Practice Point: Duration of Antibiotic Therapy for Common Infections

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Historically, durations of antimicrobial therapy for common infections have been largely driven by habits or cultural norms rather than robust scientific data. (1,2) In general, the durations have increased compared to the early days of antimicrobials when patients with pneumococcal pneumonia, for example, were treated for 1 to 4 days.(3) The long-standing belief that antimicrobials had few significant side effects likely contributed to the paucity of trials to critically evaluate minimum effective treatment durations. (4–7) However, in the last decade, increasing infections due to *Clostridioides difficile*, emergence of multidrug resistant pathogens and the concern for overall safety of antibiotics have led researchers to critically look at this issue. (8–16)

Several reports including a recent study in in England used a primary care database between 2013 and 2015 and noted that excess duration compared to recommended guidelines accounted for a staggering 1.3 million days of excess therapy. (17,18) A study among hospitalized patients in the United States reported that one third of unnecessary antibiotics were due to unnecessarily prolonged durations. (19) A recent observational study of patients with pneumonia concluded that two thirds of patients had excess durations with 93.2% of the excess being in the form of discharge antibiotics. Each excess day was associated with a 5% increase in the odds of a patient having an antibiotic-associated adverse event. (20) Many experts have made rational arguments and coined useful slogans such as "shorter is still better" to emphasize the importance of reducing durations of antimicrobials and preserve the efficacy of our antibiotics. (21–23)

The purpose of this practice point is to disseminate contemporary treatment durations for common infectious syndromes for which there are either infectious disease guidelines or substantial evidence to support shorter durations of therapy. Search strategies for appropriate guidelines from North America or Europe where similar health systems exist as well as applicable cohort or randomized controlled studies were carried out between January 2 and June 30, 2020. Subsequently, the draft document was reviewed by the Antimicrobial Stewardship and Resistance Committee (ASRC) of the Association of Medical Microbiology and Infectious Disease (AMMI) Canada, other members at large and approved by the Council of AMMI Canada.

The recommendations do not apply to individuals with genetic immune defects, individuals who are or have received immune modulating agents, chemotherapy or corticosteroids. Decisions regarding duration of treatment of individual patients should still take into consideration the underlying host, the certainty of the clinical diagnosis and clinical response to treatment. Modifications of duration can also be re-evaluated on a case-by-case basis with ongoing follow-up of patients. Table 1 summarizes current AMMI Canada recommendations for durations of treatment for common infectious syndromes in patients without special host factors such as underlying immunodeficiency.

Adults

UPPER RESPIRATORY TRACT INFECTIONS

Community acquired bacterial sinusitis

Community acquired bacterial sinusitis is usually secondary to a primary viral infection of the upper respiratory tract (viral rhinitis) that results in sinus ostia obstruction and subsequent bacterial proliferation. Patients with bacterial sinusitis either have > 10 days of persistent symptoms, severe symptoms or have initial improvement followed by relapse of symptoms. Symptoms that last greater than 12 weeks suggest chronic sinusitis and are not in the scope of this practice point. In adults, a meta-analysis of 12 randomized controlled trials (RCT) for acute bacterial sinusitis showed that a duration of 3 to 7 days was equally as effective as 6-10 days and a sensitivity analysis of 5 versus 10 days came to a similar conclusion. (24)

Guidelines for adult patients from the American Academy of Otolaryngology in 2015 recommends 5 to 10 days (based on randomized controlled trials (Grade A), but low to moderate certainty)) with a clinical re-evaluation at 7 days to ensure improvement. (25) The Infectious Diseases Society of America (IDSA) recommends 5-7 days (based on weak, low quality evidence) of antibiotics with a re-evaluation at 3-5 days to ensure improvement and no extension of infection.(26)

Children

Recommended durations of therapy for children and youth with acute bacterial sinusitis have varied because of scant evidence and difficulty in assessment of chronicity. A proposed practical alternative to prevent longer durations may be to treat for 7 days after the patient is symptom free. (27) Pneumococcus and *H. influenzae* isolates may be resistant to trimethoprim-sulphamethoxazole and azithromycin so these antibiotics are not included in the duration recommendations.

AMMI Canada Recommendations

The duration of treatment for acute uncomplicated community acquired sinusitis should be 5-7 days with a planned re-evaluation at 7 days to ensure clinical resolution. Children should also receive about 7-10 days of therapy with a beta-lactam antibiotic with a planned re-evaluation at seven days.

Acute Otitis Media (AOM)

A critical issue in therapy for AOM in children is to ensure that criteria for diagnosis are met (a bulging tympanic membrane is more likely to indicate a bacterial infection) to prevent over treatment of viral otitis media. Trials in children over 2 years of age have favoured a duration of 5-7 days however a trial in children under the age of 2 years noted that 5 days was less effective than 10 days of therapy.(28,29)

The Canadian Pediatric Society recommends durations of amoxicillin therapy for acute otitis media meeting specific diagnostic criteria in children are 10 days in children under 2 years of age and 5 days in

older children. (30) However any child with a tympanic membrane perforation or a recurrent AOM should be given a 10-day course.

<u>AMMI Canada Recommendations</u>

Duration of therapy for bacterial AOM is 10 days in children under 2 years and 5 days in children over 2 years of age.

Streptococcal pharyngitis

Streptococcal pharyngitis if left untreated may lead to acute rhematic fever or local suppurative complications. A meta-analysis demonstrated that there appears to be better bacteriological eradication with a 10 day course of penicillin versus 5-7 days but no differences in the rate of relapse or recurrence was noted. (31) Another study also non-inferior bacterial eradication with penicillin four times daily for five days versus three times a day for 10 days however the incidence of acute rheumatic fever was not assessed. (32)

Guidelines from the United Kingdom recommend a 5-10-day course of penicillin (10 days if recurrent infection) whereas the Canadian Pediatric Society recommends 10 days of oral penicillin or amoxicillin. (Sauve et al, In Press) (33)

<u>AMMI Canada Recommendations</u>

Penicillin V or amoxicillin for 10 days is the recommended duration of therapy for Streptococcal pharyngitis.

LOWER RESPIRATORY TRACT INFECTIONS

Community acquired pneumonia

Acute community acquired pneumonia is most commonly due to viruses (such as influenza) but common pathogens causing bacterial pneumonia are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Mycoplasma pneumoniae* with some special populations such as nursing home residents possibly infected with Gram negative pathogens that may be multi-drug resistant.

A systematic review and meta-analysis of randomized controlled trials predominantly of ambulatory or mixed inpatient/outpatients with low severity of illness concluded that ≤ 6 days provided equally effective treatment compared to longer durations and may confer a safety benefit due to fewer side effects. (34) Failure to respond may indicate local complications such as empyema, or other pathogens not commonly seen such as *Mycobacterium tuberculosis* or endemic fungi such as *Blastomyces dermatitidis/gilchristii*. One recent observational study reported significantly more antibiotic adverse events in patients who received therapy longer than recommended, predominatly discharge antibiotics, supporting the shorter durations as a safer option. (20) *S. pneumoniae* bacteremia associated with uncomplicated pneumonia (not meningitis or other serious infections such as septic arthritis which

requires longer courses of therapy) is effectively treated with 5 days of IV therapy, assuming clinical improvement before the discontinuation of therapy. (35)

The 2019 joint American Thoracic Society (ATS) and the IDSA guideline recommend at least 5 days duration for both severe and non-severe pneumonia with the caveat that the total duration depends on the achievement of clinical stability for 48 to 72 hours prior to discontinuing antimicrobial therapy. (36) Clinical stability was defined as normalization of vital signs, ability to eat and normal mentation. While historically there were recommendations for longer therapy (14 d) for *Staphylococcus aureus*, *Pseudomonas aeruginosa* and other non-fermenting bacteria, more recent recommendations are for 7 days of therapy in these instances, unless there another reason to extend therapy (e.g. *S. aureus* bacteremia). In complicated pneumonias (e.g. empyema), the duration is likely longer, but surgical intervention plays a key role in management and decreasing durations of antibiotics.

Children

CAP that is considered to be bacterial in origin in children is commonly due to *S pneumoniae*. Children who have prolonged cough or are older are more likely to have *Mycoplasma pneumonia*. One study in preschool children found that pneumonia treated with amoxicillin for 5 days in the outpatient setting was non-inferior to a 10 day course. (37)

The CPS practice point currently recommend a 7-10 day course of antimicrobials for uncomplicated pneumonia with the caveat that shorter courses may be just as effective for children with non-severe uncomplicated pneumonia. (38,39) Pneumonia complicated by empyema could require drainage and a slightly longer duration of therapy of 14 -21 days.

AMMI Canada Recommendations

The duration of therapy for acute uncomplicated community acquired pneumonia in adults should be a minimum of 5 days provided there is clinical stability for 48-72 hours. Duration can be extended to 7 days if there is slower resolution or pathogens such as *S. aureus* or *Pseudomonas* are identified.

Since viral infections are more common in children, clinicians should use clinical and radiological criteria to distinguish bacterial pneumonia from bronchiolitis in younger infants. Duration of therapy should be 7 days for uncomplicated pneumonia in children.

Lower Respiratory Tract Infections acquired in hospital:

Hospital acquired pneumonia (HAP) is associated with significant morbidity and a high case fatality rate. The entity previously labeled as health care associated pneumonia (HCAP) – which included patients with significant health care contact (e.g. dialysis) and those living in long-term care – has been retired and collapsed back into CAP as the microbiological etiologies are similar. In contrast, HAP and ventilator

associated pneumonia (VAP) are more likely to be associated with antibiotic-resistant organisms, depending on local hospital epidemiology, host factors and duration of hospital stay. Empiric therapy is usually broad. Historically, therapy for VAP (and HAP) was prolonged, up to 21 days, until investigators evaluated the relative efficacy of shorter (8 days) versus longer (15 days) therapy and showed no difference in mortality, intensive care unit (ICU) stay, mechanical ventilation-free days or organ failure free days. (40) Patients who received fewer days of antibiotics had less re-infection with resistant organisms. Subsequent studies are summarized in a meta-analysis confirming that 7-8 days of therapy is as effective as longer courses, except possibly for patients infected with non-fermenting Gram negative bacilli (e.g. *P. aeruginosa*) where there may be more recurrences with a shorter course, however this did not affect clinical outcome. (41)

European (2017) and IDSA guidelines (2016), both recommend durations of 7 days for VAP (moderate quality evidence) and HAP (very low quality evidence). (42–44) However, allowance is made to alter durations both for shorter and longer courses based on clinical response and microbiologic etiology.

AMMI Canada Recommendations

The duration of therapy for hospital acquired pneumonias without abscesses (ventilator associated or not) should be limited to less than or equal to 7 days.

Chronic Obstructive Pulmonary Disease Exacerbation:

Acute exacerbations (AE) of Chronic Obstructive Pulmonary Disease (COPD) caused by infection are most frequently caused by viruses, with bacteria playing a secondary role. AE-COPD should be managed with bronchodilators, anti-inflammatory therapy and correction of any reversible underlying cause such as environmental or other medical conditions (e.g. heart failure, pulmonary embolism). Antibiotics should only be considered when patients fail to respond to the above measures or when clinical findings such as fever suggest bacteria as a likely cause or when severely ill. (45)

A recent review showed no difference in clinical outcome of durations of <6 days versus 7 or more days but the shorter duration group had a significantly fewer side effects. (46) Durations of therapy of up to 5 days have been compared to longer therapies in a meta-analysis of 21 randomized controlled trials. (47) The meta-analysis supported the effectiveness of short courses of 5 days were equivalent for clinical and bacteriologic cure. Results were the same regardless of antibiotic class.

The Global Initiative for Chronic Obstructive Lung disease initiative (2019) recommend 5-7 days of antimicrobial therapy in patients with severe disease, or signs of bacterial infection.(45) Likewise the United Kingdom National Institute for Health and Care Excellence (NICE) guidelines recommend a 5 day course (if antibiotics are indicated) of any antimicrobial class. (48) The European Respiratory Society and the American Thoracic Society (ATS) guidelines recommend antimicrobial therapy, but do not comment on duration. (49)

The duration of treatment for AE-COPD believed to be due to bacterial infection should be 5 -7 days.

PREOPERATIVE ANTIMICROBIAL PROPHYLAXIS

Surgeries with no implantable devices: Prophylactic antimicrobials should be administered only when recommended, as many types of surgery do not require prophylaxis. (50,51) For effective prevention of surgical site infections, when recommended, antimicrobials should be given 30-60 minutes before surgical incision. There is no evidence to show benefit of antimicrobials continued post-surgically. A study of almost 80,000 patients showed that the risk of *C. difficile* and acute kidney injury increased in a duration dependent fashion in adults who received antimicrobials for prophylaxis for > 24 hours strongly suggesting that prolonging duration adds adverse events without preventing more surgical site infections. (52,53)

World Health Organization is definitive in its recommendations that for surgeries that do not include implants, there is no benefit to prolonging antimicrobials in the post-operative period and antibiotics should be discontinued at the time of skin closure. (54)

Women undergoing caesarean sections should also receive a timely preoperative dose of cefazolin to reduce the likelihood of surgical wound infection and endometritis with no benefit of prolonging after the surgery. (55)(56) In women with preterm labour with ruptured membranes when a gestational age is less than 32 weeks, it is recommended to receive 48 hours of intravenous (IV) ampicillin followed by 5 days of oral amoxicillin and either 1 dose of IV azithromycin or 2 days of IV erythromycin followed by 5 days of oral erythromycin. (56)

AMMI Canada Recommendations

Surgical prophylaxis, including for caesarian sections, should be stopped after skin closure. Pregnant women in pre-term labour with ruptured membranes should receive 7 days of ampicillin and a macrolide as above to decrease the risk of ascending infection to the fetus.

Duration of surgical prophylaxis for surgeries involving implants or valves can be extended 24-48 hours after surgery but this recommendation is mainly due to lack of data. (54,57)

INTRA-ABDOMINAL INFECTIONS

Treatment of intra-abdominal infections involves drainage of infected fluid collections or abscesses (source control) as this removes the source of infection, reduces bacterial load, leads to decreased days of antimicrobials and better overall outcomes.

Infections With Source Control: Patients with non-perforated appendicitis need only pre-operative antibiotics. (58) Two large studies of intra-abdominal infections support using shorter courses of therapy emphasizing that source control and drainage of abscesses are key in management. The first study done

compared 4 versus 8 days of therapy after source control and concluded that recurrent surgical-site or intra-abdominal infections were similar. (59)   A second large randomised controlled trial done in intensive care units determined that patients treated with shorter courses of 8 days had no difference in length of stay nor mortality or re-operation rates compared to those treated for 15 days. (60) For cholangitis, a systematic review summarizing available literature to 2018 reported 4 studies that met inclusion criteria. The authours concluded that provided there was source control, a shorter course of less than a week did not result in higher mortality, duration of fever or higher rates of recurrence. (61)

Guidelines from the Surgical Infection Society (SIS) and the IDSA advocate <7 days of therapy for patients with source control. (58,62) Tokyo Guidelines for management of acute cholangitis recommend drainage or source control as the mainstay of therapy followed by 4-7 days of appropriate targeted antimicrobial therapy. (63,64)

AMMI Canada Recommendations

Physicians should strongly advocate for source control (drainage of collections) in the setting of intraabdominal infections. Duration of therapy for intraabdominal infections with source control should be less than 7 days.

URINARY TRACT INFECTIONS

Cystitis or lower tract infection:

Acute dysuria, urgency and frequency, without flank pain or fever, accompanied by pyuria, and a positive single uropathogen in urine define cystitis. Since bacteria are limited to the bladder, short courses of antibiotics are sufficient. Cystitis in men is infrequent and likely indicate prostatitis or upper tract infection. Bacteriuria in pregnancy or in post renal transplant situations is beyond the scope of this document. Aside from pregnancy and prior to urologic surgery, asymptomatic bacteriuria should not be treated. (65) AMMI Canada has published a useful toolkit including educational materials for managing asymptomatic bacteriuria "Symptom Free Let it Be" available at https://www.ammi.ca/?ID=127.

Short courses of therapy (3-5 days, depending on antibiotic class) for uncomplicated cystitis in otherwise healthy, young women is well-supported by robust data and recommended in IDSA guidelines. (66) Single dose Fosfomycin (or 3 days if recurrent/complicated cystitis) also holds promise as a treatment for cystitis due to high concentrations and prolonged half-life in the urine. (67,68) Fluoroquinolones are not recommended as empiric therapy as their safely profile and propensity to increase resistance are notable. (69,70)

Children

Non febrile urinary tract infections are uncommon in infants and children but typically occur in adolescents who are sexually active. The same principles of treatment duration in adults apply to adolescents. (71)

Duration of therapy for uncomplicated cystitis in women is 3-5 days unless using fosfomycin which is one day.

Pyelonephritis

Treatment duration for uncomplicated pyelonephritis in non-pregnant women is well established. For adult men, urinary tract infections are usually considered complicated since this may indicate obstruction, stone or a prostatic focus. Studies of patients with normal male or female anatomy support a 7 day course of antimicrobials. (72–75) A meta-analysis of treatment durations for pyelonephritis comparing ≤ 7 days to >7 days resulted in 8 evaluable trials. The conclusion (irrespective of whether fluoroquinolones had been used) was that there were no differences in clinical or microbiological failure between the short and long-treatment arms. Longer treatment courses may be required for pyelonephritis complicated by abscess or stones as patients with urogenital abnormalities had more microbiological failure at the end of follow-up compared to those with normal anatomy. In this meta-analysis the percentage of bacteremic patients ranged from 3% to 29%. (72) A recent study used a median of 4.5 days of aminoglycoside therapy versus 5 days of non-aminoglycoside based therapy for adults with pyelonephritis with similar outcomes. (76)

In 2011, practice guidelines by IDSA and the European Society for Microbiology and Infectious Diseases recommended a 7 day course of antibiotics for women with uncomplicated pyelonephritis in women (without septic shock or abscesses). (66) NICE Guidelines from the United Kingdom, vary durations according to class of antimicrobial; 7 days for fluoroquinolones (consider safety issues) , 7-10 days for ß-lactams, however rising rates of resistance emphasize the critical importance of proper cultures and non-response to therapy requires prompt re-evaluation. (77) Some experts have suggested an initial intravenous dose of an aminoglycoside or ceftriaxone or ertapenem especially if oral beta-lactams are planned as definitive therapy.

Children

Pyelonephritis in children refers to the clinical syndrome of fever and symptoms compatible with a urinary tract infection (dysuria, incontinence, urgency) with pyuria and an abnormal urinalysis. No randomised controlled trials specifically examining duration of therapy in children with febrile urinary tract infections (presumed pyelonephritis) have been published. A 2014 Cochrane review determined that 10 to 14 days of therapy was appropriate for clinical success. (78) A more recent 2019 publication a study of almost 800 children with febrile UTI reported similar outcomes with courses of 6-9 days versus ≥ 10 days of therapy. However, children with urologic abnormalities had more treatment failures with short courses. (79) A randomised controlled trial conducted in neonates with Gram-negative bacteremia (of which 69% had a urinary tract source) reported that those treated with 7 days of antibiotics had non-inferior outcomes compared to those treated for 14 days. (80) In children older than one month, treatment durations for bacteremia associated with pyelonephritis have not been the subject of a

randomized controlled trial. A recent retrospective cohort study of pyelonephritis has too few cases of associated bacteremia to determine duration of therapy. (79) Guidelines from the Canadian Paediatric Society and the American Academy of Pediatrics currently recommend 7-14 days of therapy. (81)

AMMI Canada Recommendations

In adults and children with no underlying anatomic abnormalities and rapid response to therapy, duration of therapy for uncomplicated pyelonephritis or urosepsis is 7 days with slightly longer courses if there is a slow response to therapy or development of abscess. Patients with diabetes, underlying immunocompromising conditions or recurrent pyelonephritis may require more individualized plans for slightly longer durations and a slower IV to oral conversion. When considering oral therapy at presentation one dose of IM/IV aminoglycoside or ceftriaxone at diagnosis.

CELLULITIS

Purulent and Non-purulent Cellulitis:

Acute cellulitis is most commonly due to *S. aureus* (usually a purulent cellulitis characterized by abscesses or pus that is visible or can be expressed locally) or *Streptococcus pyogenes* (usually a non-purulent cellulitis characterized primarily by rapid onset of pain, erythema and swelling without abscesses). There may be some overlap in these presentations in persons with underlying dermatitis. Cellulits associated with bites (animal or human), deeper infections (such as necrotizing fasciitis), fish or water exposure, or in patients who are neutropenic is beyond the scope of this practice point. Cellulitis should also be differentiated from venous stasis, erythema migrans due to Lyme disease and cutaneous herpes infections. One randomized controlled study of patients with uncomplicated cellulitis (both outpatients and inpatients) concluded that despite some residual erythema, 5 days of therapy resulted in similar cure rates compared to 10. (82) In a study involving patients admitted to hospital with cellulitis, there appeared to be more readmissions in the shorter (6 days) duration group suggesting that some hospitalized patients may have more extensive disease requiring longer durations of therapy to prevent relapse. (83) In cases or recurrent cellulitis, consideration should be given to penicillin prophylaxis and other supportive measures. (84)

Guidelines from IDSA recommend 5 days of therapy for uncomplicated non-purulent cellulitis however, the duration should be extended to 10 days if the infection has not improved within the 5 day period or if the patient is hospitalized for more severe or extensive disease (85)

AMMI Canada Recommendations

Duration of therapy for uncomplicated cellulitis for adults and children is 5-7 days. Hospitalized patients with more extensive disease may need slightly longer courses of 10 days.

BONE AND JOINT INFECTIONS

A randomized controlled trial of therapy for patients with vertebral osteomyelitis showed similar outcomes for 6 weeks versus 12 weeks of antibiotic therapy. (86) A non-inferiority trial of 154 adult patients with native joint septic arthritis (64% hand and wrist) randomized patients to two versus four weeks of antibiotic therapy post-surgical drainage and reported similar outcomes (not inferior) in the shorter duration group. However, the findings may not be applicable to large joints such as hips and knees since these were underrepresented. (87) Appropriate surgical source control including drainage of joint fluid is paramount to reducing morbidity from joint infections. Management of prosthetic joint infections or septic arthritis due to *Neisseria gonorrhoea* is outside the scope of this article.

Guidelines currently recommend a 6 week course of antimicrobials for acute native vertebral osteomyelitis commonly due to *S. aureus*. (88) There are no current guidelines from North American or European organizations for other native joint infections. The British Society for Antimicrobial Chemotherapy (BSAC) made recommendations in 2006 in conjunction with other specialty societies and recommended 2 weeks of IV therapy, followed by a further 4 weeks of oral therapy however, acknowledged that there exists little evidence. (89) Shorter durations of 3-4 weeks could be considered for non-*Staphylococcus aureus* septic arthritis with a susceptible pathogen and adequate surgical drainage.

Children

In children multiple studies have determined that shortening the duration of antimicrobial therapy for acute hematogenous osteoarticular infection that is uncomplicated from 4-6 weeks to 3-4 weeks has not changed the uniformly good outcomes for in children.(90–92) The common bacteria are *S. aureus* and *Kingella kingae*. Treatment duration for osteomyelitis due to methicillin resistant *S. aureus* (MRSA) may be longer.

CPS practice point on hematogenous osteomyelitis recommends 3- 4 weeks of therapy with step-down to oral therapy for uncomplicated osteomyelitis. (93) Similar recommendations are outlined in European guidelines. (94)

AMMI Canada Recommendations

Uncomplicated vertebral osteomyelitis should be treated for 6 weeks. There is less data available for native joint septic arthritis (excludes *Neisseria gonorrhoea*). Once source control has been achieved septic arthritis of native joints involving the hand and fingers can be treated for two weeks whereas infection of larger joints will require 4 weeks. In children, duration of therapy for acute osteoarticular infections is usually 3-4 weeks with longer courses reserved for complicated infections.

Acute Osteoarticular Infections

<u>AMMI Canada Recommendations</u>

BACTEREMIA

***Staphylococcus aureus* bacteremia**

Bacteremia due to *S. aureus* is common, is always considered pathologic and must be treated and managed appropriately. It may be associated with an implantable or intravascular line or a detectable focus of infection such as osteoarticular infection or infective endocarditis. All prosthetic devices or intravascular catheters should be removed, if possible, to effect cure and an echocardiogram is recommended to look for endocarditis.

Current data supports treatment of uncomplicated *S. aureus* bacteremia with 14 days of intravenous antimicrobials from the first negative blood culture. Uncomplicated bacteremia is defined as *S. aureus* bacteremia without evidence of infective endocarditis using echocardiography nor metastatic sites of infection (clinically or other imaging modalities), rapid (3 days) sterilization of blood cultures and rapid (<72 hours) defervescence after appropriate antibiotics, and absence of prosthetic devices.(95) Newborns with *S. aureus* bacteremia treated with less than 14 days are also more likely to have relapse of infection. (96) Persistent *S. aureus* bacteremia beyond 72 hours despite adequate therapy may be indicative of an endovascular or other deep seated infection requiring prolonged therapy, usually 4-6 weeks. (97) There is also accumulating data indicating improved outcomes and lower mortality in patients with *S. aureus* bacteremia whose management includes infectious diseases consultation. (98,99)

<u>AMMI Canada Recommendations</u>

Fourteen days of IV antimicrobials is required for cases of uncomplicated *S. aureus* bacteremia (see above for important caveats) or associated with a central line provided the catheter has been removed. Most cases of *S. aureus* bacteremia require 4-6 weeks of therapy and should be managed in conjunction with infectious diseases consultation or input.

Non- S. aureus bacteremia

Central Line Associated

Bacteremia due to coagulase negative Staphylococci associated with an intravascular device that has been removed has generally been treated with for 5-7 days after catheter removal. (100,101) Recently some authors have reported equivalent outcomes in this group of patients who only had catheter removal as definitive therapy. Shorter durations of <5 days should be considered in circumstance where early catheter removal and rapid response is seen. (102)

Catheter associated central line infections due to Enterobacteriaceae should include catheter removal followed by 7-14 days of antimicrobial therapy. (100,101) Similar durations of therapy are

recommended for implantable venous access devices provided they are removed, providing source control and not due to *S. aureus*. (103)

<u>AMMI Canada Recommendations</u>

Compared to uncomplicated *S. aureus* catheter related bacteremias which require 14 days of therapy, uncomplicated central line associated bacteremias due to Enterobaceteraciae can be treated for 7 days after catheter removal.   If the pathogen is a coagulase negative Staphylococcus shorter duration of 5 days after removal of intravascular catheter are recommended especially if there is early catheter removal and good clinical response.

Non- central line associated bacteremia

Bacteremia associated with pyelonephritis, generally due to enterobacteraciae (such as *E. coli* or *Klebsiella*) has been traditionally treated with 7-14 days of antibiotics. A meta-analysis of outcome in 7,695 patients studied outcome in patients treated with shorter (≤ 7 days) versus longer courses of antibiotics. There were no differences in clinical outcome, microbiologic cure nor mortality between patients in the two groups. (104) Subsequent to this meta-analysis several randomised controlled trials of 7-8 versus 14-15 days of antibiotics in patients with Gram-negative bacteremia (of which the majority had a urinary tract source) found that the shorter course was non-inferior to longer courses in clinical outcome. (80,105,106) A more recent meta-analysis comparing ≤ 10 days to > 10 days of therapy in patients with bacteremia showed no differences in clinical or microbiologic cure nor mortality, however there were only 4 studies available to assess specifically this duration.(107) In an observational study, when source control had been achieved, investigators found that patients with *Pseudomonas* bacteremia receiving a median of 9 days of therapy (IQR 8-10) had a similar odds of recurrent infection and death as patients who received a median of 16 days (IQR,14-17). (108) A recent randomised clinical trial of 7 versus 14 days versus a C-reactive protein guided duration study for Gram negative bacteremia found no significant differences in clinical outcome between groups with very few recurrences. (109)

<u>AMMI Canada Recommendations</u>

For bacteremia due to enterobacteriaceae, there appears to be a wide variation in duration of antimicrobial therapy however, emerging literature would support a 7-day course for uncomplicated bacteremias due to pyelonephritis, or from a source which has been successfully controlled.

CONCLUSIONS

Antibiotics are societal resources and the emerging potential impact of losing these precious resources is enormous as detailed in a recent Canadian report. (12) Notwithstanding the societal benefits of using less antimicrobials, shortening durations of antibiotic therapy for individual patients is increasingly recommended as a better practice choice. Clinicians should be aware of new data, current guidelines and recommendations and adjust their practices accordingly to provide the best patient care while preserving antibiotics for future use.

Table 1: Summary of recommendations for duration of therapy in selected common infections

Infection	Recommended duration	Comments
Urinary Tract Infections		
Children and Adults		
Women/adolescents Uncomplicated Cystitis	Nitrofurantoin – 5 days TMP-SMX- 3 days Fosfomycin – 1 day	Young non- pregnant female adolescents or adults with normal urinary tracts and normal renal function
Children Febrile Urinary tract infection	7 to 14 days	Assumes upper tract involvement if febrile
Adults Pyelonephritis and Urosepsis	Consider an initial dose of IV dose aminoglycoside or ceftriaxone at outset Quinolones or beta-lactams 7 days	Excludes patients with urogenital abnormalities or stents/ drains Duration depends on rapidity of response to appropriate therapy
Respiratory Tract Infections		
Children and Adults		
Streptococcal pharyngitis	10 days (penicillin V or amoxicillin)	Studies limited to pediatrics. Some studies suggest 5 days of QID penicillin for bacterial eradication only
Acute Otitis Media	6 months to 2 years – 10 days Over 2 years – 5 days	Should meet diagnostic criteria such as moderately to severely ill with bulging tympanic membrane.
Acute sinusitis (uncomplicated)	5-7 days	Excludes Complicated sinusitis (e.g. epidural, subdural or orbital collection). Revaluation recommended at 7 days.
Community Acquired Pneumonia	5-7 days	Patients with underlying lung disease, immunosupression or empyema. Must be improved and have normal vital signs for 2 days when using 5 days of therapy
Acute sinusitis	5 to 7 days	Clinical re-evaluation at 7 days Excludes Complicated sinusitis (e.g. epidural, subdural or orbital collection)
Hospital and Ventilator Acquired Pneumonia (HAP/VAP)	≤7 days	Severely immune suppressed patients with collections or abscesses, associated *S. aureus* infection
Acute bacterial Chronic Obstructive Pulmonary Disease (COPD) exacerbation	5-7 days	Only for patients meeting criteria for antibiotic treatment
Intraabdominal infections		
Children and Adults		
Uncomplicated appendicitis	Pre-operative antibiotics only	Gangrenous appendicitis or perforated appendicitis should be treated for an additional 24-48 hours after source control
Traumatic bowel perforation	No more than 24 hours post-operatively	Operated on within 12 hours of trauma
Gastroduodenal perforation	No more than 24 hours post-operatively	Operated on within 24 hours
Intraabdominal infection/abscess	<7 days	Source control required with drainage of infection. No additional days required if adequate drainage is in place
Skin Infections		
Children and Adults		
Uncomplicated non-purulent or purulent cellulitis	5-7 days	Usually due to *Streptococcus pyogenes* (Group A streptococcus) or *Staphylococcus aureus*
Osteo-articular infections		

Children Acute osteoarticular infections	3-4 weeks	Should be transitioned to oral therapy once clinically able to use limb and C reactive protein (CRP) decreasing
Adults Acute Vertebral Osteomyelitis	6 weeks	Not associated with implantable device Assumes *S. aureus* but could be longer for Salmonella or Brucella infections
Adults Acute native joint osteoarticular infections	2 weeks for small joints after drainage 4 weeks for large joints after drainage	Duration recommendation for patients post-surgical drainage, with causal organism and susceptibility profile
Bacteremia		
Children and Adults		
Gram negative enterobacteriacea such as *E. coli*	7 days	Assumes source controlled, (i.e. removal of central line, abscess drainage etc) and not associated with a clinical syndrome requiring longer therapy.
Staphylococcus aureus bacteremia (uncomplicated)	14 days intravenously if uncomplicated or following intravenous line removal	Must ensure absence of endocarditis with echocardiogram and or other foci of infection (such as osteomyelitis); infectious diseases consult recommended.
Staphylococcus aureus bacteremia (complicated)	4-6 weeks intravenously	Endocarditis, metastatic foci of infection, prolonged bactereremia > 72 hours while on appropriate therapy. Infectious Diseases consult recommended.
Streptococcus pneumonia associated with pneumonia	5 -7 days	Must show clinical improvement and meet criteria for discontinuation of antibiotics for pneumonia

References:

1. Livorsi D, Comer A, Matthias MS, Perencevich EN, Bair MJ. Factors influencing antibiotic-prescribing decisions among inpatient physicians: A qualitative investigation. Infect Control Hosp Epidemiol. 2015;36(9):1065–72.

2. The McDonnell Norms Group. Antibiotic Overuse: The Influence of Social Norms. J Am Coll Surg. 2008;207(2):265–75.

3. Tillett WS, McCormack JE, Cambier MJ. The Treatment of Lobar Pneumonia with Penicillin. J Clin Invest. 1945 Jul 1;24(4):589–94.

4. Spellberg B, Rice LB. Duration of Antibiotic Therapy: Shorter Is Better. Ann Intern Med. 2019 Aug 6;171(3):210.

5. Aliberti S, Giuliani F, Ramirez J, Blasi F. How to choose the duration of antibiotic therapy in patients with pneumonia. Curr Opin Infect Dis. 2015 Apr;28(2):177–84.

6. Wald-Dickler N, Spellberg B. Short-course Antibiotic Therapy - Replacing Constantine Units with "shorter Is Better." Clin Infect Dis. 2019;69(9):1476–9.

7. Royer S, DeMerle KM, Dickson RP, Prescott HC. Shorter Versus Longer Courses of Antibiotics for Infection in Hospitalized Patients: A Systematic Review and Meta-Analysis. J Hosp Med. 2018 Jan 25;13(5):336–42.

8. Hanretty AM, Gallagher JC. Shortened Courses of Antibiotics for Bacterial Infections: A Systematic Review of Randomized Controlled Trials. Pharmacotherapy. 2018 Jun 1;38(6):674–87.

9. Pouwels KB, Hopkins S, Llewelyn MJ, Walker AS, McNulty CA, Robotham J V. Duration of antibiotic treatment for common infections in English primary care: Cross sectional analysis and comparison with guidelines. BMJ. 2019;364:1–21.

10. Esposito S, Esposito I, Leone S. Considerations of antibiotic therapy duration in community- and hospital-acquired bacterial infections. J Antimicrob Chemother. 2012;67(11):2570–5.

11. Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Heal. 2018;6(6):e619–29.

12. Finlay B, Conly J, Coyte P. When Antibiotics Fail. Ottawa (ON): the Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada, Council of Canadian Academics [Internet]. Ottawa (ON); 2019. Available from: https://cca-reports.ca/reports/the-potential-socio-economic-impacts-of-antimicrobial-resistance-in-canada/

13. Bonomo RA, Burd EM, Conly J, Limbago BM, Poirel L, Segre JA, et al. Carbapenemase-Producing Organisms: A Global Scourge. Clin Infect Dis. 2018;66(8):1290–7.

14. Bhalodi AA, van Engelen TSR, Virk HS, Wiersinga WJ. Impact of antimicrobial therapy on the gut microbiome. J Antimicrob Chemother. 2019 Jan 1;74(Supplement_1):i6–15.

15. Baxter R, Ray GT, Fireman BH. Case-control study of antibiotic use and subsequent Clostridium difficile-associated diarrhea in hospitalized patients. Infect Control Hosp Epidemiol. 2008 Jan;29(1):44–50.

16. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis. 2014;14(1):1–25.

17. Pouwels KB, Hopkins S, Llewelyn MJ, Walker AS, McNulty CA, Robotham J V. Duration of antibiotic treatment for common infections in English primary care: cross sectional analysis and comparison with guidelines. BMJ. 2019 Feb 27;364(Feb 27):l440.

18. Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary Use of Antimicrobials in Hospitalized Patients. Arch Intern Med. 2003;163(8):972.

19. Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. Arch Intern Med. 2003 Apr 28;163(8):972–8.

20. Vaughn VM, Flanders SA, Snyder A, Conlon A, Rogers MAM, Malani AN, et al. Excess antibiotic treatment duration and adverse events in patients hospitalized with pneumonia: A multihospital cohort study. Ann Intern Med. 2019;171(3):153–63.

21. Spellberg B. The maturing antibiotic mantra: "Shorter is still better." J Hosp Med. 2018;13(5):361–2.

22. Rice LB. The Maxwell Finland Lecture: For the Duration-- Rational Antibiotic Administration in an Era of Antimicrobial Resistance and Clostridium difficile. Clin Infect Dis. 2008;46(4):491–6.

23. Pulcini C, Binda F, Lamkang AS, Trett A, Charani E, Goff DA, et al. Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach. Clin Microbiol Infect. 2019;25(1):20–5.

24. Falagas ME, Karageorgopoulos DE, Grammatikos AP, Matthaiou DK. Effectiveness and safety of short vs . long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. Br J Clin Pharmacol. 2009 Feb;67(2):161–71.

25. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M, et al. Clinical practice guideline (update): Adult sinusitis. Otolaryngol - Head Neck Surg (United States). 2015;152:S1–39.

26. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJC, Hicks LA, et al. IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults. Clin Infect Dis. 2012 Apr 15;54(8):e72-112.

27. Wald ER, Applegate KE, Bordley C, Darrow DH, Glode MP, Marcy SM, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013 Jul 1;132(1).

28.   Paula A. Tähtinen, M.D., Miia K. Laine, M.D., Pentti Huovinen, M.D. PD, Jari Jalava, Ph.D., Olli Ruuskanen, M.D., Ph.D., and Aino Ruohola, M.D. PD. A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media. N Engl J Med. 2011;364:116–26.

29.   Hoberman A, Paradise JL, Rockette HE, Kearney DH, Bhatnagar S, Shope TR, et al. Shortened antimicrobial treatment for acute Otitis media in young children. N Engl J Med. 2016;375(25):2446–56.

30.   Le Saux N, Robinson JL, Canadian Pediatric Society, Saux N Le, Robinson JL, Society CP. Management of acute otitis media in children six months of age and older. Paediatr Child Health. 2016 Jan;21(1):39–50.

31.   Falagas ME, Vouloumanou EK, Matthaiou DK, Kapaskelis AM, Karageorgopoulos DE. Effectiveness and safety of short-course vs long-course antibiotic therapy for group A β-hemolytic streptococcal tonsillopharyngitis: A meta-analysis of randomized trials. Mayo Clin Proc. 2008 Aug;83(8):880–9.

32.   Skoog Ståhlgren G, Tyrstrup M, Edlund C, Giske CG, Mölstad S, Norman C, et al. Penicillin v four times daily for five days versus three times daily for 10 days in patients with pharyngotonsillitis caused by group A streptococci: Randomised controlled, open label, non-inferiority study. BMJ. 2019;367.

33.   National Institute for Health and Care Excellence (NICE). Sore throat (acute): antimicrobial prescribing [Internet]. NICE Guideline. 2018. Available from: https://www.nice.org.uk/guidance/ng84

34.   Tansarli GS, Mylonakis E. Systematic Review and Meta-analysis of the Efficacy of Short-Course Antibiotic Treatments for Community-Acquired Pneumonia in Adults. Antimicrob Agents Chemother. 2018 Jul 9;62(9):e00365-18.

35.   Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. Am J Respir Crit Care Med. 2019 Oct 1;200(7):E45–67.

36.   Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45–67.

37.   Greenberg D, Givon-Lavi N, Sadaka Y, Ben-Shimol S, Bar-Ziv J, Dagan R. Short-course antibiotic treatment for community-acquired alveolar pneumonia in ambulatory children: a double-blind, randomized, placebo-controlled trial. Pediatr Infect Dis J. 2014 Feb;33(2):136–42.

38.   Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011 Oct;53:617–30.

39.   Le Saux N, Robinson JL, on behalf of the Canadian Pediatric Society ID and IC. Uncomplicated pneumonia in healthy Canadian children and youth: Practice points for management. Paediatr Child Health. 2011 Dec 4;16(7):417–20.

40. Chastre J, Wolff M, Fagon J-Y, Chevret S, Thomas F, Wermert D, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA. 2003 Nov 19;290(19):2588–98.

41. Dimopoulos G, Poulakou G, Pneumatikos IA, Armaganidis A, Kollef MH, Matthaiou DK. Short- vs long-duration antibiotic regimens for ventilator-associated pneumonia: A systematic review and meta-analysis. Chest. 2013;144(6):1759–67.

42. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1;63(5):e61–111.

43. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. Eur Respir J. 2017 Sep 10;50(3):1700582.

44. Martin-Loeches I, Rodriguez AH, Torres A. New guidelines for hospital-acquired pneumonia/ ventilator-associated pneumonia: USA vs. Europe. Curr Opin Crit Care. 2018;24(5):347–52.

45. Global Initiative for Chronic Obstructive Lung Disease. Pocket Guide to COPD Diagnosis, Managememt, and Prevention [Internet]. 2018. Available from: www.goldcopd.org

46. Stolbrink M, Amiry J, Blakey JD. Does antibiotic treatment duration affect the outcomes of exacerbations of asthma and COPD? A systematic review. Chron Respir Dis. 2018 Aug 1;15(3):225–40.

47. El Moussaoui R, Roede BM, Speelman P, Bresser P, Prins JM, Bossuyt PMM. Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: A meta-analysis of double-blind studies. Thorax. 2008 May;63(5):415–22.

48. Hopkinson NS, Molyneux A, Pink J, Harrisingh MC. Chronic obstructive pulmonary disease: diagnosis and management: summary of updated NICE guidance. BMJ. 2019 Jul 29;366:l4486.

49. Wedzicha JA, Miravitlles M, Hurst JR, Calverley PMA, Albert RK, Anzueto A, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2017;49(3).

50. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Heal Pharm. 2013 Jan 1;70(3):195–283.

51. Berriós-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg. 2017;152(8):784–91.

52. Branch-Elliman W, O'Brien W, Strymish J, Itani K, Wyatt C, Gupta K, et al. Association of Duration and Type of Surgical Prophylaxis with Antimicrobial-Associated Adverse Events. JAMA Surg. 2019 Jul 1;154(7):590–8.

53. Yudin M, van Schalkwyk J, Van Eyk N. Antibiotic Therapy in Preterm Premature Rupture of the Membranes. J Obstet Gyenecology Canada. 2009;31(9):863–7.

54.   World Health Organization. Global Guidelines for the Prevention of Surgical Site Infection, second edition. World Heal Organ [Internet]. 2018; Available from: http://www.who.int

55.   Smaill FM, Grivell RM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database Syst Rev. 2014;2014(10).

56.   American College of Obstetricians and Gynecologists. Clinical Management Guidelines for Obstetricians & Gynecologists-Use of Prophylactic Antibiotics in Labor and Delivery. Obstet Gynecol. 2018;132(3):103–19.

57.   Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, et al. Executive summary of the American College of Surgeons/Surgical Infection Society Surgical Site Infection Guidelines -2016 Update. J Am Coll Surg. 2017;18(4):379–82.

58.   Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJC, Baron EJ, et al. 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. Clin Infect Dis. 2010 Jan 15;50(2):133–64.

59.   Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015 May 21;372(21):1996–2005.

60.   Montravers P, Tubach F, Lescot T, Veber B, Esposito-Farèse M, Seguin P, et al. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. Intensive Care Med. 2018 Mar 1;44(3):300–10.

61.   Tinusz B, Szapáry L, Paládi B, Tenk J, Rumbus Z, Pécsi D, et al. Short-Course Antibiotic Treatment Is Not Inferior to a Long-Course One in Acute Cholangitis: A Systematic Review. Dig Dis Sci. 2019 Feb 27;64(2):307–15.

62.   Mazuski JE, Tessier JM, May AK, Sawyer RG, Nadler EP, Rosengart MR, et al. The surgical infection society revised guidelines on the management of intra-abdominal infection. Surg Infect (Larchmt). 2017 Jan 1;18(1):1–76.

63.   Gomi H, Solomkin JS, Schlossberg D, Okamoto K, Takada T, Strasberg SM, et al. Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2018 Jan;25(1):3–16.

64.   Mayumi T, Okamoto K, Takada T, Strasberg SM, Solomkin JS, Schlossberg D, et al. Tokyo Guidelines 2018: management bundles for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2018;25(1):96–100.

65.   Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. Clin Infect Dis. 2019;68(10):E83–E75.

66.   Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011 Mar 1;52(5).

67.   Huttner A, Kowalczyk A, Turjeman A, Babich T, Brossier C, Eliakim-Raz N, et al. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women. JAMA. 2018 May 1;319(17):1781.

68.   Falagas ME, Vouloumanou EK, Samonis G, Vardakas KZ. Fosfomycin. Clin Microbiol Rev. 2016 Apr 9;29(2):321–47.

69.   Tandan M, Cormican M, Vellinga A. Adverse events of fluoroquinolones vs. other antimicrobials prescribed in primary care: A systematic review and meta-analysis of randomized controlled trials. Int J Antimicrob Agents. 2018 Nov 1;52(5):529–40.

70.   Gorelik E, Masarwa R, Perlman A, Rotshild V, Abbasi M, Muszkat M, et al. Fluoroquinolones and Cardiovascular Risk: A Systematic Review, Meta-analysis and Network Meta-analysis. Drug Saf. 2019 Apr 5;42(4):529–38.

71.   Robinson JLJLJL, Finlay JCJC, Lang MEME, Bortolussi R, Bridger NANANA, Martin S, et al. Urinary tract infection in infants and children: Diagnosis and management. Paediatr Child Heal. 2014;19(6):1–7.

72.   Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection-7 days or less versus longer treatment: Systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2013 Oct;68(10):2183–91.

73.   van Nieuwkoop C, van der Starre WE, Stalenhoef JE, van Aartrijk AM, van der Reijden TJKK, Vollaard AM, et al. Treatment duration of febrile urinary tract infection: A pragmatic randomized, double-blind, placebo-controlled non-inferiority trial in men and women. BMC Med. 2017 Dec 3;15(1):1–9.

74.   Kyriakidou KG, Rafailidis P, Matthaiou DK, Athanasiou S, Falagas ME. Short- versus long-course antibiotic therapy for acute pyelonephritis in adolescents and adults: a meta-analysis of randomized controlled trials. Clin Ther. 2008 Oct;30(10):1859–68.

75.   Sandberg T, Skoog G, Hermansson AB, Kahlmeter G, Kuylenstierna N, Lannergard A, et al. Ciprofl oxacin for 7 days versus 14 days in women with acute pyelonephritis: A randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. Lancet. 2012;380(9840):484–90.

76.   Elbaz M, Zadka H, Weiss-Meilik A, Ben-Ami R. Effectiveness and safety of an institutional aminoglycoside-based regimen as empirical treatment of patients with pyelonephritis. J Antimicrob Chemother. 2020 May 25;epub ahead(March).

77.   National Institute for Health and Care Excellence. Pyelonephritis (acute): antimicrobial prescribing [Internet]. 2018. Available from: https://www.nice.org.uk/guidance/ng111/resources/pyelonephritis-acute-antimicrobial-prescribing-pdf-66141593379781

78.   Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC. Antibiotics for acute pyelonephritis in children. Cochrane Database Syst Rev. 2014 Jul 28;28(7):CD003772.

79.   Fox MT, Amoah J, Hsu AJ, Herzke CA, Gerber JS, Tamma PD. Comparative Effectiveness of Antibiotic Treatment Duration in Children With Pyelonephritis. JAMA Netw Open. 2020 May

4;3(5):e203951.

80. Yahav D, Franceschini E, Koppel F, Turjeman A, Babich T, Bitterman R, et al. Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia : A Noninferiority Randomized Controlled Trial. Clin Infect Dis. 2019 Sep 13;69(7):1091–8.

81. Robinson JL, Finlay JC, Lang ME, Bortolussi R, Canadian Paediatric Society, Infectious Diseases and Immunization Committee CPC. Urinary tract infections in infants and children: Diagnosis and management. Paediatr Child Health. 2014 Jun;19(6):315–25.

82. Cranendonk DRR, Opmeer BCC, van Agtmael MAA, Branger J, Brinkman K, Hoepelman AIMIM, et al. Antibiotic treatment for 6 days versus 12 days in patients with severe cellulitis: a multicentre randomized, double-blind, placebo-controlled, non-inferiority trial. Clin Microbiol Infect. 2020 May;26(5):606–12.

83. Hepburn MJ, Dooley DP, Skidmore PJ, Ellis MW, Starnes WF, Hasewinkle WC. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. Arch Intern Med. 2004 Aug 9;164(15):1669–74.

84. Chlebicki MP, Oh CC. Recurrent Cellulitis: Risk Factors, Etiology, Pathogenesis and Treatment. Curr Infect Dis Rep [Internet]. 2014 Sep 1;16(9):422-. Available from: http://link.springer.com/10.1007/s11908-014-0422-0

85. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJCC, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014 Jul 15;59(2).

86. Bernard L, Dinh A, Ghout I, Simo D, Zeller V, Issartel B, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. Lancet (London, England). 2015 Mar 7;385(9971):875–82.

87. Gjika E, Beaulieu J-Y, Vakalopoulos K, Gauthier M, Bouvet C, Gonzalez A, et al. Two weeks versus four weeks of antibiotic therapy after surgical drainage for native joint bacterial arthritis: a prospective, randomised, non-inferiority trial. Ann Rheum Dis. 2019 Aug;78(8):1114–21.

88. Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. Clin Infect Dis. 2015 Jun 8;61(6):e26–46.

89. Coakley G, Mathews C, Field M, Jones A, Kingsley G, Walker D, et al. BSR & BHPR, BOA, RCGP and BSAC guidelines for management of the hot swollen joint in adults. Rheumatology (Oxford). 2006;45(8):1039–41.

90. Peltola H, Pääkkönen M, Kallio P, Kallio MJT. Short- Versus Long-term Antimicrobial Treatment for Acute Hematogenous Osteomyelitis of Childhood. Pediatr Infect Dis J. 2010 Dec;29(12):1123–8.

91. Jagodzinski NA, Kanwar R, Graham K, Bache CE. Prospective evaluation of a shortened regimen of treatment for acute osteomyelitis and septic arthritis in children. J Pediatr Orthop. 2009 Jan;29(5):518–25.

92. Keren R, Shah SS, Srivastava R, Rangel S, Bendel-Stenzel M, Harik N, et al. Comparative Effectiveness of Intravenous vs Oral Antibiotics for Postdischarge Treatment of Acute Osteomyelitis in Children. JAMA Pediatr. 2015 Feb 1;169(2):120.

93. Le Saux N. Diagnosis and management of acute osteoarticular infections in children. Paediatr Child Health. 2018 Jul 18;23(5):336–43.

94. Saavedra-Lozano J, Falup-Pecurariu O, Faust SN, Girschick H, Hartwig N, Kaplan S, et al. Bone and Joint Infections. Pediatr Infect Dis J. 2017 Aug;36(8):788–99.

95. Chong YP, Moon SM, Bang KM, Park HJ, Park SY, Kim MN, et al. Treatment duration for uncomplicated staphylococcus aureus bacteremia to prevent relapse: Analysis of a prospective observational cohort study. Antimicrob Agents Chemother. 2013;57(3):1150–6.

96. Chowdhary G, Dutta S, Narang A. Randomized controlled trial of 7-day vs. 14-day antibiotics for neonatal sepsis. J Trop Pediatr. 2006;52(6):427–32.

97. Holland TL, Arnold C, Fowler VG. Clinical management of staphylococcus aureus bacteremia: A review. JAMA - J Am Med Assoc. 2014 Oct 1;312(13):1330–41.

98. Pragman AA, Kuskowski MA, Abraham JM, Filice GA. Infectious disease consultation for Staphylococcus aureus bacteremia improves patient management and outcomes. Infect Dis Clin Pract. 2012;20(4):261–7.

99. Sherbuk JE, Mcmanus D, Topal JE, Malinis M. Improved mortality in Staphylococcus aureus bacteremia with the involvement of antimicrobial stewardship team and infectious disease consultation. Infect Control Hosp Epidemiol. 2019;40(8):932–5.

100. Chesshyre E, Goff Z, Bowen A, Carapetis J. The prevention, diagnosis and management of central venous line infections in children. Vol. 71, Journal of Infection. 2015. p. S59–75.

101. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the infectious diseases society of America. Clin Infect Dis. 2009;49(1):1–45.

102. Hebeisen UP, Atkinson A, Marschall J, Buetti N. Catheter-related bloodstream infections with coagulase-negative staphylococci: Are antibiotics necessary if the catheter is removed? Antimicrob Resist Infect Control. 2019;8(1):1–8.

103. Lebeaux D, Fernández-Hidalgo N, Chauhan A, Lee S, Ghigo JM, Almirante B, et al. Management of infections related to totally implantable venous-access ports: Challenges and perspectives. Lancet Infect Dis. 2014;14(2):146–59.

104. Havey TC, Fowler RA, Daneman N. Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. Crit Care. 2011;15(6):R267.

105. Daneman N, Rishu AH, Pinto R, Aslanian P, Bagshaw SM, Carignan A, et al. 7 versus 14 days of antibiotic treatment for critically ill patients with bloodstream infection: A pilot randomized clinical trial. Trials. 2018 Feb 17;19(1).

106. Chotiprasitsakul D, Han JH, Cosgrove SE, Harris AD, Lautenbach E, Conley AT, et al. Comparing the

Outcomes of Adults with Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score-Matched Cohort. Clin Infect Dis. 2018;66(2):172–7.

107. Tansarli GS, Andreatos N, Pliakos EE, Mylonakis E. A Systematic Review and Meta-analysis of Antibiotic Treatment Duration for Bacteremia Due to Enterobacteriaceae. Antimicrob Agents Chemother. 2019 Feb 25;63(5):e02495-18.

108. Fabre V, Amoah J, Cosgrove SE, Tamma PD. Antibiotic Therapy for Pseudomonas aeruginosa Bloodstream Infections: How Long Is Long Enough? Clin Infect Dis. 2019 Nov 13;69(11):2011–4.

109. Von Dach E, Albrich WC, Brunel AS, Prendki V, Cuvelier C, Flury D, et al. Effect of C-Reactive Protein-Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on 30-Day Clinical Failure Rate in Patients with Uncomplicated Gram-Negative Bacteremia: A Randomized Clinical Trial. JAMA - J Am Med Assoc. 2020;323(21):2160–9.