Ampicillin

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.1. Access group antibiotics

EMLc | ATC codes: J01CA01

Indication	Peritonitis ICD11 code: DC50.Z
INN	Ampicillin
Medicine type	Chemical agent
Antibiotic groups	A ACCESS
List type	Core
Formulations	**Parenteral > General injections > unspecified:** 500 mg in vial (as sodium salt) powder for injection (EMLc) ; 1 g in vial (as sodium salt) powder for injection (EMLc)
EML status history	First added in 2021 (TRS 1035)
Sex	All
Age	Children (1 month - 12 years)
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Ampicillin
DrugBank	Ampicillin

Expert Committee recommendation

1. Application to extend the indications for ampicillin and gentamicin on the EMLc to include treatment of complicated intra-abdominal infections in neonates and children. The Committee noted that ampicillin and gentamicin are recommended as treatment options for complicated intra-abdominal infections in children in several WHO and other international guidelines. In addition, there is extensive clinical experience using ampicillin and gentamicin, usually combined with metronidazole, for this indication in the paediatric population. To ensure alignment of the EMLc with these recommendations, the Expert Committee therefore recommended extending the indications for ampicillin and gentamicin on the EMLc to include treatment of complicated intra-abdominal infections in children, as first-choice treatment options. ---------- 2. Application to include new higher strength formulations of various antibiotics currently included on the EML to better align with the dosing needs of adults. The Expert Committee recommended the addition of the new strength formulations of amoxicillin, cefalexin, ceftriaxone, ciprofloxacin, clindamycin, phenoxymethylpenicillin and vancomycin to the existing listings of these medicines on the EML for the indications for which they are proposed. The Expert Committee recommended the addition of new higher strength formulations of ceftriaxone injection and ciprofloxacin solid oral dosage form to the existing listings on the EML for use in the treatment of adults and adolescents with complicated intra-abdominal infections. The Committee noted that the proposed strength formulations are higher than those currently included on the Model List, and are appropriate and aligned to meet recommended doses for treatment of adults, with the advantages of a reduced pill burden in the case of oral formulations, and facilitating a simplified and safer dose administration in the case of intravenous formulations. ---------- 3. Application to include a new

strength formulation (875 mg + 125 mg) of amoxicillin + clavulanic acid on the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults. The Expert Committee noted that the proposed formulation of amoxicillin + clavulanic acid will provide a higher dose of amoxicillin, without increasing the dose of clavulanic acid, and is particularly suitable for more unwell patients. In addition, the Committee noted that a higher ratio of amoxicillin to clavulanic acid is generally associated with less diarrhoea, a recognized adverse effect of this combination. The addition of this new formulation will also allow recommended amoxicillin doses to be achieved with a reduced pill burden for patients. The Committee therefore recommended the addition of the new strength formulation of amoxicillin + clavulanic acid 875 mg + 125 mg tablets to the core list of the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults. ---------- 4. Following the review of square box listings on the EML and EMLc, the Expert Committee recommended imipenem + cilastatin be specified as a therapeutic alternative under the square box listing for meropenem on the EML and EMLc for this indication.

Background

1. Application to extend the indications for ampicillin and gentamicin on the EMLc to include treatment of complicated intra-abdominal infections. Ampicillin and gentamicin are currently included in the EML and EMLc for multiple other indications. The combination of ampicillin and gentamicin is listed as first choice for: acute malnutrition in infants, children or adolescents; severe community-acquired pneumonia in children; and sepsis in neonates and children. Ampicillin is also listed as second choice for the treatment of acute bacterial meningitis in children and adults, and gentamicin is also listed as second choice for surgical prophylaxis in children and adults, and for gonococcal infection. Inclusion of ampicillin and gentamicin for the treatment of intra-abdominal infections in children will align the EMLc with current WHO guidance documents, in particular with the Pocket book of hospital care for children (1). Community-acquired intra-abdominal infections occur in children worldwide and are caused by a variety of conditions, the most frequent of which are acute appendicitis and intestinal perforation occurring as a complication of enteric fever in endemic settings (2). Acute appendicitis is particularly frequent in children (3) and most cases (70%) are uncomplicated and with a very low short-term postappendectomy mortality (1%) However, the incidence of appendicitis varies across settings; while a decrease has been observed in western Europe and North America since the 1990s, increasing trends are reported in Asia, South America and the Middle East (4). ---------- 2. Application to include new higher strength formulations of various antibiotics currently included on the EML to better align with the dosing needs of adults. The application requested the inclusion of new higher strengths of the following antibiotics on the EML to better align with the dosing needs of adults: Amoxicillin: solid oral dosage form 1 g Cefalexin: solid oral dosage form 500 mg Ceftriaxone: powder for injection 2 g Ciprofloxacin: solid oral dosage form 500 mg Clindamycin: injection 600 mg/4 mL, 900 mg/6 mL Phenoxymethylpenicillin: tablet 500 mg Vancomycin: powder for injection 500 mg, 1 g All of the antibiotics for which additional strength formulations are proposed are currently included on the EML is various other formulations and strengths for the indications described below (1). ---------- 3. Application to include a new strength formulation (875 mg + 125 mg) of amoxicillin + clavulanic acid on the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults. Amoxicillin + clavulanic acid, in multiple formulations, has been included on the Model Lists since 1997. Amoxicillin + clavulanic acid is currently included on the EML and EMLc as a first- or second-choice empiric treatment for several bacterial infections. The EML currently recommends amoxicillin + clavulanic acid as a second-choice option for community-acquired pneumonia because in most cases there is no need to broaden the spectrum of antibacterial activity to cover more resistant pathogens and amoxicillin (or phenoxymethylpenicillin) can safely be used. The other reason is that amoxicillin + clavulanic is associated with more frequent side-effects than amoxicillin alone – mostly diarrhoea, including Clostridioides difficile infection (1). Amoxicillin + clavulanic acid is also recommended in the EML as a first-choice option for the empiric treatment of mild, community-acquired intra-abdominal infections in patients who are not critically ill and there is no suspicion of sepsis or septic shock. Community-acquired pneumonia is common worldwide and is a leading cause of morbidity and mortality, with an especially high burden in low-income countries (2). According to the Global Burden of Disease study, in 2017 among all ages and sexes combined, an estimated 471 million new cases of lower respiratory tract infections (including community-acquired pneumonia) occurred globally (3). The most

common causative pathogen worldwide is Streptococcus pneumoniae, and viral co-infection is not unusual. In general, the incidence of community-acquired pneumonia and risk of death increase with age (4). Community-acquired pneumonia is curable and preventable. Most people who develop this infection can be successfully treated with a 5-day antibiotic regimen. Vaccines to prevent community-acquired pneumonia caused by certain pathogens (e.g. Streptococcus pneumoniae, Haemophilus influenzae type b and influenza virus). Intra-abdominal infections include uncomplicated infections with no involvement of the peritoneal cavity and no abscess formation and complicated infections with involvement of the peritoneal cavity and/or abscess formation. The most frequent intraabdominal infections include acute appendicitis, acute cholecystitis, acute cholangitis, acute diverticulitis and pyrogenic liver abscess. Treatment of these infections usually requires a combination of antibiotics and surgery to achieve adequate control of the source of infection.

Summary of evidence

1. Application to extend the indications for ampicillin and gentamicin on the EMLc to include treatment of complicated intra-abdominal infections. Both ampicillin and gentamicin are commonly used in neonates and children and the evidence of benefits has already been extensively revised by the EML Working Group and Expert Committee. In the context of the review of antibacterial medicines undertaken for the 2017 EML update, aminoglycosides were identified as alternative, targeted treatment options to the core antibiotics listed for complicated intra-abdominal infections, based on local resistance data. The review noted that ampicillin could be considered as a treatment option if additional enterococcal coverage is needed, e.g. because the regimen used would otherwise not be covering Enterococcus spp. (e.g. ceftriaxone plus metronidazole). Since the systematic reviews gave inconclusive results, the treatment options proposed for adults and children were based on the review of national and international guidelines, notably the 2010 Infectious Diseases Society of America/Surgical Infection Society guidelines (5) and the guidelines developed at the 2010 consensus conference of the World Society of Emergency Surgery (6). In 2017, the Surgical Infection Society revised the 2010 guidelines (without Infectious Diseases Society of America collaboration) (7). The revised guidelines confirmed aminoglycoside-based regimens for neonates; in particular, the guidelines say, “Use ampicillin, gentamicin, and either metronidazole or clindamycin; ampicillin, cefotaxime, and either metronidazole or clindamycin; or meropenem in paediatric patients less than one month of age (45 weeks postconceptional age)” (7). The evidence of harms and toxicity has already been extensively reviewed by the EML Working Group and Expert Committee and a separate review was not done for this application. No additional evidence has emerged that would discourage use of ampicillin and gentamicin for treatment of intra-abdominal infections in neonates and children. ---------- 2. Application to include new higher strength formulations of various antibiotics currently included on the EML to better align with the dosing needs of adults. Amoxicillin: solid oral dosage form 1 g Most adult and adolescent patients with mild community-acquired pneumonia or acute bacterial sinusitis can be successfully treated with amoxicillin 1 g every 8 hours for 5 days. The proposed 1 g oral formulation will allow for a reduced pill burden to complete the course of treatment compared with the currently listed 500 mg strength formulation, and should facilitate adherence to treatment. Cefalexin: solid oral dosage form 500 mg Most adult patients diagnosed with exacerbations of chronic obstructive pulmonary disease, can be successfully treated with cefalexin 500 mg every 12 hours for 5 days. For bacterial pharyngitis and mild skin and soft tissue infections, most adult and adolescent patients can be successfully treated with cefalexin 500 mg every 8 hours for 5 days. The proposed 500 mg oral formulation will allow for a reduced pill burden to complete a course of treatment compared with the currently listed 250 mg strength formulation, and should facilitate adherence to treatment. Ceftriaxone: powder for injection 2 g This higher strength formulation is preferable for the treatment of certain infections because it maximizes the chances of bacterial eradication in order to achieve clinical success. For example, in the case of acute bacterial meningitis, a ceftriaxone dose of 2 g every 12 hours is needed to achieve adequate concentrations of the drug in the central nervous system. The recommended duration of treatment is 10 days. For adult patients with hospital-acquired pneumonia and no risk factors for multidrug-resistant infections, ceftriaxone 2 g a day for 7 days is a recommended treatment regimen. For complicated intra-abdominal infections, ceftriaxone 2 g per day for 5 days (in combination with metronidazole) is a recommended treatment in cases where extended-spectrum beta-lactamase strains are not suspected. For severe cases of enteric fever, if ceftriaxone is used, a dose of 2 g per day

for 10 days is recommended. Ciprofloxacin: solid oral dosage form 500 mg The proposed higher strength formulation will benefit adult and adolescent patients prescribed ciprofloxacin for infections including acute invasive bacterial diarrhoea, cholera, complicated intra-abdominal infections, enteric fever, low-risk febrile neutropenia and upper urinary tract infections. Treatment regimens recommend ciprofloxacin doses of 500 mg every 12 hours for 3, 5 or 7 days, depending on the indication or, in the case of cholera, a single dose of 1 g. The proposed 500 mg oral formulation will allow for a reduced pill burden to complete the course of treatment compared with the currently listed 250 mg strength formulation, and should facilitate adherence to treatment. Clindamycin: injection 600 mg/4 mL, 900 mg/6 mL The higher strength formulations of clindamycin are preferable for the treatment of bone and joint infections to maximize the chance of bacterial eradication in order to achieve clinical success. For adults and adolescents diagnosed with osteomyelitis, clindamycin is an acceptable treatment option when methicillin-resistant Staphylococcus aureus (MRSA) is suspected or confirmed when antimicrobial susceptibility of MRSA to clindamycin is proven or likely. Intravenous clindamycin at a dose of 600 mg every 8 hours for 4–6 weeks is a recommended dosage regimen in most cases. Clindamycin may also be used in patients allergic to penicillin. Phenoxymethylpenicillin: solid oral dosage form 500 mg Most adult and adolescent patients with mild community-acquired pneumonia, bacterial pharyngitis or dental infections can be successfully treated with phenoxymethylpenicillin 500 mg every 6 hours for 5 days; however, a longer treatment duration may be recommended in some circumstances. The proposed 500 mg strength oral formulation will allow for a reduced pill burden to complete the course of treatment compared with the currently listed 250 mg strength formulation and should facilitate adherence to treatment. Vancomycin: powder for injection 500 mg, 1 g For adult and adolescent patients with high-risk febrile neutropenia when MRSA infection is suspected, weight-based dosing of vancomycin is recommended (15–20 mg/kg every 12 hours). The 500 mg and 1 g strength formulations will allow for the achievement of recommended dose using fewer vials, compared with the currently listed 250 mg strength. ----------
3. Application to include a new strength formulation (875 mg + 125 mg) of amoxicillin + clavulanic acid on the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults. Benefits: The rationale for the inclusion of the 875 mg + 125 mg formulation of amoxicillin + clavulanic acid is to increase the amoxicillin to clavulanic acid ratio from 4:1 (500 mg + 125 mg formulation) to 7:1. There is limited evidence about differences in clinical and microbiological efficacy of the different ratios of amoxicillin to clavulanic acid. However, the advantage of the 7:1 ratio formulation is increased exposure to amoxicillin without increased exposure to clavulanic acid. The reason for limiting exposure to clavulanic acid is that increasing its dose exposes patients to a higher risk of gastrointestinal side-effects (especially diarrhoea) with only a minimal increase in efficacy against beta-lactamases (5). Amoxicillin + clavulanic acid is recommended for the treatment of mild community-acquired pneumonia because it is effective against the most likely bacterial pathogens responsible for this syndrome (notably Streptococcus pneumoniae and Haemophilus influenzae, including strains that produce beta-lactamases) and because it is safe, inexpensive and readily available in many settings. In general, amoxicillin alone remains effective against Streptococcus pneumoniae isolates in most cases because these isolates are not known to produce beta-lactam enzymes (5). However, other pathogens (mostly Haemophilus influenzae) produce beta-lactamases in a large proportion of cases (6,7) and could therefore be resistant to amoxicillin alone. Such cases would therefore benefit from treatment with amoxicillin + clavulanic acid. A key element of the treatment of community-acquired pneumonia is to maximize the chance of bacterial eradication in order to achieve clinical success and to reduce the risk of resistance developing. For beta-lactam agents, maximal clinical efficacy depends on the time that the plasma concentration of the drug remains above the level of the minimal inhibitory concentration (MIC) for the target pathogen (T>MIC). For amoxicillin, a T>MIC of at least 30–40% between dosing intervals is required to effectively treat most pathogens responsible of mild community-acquired pneumonia. Therefore, the advantage of a formulation with a higher dose of amoxicillin is that it can improve the efficacy of amoxicillin + clavulanic acid for the treatment of pathogens with higher MICs (8). In particular, the 875 mg +125 mg formulation (given three times a day) would achieve bacteriological efficacy against strains with amoxicillin MICs of up to 4 mg/L (T>MIC 34% for MICs of 4 mg/L, 57% for MICs of 2 mg/L and 69% for MICs of 1 mg/L), while the 500 mg + 125 mg formulation (three times a day) would only achieve bacteriological efficacy against strains with MICs of up to 2 mg/L (T>MIC 43% for MICs of 2 mg/L and 55% for MICs of 1 mg/L) (9). An additional advantage of amoxicillin + clavulanic acid that applies to both its use for the treatment of mild community-acquired pneumonia and mild community-acquired intra-abdominal infections is its lower potential for resistance compared

with other antibiotic options that are sometimes used for the treatment of these syndromes, most notably fluoroquinolones. In patients with community-acquired pneumonia, amoxicillin + clavulanic acid is a particularly valid option in patients who would be at higher risk of poor outcomes if initial empiric treatment were inadequate (e.g. patients with multiple comorbidities who are often more vulnerable to infections or patients with a higher risk of resistant infections due to frequent antibiotic exposure). The clinical and bacteriological efficacy of the 875 mg +125 mg formulation is high (> 90% for clinical efficacy and 80–90% for microbiological efficacy at the end of treatment in trials where this formulation has been used (10)) including in settings with a high prevalence of penicillin-resistant Streptococcus pneumoniae (11). Many patients with intra-abdominal infections may not be able to tolerate oral treatment in the initial phase of treatment, especially those with complicated infections that require surgery; therefore, patients are often started on intravenous treatment. For the treatment of intra-abdominal infections, the use of the 875 mg +125 mg oral formulation of amoxicillin + clavulanic would apply in only certain circumstances: initial empiric treatment of mild cases in patients who can tolerate oral treatment (e.g. patients managed in the outpatient setting) and intravenous to oral switch to complete the course of treatment initiated with intravenous therapy. Amoxicillin + clavulanic acid has a range of antibacterial activity that allows for the coverage of the most likely pathogens responsible for intra-abdominal infections (most notably Escherichia coli, enteric streptococci and anaerobic bacteria) even though amoxicillin + clavulanic resistance rates among E. coli isolates may be of concern in some settings (12). No clinical trial was identified that directly compared the efficacy of different doses of oral amoxicillin + clavulanic acid for intra-abdominal infections. However, the 875 mg + 125 mg oral formulation has been used in several trials, especially for the treatment of uncomplicated acute appendicitis with antibiotics alone (13,14), while lower doses of amoxicillin + clavulanic acid (500 mg + 25 mg) are generally used when treatment is started intravenously and then later switched to oral treatment (15). As detailed above for community-acquired pneumonia, the use of a higher dose of amoxicillin in combination with clavulanic acid, improves efficacy for the treatment of pathogens with higher MICs; therefore, the 875 mg +125 mg is preferable to achieve cure and reduce the risk of resistance developing when oral treatment is chosen. In serious infections, such as intra-abdominal infections, high protein binding of beta-lactams and rapid elimination can reduce the amount of antibiotic available in both the plasma and tissue, increasing the risk of treatment failure, especially in cases of pathogens with higher MICs (16). Therefore, doses should be increased and the interval between doses reduced, especially when oral beta-lactam treatment is used. In order to appropriately treat resistant pathogens, the daily dose of amoxicillin can be more safely increased than the dose of other antibiotics used to treat intra-abdominal infections such as fluoroquinolones. Fluoroquinolones have a worse safety profile, both for gastrointestinal and mild neurological reactions (nausea, vomiting, dizziness, insomnia and headache) but also for more serious adverse events such as tendinitis and tendon rupture (17), risk of arrhythmias (18) or possibly rupture of an aortic aneurysm (19). Harms: Potential harms associated with the 875 mg + 125 mg formulation of amoxicillin + clavulanic acid are not expected to differ from the 500 mg + 125 mg preparation, as the dose of clavulanic acid (responsible for common side-effects such as diarrhoea) remains the same. Moreover, in published trials, even higher doses of amoxicillin + clavulanic acid (2000 mg + 125 mg) have been safely used and were well tolerated (10).

Guidelines

1. Application to extend the indications for ampicillin and gentamicin on the EMLc to include treatment of complicated intra-abdominal infections. The WHO Pocket book of hospital care for children includes the following recommendations for treatment of intra-abdominal infections in children (1). • Appendicitis: Give antibiotics once the diagnosis is established: ampicillin (25–50 mg/kg intramuscular or intravenous four times a day), gentamicin (7.5 mg/kg intramuscular or intravenous once a day) and metronidazole (10 mg/kg intravenous or oral three times a day). • Necrotizing enterocolitis: Start antibiotics and give ampicillin (or penicillin) plus gentamicin plus metronidazole for 10 days. The WHO recommendations on newborn health recommend that young neonates with suspected necrotizing enterocolitis should be treated with intravenous or intramuscular ampicillin (or penicillin) and gentamicin as first-line antibiotic treatment for 10 days. (Strong recommendation, low quality of evidence) (8). ---------- 2. Application to include new higher strength formulations of various antibiotics currently included on the EML to better align with the dosing needs of adults. Not applicable. ---------- 3. Application to include a new

strength formulation (875 mg + 125 mg) of amoxicillin + clavulanic acid on the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults. Not applicable.

Committee considerations

1. Application to extend the indications for ampicillin and gentamicin on the EMLc to include treatment of complicated intra-abdominal infections. As the proposed medicines are already included on the Model Lists and on many national essential medicine lists, a review of the comparative costs and cost–effectiveness was not done. Ampicillin and gentamicin have regulatory approval globally and are widely available in brand and generic forms. ---------- 2. Application to include new higher strength formulations of various antibiotics currently included on the EML to better align with the dosing needs of adults. All proposed formulations are approved by several regulatory agencies including the US Food and Drug Administration and European Medicines Agency, and are available in most countries. ---------- 3. Application to include a new strength formulation (875 mg + 125 mg) of amoxicillin + clavulanic acid on the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults. There are several suppliers of the 875 mg +125 mg formulation globally at a cost of about US$ 10 per pack (12 tablets) in high-income countries. Amoxicillin + clavulanic acid 875 mg + 125 mg has regulatory approval globally and is available in most countries.

EML recommendations: Peritonitis

First choice	Second choice
MILD-MODERATE	
ampicillin	ciprofloxacin
amoxicillin + clavulanic acid	
ceftriaxone	
cefotaxime	
SEVERE	
piperacillin + tazobactam	meropenem
ampicillin	
ceftriaxone	
cefotaxime	

1. Application to extend the indications for ampicillin and gentamicin on the EMLc to include treatment of complicated intra-abdominal infections.

1. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. Second

edition. Geneva, World Health Organization; 2013 (https://apps.who.int/iris/handle/10665/81170, accessed 13 August 2021).
2. Seyi-Olajide JO, Ezidiegwu U, Ameh EA. Burden of complicated intra-abdominal infections in children in Nigeria: recent experience and systematic review. Surg Infect (Larchmt). 2020;21(6):501–8.
3. Kotaluoto S, Ukkonen M, Pauniaho SL, Helminen M, Sand J, Rantanen T. Mortality related to appendectomy; a population based analysis over two decades in Finland. World J Surg. 2017;41(1):64–9.
4. Ferris M, Quan S, Kaplan BS, Molodecky N, Ball CG, Chernoff GW, et al. The global incidence of appendicitis: a systematic review of population-based studies. Ann Surg. 2017;266(2):237–41.
5. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, 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;50(2):133–64.
6. Sartelli M, Viale P, Koike K, Pea F, Tumietto F, van Goor H, et al. WSES consensus conference: guidelines for first-line management of intra-abdominal infections. World J Emerg Surg. 2011;6:2.
7. 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;18(1):1–76.
8. WHO recommendations on newborn health: guidelines approved by the WHO Guidelines Review Committee. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/259269, accessed 13 August 2021).

---

2. Application to include new higher strength formulations of various antibiotics currently included on the EML to better align with the dosing needs of adults.

1. WHO Model List of Essential Medicines. 21st List. Geneva, World Health Organization; 2019. (https://apps.who.int/iris/handle/10665/330668, accessed 13 August 2021).

---

3. Application to include a new strength formulation (875 mg + 125 mg) of amoxicillin + clavulanic acid on the EML for the treatment of mild community-acquired pneumonia and intra-abdominal infections in adults.

1. Salvo F, Polimeni G, Moretti U, Conforti A, Leone R, Leoni O, et al. Adverse drug reactions related to amoxicillin alone and in association with clavulanic acid: data from spontaneous reporting in Italy. J Antimicrob Chemother. 2007;60(1):121–6.
2. Peyrani P, Mandell L, Torres A, Tillotson GS. The burden of community-acquired bacterial pneumonia in the era of antibiotic resistance. Expert Rev Respir Med. 2019;13(2):139–52.
3. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1789–858.
4. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67(1):71–9.
5. Huttner A, Bielicki J, Clements MN, Frimodt-Møller N, Muller AE, Paccaud JP, et al. Oral amoxicillin and amoxicillin–clavulanic acid: properties, indications and usage. Clin Microbiol Infect. 2020;26(7):871–9.
6. Jacobs MR, Felmingham D, Appelbaum PC, Grüneberg RN. The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. J Antimicrob Chemother. 2003;52(2):229–46.
7. Leven M, Coenen S, Loens K, Lammens C, Coenjaerts F, Vanderstraeten A, et al. Aetiology of lower respiratory tract infection in adults in primary care: a prospective study in 11 European countries. Clin Microbiol Infect. 2018;24(11):1158–63.
8. Woodnutt G, Berry V. Two pharmacodynamic models for assessing the efficacy of amoxicillin-clavulanate against experimental respiratory tract infections caused by strains of Streptococcus pneumoniae. Antimicrob Agents Chemother. 1999;43(1):29–34.
9. White AR, Kaye C, Poupard J, Pypstra R, Woodnutt G, Wynne B. Augmentin (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent. J Antimicrob Chemother. 2004;53(Suppl 1):i3–20.
10. File TM, Jr., Lode H, Kurz H, Kozak R, Xie H, Berkowitz E. Double-blind, randomized study of the efficacy and safety of oral pharmacokinetically enhanced amoxicillin-clavulanate (2000/125 milligrams) versus those of amoxicillin-clavulanate (875/125 milligrams), both given twice daily for 7 days, in treatment of bacterial community-acquired pneumonia in adults. Antimicrob Agents Chemother. 2004;48(9):3323–31.
11. Siquier B, Sánchez-Alvarez J, García-Mendez E, Sabriá M, Santos J, Pallarés R, et al. Efficacy and safety of twice-daily pharmacokinetically enhanced amoxicillin/clavulanate (2000/125 mg) in the treatment of adults with community-acquired pneumonia in a country with a high prevalence of penicillin-resistant Streptococcus pneumoniae. J Antimicrob Chemother. 2006;57(3):536–45.
12. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, 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;50(2):133–64.
13. Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. Lancet. 2011;377(9777):1573–9.
14. Di Saverio S, Sibilio A, Giorgini E, Biscardi A, Villani S, Coccolini F, et al. The NOTA Study (Non Operative Treatment for Acute Appendicitis): prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. Ann Surg. 2014;260(1):109–17.

15. Daniels L, Ünlü Ç, de Korte N, van Dieren S, Stockmann HB, Vrouenraets BC, et al. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. Br J Surg. 2017;104(1):52–61.
16. Mazzei T, Novelli A. Pharmacological rationale for antibiotic treatment of intra-abdominal infections. J Chemother. 2009;21(Suppl 1):19–29.
17. Wise BL, Peloquin C, Choi H, Lane NE, Zhang Y. Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. Am J Med. 2012;125(12):1228.e23–e28.
18. 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;42(4):529–38.
19. Noman AT, Qazi AH, Alqasrawi M, Ayinde H, Tleyjeh IM, Lindower P, et al. Fluoroquinolones and the risk of aortopathy: a systematic review and meta-analysis. Int J Cardiol. 2019;274:299–302.

