The antibiotic puzzle: Guidelines for the family physician

G Harding, S Field, R MacMahon, T Louie and the Prairie Consensus Conference Group. The antibiotic puzzle: Guidelines for the family physician. Can J Infect Dis 1997;8(Suppl C):2C-16C. Choosing the most appropriate antibiotic for the treatment of common infections is becoming increasingly complex. New drugs and new classes of antibiotics are being developed and made available, and emerging resistance and pharmacoeconomics play important roles. The Canadian healthcare system presents a unique challenge for prescribing physicians because pharmacoeconomic considerations are becoming increasingly important. It is important that Canadian guidelines be developed to address the needs of Canadian physicians. A consensus conference was held in October 1996 to discuss appropriate guidelines for antibiotic recommendations for common adult respiratory, urinary tract and diabetic foot infections. In August 1997, the guidelines were reviewed and updated as part of a second meeting of the group on antimicrobial resistance. The final recommendations constitute the information in this document. The panel of physicians and pharmaceutical doctors from the Prairie provinces of Alberta, Saskatchewan and Manitoba included family physicians and specialists in internal medicine, respirology, urology, infectious diseases, medical microbiology and pharmacoeconomics.

Key Words: *Antibiotic guidelines, Diabetic foot infections, Family physician, Infection guidelines, Prostatitis, Respiratory tract infections, Urinary tract infections*

Le casse-tête de l'antibiothérapie Directives à l'intention du médecin de famille

RÉSUMÉ : Le choix de l'antibiotique le plus approprié pour le traitement des affections courantes devient de plus en plus complexe. De nouveaux médicaments et de nouvelles classes d'antibiotiques font constamment leur apparition sur le marché, sans compter que l'émergence des souches résistantes et que la pharmacoéconomie jouent aussi un rôle prépondérant. Le système canadien de soins de santé pose un défi unique aux médecins de premier recours à cause de l'importance croissante accordée aux principes de pharmacoéconomie. Il est important de mettre au point des directives qui puissent répondre spécifiquement aux besoins des médecins canadiens. Une conférence consensuelle a eu lieu en octobre 1996; on y a discuté des directives relatives à l'antibiothérapie appliquée aux infections respiratoires et urinaires courantes de l'adulte, ainsi qu'aux infections du pied chez le diabétique. En août 1997, les directives ont été passées en revue et mises à jour dans le cadre d'une seconde rencontre du groupe formé pour traiter de la résistance aux antimicrobiens. Les recommandations finales forment l'essentiel du présent document. Un comité de médecins et de pharmacologues des provinces de l'Ouest (Alberta, Saskatchewan et Manitoba) été formé et regroupait des médecins de familles, des internistes, des pneumologues, des urologues, des infectiologues, des microbiologistes et des spécialistes de la pharmacoéconomie.

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Choosing the most appropriate antibiotic for the treatment of common infections is becoming increasingly complex. New drugs and new classes of antibiotics are being developed and made available, emerging resistance is still a factor and pharmacoeconomics plays a very important role. In addition, at times, standard first-line treatment may not be appropriate, especially when the risk and consequences of treatment failure are particularly high.

The plan: With changing resistance profiles, regional microbiological prevalence differences and the availability of new anti-infective agents, therapeutic guidelines must be reviewed regularly and updated. It is important that Canadian guidelines be developed to address the needs of Canadian physicians. The need for practical guidelines for family physicians was identified.

The Canadian healthcare system presents a unique challenge for prescribing physicians because pharmacoeconomic considerations are becoming increasingly important. It is no longer acceptable to look at the cost of a drug alone. Cost analysis should consider indirect costs such as those associated with adverse effects, time lost from work and treatment failure, and intangible costs such as the cost of a life saved. In some instances the higher cost of second-line antibiotics can be justified if treatment is expected to reduce the risk of deterioration, which may result in hospitalization. Thus, where appropriate, pharmacoeconomics should be considered when making therapeutic recommendations.

The panel: In October 1996, Dr Godfrey Harding brought together a panel of physicians and pharmaceutical doctors from the Prairie provinces of Alberta, Saskatchewan and Manitoba for a consensus conference to discuss appropriate guidelines for antibiotic recommendations for common adult respiratory, urinary tract and diabetic foot infections. The panel included family physicians and specialists in internal medicine, respirology, urology, infectious diseases, medical microbiology and pharmacoeconomics. The panel's mandate was to develop practical, current antibiotic treatment guidelines that would be useful to a family physician in everyday practice.

Team leaders (chairs) were identified before the workshop and included Drs Stephen Field, Ross MacMahon and Thomas Louie. After reviewing the pertinent literature, they developed working documents with references, which were handed out before the plenary sessions. The working documents with proposed recommendations were presented at a plenary session before the entire group for discussion. In addition, Dr George Zhanel gave a talk on pharmacoeconomic issues pertinent to these topic areas. The next day, the team leaders chaired small group breakout sessions on their respective topic areas, and the recommendations were revised. These recommendations were presented to the entire group and agreed upon at a second plenary session. In August 1997, the proposed guidelines were reviewed and updated as part of a second meeting of the group on antimicrobial resistance. The final recommendations, which constitute the information in this document, were agreed upon at the final plenary session

TABLE 1
First-line antibiotic treatment for acute sinusitis

Grade D recommendations	
Antibiotic	**Dose**
Co-trimoxazole	160/800 mg bid for seven to 10 days
Doxycycline	200 mg first day, then 100 mg once daily for seven to 10 days
Amoxicillin	250 to 500 mg tid for seven to 10 days

If a course of first-line treatment fails, a second course with a different first-line antibiotic should be tried. Second-line antibiotics are indicated when first-line antibiotics have failed or there is a history of recent first-line failure

TABLE 2
Second-line antibiotic treatment for acute sinusitis

Grade D recommendations	
Antibiotic	**Dose**
Amoxicillin/ clavulanate	250/125 to 500/125 mg tid for 10 to 14 days
Clarithromycin	500 mg bid for 10 to 14 days
Azithromycin	500 mg first day, then 250 mg for four days
Ciprofloxacin	500 mg bid for 10 to 14 days
Ofloxacin	400 mg bid for 10 to 14 days
Cefaclor	250 to 500 mg tid for 10 to 14 days
Cefuroxime axetil	250 to 500 mg bid for 10 to 14 days
Cefixime	400 mg once daily for 10 to 14 days

If second-line treatment fails, refer patient to specialist. Other reasons to consider referral are recurrent disease (greater than three episodes per year) and the development of complications such as mucoceles or orbital extension

TABLE 3
Group 1 – Acute bronchitis: Previously healthy patients with no other respiratory problems or comorbidity

Grade D recommendations Considerations	Antibiotic	Dose and duration
	No treatment or erythromycin*	1 g/day in divided doses for 10 to 14 days
If macrolide allergy	Doxycycline	200 mg first day, then 100 mg once daily for nine days
If gastrointestinal intolerance to erythromycin or if smoker with possible *Hemophilus influenzae*	Azithromycin or clarithromycin	500 mg first day, then 250 mg once daily for four days 250 to 500 mg bid for 10 days

**If purulent sputum and/or fever is present, the physician may consider prescribing an antibiotic. Amoxicillin, second generation cephalosporins or amoxicillin/clavulanate were not recommended because they fail to provide coverage for* Mycoplasma pneumoniae *and* Chlamydia pneumoniae.

TABLE 4
Group 2 – Exacerbations of simple chronic bronchitis: Patients less than 65 years of age, forced expiratory volume in 1 s less than 50% predicted, less than four exacerbations per year and no comorbidity

Grade A recommendations Considerations	Antibiotic	Dose and duration
Type 3	No antibiotic required	–
Type 1 or Type 2	Co-trimoxazole or	160/800 mg bid for 10 days
	doxycycline or	200 mg first day, then 100 mg once daily for nine days
	amoxicillin	250 to 500 mg tid for 10 days

chaired by Dr Harding after the breakout sessions. The antibiotic recommendations are for average-sized adults with normal renal function.

USE OF ANTIBIOTICS IN RESPIRATORY TRACT INFECTIONS

The etiological organisms involved in a respiratory tract infection are usually unknown when therapy is initiated, and an antibiotic must be chosen without the benefit of microbiological diagnosis. It may be difficult to confirm a diagnosis because of previous antibiotic therapy, normal flora or the presence of other contaminating potential pathogens in culture specimens. Antibiotic selection is based on the spectrum of pathogens usually seen in a particular setting.

Acute sinusitis: Seventy per cent of bacterial isolates found in adults and children with acute sinusitis are *Streptococcus pneumoniae* and *Hemophilus influenzae* (1). Nasal swab results do not correlate well with antral cultures, and such swabs are not recommended for culture.

Decongestants and analgesics are helpful in acute sinusitis, but nasal decongestants should not be given for more than five days to prevent rebound vasodilation. Antihistamines should be avoided because their anticholinergic effect can interfere with normal mucociliary clearance (1).

Although 40% of cases of acute sinusitis resolve spontaneously, a therapeutic advantage to antibiotic therapy was demonstrated in some but not all studies (1-4). Tables 1 and 2 reflect the consensus agreement by the panel, with the caveat that local resistance profiles be considered when choosing therapy. Recent microbiological sensitivity surveys have shown a rising prevalence of penicillin-resistant *S pneumoniae* and beta-lactamase-producing *H influenzae*, which may be as high as 40% (5). In view of the steady rise of antibiotic resistance, amoxicillin may not remain a first-line antibiotic choice in the future.

Chronic sinusitis: Chronic sinusitis is usually the result of ostial obstruction due to allergy, deviated septum or nasal polyps. Topical steroids and antihistamines may

TABLE 5
Group 3 and 4 – Exacerbations of complicated chronic bronchitis: Patients with four or more exacerbations per year, forced expiratory volume in 1 s less than 50% predicted, older than 65 years of age or comorbidity

Grade D recommendations

Considerations	Antibiotic	Dose and duration
The use of second-line antibiotics may be justified to minimize treatment failure	Azithromycin or	500 mg first day, 250 mg once daily for four days
	clarithromycin or	500 mg bid for 10 to 14 days
	ciprofloxacin or	500 mg bid for 10 to 14 days
	ofloxacin or	400 mg bid for 10 to 14 days
	cefaclor or	500 mg tid for 10 to 14 days
	cefuroxime axetil or	500 mg bid for 10 to 14 days
	cefixime	400 mg once daily for 10 to 14 days

Treatment failure suggests inflammation rather than bacterial infection. Consider sputum Gram stain and culture, and referral to a specialist

be beneficial. If infection is present, a prolonged course of antibiotics for two to four weeks may be required.

Opportunistic organisms that can grow in obstructed sinuses include the anaerobes *H influenzae* and *S aureus*. Amoxicillin/clavulanate is effective against most anaerobes. *Pseudomonas aeruginosa* may be found if polyps are present and may be treated with ciprofloxacin.

Referral to a specialist is recommended for most patients. Surgery may be necessary if medical therapy is unsuccessful.

Recommendation for treatment of chronic sinusitis
- Topical steroids and antihistamines
- Prolonged antibiotic therapy for bacterial infection
- Referral if medical treatment is unsuccessful

Acute exacerbations of chronic bronchitis: Measures to prevent acute exacerbation of chronic bronchitis include smoking cessation, vaccination against influenza and, in selected cases, vaccination against *S pneumoniae*. Exacerbations can be precipitated by a variety of triggers, both infectious and noninfectious. Patients should be advised to avoid irritants such as cigarette smoke during an exacerbation. Exacerbations should be treated with bronchodilators, corticosteroids, supplemental oxygen if the patient is hypoxemic and antibiotics.

Recommendations for treatment of acute exacerbations of chronic bronchitis
- Bronchodilators
- Corticosteroids
- Supplemental oxygen
- Antibiotics

Canadian guidelines for the management of chronic bronchitis were published in 1994 (6). These recommendations stratified patients into five groups on the basis of severity of disease, partly defined by the forced expiratory volume in 1 s, number of exacerbations per year and presence of comorbidity. The panel adopted the guidelines mentioned above and agreed with the antibiotic choices detailed there, which were based on the likelihood of bacterial infection in a particular setting, risk of treatment failure and pharmacoeconomic considerations (Tables 3-5). In addition, the panel felt that the stratification system for exacerbations developed by Anthonisen et al (7) was helpful. Type 1 exacerbations are characterized by increased dyspnea, increased sputum volume and purulence. Type 2 exacerbations are characterized by two of the above three symptoms. Type 3 exacerbations are characterized by one of the three symptoms and one other finding of fever, sore throat, nasal discharge, wheeze or cough. The efficacy of antibiotic therapy for Type 1 exacerbations of chronic bronchitis is well documented (7).

In general, treatment failure suggests inflammation rather than infection, and the panel recommended sputum Gram stain and culture, and referral to a specialist for such cases.

Group 5 – Bronchiectasis: Bronchiectasis is characterized by recurrent infections and ongoing sputum purulence. The panel recommended that patients in this group be referred for investigation and treatment. Patients should receive antibiotics tailored to the specific pathogens and the susceptibility of the pathogens found in the patient's sputum culture.

Community-acquired pneumonia: Most patients with community-acquired pneumonia (CAP) can be managed as out-patients; however, CAP severe enough to warrant hospitalization has a mortality rate that may exceed 20% (8). Mortality is dependent on the extent of lung involvement, age, comorbidity and the need for mechanical ventilation. In nursing homes, the mortality rate may be as high as 40% (9).

For the majority of patients (Table 6), diagnostic information on the etiological agent is not available until several days after presentation. In most cases, sputum cultures are inconclusive, and it may be impossible to distinguish colonizing organisms from invasive organisms. Chest radiograph is often unhelpful in distinguishing among the common etiological causes of CAP (10). Although microbiological evidence is preferred, the selection of an antibiotic is often made on the basis of epidemiological data, and clinical presentation and findings.

The Canadian Conference Group on Community-Acquired Pneumonia stratified CAP patients into four groups based on severity of illness, setting in which pneumonia developed, age, comorbidity and need for hospitalization (8). The recommendations presented here (Table 7) are based on their guidelines; local modification may be necessary to account for varying organism prevalence or antibiotic resistance profiles. These recommendations assume that documented evidence of pneumonia will be available during the course of treatment.

The panel also felt that nursing home patients should be considered separately because diagnosis and treatment are often unique in the nursing home setting. Patients with human immunodeficiency virus (HIV) and other forms of immunodeficiency were not included because these patients require consideration of a large number of opportunistic infections.

Hospital-acquired pneumonia: Nosocomial pneumonia is the second most common hospital-acquired infection and the one that is most commonly fatal. The overall mortality rate in Canada is estimated to be 32% (10). The incidence varies greatly depending on the type of medical service – Canadian tertiary care hospitals report incidence rates between 2.5 per 1000 admissions to the gynecology service and 67 per 1000 in the intensive care unit (8). Family physicians are rarely called upon to treat hospital-acquired pneumonia, and this condition was not addressed by the panel.

TABLE 6
Suggested diagnostic tests for community-acquired pneumonia

Test	Rationale
Chest x-ray	Confirm suspected pneumonia Rule out effusion or abscess Determine extent of involvement
Blood work including blood cultures, oximetry or arterial blood gases	Only warranted if the patient is to be admitted
Thoracentesis	Rule out empyema if effusion is greater than 10 mm on lateral decubitus view or patient is toxic

THE USE OF ANTIBIOTICS IN URINARY TRACT INFECTIONS AND PROSTATITIS

Thirty-five per cent of women aged 20 to 40 years will have at least one urinary tract infection (UTI) in their lifetime. In the general population, there are 25 times more UTIs in females than in males, although in institutional settings, the ratio is equivalent.

Over the past decade, the management of acute and recurrent cystitis and uncomplicated pyelonephritis has advanced, and there is now a general consensus on treatment (12). Conversely, there have been few advances in the management of complicated UTIs or chronic prostatitis, and antibiotic regimens for these conditions remain empirical (13).

Acute uncomplicated UTI: Because the infecting organisms and their antimicrobial susceptibility profiles are predictable in young, healthy, nonpregnant females with typical symptoms of acute uncomplicated cystitis, pretreatment urine cultures are not recommended in this population. The diagnosis can be presumed if pyuria is present on microscopy or leukocyte esterase testing. A short course of empirical antimicrobial therapy can be prescribed. No follow-up visit or culture after therapy is necessary unless symptoms persist or recur. If pyuria is

TABLE 7
Antibiotic treatment of community-acquired pneumonia

Patient characteristics	Organisms	Antibiotic recommendations
Grade D recommendations		
Group 1		
Healthy out-patients Less than 65 years of age No comorbidity	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* Respiratory viruses *Chlamydia pneumoniae* *Haemophilus influenzae* *Legionella* species *Staphylococcus aureus* *Mycobacterium tuberculosis* Endemic fungi (depending on geographic location)	Erythromycin 1 g/day in divided doses for 10 days If macrolide allergy, use doxycycline 200 mg first day, then 100 mg once daily for nine days If gastrointestinal intolerance or a smoker, azithromycin 500 mg first day, then 250 mg for four days or clarithromycin 250 to 500 mg bid for 10 days
Group 2 non-nursing home patients		
More than 65 years of age With comorbidity Do not require hospitalization	*S pneumoniae* Respiratory viruses *H influenzae* Aerobic Gram-negative bacilli *S aureus* *C pneumoniae* *Legionella* species *M tuberculosis* Endemic fungi	Amoxicillin/clavulanate 500/125 mg tid for 10 days or cefaclor 500 mg tid for 10 days or cefuroxime axetil 500 mg bid for 10 days If allergic to penicillin, use co-trimoxazole 160/800 mg bid for 10 days If *C pneumoniae* or *Legionella* species are a concern add erythromycin 2 g/day in divided doses for 10 days or clarithromycin 500 mg bid for 10 days or azithromycin 500 mg on day 1, then 250 mg daily for four days
Group 2 nursing home patients		
Oral therapy required Evidence of respiratory distress Evidence of consolidation	*S pneumoniae* *H Influenzae* Anaerobes Gram-negative bacilli *S aureus* *C pneumoniae* *Legionella* species	Amoxicillin/clavulanate 500/125 mg tid or cefuroxime axetil 500 mg bid or cefaclor 500 mg tid or co-trimoxazole 160/800 mg bid If *C pneumoniae* or *Legionella* species are a concern, add erythromycin 1 g/day in divided doses In the severely ill, use amoxicillin 500 mg tid with ciprofloxacin 500 to 750 mg bid for 10 days or cefuroxime axetil 500 mg bid for 10 days with erythromycin 1 g/day in divided doses If allergic to penicillin, use clindamycin 300 to 450 mg tid with ciprofloxacin 500 to 750 mg bid for 10 days If *C pneumoniae* or *Legionella* species are a concern, add erythromycin 2 g/day in divided doses
Group 3		
Require hospitalization Parenteral therapy Consider switching to oral therapy 48 to 72 h after defervescence	*S pneumoniae* *H influenzae* Polymicrobial (including anaerobes) aerobic Gram-negative bacilli *S aureus* *M pneumoniae* *C pneumoniae* Respiratory viruses *Legionella* species	Cefuroxime 750 mg intravenously every 8 h or ceftriaxone 1 g intravenous or intramuscular every 24 h or cefotaxime 1 g intravenous every 8 h If allergic to cephalosporin, use co-trimoxazole 160 to 240/800 to 1200 mg intravenous every 6 to 8 h with or without erythromycin If *C pneumoniae* or *Legionella* species are a concern, add erythromycin 2 to 4 g/day in divided doses for 14 days

Continued on next page

TABLE 7 continued
Antibiotic treatment of community-acquired pneumonia

Grade D recommendations Patient characteristics	Organisms	Antibiotic recommendations
Group 4		
Severely ill patients Require intensive care unit therapy High risk of mortality	*S pneumoniae* *Legionella* species Aerobic Gram-negative bacilli *M pneumoniae* Respiratory viruses *H influenzae* *C pneumoniae*	Intravenous or intramuscular ceftriaxone 1 g every 24 h or cefotaxime 1 g intravenous every 8 h* If *Pseudomonas aeruginosa* or antibiotic-resistant Gram-negatives are a concern, use intravenous piperacillin/tazobactam 3/0.375 g every 6 h or intravenous imipenem/cilastatin 500/100 g every 6 h of each or intravenous meropenem 1 g every 8 h or intravenous ciprofloxacin 400 mg every 12 h Add erythromycin 2 to 4 g/day in divided doses to cover *Legionella* species, *M pneumoniae* or *C pneumoniae* When *Pseudomonas* species are suspected, combination therapy is required, eg, ceftazidime, piperacillin, piperacillin/tazobactam, imipenem/cilastatin, meropenem or ciprofloxacin in combination with an aminoglycoside

**With the exception of ceftriaxone, the antibiotics may have to be adjusted for impaired renal function. Comorbidity: Chronic obstructive lung disease, diabetes mellitus, renal insufficiency, congestive heart failure, hospitalization within previous year, postsplenectomy state, chronic alcoholism, malnutrition, altered mental status or suspected aspiration*

TABLE 8
Antibiotic recommendations for acute cystitis in women

Grade A recommendations Considerations	Antibiotic	Dose
Uncomplicated presentation	Co-trimoxazole	160/800 mg bid for three days
Postmenopausal	Co-trimoxazole	160/800 mg bid for seven days
Allergy to sulfa	Trimethoprim or nitrofurantoin	100 mg bid for three days 50 to 100 mg qid for three days
Intolerant to first-line antibiotic	Amoxicillin/clavulanate or ciprofloxacin or ofloxacin or norfloxacin	250/125 mg tid for three days 100 to 250 mg bid for three days 200 mg bid for three days 400 mg bid for three days

It should be noted that resistance rates to co-trimoxazole continue to rise and currently are in the order of 15% to 20% in the Canadian prairie provinces

absent, or there are atypical clinical features or factors that suggest a complicated infection, a culture should be performed before therapy is started. In males, a culture is generally recommended.

The efficacy of a three-day course of antibiotic is well documented (Table 8) (14-18). However, patients should be advised that some symptoms will not resolve immediately and may continue for more than three days.

Acute cystitis is very uncommon in young men. Sexual activity is a risk factor, whether the patient is heterosexual (19) or homosexual (20). Because of the relative rarity of the condition there are no controlled

TABLE 9
Antibiotic treatment of recurrent cystitis

Type of Recurrence	Antibiotic options	Dose and duration
Grade A recommendations		
Frequent reinfections (three or more infections per year)	Continuous prophylaxis at bedtime	Co-trimoxazole 40/200 mg once daily at bed time or every other night for six months If allergy to sulfa, nitrofurantoin 50 to 100 mg once daily at bedtime or trimethoprim 100 mg once daily at bedtime If intolerant or resistant, norfloxacin 200 mg once daily at bedtime
	Postcoital prophylaxis	Co-trimoxazole 40 to 80/200 to 400 mg single dose If allergy to sulfa, nitrofurantoin 50 to 100 mg single dose or cephalexin 250 mg single dose or ciprofloxacin 250 mg single dose
	Intermittent self-therapy	Co-trimoxazole 320/1600 mg as a single dose or co-trimoxazole 160/800 mg bid for three days or any of the aforementioned antibiotics for three days (grade D recommendations)
Grade D recommendations		
Early Recurrence/relapse (recurrence within four weeks of first infection) Urine culture required	Second course of first-line antibiotic or	Co-trimoxazole 160/800 mg bid for seven days or trimethoprim 100 mg bid for seven days or nitrofurantoin 50 to 100 mg qid for seven days
	second-line antibiotic	Amoxicillin/clavulanate 250 to 500/125 mg tid for seven days or ciprofloxacin 250 mg bid for seven days or ofloxacin 200 mg bid for seven days or norfloxacin 400 mg bid for seven days

treatment studies. A seven-day course of co-trimoxazole will cure most patients, and prolonged antibiotic therapy (four to six weeks of co-trimoxazole or a quinolone) is reserved for patients who develop recurrence (21).

Recurrent cystitis: Patients whose cystitis recurs after a three-day course of treatment for acute cystitis were stratified by the panel into two groups: those who relapse (early recurrence with the same organism within four weeks) and those who have reinfections. Patients who relapse should have culture and susceptibility testing performed and require a second seven-day course of treatment (Table 9). For patients with frequent reinfections (more than three in the preceding year), there are several options available – continuous low-dose prophylaxis (21-24), postcoital prophylaxis (25-27) and intermittent self-therapy (28). Patient involvement is important in selecting the most appropriate strategy.

Acute uncomplicated pyelonephritis: Symptoms of acute pyelonephritis are fever, flank pain and, in some cases, lower urinary tract symptoms. A midstream urine culture is recommended. In patients who are severely ill, are hemodynamically unstable, or have signs of septicemia or septic shock, hospital admission and parenteral therapy (Table 10) are indicated (29). If the patient fails to improve in 48 to 72 h, the likelihood of a complicated infection or a resistant pathogen must be considered. Investigation with a renal sonogram or computerized tomography should be considered in patients who are hemodynamically unstable or fail to improve. All patients should have a follow-up urine culture five to nine days after completion of therapy because there is a relapse rate of approximately 30%. Stable patients without nausea and vomiting can be managed safely with oral antibiotics on an out-patient basis (30).

Acute pyelonephritis in pregnancy usually requires admission to hospital, and treatment with parenteral ampicillin and gentamicin (12). Quinolones are contraindicated in pregnancy.

Table 10
Antibiotic treatment of uncomplicated pyelonephritis:

Grade A recommendations

Patient characteristics	Antibiotic	Dosage and duration
Mild acute pyelonephritis: No nausea or vomiting Can tolerate oral therapy	Co-trimoxazole or	160/800 mg bid for 14 days
	ciprofloxacin or	500 mg bid for 14 days
	norfloxacin or	400 mg bid for 14 days
	ofloxacin or	200 mg bid for 14 days
	amoxicillin/clavulanate	250/125 to 500/125 mg tid for 14 days
Severe systemic illness: Nausea and vomiting Possible urosepsis Overnight admission to hospital or observation unit necessary	Gentamicin intravenous	1.5 mg/kg/day intravenous 8 h or once daily (5 to 7 mg/kg/day)
	with or without ampicillin intravenous	1 to 2 g intravenous every 4 to 6 h
When clinically improved, switch to oral therapy based on urine culture results	Co-trimoxazole or	160/800 mg bid for 14 days
	ciprofloxacin or	500 mg bid for 14 days
	norfloxacin or	400 mg bid for 14 days
	ofloxacin	200 mg bid for 14 days

TABLE 11
Antibiotics to be used in acute pyelonephritis in pregnancy

Antibiotic
First-line
Intravenous gentamicin 1.5 mg/kg every 8 h or once daily (5 to 7 mg/kg/day) with intravenous ampicillin 1 to 2 g every 4 to 6 h
Second-line
Intravenous cefotaxime 1 g every 8 h
Ceftriaxone 1 g every 24 h

This regimen is to be followed by one with an oral antibiotic appropriate for use during pregnancy to complete a two-week course

The recommendations defined below were derived from a substantial amount of clinical work in this area (31-33). Local resistance patterns must also be considered when choosing antibiotic therapy.

Asymptomatic bacteriuria: Bacteriuria is common in the elderly, and the majority of patients are asymptomatic (34). Treatment is associated with a high incidence of recurrence and may lead to development of antibiotic-resistant organisms (35). Untreated patients do not appear to have a higher morbidity or mortality rate. For this reason, asymptomatic infections are not routinely treated, although infections should be eradicated before genitourinary surgery or insertion of a prosthesis. In younger patients, the significance and management of asymptomatic bacteriuria is less clear. It should be eradicated in pregnant females, but repeated treatment of asymptomatic bacteriuria in healthy young females is not warranted (36).

Asymptomatic bacteriuria
No treatment except before instrumentation of the urinary tract or prosthetic surgery and during pregnancy.

UTI in pregnancy: Patients with UTIs during pregnancy should be treated whether symptomatic or not (Table 11) (37). Approximately 30% of females with untreated asymptomatic bacteriuria in pregnancy develop acute

symptomatic infection later in pregnancy, which may be associated with premature delivery (38). The choice of antibiotics in pregnancy is limited, and quinolones are contraindicated (Table 12) (12,39,40). Management of acute pyelonephritis in pregnancy usually requires admission to hospital and treatment with parenteral therapy, although out-patient therapy is safe and effective in selected patients.

Catheter-associated UTI: Treatment of asymptomatic bacteriuria in patients with indwelling catheters has minimal benefit (41). Infection should be treated before urological surgery or insertion of a prosthesis (42). Within two weeks of catheter removal, 25% of untreated patients become symptomatic with either upper or lower UTI (43).

Although diagnosis of infection is often difficult, approximately 50% of febrile episodes in patients with in-

TABLE 12
Antibiotics that may be used in pregnancy

Antibiotic	Concerns
Cephalexin 250 mg qid for three to seven days	
Nitrofurantoin 50 to 100 mg qid for three to seven days	Risk of hemolytic anemia in G6PD deficient patients
Co-trimoxazole 160/800 mg bid for three to seven days	Risk of kernicterus if used near term Possible teratogenesis
Amoxicillin 250 to 500 mg tid for three to seven days	High resistance rates

It is recommended that a follow-up urine sample be taken

TABLE 13
Antibiotic treatment of prostatitis

Type of Prostatitis	Antibiotic	Dose
Grade B recommendations		
Acute bacterial	Ampicillin with	1 to 2 g intravenous every 4 to 6 h
	gentamicin followed by	3 to 5 mg/kg/day intravenous every 8 h or 5 to 7 mg/kg/day once daily
	co-trimoxazole or	160/800 mg bid orally for four to six weeks
	ciprofloxacin or	500 mg bid orally for four to six weeks
	norfloxacin or	400 mg bid orally for four to six weeks
	ofloxacin	300 mg bid orally for four to six weeks
Grade A recommendations		
Chronic bacterial	Co-trimoxazole or	160/800 mg bid orally for six to 12 weeks
	ciprofloxacin or	500 mg bid orally for six to 12 weeks
	norfloxacin or	400 mg bid orally for six to 12 weeks
	ofloxacin	300 mg bid orally for six to 12 weeks
Grade D recommendations		
Chronic nonbacterial	Co-trimoxazole or	160/800 mg bid orally for four to six weeks
	erythromycin or	500 mg bid orally for four to six weeks
	ciprofloxacin or	250 to 500 mg bid orally for four to six weeks
	ofloxacin or	300 mg bid orally for four to six weeks
	doxycycline	100 mg bid orally for four to six weeks

TABLE 14
Investigation of diabetic foot infections

Objectives	Considerations
Assess neuropathy	• Testing for pain, temperature and vibration sensation reinforces patient's education regarding the role of recurring trauma • The nylon monofilament test of pain/touch is a quick effective monitoring device (57,58)
Assess perfusion	• In addition to large vessel arterial occlusive disease, peripheral vascular bypass grafts in the lower leg have reduced amputation rates (59,60) • Adequate perfusion is often a prerequisite for optimal outcome
Cultures as a guide to antimicrobial treatment	• Aerobic culture results can be used to guide antibiotic selection, keeping in mind situations where anaerobic coverage is required. Culture-guided therapy is the most cost effective strategy (61)
Imaging studies	• X-rays: Baseline and serially as clinically indicated • Bone and white blood cell scans are not cost effective in uncomplicated infections (61)

dwelling catheters appear to originate from the urinary tract (44). Parenteral treatment with ampicillin and gentamicin for 48 to 72 h until afebrile was recommended (12).

Grade B recommendations for catheter-associated urinary tract infection (catheter in situ)
- Asymptomatic bacteriuria – No treatment except before urological or prosthetic surgery
- Symptomatic infection – Parenteral ampicillin and gentamicin until afebrile for 48 to 72 h

Prostatitis: Acute prostatitis (Table 13) is a severe systemic illness characterized by a tender enlarged prostate, dysuria and urinary retention. Admission to hospital is often required.

Stratification of chronic prostatitis has proven to be of limited value in developing guidelines for patient treatment. Diagnosis remains difficult because localization studies are time consuming, expensive and can cause discomfort to the patient. Treatment with antibiotics is moderately successful, and short term cure rates of 60% have been reported (45-47). The relapse rate following antibiotic treatment for chronic bacterial prostatitis is high.

The cause of chronic nonbacterial prostatitis is largely unknown. In the absence of inflammatory cells in prostatic secretions or bacteriuria, prolonged antibiotic therapy is not indicated.

Complicated UTIs: UTIs are associated with an underlying urinary tract abnormality, which may be caused by stones, recent urological surgery or renal cystic disease, or may be due to a significant systemic disorder such as diabetes, immunosuppression or a neurogenic bladder. There have been few controlled clinical trials, and therapy must be individualized according to presenting symptoms and comorbidity (12). The majority of patients are managed in the same way as those with acute pyelonephritis. Radiological investigation and urological consultation are often necessary.

ANTIBIOTIC TREATMENT OF DIABETIC FOOT INFECTIONS

Assessment and investigation: Diabetes mellitus affects close to 5% of the Canadian population, and foot infections are the most common reason for hospital admission among diabetics. At least half of the foot amputations performed each year are the result of diabetic foot infections (48).

The pathogenetic processes leading to foot infection include peripheral neuropathy and occlusive vascular disease involving arteries in the lower third of the leg (49), each of which are accelerated by poor diabetic control (50). Recurrent (and unappreciated) trauma and re-

TABLE 15
Antibiotic treatment for diabetic foot infections

Grade D recommendations

Infection	Patient characteristics	Organism coverage	Antibiotic, dose and duration
Superficial uncomplicated	• 80% of initial presentations • one month duration • 2 cm inflammation • Negative probe to bone • Negative x-ray for osteomyelitis	*Staphylococcus aureus* *Streptococcus* species Anaerobes	Cephalexin 500 to 1000 mg qid for 14 days or co-trimoxazole 320/1600 mg bid for 14 days or amoxicillin clavulanate 500/125 mg tid for 14 days or cloxacillin 500 to 1000 mg qid for 14 days* If penicillin allergy, clindamycin 300 mg tid for 14 days
Complicated nonlimb threatening	• 20% of infections • Acute aggressive • Chronic progressive • 2 cm cellulitis • Deep soft tissue involvement • Bone or joint involvement • Out-patient management	*S aureus* *Streptococcus* species Anaerobes Coliforms (enteric Gram-negative bacilli)	Cephalexin 500 to 1000 mg qid for 2 to 12 weeks with metronidazole 500 mg bid for two to 12 weeks or co-trimoxazole 320/1600 mg bid for two to 12 weeks† with metronidazole 500 mg bid for two to 12 weeks or amoxicillin/clavulanate 500/125 mg tid for two to 12 weeks or co-trimoxazole 320/1600 mg bid for two to 12 weeks with clindamycin 300 mg qid for two to 12 weeks or clindamycin 300 mg qid for two to 12 weeks with ciprofloxacin 500 mg bid for two to 12 weeks
Limb and life-threatening infections	• Acutely evolving • Sepsis • Bacteremia • In-patient management including surgical intervention if necessary	*S aureus* *Streptococcus* species Anaerobes Coliforms (enteric Gram-negative bacilli) Add aminoglycoside for 48 to 72 h pending cultures if hospital-acquired Gram-negative bacilli is suspected	Intravenous ceftriaxone 1 g every 24 h with intravenous metronidazole 500 mg every 8 h or intravenous clindamycin 600 mg every 8 h or intravenous cefotaxime 1 g every 8 h with intravenous metronidazole 500 mg every 8 h or intravenous clindamycin 600 mg every 8 h
		Broad spectrum coverage including antipseudomonal coverage Add aminoglycoside for 48 to 72 h pending cultures	Intravenous piperacillin/tazobactam 4.5 g every 8 h or 3.375 g every 6 h or intravenous ceftazidime 1 to 2 g with intravenous clindamycin 600 mg every 8 h or intravenous imipenem/cilastatin 500/500 mg every 6 h

**Add metronidazole 250 to 500 mg bid for 14 days if patient responds suboptimally; †For osteomyelitis*

duced tissue perfusion increase the susceptibility of the foot to soft tissue infection, or to ulceration and chronic microbial colonization of foot lesions (51). Subsequent deeper infection of joints, bone or soft tissue planes may supervene.

When examining the infected foot (Table 14), the extent of cellulitis, necrosis and abscess formation and the presence of osteomyelitis must be assessed. A pedal pulse evaluation is important, and if the vascular system is compromised, further investigation with Doppler

ultrasound and angiography may be necessary. The chronic stable neuropathic foot ulcer, though colonized by microbes, seldom requires antimicrobial therapy. In this situation, treatment should be directed at relief from pressure and foot trauma (52).

Carefully obtained cultures are useful to guide antimicrobial selection. Superficial swabs are discouraged because surface contaminants are mixed with potential pathogens. More reliable cultures are collected from curettage material from a cleaned ulcer base, excised deep tissue or sinus cultures, particularly when probing of the sinus leads to subjacent bone (53). A wire swab, used elsewhere for urethral cultures, is a convenient tool to probe draining sinuses. When the wire probe leads to bone, there is an 89% positive predictive value for underlying osteomyelitis, a finding that reduces the need for nuclear imaging studies (53). In cases of osteomyelitis, especially when necrotic bone is present, open debridement of infected tissue provides more reliable culture material.

Aerobic and anaerobic cultures usually reveal a polymicrobial infection, particularly in chronic and deep infections (51,54). Predominant pathogens include *Staphylococcus aureus*, anaerobic Gram-positive cocci, *Bacteroides* species, and enteric Gram-negative bacilli. On the other hand, early acute infections are more likely to involve streptococcal and staphylococcal organisms as primary pathogens – Gram-negative organisms recovered from ulcer lesions are more likely colonizers in this situation (55).

Treatment: A team approach involving diabetology, diagnostic imaging, peripheral vascular surgery, orthopedic surgery, foot clinics and home care was recommended for the treatment of foot infections (56-60). Interventions include relief of trauma, pressure release, debridement of necrotic tissue, good diabetic control and referral to foot care. When indicated, vascular reconstructive surgery, including pedal bypass, was shown to reduce amputations and accelerate healing. Antibiotic therapy (Table 15) can be initiated empirically on clinical grounds, but subsequent therapy should depend on the type of pathogens recovered from cultures.

The duration of therapy of acute cellulitis is generally 10 to 14 days. If patients are started on intravenous therapy, stepdown to oral therapy should be considered once the infection is controlled (61). For patients with underlying osteomyelitis, prolonged therapy for as long as 12 to 15 weeks is required for durable cures (62,63). Surgical debridement of dead bone is essential for cure.

Regarding the recommendations for antimicrobial therapy, equivalent outcomes are expected for each of the choices within each patient grouping. Ranking or selection is based on convenience, cost and adverse effect profiles. Enterococcal coverage may need to be considered when this organism is shown to persist in serial cultures from patients responding suboptimally, or when the organism is recovered in limb and life-threatening infections.

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