AMOXICILLIN

Indications

Therapeutic indications of amoxicillin:

1) Amoxicillin is indicated for the treatment of bacterial infections caused by susceptible pathogens in the following conditions:
    a. Respiratory tract infections (pharyngitis, tonsillitis, sinusitis, acute and chronic otitis media, acute and chronic bronchitis, tracheobronchitis, bronchopneumonia, pneumonia, bronchiectasis, lung abscess). In the treatment of acute otitis media (AOM), amoxicillin is the drug of choice, either alone or in combination with clavulanic acid.
    b. Otorhinolaryngological and stomatological infections
    c. Urogenital tract infections (cystitis, urethritis, pyelonephritis, gonorrhea)
    d. Skin and soft tissue infections
    e. Gastrointestinal infections, including biliary infections, salmonellosis
    f. Splenic infections
    g. Septicemia
    h. Peritonitis
    i. Endocarditis
    j. Listeria meningitis
    k. Actinomycosis
    l. Typhoid and paratyphoid fever
    m. Postoperative sepsis
2) Amoxicillin is indicated for the eradication of Helicobacter pylori in combination with metronidazole, omeprazole, or bismuth subsalicylate plus metronidazole;
3) Amoxicillin is indicated for surgical prophylaxis (amoxicillin plus clavulanic acid);
4) Amoxicillin is indicated for the treatment of Chlamydia infection in pregnant patients with erythromycin intolerance (Morbid. Mortal. Weekly Rep., 1993);
5) Amoxicillin is indicated for the treatment of Lyme disease, especially in children under 8 years of age and in pregnant or breastfeeding women. Amoxicillin is used as an alternative to doxycycline when the disease presents with erythema migrans, neurological involvement (facial nerve paralysis), cardiac involvement (first-degree AV block, PR <300 msec), and arthritis without neurological symptoms.

Dosage

The dosage of amoxicillin varies depending on the type of bacterial infection, the age of the patient, and renal function. Below are therapeutic guidelines for amoxicillin.

Monotherapy

Bacterial infections susceptible to amoxicillin

Oral administration.

Adults, children (weight ≥40 kg): 500 mg every 8 hours (1500 mg/day) or 1 g every 12 hours (2 g/day) of amoxicillin.

Children (up to 10 years): 125-250 mg every 8 hours of amoxicillin.

Children (less than 20 kg in weight): 20-40 mg/kg/day of amoxicillin.

Intramuscular administration.

Adults, children (weight ≥40 kg): 500 mg every 12 hours (1 g/day) of amoxicillin. Children (weight <40 kg): 50-100 mg/kg/day of amoxicillin in 2-3 administrations. Intravenous administration

Adults, children (weight ≥40 kg): 500 mg of amoxicillin every 8 hours (1500 mg/day) via slow infusion; in severe infections, increase the dose to 1 g IV every 6 hours with an infusion duration of 3-4 minutes or slow infusion over 30-60 minutes.

Children (weight <40 kg): up to a maximum of 100 mg/kg/day of amoxicillin in 2-4 administrations (25 mg/kg every 6 hours) via a 30-minute infusion or slow intravenous injection. In severe infections, the dosage may be doubled, to be administered only as a 30-minute infusion.

Children (up to 3 months): maximum dose of 50 mg/kg of amoxicillin every 8 hours via a 30-minute IV infusion.

Premature infants: maximum dose of 50 mg/kg of amoxicillin every 12 hours via a 30-minute IV infusion.

Renal impaired patients

Oral administration.

Adults, children (weight ≥40 kg) (CLcr: 10-30 ml/min): 500 mg of amoxicillin every 12 hours (1 g/day).

Adults, children (weight ≥40 kg) (CLcr < 10 ml/min): 500 mg/day of amoxicillin as a single administration.

Adults, children (weight ≥40 kg) (peritoneal dialysis): maximum dose of 500 mg/day of amoxicillin as a single administration.

Children (weight <40 kg; CLcr 10-30 ml/min): 30 mg/kg of amoxicillin to be divided into two administrations every 12 hours.

Children (weight <40 kg; CLcr <10 ml/min): 15 mg/kg/day of amoxicillin as a single administration.

Children (weight <40 kg, hemodialysis): 15 mg/kg/day of amoxicillin as a single administration. Prior to dialysis, an additional dose of 15 mg/kg should be administered, followed by an equal dose after the dialysis session.

Intramuscular administration.

Adults, children (weight ≥40 kg) (CLcr: 10-30 ml/min): 500 mg of amoxicillin every 12 hours (1 g/day).

Adults, children (weight ≥40 kg) (CLcr < 10 ml/min): 500 mg/day of amoxicillin as a single administration.

Adults, children (weight ≥40 kg) (peritoneal dialysis): 500 mg/day of amoxicillin as a single administration.

Adults, children (weight ≥40 kg) (hemodialysis): 500 mg during dialysis, 500 mg of amoxicillin at the end of the dialysis session, followed by 500 mg every 24 hours.

Children (weight <40 kg; CLcr: 10-30 ml/min): 30 mg/kg/day of amoxicillin in 2 daily administrations.

Children (weight <40 kg; CLcr < 10 ml/min): 15 mg/kg/day of amoxicillin as a single administration.

Children (weight <40 kg; peritoneal dialysis): 15 mg/kg/day of amoxicillin as a single administration.

Children (weight <40 kg; hemodialysis): an initial dose of 25 mg/kg of amoxicillin, followed by 12.5 mg/kg at the end of the dialysis. Maintenance dose of 25 mg/kg/day as a single administration.

Intravenous Administration

Adults, children (weight ≥40 kg) (CLcr: 10-30 ml/min): Initial dose of 1 g of amoxicillin followed by 1 g/day divided into 2 daily doses every 12 hours (maintenance dose).

Adults, children (weight ≥40 kg) (CLcr <10 ml/min): Initial dose of 1 g of amoxicillin followed by 500 mg/day as a single administration (maintenance dose). Adults, children (weight ≥40 kg) (peritoneal dialysis): Initial dose of 1 g of amoxicillin followed by 500 mg/day as a single administration (maintenance dose). Adults, children (weight ≥40 kg) (hemodialysis): 1 g of amoxicillin at the end of dialysis, followed by a maintenance dose of 500 mg every 24 hours.

Children (weight 40 kg) (CLcr: 10-30 ml/min): 50 mg/kg/day of amoxicillin divided into two daily doses every 12 hours.

Children (weight <40 kg; CLcr < 10 ml/min): 25 mg/kg/day of amoxicillin as a single administration.

Children (weight <40 kg; peritoneal dialysis): 25 mg/kg/day of amoxicillin as a single administration.

Children (weight <40 kg; hemodialysis): Initial dose of 25 mg/kg of amoxicillin followed by 12.5 mg/kg at the end of dialysis. Maintenance dose of 25 mg/kg/day as a single administration.

Upper respiratory tract and skin infections

Oral administration.

Adults: 250-500 mg of amoxicillin every 8 hours (750-1500 mg/day).

Children: 20-40 mg/kg/day of amoxicillin divided every 8 hours.

Acute otitis media

Oral administration.

Children: 50 mg/kg/day of amoxicillin, which can be increased to 80-90 mg/kg/day. Divide the total daily dose into three administrations and continue the therapy for 10 days. In some patients, antibiotic therapy can be limited to 5-7 days if the risk of amoxicillin resistance is low. To enhance treatment adherence, amoxicillin can be administered twice daily instead of three times daily.

Lower respiratory tract infections

Oral administration.

Adults, children (over 20 kg): 500 mg of amoxicillin every 8 hours (1500 mg/day).

Children (older than one month and weighing less than 20 kg): 40 mg/kg/day of amoxicillin, divided into equal doses and administered every 8 hours.

Dental abscess

Oral administration.

Adults: 3 g of amoxicillin, to be repeated after 8 hours.

Complicated cystitis

Oral administration.

Adults: 3 g/day of amoxicillin, divided into three daily administrations. Administer the antibiotic for 5 days.

Urinary tract infections in pregnancy

Oral administration.

Adults: 3 g/day of amoxicillin, divided into three daily administrations. Administer the antibiotic for 5 days.

Gonorrhea

Oral administration.

Adults and adolescents (over 45 kg): 3 g of amoxicillin as a single administration, in combination with probenecid (1 g administered 30-60 minutes prior).

Adolescents (12 years and older, weighing less than 45 kg): 50 mg/kg of amoxicillin as a single administration, in combination with probenecid (25 mg/kg). Do not exceed 3 g of amoxicillin and 1 g of probenecid.

Chlamydia infection in pregnant patients and those intolerant to erythromycin

Oral administration.

Adults: 1500 mg/day of amoxicillin divided into 3 administrations for 7-10 days.

Salmonellosis (Salmonella enteritidis and typhi)

Oral administration.

Adults (AIDS patients): 3 g/day of amoxicillin divided into 3 administrations (Smith, 1992).

Duodenal ulcer

Oral administration.

Adults: 2000 mg/day of amoxicillin divided into 4 administrations for 14 days in combination with omeprazole; or 2250 mg/day divided into 3 administrations for 12 days in combination with metronidazole; or 2000 mg/day divided into 4 administrations in combination with bismuth salicylate and metronidazole.

Endocarditis prophylaxis

Oral administration.

Adults: 2 g of amoxicillin administered 1 hour before the surgical procedure. Children: 50 mg/kg of amoxicillin 1 hour before the surgical procedure.

Endocarditis treatment

Intravenous administration.

Adults: 8 g/day of amoxicillin by IV infusion, divided into 4 administrations (2 g every 6 hours), in combination with other antibiotics.

Enterococcal endocarditis

Intravenous administration.

Adults: 12 g/day of amoxicillin by IV infusion, divided into 4 administrations (2 g every 4 hours), in combination with gentamicin (160 mg/day IV) for 4 weeks.

Lyme disease

(Alternative to doxycycline in children under 8 years, during pregnancy, and while breastfeeding).

Erythema Migrans

Oral administration.

Adults: 1500 mg/day of amoxicillin divided into 3 administrations for a period of 14-21 days.

Children: 50 mg/kg/day of amoxicillin divided into 3 administrations for 14-21 days.

Neurological Disease (Facial Nerve Paralysis)

Oral administration.

Adults: 1500 mg/day of amoxicillin divided into 3 administrations for 14-21 days.
Children: 50 mg/kg/day of amoxicillin divided into 3 administrations for 14-21 days.

Cardiac Disease (1st Degree AV Block)

Oral administration.

Adults: 1500 mg/day of amoxicillin divided into 3 administrations for 14-21 days.

Children: 50 mg/kg/day of amoxicillin divided into 3 administrations for 14-21 days.

Arthritis (Without Neurological Disease)

Oral administration.

Adults: 1500 mg/day of amoxicillin divided into 3 administrations for 28 days.

Children: 50 mg/kg/day of amoxicillin divided into 3 administrations for 14-21 days.

Anthrax (post-exposure treatment and prophylaxis)

Oral administration.

Adults, children (weight >/= 20 kg): 1500 mg/day of amoxicillin divided into 3 administrations (500 mg every 8 hours).

Children (weight < 20 kg): 80 mg/kg/day of amoxicillin divided into 3 administrations.

Intramuscular administration.

Adults: 1500 mg/day of amoxicillin divided into 3 administrations (500 mg every 8 hours).

Children: 50-100 mg/kg/day of amoxicillin in multiple doses.

Intravenous administration.

Adults: 1500 mg/day of amoxicillin divided into 3 administrations (500 mg every 8 hours). In severe infections, administer 1 g every 6 hours.

Children: 50 mg/kg/day of amoxicillin in multiple administrations.

Combinations

Antibacterial Preparations

In combination with clavulanic acid (Antibacterial Preparations)

Oral administration.

Adults: 1750-2625 mg/day (amoxicillin) plus 250-375 mg/day (clavulanic acid) divided into 2-3 administrations.

Children (5-10 kg): 4 ml/day of suspension (containing amoxicillin 5 g/100 ml plus clavulanic acid 1.25 g/100 ml) divided into 2 administrations 12 hours apart

Children (10-13 kg): 8 ml/day of suspension (containing amoxicillin 5 g/100 ml plus clavulanic acid 1.25 g/100 ml) divided into 2 administrations 12 hours apart. Alternatively, 500 mg/day (amoxicillin) plus 125 mg/day (clavulanic acid) divided into 2 administrations 12 hours apart.

Children (24-45 kg): 10 ml/day of suspension (containing amoxicillin 5 g/100 ml plus clavulanic acid 1.25 g/100 ml) divided into 2 administrations 12 hours apart. Alternatively, 1000 mg/day (amoxicillin) plus 250 mg/day (clavulanic acid) divided into 2 administrations 12 hours apart.

Children (over 45 kg): 750 mg/day (amoxicillin) plus 187.5 mg/day (clavulanic acid) divided into 3 administrations 8 hours apart.

Intravenous administration.

Adults: 500 mg-1 g (amoxicillin) plus 100-200 mg (clavulanic acid) by slow IV infusion every 8 hours. In severe infections, administer 2 g (amoxicillin) plus 200 mg (clavulanic acid) by IV infusion over 30 minutes every 8-6 hours. For prophylaxis in colon-rectal surgery, the amoxicillin plus clavulanic acid combination should be administered at anesthesia induction (dose of 2.2 g) (Arnaud, 1992; Tonelli, 2002). In abdominal surgery, the chemotherapeutic combination should be administered 30 minutes before the procedure (percutaneous endoscopic gastrostomy, dose of 2.2 g) or at surgical induction (cholecystectomy and biliary surgery, dose of 1.2 g) (Preclik, 1999; Orozco et al., 2000). In neurosurgery, the pharmacological combination (dose of 2.2 g) can be administered half an hour before the procedure (Cormio et al., 2002).

Contraindications

The use of amoxicillin is contraindicated in the following cases:

1) Hypersensitivity to penicillins and cephalosporins;
2) Patients with infections caused by beta-lactamase-producing pathogens (this contraindication applies when amoxicillin is not co-administered with clavulanic acid);
3) Patients with a positive history of allergy (patients with a known risk of allergy);
4) Patients suffering from mononucleosis, viral infections, lymphocytic leukemia (high risk of cutaneous rashes).

Warnings

Allergic history: patients with a positive history of allergies should undergo hypersensitivity testing for penicillins.

Hypersensitivity reactions: in the event of allergic reactions, discontinue antibiotic administration and initiate appropriate therapy. Use caution in patients with hypersensitivity to cephalosporins and imipenem. Also, exercise caution in patients with allergic conditions such as asthma, allergic eczema, urticaria, and hay fever.

Monitoring: conduct hematological, hepatic, and renal function assessmentsduring long-term treatments.

Superinfections: antibiotic therapy may lead to the development of fungal or bacterial superinfections.

Infections caused by Hemolytic Streptococci: prolong amoxicillin therapy for at least 10 days after symptom remission (to prevent rheumatic fever or glomerulonephritis).

Chlamydia infections in pregnancy: recommend microbiological testing 3 weeks after completing antibiotic therapy and between the 36^{th} and 40^{th} week of gestation.

Colitis: patients with colitis may experience exacerbated gastrointestinal side effects induced by the antibiotic.

Nephropathic patients: in patients with creatinine clearance (CLcr) less than or equal to 50 ml/min, reduce the dose of amoxicillin and/or the daily administrations frequency. High doses of amoxicillin can lead to neurotoxicity manifesting as seizures (Nicholls, 1980).

High dosages: maintain adequate hydration in patients receving high doses.

Persistent and severe diarrhea: perform necessary tests to detect potential antibiotic-induced pseudomembranous colitis. In case of a positive result, discontinue amoxicillin therapy and, if necessary, administer fluids, electrolytes, protein supplements, and effective antibacterial drugs against Clostridium difficile, the causative agent of pseudomembranous colitis.

Hepatotoxicity: the combination of amoxicillin and clavulanic acid can rarely induce liver damage. Symptoms include itching, jaundice, and gastrointestinal disturbances. Onset may occur between 2 and 45 days after starting treatment, but hepatic complications could manifest even months after antibiotic therapy cessation. Most cases result in complete recovery but may require several months. Liver damage is more common in elderly patients and with prolonged therapy (over 14 days) and has been reported less frequently in pediatric patients.

Liver insufficiency: literature reports of amoxicillin-induced hepatotoxicity in monotherapy are very rare, but more frequent when combined with clavulanic acid (Bolzan et al., 2000). The amoxicillin-clavulanic acid combination can rarely lead to acute liver toxicity. Patients who previously experienced drug-induced hepatotoxicity

unrelated to the amoxicillin-clavulanic acid combination may have a higher risk of hepatotoxicity from this combination (literature reports cases of patients with hepatotoxicity rom amoxicillin-clavulanic acid who had previously experienced hepatotoxicity from terbinafine or chlorpromazine) (Lewe et al., 1993; Watson et al., 1998). Monitor liver function parameters in patients with liver insufficiency, especially when amoxicillin is administered in combination with clavulanic acid.

Glycosuria measurements: amoxicillin interferes with the glucose detection test (false-positive) in urine when using the Benedict's or Fehling's reagent.

Oral contraceptives: amoxicillin antibiotic treatment may reduce the effectiveness of oral contraceptives (reduced absorption). Therefore, additional contraception measures are recommended alongside combined estrogen-progestin contraceptives for the entire duration of therapy and up to one week after. If the 7th day coincides with the last pill of the oral contraceptive, start a new cycle without the usual week-long break between cycles.

Antibiotic prophylaxis for preterm birth due to premature rupture of membranes: some literature data indicate that the use of amoxicillin and clavulanic acid alone or in combination with erythromycin is associated with a significant increase in neonatal necrotizing enterocolitis (Kenyon et al., 2004; Kenyon et al., 2001).

Injectable pharmaceutical forms: avoid dilution with saline or acidic solutions (infusion preparations).

Pregnancy: amoxicillin can be prescribed during pregnancy. The FDA has classified the antibiotic as category B for use during pregnancy. This category includes drugs for which animal reproduction studies have not shown fetal risk, but human-controlled studies are lacking, or drugs for which animal studies have shown an harmful effects (in addition to decreased fertility), but these effects have not been confirmed in controlled studies in women during the first trimester (and there is no evidence of harm in later stages of pregnancy).

Breastfeeding: administration of amoxicillin during breastfeeding may lead to diarrhea, candidiasis, and skin rashes in the infant.

Interactions

The pharmacological interactions of amoxicillin can be classifield as either pharmacokinetic or pharmacodynamic. A pharmacokinetic drug-drug interaction occurs at the level of drug absorption, distribution, metabolism, or excretion, affecting one or both of the drugs involved. A pharmacodynamic drug-drug interaction, on the other hand, influences the mechanism of action of the drugs.

Acetylsalicylic acid (aspirin), NSAIDs: at high doses, they can increase the plasma levels and half-life of amoxicillin.

Clavulanic acid: enhances the pharmacological activity of amoxicillin by protecting the antibiotic from the action of beta-lactamases.

Allopurinol: increases the incidence of amoxicillin-induced skin rashes.

Amiloride: slows intestinal absorption (increasing the peak plasma time from 1 hour to 1.6 hours) and decreases the bioavailability (by 27%) of amoxicillin (Westphal et al., 1995). As amiloride is an inhibitor of the Na+/H+ exchange, it is possible that the interaction occurs at the exchange of these two ions, which is crucial for intestinal absorption of peptides shared with amoxicillin.

Bacteriostatic antibiotics: they may mask the effect of amoxicillin by blocking protein synthesis.

Bromelain: increases the absorption and tissue levels of amoxicillin (Tinozzi, Venegoni, 1978).

Oral contraceptives: amoxicillin reduces their absorption.

Ethanol: alters the rate of amoxicillin absorption with no significant changes in peak plasma concentration and area under the curve (AUC) (Morasso et al., 1988).

Methotrexate: amoxicillin significantly increases the blood concentration of high-dose administered methotrexate due to reduced renal secretion. This interaction was observed in a patient treated with high-dose methotrexate (8 g/m2 IV every 6 hours) for 10 cycles for malignant osteosarcoma. During the last cycle, amoxicillin (1 g every 6 hours) was administered. The antibiotic likely reduced methotrexate clearance, possibly through tubular secretion competition. The patient exhibited acute and subacute toxicity, including renal insufficiency, myelosuppression, mucositis, nausea, vomiting, fever, and skin toxicity (Ronchera et al., 1993). The pharmacological combination requires caution and monitoring for potential signs and symptoms of toxicity.

Probenecid: slows the tubular secretion of amoxicillin, prolonging its presence in the bloodstream.

Simvastatin: literature reports an episode of severe rhabdomyolysis in a patient treated with simvastatin and amoxicillin. It has been hypothesized that amoxicillin-induced liver damage increased statin levels in the blood (reducing drug metabolism), leading to rhabdomyolysis (Bhatia, 2004).

Warfarin: co-administration of amoxicillin and warfarin mau increase the risk of bleeding. This pharmacological interaction has been classified as possible (Hollbrook et al., 2005).

Laboratory tests: glucosuria should be performed using enzymatic methods employing glucose oxidase. With chemical methods, the high concentration of amoxicillin in the urine can yield false positives.

Incompatibility: tetracyclines, aminoglycosides, quinolones, and amino acid solutions.

Side effects

Side effects are observed in approximately 30% of patients and tend to resolve spontaneously. Severe toxic effects have occasionally occurred when amoxicillin was administered with clavulanic acid to enhance its spectrum of activity, including cholestatic hepatitis (Stricker et al., 1989) and erythema multiforme.

In a study that considered drug-induced adverse reactions in pediatric patients (age <19 years) from January 1998 to May 2002 in Canada, amoxicillin ranked fourth (with 40 reports) among the top 5 drugs—others being isotretinoin (first), paroxetine, methylphenidate, and valproic acid—and was the drug with the highest number of units sold (in 2001: 193,089 units for amoxicillin and 7,945 for methylphenidate, the second most sold). The total reported cases were 1,139, with the majority occurring in the 13-19 age group (699 cases). Skin reactions accounted for 57.7% (23 cases) of adverse reactions reported with amoxicillin, while 25% (10 cases) were gastrointestinal, and another 25% (10 cases) were neurological.

In the 2007 annual report of Interregional Pharmacovigilance Group (GIF) comcerning spontaneous reporting, amoxicillin in monotherapy or in combination with clavulanic acid represented the active ingredient with the highest number of reports (monotherapy: 241 reports, including 30% severe; in combination: 316 reports, 29% severe). When considering these data, it is important to note that amoxicillin in monotherapy or in combination is one of the most widely used antibiotics. The high number of reports could, in fact, be attributed to both the pharmacological profile of the molecule and its widespread use, (increasing the likelihood of adverse reactions).

Cardiovascular: vasculitis.

Gastrointestinal: nausea (9%), abdominal pain (19%), vomiting, diarrhea, gastritis, anorexia, alteration of intestinal bacterial flora, dental discoloration (amoxicillin plus clavulanic acid has been associated with the appearance of yellow or gray-brown stains), esophagitis, dysphagia; (less commonly) pseudomembranous colitis; tongue discoloration, taste and/or smell alterations (GIF, 2007).

General: hypersensitivity reactions (erythema, angioedema, anaphylaxis, anemia, eosinophilia, hemolysis, thrombocytopenia, leukopenia, and agranulocytosis). These reactions usually disappear with treatment discontinuation. Maculopapular rash, urticaria, Stevens-Johnson syndrome, interstitial nephritis, renal tubular necrosis, and nephrotic syndrome have also been reported; phlebitis and thrombophlebitis (intravenous administration); pain and inflammatory reaction (intramuscular administration); candidiasis; pancreatitis.

Amoxicillin can cause severe anaphylaxis, which, if untreated, can lead to death. The incidence is higher in patients with a history of allergy or after parenteral administration. Anaphylaxis treatment includes the administration of epinephrine, oxygen, intravenous steroids, and maintaining airway patency.

Genitourinary: interstitial nephritis, nephrotic syndrome, vaginal bleeding.

Vaginal bleeding has been reported in a patient receiving niflumic acid and amoxicillin-clavulanic acid (2 g/day). The bacterial combination was associated with Candida vaginitis and hematological abnormalities following therapy cessation, such as platelet abnormalities, prolonged PTT, and bleeding time. The correlation between vaginal bleeding and amoxicillin/clavulanic acid was considered "possible" (Pharmasearch, 2008).

Hematological: (post-marketing) altered platelet function, prolonged bleeding time and activated partial thromboplastin time, anemia, hemolytic anemia, purpura, neutropenia, leukopenia, thrombocytopenia, pancytopenia, reversible agranulocytosis, petechiae.

Epidemiological data have shown an increased relative risk of blood dyscrasias in patients on antibiotic therapy compared to those not exposed to antibiotic therapy (RR: 4.4, 95% CI 2.6-7.5); this risk further increases when antibiotic therapy involves the use of multiple drugs from different classes (RR: 29.1, 95% CI 9.1-92.8). Penicillins have been found to have a relative risk of 3.1 (statistically significant), lower than that observed for cephalosporins (RR: 13.8, 95% CI 3.6-52.6) (Huerta et al., 2002). Adverse hematological effects are likely to be mediated by an immune mechanism: penicillin acts as a hapten and stimulates the immune system to produce anti-penicillin antibodies or autoantibodies (a hapten is a low molecular weight molecule that is non-immunogenic itself but acquires this property when bound to a protein). The Italian Pharmacovigilance Network includes 38 reports of hematological adverse reactions associated with amoxicillin plus clavulanic acid, half of which were considered severe and mainly reported in elderly patients (ReA, 2010).

Liver/biliary: elevated transaminases, jaundice, and cholestatic hepatitis (most cases reported in combination with clavulanic acid).

Symptoms of hepatotoxicity include increased transaminases (ALT and AST), serum bilirubin, and/or alkaline phosphatase. The estimated incidence of liver damage ranges from 1/10,000 to 1/100,000, but this range is likely underestimated (a study conducted in France reported an incidence of drug-induced hepatotoxicity 16 times higher than estimated) (Sgro et al., 2002). The risk of cholestatic jaundice with the amoxicillin-clavulanic acid combination is six times higher than with amoxicillin monotherapy, and it is more common in patients over 65 years of age, males, and after prolonged treatment. It has also been noted that rechallenge with amoxicillin in patients who had previously experienced amoxicillin-clavulanic acid-induced hepatitis was well tolerated, while rechallenge with the combination led to a second episode of hepatitis (Eur. J. Med. Res., 2001; Am. J. Gastroenterol., 1998). Cholestatic jaundice is usually self-limiting, and fatal cases have been very rare. The onset of the reaction ranges from 2 to 45 days after start of treatment; hepatic complications may occur more than 6 weeks after treatment discontinuation. Acute liver toxicity has been rarely reported in pediatric patients.

Nervous system: migraine and dizziness (11%); seizures (at high doses of amoxicillin in patients with impaired renal function); behavioral disorders (in pediatric patients treated with amoxicillin/clavulanic acid combination), acute psychosis

(amoxicillin plus clavulanic acid) (Bell et al., 2008); drug-induced aseptic meningitis (Czerwenka et al., 1999); insomnia.

The English pharmacovigilance system reports 3,935 adverse reactions to amoxicillin, of which 2.6%are psychiatric in nature.

Skin: skin rashes, erythema multiforme, toxic epidermal necrolysis, exfoliative dermatitis, bullous rash, maculopapular rash.

In a prospective study that examined allergic reactions reported in pediatric patients undergoing antibiotic therapy for otolaryngological infections, amoxicillin had the highest number of reports (38.2%). A total of 47 patients were examined over a 12-month period. Over 80% of patients experienced at least one cutaneous adverse reaction. Amoxicillin-related skin eruptions included maculopapular rash, urticaria, and fixed drug eruption. Most reactions occurred within the first week of treatment and resolved with antibiotic discontinuation and/or the administration oforal antihistamines or topical corticosteroids (Ralis et al., 2006).

Toxicity

Hepatic toxicity: the combination of amoxicillin and clavulanic acid can induce hepatic damage (estimated incidence: 1/10,000-1/100,000). Hepatic damage caused by amoxicillin/clavulanic acid can be considered an idiosyncratic or immune-mediated adverse reaction, characterized by 1) unpredictability, 2) dose-independence, and 3) low incidence. Idiosyncratic or immune-mediated hepatic reactions are typically associated with the formation of toxic metabolites in patients with genetically altered metabolism. The onset of these reactions can occur even months or years after exposure. In cases of hepatic damage due to amoxicillin and clavulanic acid, hepatic complications can manifest more than 6 weeks after discontinuation of therapy. In triggering this adverse event, clavulanic acid appears to play a predominant role compared to the antibiotic: the incidence of cholestatic jaundice was found to be six times more frequent with the drug combination compared to amoxicillin monotherapy. Rechallenge with amoxicillin in patients who had previously experienced hepatitis from amoxicillin/clavulanic acid was well tolerated, while rechallenge with amoxicillin/clavulanic acid led to a second episode of hepatitis.

Reproductive toxicity: amoxicillin has not shown embryofetotoxic or teratogenic effects in vivo. In non-specific case-control studies, no malformations were observed with amoxicillin administered in the second and third trimester of pregnancy (Czeizel et al., 2001). In retrospective cohort studies with a control group, the relative risk (odds ratio, OR) was less than 1 for low birth weight (OR 0.63), preterm birth (OR 0.77), and spontaneous abortion (OR 0.89); slightly greater than 1 for congenital malformations (OR 1.16). These data suggest the absence of a significant increase in the risk of toxicity to the child for mothers taking amoxicillin during pregnancy, compared to mothers not exposed to the drug during pregnancy (Jepsen et al., 2003).
The FDA, Food and Drug Administration, categorizes amoxicillin as class B for use during pregnancy. This class includes drugs for which animal reproductive studies have not shown a risk to the fetus, but there are no controlled studies in humans, or drugs for which animal studies have shown a harmful effect (in addition to a decrease in fertility) that has not been confirmed in controlled studies in women during the first trimester (and there is no evidence of harm in later stages of pregnancy).

Pharmacology

Amoxicillin is an aminopenicillin with similar activity to ampicillin; chemically, it differs by the presence of a hydroxyl group on the side chain. It exhibits stability in gastric acidity and oral bioavailability greater than that of penicillin and ampicillin, respectively.

The mechanism of action is similar to that of penicillins. Amoxicillin acts at the bacterial cell wall by preventing the formation of cross-links (transpeptidation process) necessary to maintain the rigidity of cell wall. It forms a stable, inactive complex with transpeptidase, the enzyme responsible for the transpeptidation process. In the absence of cross-links, bacterial lysis and death occur.

It is used in therapy for the treatment of urinary tract infections, upper and lower respiratory tract infections, acute otitis media, acute sinusitis, uncomplicated gonorrhea, typhoid and paratyphoid fever.

Amoxicillin has a broad spectrum of action, including both Gram-positive and Gram-negative bacteria.

In vitro, it is effective against: Actinomyces sp., Bacillus anthracis, Bacteroides melaninogenicus, Bifidobacterium sp., Borrelia burgdorferi, Brucella sp., Clostridium perfringens, Clostridium tetani, Corynebacterium diphtheriae, Eikenella corrodens, Erysipelothrix rhusiopathiae, Eubacterium sp., Helicobacter pylori, Lactobacillus sp., Listeria monocytogenes, Peptococcus sp., Peptostreptococcus sp., Propionibacterium sp., Streptococcus agalactiae (Group B streptococci), Streptococcus dysgalactiae, Streptococcus pneumoniae, Streptococcus pyogenes (Group A beta-hemolytic streptococci), Treponema pallidum, Vibrio cholerae, and Viridans streptococci.

In vitro, it is also more active than ampicillin against Enterococcus faecalis and Salmonella and less active against Shigella.

It is effective in infections caused by Haemophilus influenzae (non-beta-lactamase-producing strains), Enterococcus faecalis, Escherichia coli, Proteus mirabilis, Salmonella spp.

It has less effective antibacterial action against Neisseria gonorrhoeae, N. meningitidis, and Bordetella pertussis.

For strains of Streptococcus pneumoniae with reduced penicillin sensitivity, higher doses of amoxicillin (1 g tid) than normally recommended dose (500 mg tid or 1 g bid) have been found effective in the treatment of non-neurological pneumococcal infections (Petitpretz et al., 2001; Tremolieres et al., 1998). A meta-analysis of 9 clinical studies demonstrated a high efficacy for high-dose amoxicillin (2 g every 12 hours) combined with clavulanic acid (125 mg bid) at 97% in patients with S. pneumoniae infections, such as sinusitis and pneumonia. In patients with pneumococci resistant to penicillin (MIC >/= 2 micrograms/ml), the clinical success rate was 98% (File et al., 2002).

Amoxicillin is not active against beta-lactamase-producing bacteria (penicillinase producers). Beta-lactamases, in fact, open the beta-lactam ring of the antibiotic, rendering it inactive. The administration of clavulanic acid enhances the effectiveness of amoxicillin against these bacterial strains. Clavulanic acid, produced by Streptomyces clavuligerus, forms irreversible bonds with beta-lactamases, rendering them inactive.

Resistance

There are three fundamental mechanisms of resistance:

1) Production of beta-lactamase enzymes that inactivate the antibiotic by opening its beta-lactam ring.
2) Reduced permeability of the bacterium to the molecule.
3) Modification of the proteins that bind to amoxicillin.

In Staphylococci, plasmid-mediated resistance to the drug is associated with the production of beta-lactamase.

Some bacteria are also resistant to the combination of amoxicillin and clavulanic acid. Among these microorganisms are Serratia marcescens, Morganella morganii, Acinetobacter spp., Providencia spp., and Pseudomonas spp.

Cross-resistance may occur between amoxicillin and ampicillin, cross-sensitivity between amoxicillin and cephalosporins.

Bacterial Infections

In the case of acute otitis media in children, short-term treatment with amoxicillin has proven more effective than placebo (therapeutic response: 92% vs. 86%). Long-term recurrence rates have been similar (0.6% vs. 0.7%) (Corriere Medico, 1991). In acute otitis media, amoxicillin is more effective than cefixime in Streptococcus pneumoniae infection, less effective in Haemophilus influenzae infection, and equally effective in Branhamella catarrhalis infection (Howie, Owen, 1987).

In acute respiratory tract infections, amoxicillin has a slightly higher therapeutic efficacy than cefixime (82.2% vs. 80.7% of patients), with similar recurrence rates. Amoxicillin is less effective than cefixime in eradicating the bacteria (80% vs. 94.7% of patients) (Hugues et al., 1989).

In acute bronchitis (infections caused by strains of Haemophilus, S. pneumoniae, and B. catarrhalis), the combination of amoxicillin and clavulanic acid has proven more effective than cefixime in inducing therapeutic response (74% vs. 71% of patients) but less effective in eradicating bacterial infection (52% vs. 54% of patients) (Beumer, 1989).

In the treatment of acute sinusitis, amoxicillin administration has not been effective in attenuating the severity of symptom or the duration of the acute episode. The use of antibiotics in the treatment of acute sinusitis is a a subject of debate. To assess the efficacy of amoxicillin, patients aged 16 and older with acute maxillary sinusitis were randomized to receive amoxicillin in monotherapy or in combination with topical

budesonide versus placebo. The diagnosis of sinusitis was made with at least two of the following diagnostic criteria: unilateral or bilateral predominance of purulent rhinorrhea, local pain with unilateral predominant, and the presence of pus in the nasal cavities. At the end of the study, no significant differences were observed between the different arms (antibiotic plus placebo vs. antibiotic plus steroid vs. placebo plus steroid vs. placebo plus placebo) (Williamson et al., 2007).

In cases of non-severe pediatric pneumonia (caused by S. pneumoniae and/or H. influenzae), amoxicillin administration for 3 days was as effective as a 5-day treatment (therapeutic success: 89.5% vs. 89.9%) with overlapping rates of therapeutic failure (10.3%) and relapse (5.3%) between the two treatment groups. Patients in the study were aged between 2 and 59 months and received antibiotic doses of 31 to 54 mg/kg/day. Adherence to treatment was 94% with the 3-day therapy and 85% with the 5-day therapy. No qualitative or quantitative differences were observed between the two study arms for adverse events, including hospitalization, severe vomiting, diarrhea with dehydration, rash with or without itching, and seizures in non-epileptic children (ISCAP Study Group, 2004).

In the treatment of gonococcal urethritis, amoxicillin has a therapeutic effect similar to cefixime.

Amoxicillin can be administered as an alternative to erythromycin (the preferred drug) in pregnant patients with Chlamydia infections.

In the case of uncomplicated cystitis, the combination of amoxicillin and clavulanic acid (500/125 mg bid for 3 days) was less effective than ciprofloxacin (250 mg bid), even in cases of susceptible bacterial strains, likely due to the difficulty in eradicating E. coli associated with a higher risk of reinfection (cure: 58% vs. 77%; cure in patients with susceptible strains: 60% vs. 77%; bacterial eradication after 2 weeks from the end of therapy: 76% vs. 95%; E. coli positivity after 2 weeks from the end of therapy: 45% vs. 10% of patients) (Hooton et al., 2005).

Eradication of Helicobacter pylori

Amoxicillin is indicated in the treatment of peptic ulcers: in combination with omeprazole, it has been effective in eradicating Helicobacter pylori (82.8% of patients) (Labenz et al., 1993). In combination with metronidazole, it has shown superior activity to ranitidine monotherapy in improving microbial eradication (89% vs. 2% of patients), ulcer healing (92% vs. 75% of patients), and reducing recurrence rates (2% vs. 85% of patients) (Hentschel et al., 1993).

The combination of amoxicillin plus omeprazole has been found to be less effective or equally effective as the combination of clarithromycin plus omeprazole (eradication rate: 58-87.5% vs. 72-84%). The antibacterial plus omeprazole combination (dual therapy) is less effective than triple therapy, which involves combining amoxicillin with clarithromycin plus omeprazole.

The response to therapeutic treatment is also influenced by various factors such as the antibiotic's susceptibility to stomach acid, the time interval between the

administration of the frug combination and food intake, the drug formulation, administration frequency, and bacterial strain resistance.

Endocarditis

Infective endocarditis is due to the development of bacterial infections on heart valves or other endocardial surfaces. Predisposing factors include valve prolapse, prosthetic heart valves, rheumatic or congenital heart disease. Poor oral hygiene, intravenous drug use, systemic sepsis, diabetes mellitus, chronic hemodialysis, immunosuppression, and invasive procedures can also be risk factors. Amoxicillin (12 g IV divided into 6 doses), in combination with gentamicin, has been effective in treating enterococcal endocarditis (therapy duration: 4 weeks) (Working Party of the British Society of Antimicrobial Chemotherapy, 1998). Patients who do not respond to this treatment due to gentamicin resistance (about one-quarter) may respond to the combination of amoxicillin with streptomycin (DTB, 1999). In cases of resistance to both, administer high-dose amoxicillin as monotherapy. The final therapeutic option for patients who do not respond to antibiotic treatment is valve replacement surgery.

Lyme Disease

Lyme disease is a systemic bacterial infection caused by some species of spirochetes (Borrelia) transmitted through tick bites (Ixodes scapularis or pacificus). approximately 70% of patients develop skin erythema at the tick bite site (erythema migrans) about 3-30 days after tick removal. If left untreated, the infection can progress and affect the heart, certain nerves, including the facial nerve, or present musculoskeletal involvement. Late manifestations include arthritis, neurological disorders such as peripheral neuropathy and encephalopathy with cognitive deficits. Antibiotic therapy aims to resolve erythema migrans and prevent severe late complications. Amoxicillin is recommended as an alternative to doxycycline in pediatric patients (<8 years old), pregnant women, or those breastfeeding. In more severe forms of the disease, ceftriaxone is the first-line drug; amoxicillin can be used as a second-line drug in cases of facial nerve involvement, non-severe heart block (first-degree atrioventricular block with a PR interval less than 300 msec), and arthritis without neurological symptoms.

Antibiotic Therapy in Pregnancy

Two large clinical studies (ORACLE I and II) considered the effects of antibiotic therapy in women with preterm rupture of membranes without clinical signs and in premature births. In the first study (ORACLE I), amoxicillin plus clavulanic acid (325 mg four times a day) was compared to erythromycin (250 mg four times a day) according to the following treatment regimens: amoxicillin/clavulanate plus erythromycin vs. amoxicillin/clavulanate plus placebo vs. placebo plus erythromycin vs. placebo plus placebo. Antibiotic treatment was continued for 10 days or until delivery. The study included women with preterm rupture of membranes. While erythromycin was effective in improving neonatal morbidity (the primary composite outcome included neonatal mortality, chronic lung disease, and significant

neurological abnormalities), amoxicillin/clavulanate, both alone and in combination with erythromycin, did not alter the primary composite outcome. It was effective in prolonging the latency period before delivery but was associated with a higher incidence of necrotizing enterocolitis (Kenyon et al., 2001).

In the second study (ORACLE II), women with spontaneous preterm birth, in the absence of membrane rupture, were considered. The dosing regimen and treatment duration were similar to the ORACLE I study. The primary composite outcome, identical to the previous study (neonatal death plus chronic lung disease plus significant neurological abnormalities), was comparable across the four arms of the study (5.6% vs. 5.0% vs. 5.9% vs. 5.0%, respectively, with erythromycin, amoxicillin/clavulanate, erythromycin plus amoxicillin/clavulanate, placebo) (Kenyon et al., 2001a).

In two other more recent studies, both aimed at analyzing possible antibiotic therapy in the case of premature rupture of membranes in pregnant women, early treatment (within 48 hours of birth) with gentamicin and amoxicillin/clavulonate was associated with a reduction in necrotizing enterocolitis (Krediet, 2003), and treatment with parenteral ampicillin/sulbctam followed by oral amoxicillin/clavulonate resulted in a lower rate of necrotizing enterocolitis in newborns compared to the parenteral cefazolin/erythromycin followed by oral cephalexin/erythromycin regimen (8.0% vs. 10.2%) (Ehsanipoor et al., 2008).

Pharmacokinetics

Following oral administration, the absorption of amoxicillin is rapid and greater than that of ampicillin.

Co-administration of clavulanic acid not alter the pharmacokinetics of the antibiotic.

Amoxicillin is absorbed in the intestinal lumen through a carrier responsible for dipeptide transport. The driving force for this carrier is the hydrogen ion gradient between the intracellular and luminal cell environments. This gradient is directly influenced by the Na+/H+ exchange and indirectly by the intracellular Na concentration (Westphal et al., 1995).

The presence of food delays the rate of antibiotic absorption but not the amount of drug absorbed

Oral bioavailability: 74-92%.

Time to peak plasma concentration: 1-2.5 hours.

Peak plasma concentration: approximately 3.5-5 mg/ml (250 mg dose); 5.5-7.5 mg/ml (500 mg dose); dose-dependent. Serum levels are similar after oral or intramuscular administration.

Equivalent doses of amoxicillin and ampicillin result in plasma peaks that are respectively twice as high as the other.

Effective plasma concentrations persist for up to 8 hours after oral administration.

Serum protein binding: approximately 20%.

Amoxicillin is distributed in both tissues and body fluids: it is present in the liver, gallbladder, lungs, prostate, urine; middle ear secretions, bronchial secretions, maxillary sinus secretions; synovial, peritoneal, and pleural fluids.

It is found in minimal quantities in cerebrospinal fluid when the meninges are not inflamed; however, the antibiotic concentration tends to increase in cases of meningitis.

Amoxicillin permeates the placenta and is excreted in breast milk.

It crosses the blood-brain barrier only in the presence of meningeal inflammation.

Amoxicillin is metabolized to penicilloic acid.

Half-life: 1-1.5 hours. It increases in neonates and the elderly; in patients with renal insufficiency (7-20 hours).

Amoxicillin is eliminated partly in urine and partly in feces. In urine, it is excreted both through glomerular filtration and active tubular secretion; approximately 60% of the dose is recovered as unchanged drug 6-8 hours after oral administration.

Renal excretion of amoxicillin is delayed by probenecid.

Amoxicillin is removed during hemodialysis.

Classification

Chemical formula

$C_{16}H_{19}N_3O_5S$

Molecular weight

3655.41

ATC code

J01CA04

J01CR02

Bibliography

Am. J. Gastroenterol., 1998, 93, 1363.

Arnaud J.P., J. Hospital Infect, 1992, 22 (Suppl.), 23.

Bhatia V., J. Postgrad Med., 2004, 50, 234.

Bell C. et al., BMJ, 2008, 337, a2117.

Bolzan H. et al., Gastroenterol. Hepatol., 2000, 23, 237.

Cormio G. et al., J. Chemother., 2002, 14, 618.

Czeizel A.E. et al., Eur. J. Obstet. Gynecol. Reprod. Biol., 2001, 97 (2), 188.

Czerwenka W. Et al., BMJ, 1999, 318, 1521.

DTB, 1999, 8, 9.

Ehsanipoor R.M. et al., Am. J. Obstet. Gynecol., 2008, 198 (5), e54.

Eur. J. Med. Res., 2001, 6, 535.

File T. et al., Int. J. Antimicrob. Agents, 2002, 20, 235.

GIF – Gruppo Interegionale di Farmacovigilanza, "Annual Report of Spontaneous Reports", 2007.

Hentschel E. et al., NEJM, 1993, 328, 308.

Hollbrook A.M. et al., Arch. Int. Med., 2005, 165, 1095.

Hooton t.M. et al., JAMA, 2005, 293 (8), 949.

Howie V.M., Owen M.J., Pediatr. Infect. Dis. J., 1987, 6, 989.

Hugues F.C. et al., Presse Médicale, 1989,18, 1600.

ISCAP Study Group, BMJ, 2004, 328, 791.

Jepsen P. et al., Br. J. Clin. Pharmacol., 2003, 55 (2), 216.

Kenyon S. et al., Obstet. Gynecol., 2004, 104 (5 Pt 1), 1051.

Kenyon S.L. et al., Lancet, 2001, 357 (9261), 979 (ORACLE I study).

Kenyon S.L. et al., Lancet, 2001a, 357 (9261), 989 (ORACLE II study).

Krediet T.G., Acta Pediatr., 2003, 92 (10), 1180.

Labenez J. et al., Am. J. Gastroenterol., 1993, 88, 491.

Lewe G. et al., BMJ, 1993, 306, 248.

Morasso M.I. et al., Int. J. Clin. Pharmacother. Toxicol., 1988, 26 (9), 428.

Morbid. Mortal. Weekly Rep., 1993, 42, 1.

Preclik G., BMJ, 1999, 319, 881.

Orozco H. et al., J. Gastrointest. Surg., 2000, 4, 606.

Petitpretz P. et al., Chest, 2001, 119, 185.

Pharmasearch, novembre, 2008.

Ralis E. et al., Int. J. Pediatr. Otorhinolaryngol., 2006, 70, 53.

ReA, Reactions – Pharmacovigilance Bulletin of AIFA, 2010, February, n 16.

Ronchera C.L. et al., Ther. Drug Monit., 1993, 15 (5), 375.

Sgro C. et al., Hepatology, 2002, 36, 451.

Smith P.D., Ann. Intern. Med., 1992, 116, 63.

Stricker B.H.C. et al., Dig. Dis. Sci., 1989, 34, 1576.

Tinozzi S, Venegoni A., Drug Exp. Clin. Res., 1978, 4, 39.

Tonelli F., J. Chemoth., 2002, 14, 366.

Tremolieres F. et al., Eur. J. Clin. Microbiol. Infect. Dis., 1998, 17, 447.

Westphal J.F. et al., Clin. Pharm. Ther., 1995, 57, 257.

Willianson I.G. et al., JAMA, 2007, 298, 2487.

Working Party of the British Society of Antimicrobial Chemotherapy, Heart, 1998, 79, 207.

Watson R.G. et al., J. Hepatol., 1998, 7, 72.

