serves on the speakers bureau for Pfizer Pharmaceuticals and is a member of the Surgery National Advisory Board. S.E. serves on advisory boards and the speakers' bureau for Pfizer, Cubist, and Wyeth. All other authors: no conflicts.

References

1. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults [see comments]. Chest **1991**; 100:1619–36.
2. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA **1993**; 270:2957–63 (erratum: JAMA **1994**; 271:1321).
3. Lemeshow S, Le Gall JR. Modeling the severity of illness of ICU patients: a systems update. JAMA **1994**; 272:1049–55.
4. Meyer AA, Messick WJ, Young P, et al. Prospective comparison of clinical judgment and APACHE II score in predicting the outcome in critically ill surgical patients. J Trauma **1992**; 32:747–53.
5. Swenson BR, Metzger R, Hedrick TL, et al. Choosing antibiotics for intra-abdominal infections: what do we mean by "high risk"? Surg Infect (Larchmt) **2009**; 10:29–39.
6. DeFrances CJ, Cullen KA, Kozak LJ. National Hospital Discharge Survey: 2005 annual summary with detailed diagnosis and procedure data. Vital Health Stat 13 **2007**; 165:1–209.
7. Brun-Buisson C, Doyon F, Carlet J, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults: a multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA **1995**; 274:968–74.
8. Field M, Lohr K. Clinical practice guidelines: directions for a new program. In: Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice Guidelines. Washington, DC: National Academy Press, **1990**:8.
9. Solomkin JS, Mazuski JE, Baron EJ, et al. Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections. Clin Infect Dis **2003**; 37:997–1005.
10. Mazuski JE, Sawyer RG, Nathens AB, et al. The Surgical Infection Society guidelines on antimicrobial therapy for intra-abdominal infections: an executive summary. 3rd edition. Surgical Infection Society, **2002**:161–74.
11. The periodic health examination. Canadian Task Force on the Periodic Health Examination. Can Med Assoc J **1979**; 121:1193–254.
12. Wagner JM, McKinney WP, Carpenter JL. Does this patient have appendicitis? JAMA **1996**; 276:1589–94.
13. Bundy DG, Byerley JS, Liles EA, Perrin EM, Katznelson J, Rice HE. Does this child have appendicitis? JAMA **2007**; 298:438–51.
14. Silen WW. Cope's early diagnosis of the acute abdomen. 12th ed. New York: Oxford University Press, **2005**.
15. Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med **1986**; 15:557–64.
16. Pinto LN, Pereira JM, Cunha R, Pinto P, Sirlin C. CT evaluation of appendicitis and its complications: imaging techniques and key diagnostic findings. AJR Am J Roentgenol **2005**; 185:406–17.
17. Urban BA, Fishman EK. Targeted helical CT of the acute abdomen: appendicitis, diverticulitis, and small bowel obstruction. Semin Ultrasound CT MR **2000**; 21:20–39.
18. Doria AS, Moineddin R, Kellenberger CJ, et al. US or CT for diagnosis of appendicitis in children and adults? A meta-analysis. Radiology **2006**; 241:83–94.
19. Mariak Z, White MD, Lewko J, Lyson T, Piekarski P. Direct cooling of the human brain by heat loss from the upper respiratory tract. J Appl Physiol **1999**; 87:1609–13.
20. White MD. Components and mechanisms of thermal hyperpnea. J Appl Physiol **2006**; 101:655–63.
21. Barnes BA, Behringer GE, Wheelock FC, Wilkins EW. Treatment of appendicitis at the Massachusetts General Hospital (1937–1959). JAMA **1962**; 180:122–6.
22. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med **2008**; 36:296–327.
23. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med **2006**; 34:1589–96.
24. van Nieuwenhoven CA, Buskens E, van Tiel FH, Bonten MJ. Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. JAMA **2001**; 286:335–40.
25. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Am J Surg **2005**; 189:395–404.
26. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. Clin Infect Dis **2006**; 43:322–30.
27. Marshall JC, Maier RV, Jimenez M, Dellinger EP. Source control in the management of severe sepsis and septic shock: an evidence-based review. Crit Care Med **2004**; 32(Suppl 11):S513–26.
28. Shlaes DM, Gerding DN, John JF Jr, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin Infect Dis **1997**; 25:584–99.
29. Koperna T, Schulz F. Prognosis and treatment of peritonitis. Do we need new scoring systems? Arch Surg **1996**; 131:180–6.
30. Koperna T, Schulz F. Relaparotomy in peritonitis: prognosis and treatment of patients with persisting intraabdominal infection. World J Surg **2000**; 24:32–7.
31. Mulier S, Penninckx F, Verwaest C, et al. Factors affecting mortality in generalized postoperative peritonitis: multivariate analysis in 96 patients. World J Surg **2003**; 27:379–84.
32. Grunau G, Heemken R, Hau T. Predictors of outcome in patients with postoperative intra-abdominal infection. Eur J Surg **1996**; 162:619–25.
33. Betsch A, Wiskirchen J, Trubenbach J, et al. CT-guided percutaneous drainage of intra-abdominal abscesses: APACHE III score stratification of 1-year results. Eur Radiol **2002**; 12:2883–9.
34. Bufalari A, Giustozzi G, Moggi L. Postoperative intraabdominal abscesses: percutaneous versus surgical treatment. Acta Chir Belg **1996**; 96:197–200.
35. Theisen J, Bartels H, Weiss W, Berger H, Stein HJ, Siewert JR. Current concepts of percutaneous abscess drainage in postoperative retention. J Gastrointest Surg **2005**; 9:280–3.
36. Pruett TL, Simmons RL. Status of percutaneous catheter drainage of absceses. Surg Clin North Am **1988**; 68:89–105.
37. Gerzof SG, Robbins AH, Birkett DH. Computed tomography in the diagnosis and management of abdominal abscesses. Gastrointest Radiol **1978**; 3:287–94.
38. Gerzof SG, Johnson WC, Robbins AH, Nabseth DC. Expanded criteria for percutaneous abscess drainage. Arch Surg **1985**; 120:227–32.
39. Gerzof SG, Robbins AH, Johnson WC, Birkett DH, Nabseth DC. Percutaneous catheter drainage of abdominal abscesses: a five-year experience. N Engl J Med **1981**; 305:653–7.
40. vanSonnenberg E, Mueller PR, Ferrucci JT Jr. Percutaneous drainage of 250 abdominal abscesses and fluid collections. Part I: results, failures, and complications. Radiology **1984**; 151:337–41.

41. Levison MA. Percutaneous versus open operative drainage of intra-abdominal abscesses. Infect Dis Clin North Am **1992**; 6:525–44.
42. Sones PJ. Percutaneous drainage of abdominal abscesses. AJR Am J Roentgenol **1984**; 142:35–9.
43. Maher MM, Gervais DA, Kalra MK, et al. The inaccessible or undrainable abscess: how to drain it. Radiographics **2004**; 24:717–35.
44. van Ruler O, Mahler CW, Boer KR, et al. Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis: a randomized trial. JAMA **2007**; 298:865–72.
45. Schein M, Paladugu R. Planned relaparotomies and laparostomy. In: Schein M, Marshall JC, eds. Source control: a guide to the management of surgical infections. Berlin: Springer-Verlag, **2003**:412–23.
46. Cueto J, D'Allemagne B, Vazquez-Frias JA, et al. Morbidity of laparoscopic surgery for complicated appendicitis: an international study. Surg Endosc **2006**; 20:717–20.
47. Akinci D, Akhan O, Ozmen MN, et al. Percutaneous drainage of 300 intraperitoneal abscesses with long-term follow-up. Cardiovasc Intervent Radiol **2005**; 28:744–50.
48. De Waele JJ, Hoste EA, Blot SI. Blood stream infections of abdominal origin in the intensive care unit: characteristics and determinants of death. Surg Infect (Larchmt) **2008**; 9:171–7.
49. Rashid RM, Salah W, Parada JP. '*Streptococcus milleri*' aortic valve endocarditis and hepatic abscess. J Med Microbiol **2007**; 56:280–2.
50. Dougherty SH. Antimicrobial culture and susceptibility testing has little value for routine management of secondary bacterial peritonitis. Clin Infect Dis **1997**; 25(Suppl 2):S258–61.
51. Kokoska ER, Silen ML, Tracy TF Jr, et al. The impact of intraoperative culture on treatment and outcome in children with perforated appendicitis. J Pediatr Surg **1999**; 34:749–53.
52. Montravers P, Gauzit R, Muller C, Marmuse JP, Fichelle A, Desmonts JM. Emergence of antibiotic-resistant bacteria in cases of peritonitis after intraabdominal surgery affects the efficacy of empirical antimicrobial therapy. Clin Infect Dis **1996**; 23:486–94.
53. Aldridge KE, O'Brien M. In vitro susceptibilities of the *Bacteroides fragilis* group species: change in isolation rates significantly affects overall susceptibility data. J Clin Microbiol **2002**; 40:4349–52.
54. Cuchural GJ Jr, Tally FP, Jacobus NV, et al. Susceptibility of the *Bacteroides fragilis* group in the United States: analysis by site of isolation. Antimicrob Agents Chemother **1988**; 32:717–22.
55. Snydman DR, McDermott L, Cuchural GJ Jr, et al. Analysis of trends in antimicrobial resistance patterns among clinical isolates of *Bacteroides fragilis* group species from 1990 to 1994. Clin Infect Dis **1996**; 23(Suppl 1):S54-65.
56. Snydman DR, Jacobus NV, McDermott LA, et al. Multicenter study of in vitro susceptibility of the *Bacteroides fragilis* group, 1995 to 1996, with comparison of resistance trends from 1990 to 1996. Antimicrob Agents Chemother **1999**; 43:2417–22.
57. Snydman DR, Jacobus NV, McDermott LA, et al. National survey on the susceptibility of *Bacteroides fragilis* group: report and analysis of trends for 1997–2000. Clin Infect Dis **2002**; 35(Suppl 1):S126-34.
58. Golan Y, McDermott LA, Jacobus NV, et al. Emergence of fluoroquinolone resistance among *Bacteroides* species. J Antimicrob Chemother **2003**; 52:208–13.
59. Goldstein EJ, Citron DM, Warren YA, Tyrrell KL, Merriam CV, Fernandez H. In vitro activity of moxifloxacin against 923 anaerobes isolated from human intra-abdominal infections. Antimicrob Agents Chemother **2006**; 50:148–55.
60. Snydman DR, Jacobus NV, McDermott LA, et al. In vitro activities of newer quinolones against bacteroides group organisms. Antimicrob Agents Chemother **2002**; 46:3276–9.
61. Snydman DR, Jacobus NV, McDermott LA, et al. National survey on the susceptibility of *Bacteroides fragilis* group: report and analysis of trends in the United States from 1997 to 2004. Antimicrob Agents Chemother **2007**; 51:1649–55.
62. Borbeau PJ, Riley J, Heiter BJ, Master R, Young C, Pierson C. Use of the BacT/Alert blood culture system for culture of sterile body fluids other than blood. J Clin Microbiol **1998**; 36:3273–7
63. Paterson DL, Rossi F, Baquero F, et al. In vitro susceptibilities of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: the 2003 Study for Monitoring Antimicrobial Resistance Trends (SMART). J Antimicrob Chemother **2005**; 55:965–73.
64. Yellin AE, Heseltine PN, Berne TV, et al. The role of *Pseudomonas* species in patients treated with ampicillin and sulbactam for gangrenous and perforated appendicitis. Surg Gynecol Obstet **1985**; 161:303–7.
65. Bradley JS, Behrendt CE, Arrieta AC, et al. Convalescent phase outpatient parenteral antiinfective therapy for children with complicated appendicitis. Pediatr Infect Dis J **2001**; 20:19–24.
66. Lin WJ, Lo WT, Chu CC, Chu ML, Wang CC. Bacteriology and antibiotic susceptibility of community-acquired intra-abdominal infection in children. J Microbiol Immunol Infect **2006**; 39:249–54.
67. Mosdell DM, Morris DM, Voltura A, et al. Antibiotic treatment for surgical peritonitis. Ann Surg **1991**; 214:543–9.
68. Maltezou HC, Nikolaidis P, Lebesii E, Dimitriou L, Androulakakis E, Kafetzis DA. Piperacillin/tazobactam versus cefotaxime plus metronidazole for treatment of children with intra-abdominal infections requiring surgery. Eur J Clin Microbiol Infect Dis **2001**; 20:643–6.
69. Angeras MH, Darle N, Hamnstrom K, et al. A comparison of imipenem/cilastatin with the combination of cefuroxime and metronidazole in the treatment of intra-abdominal infections. Scand J Infect Dis **1996**; 28: 513–8.
70. Luke M, Iversen J, Sondergaard J, et al. Ceftriaxone/metronidazole is more effective than ampicillin/netilmicin/metronidazole in the treatment of bacterial peritonitis. Eur J Surg **1991**; 157:397–401.
71. Barie PS, Vogel SB, Dellinger EP, et al. A randomized, double-blind clinical trial comparing cefepime plus metronidazole with imipenem-cilastatin in the treatment of complicated intra-abdominal infections. Cefepime Intra-abdominal Infection Study Group. Arch Surg **1997**; 132: 1294–302.
72. Solomkin JS, Reinhart HH, Dellinger EP, et al. Results of a randomized trial comparing sequential intravenous/oral treatment with ciprofloxacin plus metronidazole to imipenem/cilastatin for intra-abdominal infections. The Intra-Abdominal Infection Study Group. Ann Surg **1996**; 223:303–15.
73. Allo MD, Bennion RS, Kathir K, et al. Ticarcillin/clavulanate versus imipenem/cilistatin for the treatment of infections associated with gangrenous and perforated appendicitis. Am Surg **1999**; 65:99–104.
74. Meller JL, Reyes HM, Loeff DS, Federer L, Hall JR. One-drug versus two-drug antibiotic therapy in pediatric perforated appendicitis: a prospective randomized study. Surgery **1991**; 4:764–7.
75. Oliva ME, Rekha A, Yellin A, et al. A multicenter trial of the efficacy and safety of tigecycline versus imipenem/cilastatin in patients with complicated intra-abdominal infections [study ID numbers: 3074A1–301-WW; ClinicalTrials.gov identifier: NCT00081744]. BMC Infect Dis **2005**; 5:88.
76. Namias N, Solomkin JS, Jensen EH, Tomassini JE, Abramson MA. Randomized, multicenter, double-blind study of efficacy, safety, and tolerability of intravenous ertapenem versus piperacillin/tazobactam in treatment of complicated intra-abdominal infections in hospitalized adults. Surg Infect (Larchmt) **2007**; 8:15–28.
77. Solomkin JS, Yellin AE, Rotstein OD, et al. Ertapenem versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections: results of a double−blind, randomized comparative phase III trial. Ann Surg **2003**; 237:235–45.
78. Malangoni MA, Song J, Herrington J, Choudhri S, Pertel P. Randomized controlled trial of moxifloxacin compared with piperacillin-tazobactam and amoxicillin-clavulanate for the treatment of complicated intra-abdominal infections. Ann Surg **2006**; 244:204–11.
79. Bieluch VM, Cuchural GJ, Snydman DR, Gorbach SL, Tally FP. Clinical importance of cefoxitin-resistant *Bacteroides fragilis* isolates. Diagn Microbiol Infect Dis **1987**; 7:119–26.
80. Snydman DR, Cuchural GJ Jr, McDermott L, Gill M. Correlation of various in vitro testing methods with clinical outcomes in patients with

Bacteroides fragilis group infections treated with cefoxitin: a retrospective analysis. Antimicrob Agents Chemother **1992**; 36:540–4.
81. Oh H, Nord CE, Barkholt L, Hedberg M, Edlund C. Ecological disturbances in intestinal microflora caused by clinafloxacin, an extended-spectrum quinolone. Infection **2000**; 28:272–7.
82. Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. Lancet Infect Dis **2001**; 1: 101–14.
83. Cohn SM, Lipsett PA, Buchman TG, et al. Comparison of intravenous/ oral ciprofloxacin plus metronidazole versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections. Ann Surg **2000**; 232:254–62.
84. Ohlin B, Cederberg A, Forssell H, Solhaug JH, Tveit E. Piperacillin/ tazobactam compared with cefuroxime/ metronidazole in the treatment of intra-abdominal infections. Eur J Surg **1999**; 165:875–84.
85. Polk HC Jr, Fink MP, Laverdiere M, et al. Prospective randomized study of piperacillin/tazobactam therapy of surgically treated intra-abdominal infection. The Piperacillin/Tazobactam Intra-Abdominal Infection Study Group. Am Surg **1993**; 59:598–605.
86. Sirinek KR, Levine BA. A randomized trial of ticarcillin and clavulanate versus gentamicin and clindamycin in patients with complicated appendicitis. Surg Gynecol Obstet **1991**; 172(Suppl):30–5.
87. Walker AP, Nichols RL, Wilson RF, et al. Efficacy of a β-lactamase inhibitor combination for serious intraabdominal infections. Ann Surg **1993**; 217:115–21.
88. Brook I, Frazier EH. Aerobic and anaerobic microbiology in intra-abdominal infections associated with diverticulitis. J Med Microbiol **2000**; 49:827–30.
89. Christou NV, Barie PS, Dellinger EP, Waymack JP, Stone HH. Surgical Infection Society intra-abdominal infection study: prospective evaluation of management techniques and outcome. Arch Surg **1993**; 128: 193–8; discussion:198–9.
90. Dellinger EP, Wertz MJ, Meakins JL, et al. Surgical infection stratification system for intra-abdominal infection: multicenter trial. Arch Surg **1985**; 120:21–9.
91. Nystrom PO, Bax R, Dellinger EP, et al. Proposed definitions for diagnosis, severity scoring, stratification, and outcome for trials on intraabdominal infection. Joint Working Party of SIS North America and Europe. World J Surg **1990**; 14:148–58.
92. Ohmann C. Prognostic scores and design of clinical studies. Infection **1998**; 26:342–4.
93. Ohmann C, Wittmann DH, Wacha H. Prospective evaluation of prognostic scoring systems in peritonitis. Peritonitis Study Group. Eur J Surg **1993**; 159:267–74.
94. Wacha H, Hau T, Dittmer R, Ohmann C. Risk factors associated with intraabdominal infections: a prospective multicenter study. Peritonitis Study Group. Langenbecks Arch Surg **1999**; 384:24–32.
95. Bailey JA, Virgo KS, DiPiro JT, Nathens AB, Sawyer RG, Mazuski JE. Aminoglycosides for intra-abdominal infection: equal to the challenge? Surg Infect (Larchmt) **2002**; 3:315–35.
96. Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A. Back to the future: using aminoglycosides again and how to dose them optimally. Clin Infect Dis **2007**; 45:753–60.
97. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA **2007**; 298: 1763–71.
98. Montravers P, Dupont H, Gauzit R, et al. *Candida* as a risk factor for mortality in peritonitis. Crit Care Med **2006**; 34:646–52.
99. Montravers P, Lepape A, Dubreuil L, et al. Clinical and microbiological profiles of community-acquired and nosocomial intra-abdominal infections: results of the French prospective, observational EBIIA study. J Antimicrob Chemother **2009**; 63:785–94.
100. Montravers P, Chalfine A, Gauzit R, et al. Clinical and therapeutic features of nonpostoperative nosocomial intra-abdominal infections. Ann Surg **2004**; 239:409–16.
101. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest **2000**; 118:146–55.
102. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest **1999**; 115:462–74.
103. Lodise TP Jr, Patel N, Kwa A, et al. Predictors of 30-day mortality among patients with *Pseudomonas aeruginosa* bloodstream infections: impact of delayed appropriate antibiotic selection. Antimicrob Agents Chemother **2007**; 51:3510–5.
104. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. Clin Infect Dis **2004**; 38:161–89.
105. Calandra T, Bille J, Schneider R, Mosimann F, Francioli P. Clinical significance of *Candida* isolated from peritoneum in surgical patients. Lancet **1989**; 2:1437–40.
106. Solomkin JS, Flohr AB, Quie PG, Simmons RL. The role of *Candida* in intraperitoneal infections. Surgery **1980**; 88:524–30.
107. Eggimann P, Francioli P, Bille J, et al. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high- risk surgical patients. Crit Care Med **1999**; 27:1066–72.
108. Mean M, Marchetti O, Calandra T. Bench-to-bedside review: *Candida* infections in the intensive care unit. Crit Care **2008**; 12:204.
109. Hof H. Developments in the epidemiolgy of invasive fungal infections—implications for the empiric and targeted antifungal therapy. Mycoses **2008**; 51(Suppl 1):1–6.
110. Pfaller MA, Boyken L, Hollis RJ, et al. In vitro susceptibility of invasive isolates of *Candida* spp. to anidulafungin, caspofungin, and micafungin: six years of global surveillance. J Clin Microbiol **2008**; 46:150–6.
111. Pfaller MA, Messer SA, Boyken L, et al. Use of fluconazole as a surrogate marker to predict susceptibility and resistance to voriconazole among 13,338 clinical isolates of *Candida* spp. tested by clinical and laboratory standards institute-recommended broth microdilution methods. J Clin Microbiol **2007**; 45:70–5.
112. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med **2002**; 347: 2020–9.
113. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med **2007**; 356:2472–82.
114. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis **2007**; 45:883–93.
115. Blot S, De Waele JJ. Critical issues in the clinical management of complicated intra-abdominal infections. Drugs **2005**; 65:1611–20.
116. Burnett RJ, Haverstock DC, Dellinger EP, et al. Definition of the role of enterococcus in intraabdominal infection: analysis of a prospective randomized trial. Surgery **1995**; 118:716–21.
117. Sitges-Serra A, Lopez MJ, Girvent M, Almirall S, Sancho JJ. Postoperative enterococcal infection after treatment of complicated intra-abdominal sepsis. Br J Surg **2002**; 89:361–7.
118. Mascini EM, Bonten MJ. Vancomycin-resistant enterococci: consequences for therapy and infection control. Clin Microbiol Infect **2005**; 11(Suppl 4):43–56.
119. Leavis HL, Willems RJ, Top J, et al. Epidemic and nonepidemic multidrug-resistant *Enterococcus faecium.* Emerg Infect Dis **2003**; 9:1108–15.
120. Bonten MJ, Willems R, Weinstein RA. Vancomycin-resistant enterococci: why are they here, and where do they come from? Lancet Infect Dis **2001**; 1:314–25.
121. Mazuski JE. Vancomycin-resistant enterococcus: risk factors, surveillance, infections, and treatment. Surg Infect (Larchmt) **2008**; 9:567–71.
122. Fierobe L, Decre D, Muller C, et al. Methicillin-resistant *Staphylococcus aureus* as a causative agent of postoperative intra-abdominal infection: relation to nasal colonization. Clin Infect Dis **1999**; 29:1231–8.
123. Patel M, Kumar RA, Stamm AM, Hoesley CJ, Moser SA, Waites KB. USA300 genotype community-associated methicillin-resistant *Staphylococcus aureus* as a cause of surgical site infections. J Clin Microbiol **2007**; 45:3431–3.
124. Hirota M, Takada T, Kawarada Y, et al. Diagnostic criteria and severity

assessment of acute cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg **2007**; 14:78–82.
125. Yoshida M, Takada T, Kawarada Y, et al. Antimicrobial therapy for acute cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg **2007**; 14: 83–90.
126. Takada T, Kawarada Y, Nimura Y, et al. Background: Tokyo Guidelines for the management of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Surg **2007**; 14:1–10.
127. Mayumi T, Takada T, Kawarada Y, et al. Results of the Tokyo Consensus Meeting Tokyo Guidelines. J Hepatobiliary Pancreat Surg **2007**; 14: 114–21.
128. Strasberg SM. Clinical practice. Acute calculous cholecystitis. N Engl J Med **2008**; 358:2804–11.
129. Ralls PW, Colletti PM, Lapin SA, et al. Real-time sonography in suspected acute cholecystitis: prospective evaluation of primary and secondary signs. Radiology **1985**; 155:767–71.
130. Goldin AB, Sawin RS, Garrison MM, Zerr DM, Christakis DA. Aminoglycoside-based triple-antibiotic therapy versus monotherapy for children with ruptured appendicitis. Pediatrics **2007**; 119:905–11.
131. St Peter SD, Little DC, Calkins CM, et al. A simple and more cost-effective antibiotic regimen for perforated appendicitis. J Pediatr Surg **2006**; 41:1020–4.
132. Rodriguez JC, Buckner D, Schoenike S, Gomez-Marin O, Oiticica C, Thompson WR. Comparison of two antibiotic regimens in the treatment of perforated appendicitis in pediatric patients. Int J Clin Pharmacol Ther **2000**; 38:492–9.
133. Nadler EP, Reblock KK, Ford HR, Gaines BA. Monotherapy versus multi-drug therapy for the treatment of perforated appendicitis in children. Surg Infect (Larchmt) **2003**; 4:327–33.
134. St Peter SD, Tsao K, Spilde TL, et al. Single daily dosing ceftriaxone and metronidazole vs standard triple antibiotic regimen for perforated appendicitis in children: a prospective randomized trial. J Pediatr Surg **2008**; 43:981–5.
135. Sanchez AR, Rogers RS III, Sheridan PJ. Tetracycline and other tetracycline-derivative staining of the teeth and oral cavity. Int J Dermatol **2004**; 43:709–15.
136. Schaad UB. Fluoroquinolone antibiotics in infants and children. Infect Dis Clin North Am **2005**; 19:617–28.
137. Rice HE, Brown RL, Gollin G, et al. Results of a pilot trial comparing prolonged intravenous antibiotics with sequential intravenous/oral antibiotics for children with perforated appendicitis. Arch Surg **2001**; 136: 1391–5.
138. Thompson AM, Bizzarro MJ. Necrotizing enterocolitis in newborns: pathogenesis, prevention and management. Drugs **2008**; 68:1227–38.
139. Nankervis CA, Giannone PJ, Reber KM. The neonatal intestinal vasculature: contributing factors to necrotizing enterocolitis. Semin Perinatol **2008**; 32:83–91.
140. Epelman M, Daneman A, Navarro OM, et al. Necrotizing enterocolitis: review of state-of-the-art imaging findings with pathologic correlation. Radiographics **2007**; 27:285–305.
141. Hunter CJ, Chokshi N, Ford HR. Evidence vs experience in the surgical management of necrotizing enterocolitis and focal intestinal perforation. J Perinatol **2008**; 28(Suppl 1):S14–7.
142. Henry MC, Moss RL. Neonatal necrotizing enterocolitis. Semin Pediatr Surg **2008**; 17:98–109.
143. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol **2004**; 2:289–300.
144. Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis **2007**; 44:357–63.
145. Edmiston CE, Krepel C, Kelly H, et al. Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? Surgery **2004**; 136:738–47.
146. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy **2007**; 27:1081–91.
147. Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet **2005**; 44: 1009–34.
148. Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. Clin Pharmacokinet **2006**; 45:755–73.
149. Lamp KC, Freeman CD, Klutman NE, Lacy MK. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. Clin Pharmacokinet **1999**; 36:353–73.
150. Sprandel KA, Drusano GL, Hecht DW, Rotschafer JC, Danziger LH, Rodvold KA. Population pharmacokinetic modeling and Monte Carlo simulation of varying doses of intravenous metronidazole. Diagn Microbiol Infect Dis **2006**; 55:303–9.
151. Lau AH, Emmons K, Seligsohn R. Pharmacokinetics of intravenous metronidazole at different dosages in healthy subjects. Int J Clin Pharmacol Ther Toxicol **1991**; 29:386–90.
152. Ljungberg B, Nilsson-Ehle I, Ursing B. Metronidazole: pharmacokinetic observations in severely ill patients. J Antimicrob Chemother **1984**; 14: 275–83.
153. Berne TV, Yellin AW, Appleman MD, Heseltine PN. Antibiotic management of surgically treated gangrenous or perforated appendicitis: comparison of gentamicin and clindamycin versus cefamandole versus cefoperazone. Am J Surg **1982**; 144:8–13.
154. Solomkin JS, Dellinger EP, Christou NV, Busuttil RW. Results of a multicenter trial comparing imipenem/cilastatin to tobramycin/clindamycin for intra-abdominal infections. Ann Surg **1990**; 212:581–91.
155. Falagas ME, Barefoot L, Griffith J, Ruthazar R, Snydman DR. Risk factors leading to clinical failure in the treatment of intra- abdominal or skin/soft tissue infections. Eur J Clin Microbiol Infect Dis **1996**; 15:913–21.
156. Krobot K, Yin D, Zhang Q, et al. Effect of inappropriate initial empiric antibiotic therapy on outcome of patients with community-acquired intra-abdominal infections requiring surgery. Eur J Clin Microbiol Infect Dis **2004**; 23:682–7.
157. Sturkenboom MC, Goettsch WG, Picelli G, et al. Inappropriate initial treatment of secondary intra-abdominal infections leads to increased risk of clinical failure and costs. Br J Clin Pharmacol **2005**; 60:438–43.
158. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* infection. Clin Infect Dis **2008**; 46(Suppl 1):S12–8.
159. Wilton P, Smith R, Coast J, Millar M. Strategies to contain the emergence of antimicrobial resistance: a systematic review of effectiveness and cost-effectiveness. J Health Serv Res Policy **2002**; 7:111–7.
160. Mazuski JE, Sawyer RG, Nathens AB, et al. The Surgical Infection Society guidelines on antimicrobial therapy for intra-abdominal infections: evidence for the recommendations. 3rd ed. Surgical Infection Society, **2002**: 175–234.
161. Hedrick TL, Evans HL, Smith RL, et al. Can we define the ideal duration of antibiotic therapy? Surg Infect (Larchmt) **2006**; 7:419–32.
162. Lennard ES, Dellinger EP, Wertz MJ, Minshew BH. Implications of leukocytosis and fever at conclusion of antibiotic therapy for intra-abdominal sepsis. Ann Surg **1982**; 195:19–24.
163. de Vries AC, Besselink MG, Buskens E, et al. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodological quality and outcome. Pancreatology **2007**; 7: 531–8.
164. Solomkin JS, Dellinger EP, Bohnen JM, Rostein OD. The role of oral antimicrobials for the management of intra-abdominal infections. New Horiz **1998**; 6(Suppl 2):S46–52.
165. Solomkin JS, Reinhart HH, Dellinger EP, et al. Results of a randomized trial comparing sequential intravenous/oral treatment with ciprofloxacin plus metronidazole to imipenem/cilastatin for intra-abdominal infections. The Intra-Abdominal Infection Study Group. Ann Surg **1996**; 223:303–15.
166. Smink DS, Finkelstein JA, Garcia Pena BM, Shannon MW, Taylor GA, Fishman SJ. Diagnosis of acute appendicitis in children using a clinical practice guideline. J Pediatr Surg **2004**; 39:458–63.
167. Schneider C, Kharbanda A, Bachur R. Evaluating appendicitis scoring

systems using a prospective pediatric cohort. Ann Emerg Med **2007**; 49:778–84.
168. Emil S, Taylor M, Ndiforchu F, Nguyen N. What are the true advantages of a pediatric appendicitis clinical pathway? Am Surg **2006**; 72:885–9.
169. Paulson EK, Kalady MF, Pappas TN. Clinical practice: suspected appendicitis. N Engl J Med **2003**; 348:236–42.
170. Yu J, Fulcher AS, Turner MA, Halvorsen RA. Helical CT evaluation of acute right lower quadrant pain: part II, uncommon mimics of appendicitis. AJR Am J Roentgenol **2005**; 184:1143–9.
171. Yu J, Fulcher AS, Turner MA, Halvorsen RA. Helical CT evaluation of acute right lower quadrant pain: part I, common mimics of appendicitis. AJR Am J Roentgenol **2005**; 184:1136–42.
172. National Center for Health Statistics. Ambulatory and Inpatient Procedures in the United States, 1996. National Center for Health Statistics, **2004**.
173. Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. World J Surg **2006**; 30:1033–7.
174. Taylor M, Emil S, Nguyen N, Ndiforchu F. Emergent vs urgent appendectomy in children: a study of outcomes. J Pediatr Surg **2005**; 40: 1912–5.
175. Ditillo MF, Dziura JD, Rabinovic R. Is it safe to delay appendectomy in adults with acute appendicitis? Ann Surg **2006**; 244:656–60.
176. Bagi P, Dueholm S. Nonoperative management of the ultrasonically evaluated appendiceal mass. Surgery **1987**; 101:602–5.
177. Hoffmann J, Lindhard A, Jensen HE. Appendix mass: conservative management without interval appendectomy. Am J Surg **1984**; 148:379–82.
178. Jeffrey RB Jr, Federle MP, Tolentino CS. Periappendiceal inflammatory masses: CT-directed management and clinical outcome in 70 patients. Radiology **1988**; 167:13–6.
179. Lewin J, Fenyo G, Engstrom L. Treatment of appendiceal abscess. Acta Chir Scand **1988**; 154:123–5.
180. Samuel M, Hosie G, Holmes K. Prospective evaluation of nonsurgical versus surgical management of appendiceal mass. J Pediatr Surg **2002**;37: 882–6.
181. Hogan MJ. Appendiceal abscess drainage. Tech Vasc Interv Radiol **2003**; 6:205–14.
182. Andersson RE, Petzold MG. Nonsurgical treatment of appendiceal abscess or phlegmon: a systematic review and meta-analysis. Ann Surg **2007**; 246:741–8.
183. Corfield L. Interval appendicectomy after appendiceal mass or abscess in adults: what is "best practice"? Surg Today **2007**; 37:1–4.
184. Kaminski A, Liu IL, Applebaum H, Lee SL, Haigh PI. Routine interval appendectomy is not justified after initial nonoperative treatment of acute appendicitis. Arch Surg **2005**; 140:897–901.
185. Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. Cochrane Database Syst Rev **2005**; 3:CD001439.
186. Taketomo CK, Hodding JH, Kraus DM, eds. Pediatric dosage handbook. 14th ed. Hudson, OH: Lexi-Comp, **2007**.
187. Bradley JS, Sauberan J. Antimicrobial agents: principles and practice of pediatric infectious diseases. 3rd ed. Philadelphia: Churchill Livingstone, **2008**.
188. Sauberan J. Systemic anti-infectives. Nelson's pocket book of pediatric antimicrobial therapy. 16th ed. Buenos Aires: ACINES, **2006**.
189. Solomkin JS, Wilson SE, Christou NV, et al. Results of a clinical trial of clinafloxacin versus imipenem/cilastatin for intraabdominal infections. Ann Surg **2001**; 233:79–87.