Amoxicillin-clavulanate

Newborn use only

2020

Alert	Not for intramuscular administration. The pharmacokinetics of clavulanate has not been evaluated in neonates. Dose and frequency are product specific and the products are not interchangeable. **5:1 ratio of amoxicillin and clavulanate are used for intravenous and** **4:1 ratios of amoxicillin and clavulanate used for oral administrations in neonates**
Indication	Directed treatment of susceptible bacterial infections covered by amoxicillin but producing beta-lactamase when amoxicillin alone is ineffective; including skin infection, ear infection, sinusitis, urinary tract infection, upper and lower respiratory tract infection, and animal bites. [1,2]
Action	Semi-synthetic penicillin with similar antibacterial spectrum as ampicillin. It is bactericidal against both gram-positive and gram-negative bacteria but is destroyed by beta-lactamase produced by many of these bacteria. Clavulanate binds irreversibly with beta-lactamases produced by a variety of gram-positive and gram-negative microorganisms and protects amoxicillin from degradation. Thus extending the spectrum of amoxicillin. [1] Amoxicillin is better-absorbed than ampicillin, following oral administration. [1]
Drug type	Antimicrobial agent – Beta-lactam aminopenicillin and Beta-lactamase inhibitor combination
Trade name	Oral: Curam 125mg/31.25mg Powder for Suspension IV: Amoxiclav Juno 1000/200, Curam 500/100, Curam 1000/200
Presentation	**IV** 500mg/100mg vial (500 mg of amoxicillin and 100 mg of clavulanic acid) [5:1 ratio] 1000mg/200mg vial (1000 mg of amoxicillin and 200 mg of clavulanic acid) [5:1 ratio]. Vials containing alternative ratios have not been included in this formulary. **Oral** Reconstituted suspension (125 mg amoxicillin and 31.25 mg clavulanate per 5 mL) [4:1 ratio].
Dosage	**Doses are based on amoxicillin component** **IV:** 25 mg (of amoxicillin component)/kg/dose, 12 hourly. [1-4] **Oral:** 15-20 mg (of amoxicillin component)/kg/dose, 12 hourly. [5]
Dose adjustment	Therapeutic hypothermia: Insufficient information to recommend any specific dose adjustment. ECMO: 25 to 50 mg/kg every 6 hours in paediatric intensive care patients after cardiac surgery may not be adequate. Renal impairment: Consider alternate antibiotic in moderate to severe renal impairment. Hepatic: No dose adjustment required. Monitor hepatic function closely. [3]
Maximum dose	ORAL –90 mg/kg/day.
Total cumulative dose	
Route	IV Oral
Preparation	**IV** Add 9.5 mL of water for injection to the **500mg/100 mg vial** to make a 50 mg/mL solution OR Add 19.1 mL of water for injection to the **1000mg/200 mg** vial to make a 50 mg/mL solution [6] **FURTHER DILUTE** Draw up 3 mL (150mg of amoxicillin equivalent) of the above solution and add 12 mL of sodium chloride 0.9% to make a final volume of 15 mL with a final concentration of 10 mg/mL. [6] **ORAL** Reconstitute powder for oral suspension with 71 mL of water for irrigation and shake vigorously until suspended to make a final volume of 75 mL with a final concentration of 25 mg/mL amoxicillin equivalent
Administration	**IV infusion**: over 30 to 40 minutes. [4] **Oral**: Administer at the start of a feed (to increase absorption and decrease stomach upset); administer around-the-clock to promote less variation in peak and trough serum levels. Shake suspension well before measuring the dose. The dose may be mixed with milk. After mixing, administer immediately.

Monitoring	Renal and hepatic function, full blood count if on prolonged therapy.
Contraindications	Hypersensitivity to penicillins, cephalosporins and carbapenems. Previous history of jaundice/hepatic dysfunction associated with the combination or amoxicillin or clavulanic acid. Severe renal impairment (creatinine clearance less than 30 mL/minute). Note: infants <7 days, very preterm infants and sick infants frequently have a creatinine clearance <30 mL/minute.
Precautions	In moderate renal impairment: increase the dosing interval and maintain adequate fluid intake, especially with IV doses, to reduce the possibility of amoxicillin crystalluria. Hepatic dysfunction: monitor liver function tests. Concurrent use in CMV infection increases risk of rash. Oral suspension - contains aspartame (source of phenylketonuria), therefore use with caution in patients with phenylketonuria.
Drug interactions	Warfarin: increased risk of bleeding. Tetracycline: reduction of efficacy.
Adverse reactions	Mucositis, oral candidiasis, mild to life-threatening Clostridium difficile-associated diarrhoea, life-threatening hepatic dysfunction, and skin rashes including Stevens-Johnson syndrome, Toxic epidermal necrolysis and severe hypersensitivity reactions such as anaphylaxis have been reported.
Compatibility	Fluids: sodium chloride 0.9%, glucose 5% (by Y-site only), Hartmann's, Ringer's. Y-site: No information.
Incompatibility	Fluids : Glucose 5% Drugs: amikacin, gentamicin, tobramycin, amiodarone, ciprofloxacin, metronidazole, sodium bicarbonate.
Stability	IV: the reconstituted solution is stable for 20 minutes at 25 °C. Diluted IV solution: stable in sodium chloride 0.9% for 4 hours and in Hartmann's and Ringer's for 3 hours at 25 °C. Stable in sodium chloride 0.9% for 8 hours at 2 to 8 °C when added to a pre-refrigerated bag. Oral: The medication mixed with milk should be administered immediately.
Storage	Vial: store below 25 °C. Protect from light. Oral: Store dry powder for oral suspension at 20 to 25°C. Store reconstituted suspension at 2 to 8 °C. Discard unused suspension after 7 days.
Excipients	Oral Curam Powder for Suspension: Lemon Flavouring , Peach-Apricot Flavouring, citric acid, sodium citrate, aspartame, purified talc, Orange Flavouring, Guar Gum and silicon dioxide. Contains sulfites. When reconstituted as directed, Curam 125/31.25 contains aspartame 8.5mg/5mL. Each 5mL of suspension contains 0.16mmol of potassium.
Special comments	
Evidence	Amoxicillin-clavulanate shows good activity against organisms associated with acute otitis media and community acquired pneumonia in childhood including penicillin-susceptible and -intermediate strains of Streptococcus pneumoniae, and β-lactamase producing strains of Haemophilus influenzae and Moraxella catarrhalis. A high-dose formulation has been developed with the aim of providing better coverage for penicillin-resistant strains. [7] Gram-negative organisms require higher and more sustained levels of both amoxicillin and clavulanic-acid for optimal therapy. For clinical syndromes in which Gram-negative pathogens are causative (e.g. urinary tract infection), a narrower ratio (e.g. 4:1) with more frequent dosing (three or four rather than two times daily) is needed for efficacy. [8] **Oral antibiotics for neonatal infections:** A systematic review of studies that assessed oral versus parenteral antibiotics and switching to oral therapy from parenteral antibiotics in newborns included 31 studies. Oral antibiotics reached maximum concentrations later and had lower bioavailability, but in the majority of cases, adequate serum levels for bacterial killing were reached. Furthermore, studies on efficacy of oral antibiotics showed similar relapse rates (OR 0.95; 95% CI 0.79–1.16; I^2 0%) and mortality (OR 1.11; 95% CI 0.72–1.72; I^2 0%), and a reduction in hospital stay. Although early switch to oral antibiotics after a short course of IV antibiotics is promising in term neonates with a (probable) bacterial infection, the lack of large well-designed studies in a high-income setting requires further trials to establish the safety and efficacy of iv-to-oral switch therapy in neonates. [9] [LOE I GOR C] **Efficacy of amoxicillin-clavulanate:**

Efficacy data on the use of amoxicillin-clavulanate in neonates are limited to case series in infants with urinary tract infection (UTI) and infants with 'bacterial colonisation' treated with antibiotics. [5,10] In a retrospective case, series of infants with median age 19 days with UTI, 49 were treated with ampicillin and gentamicin and 105 with amoxicillin-clavulanate and gentamicin. Switch to oral amoxicillin-clavulanate was used in 75%. No treatment failure or relapse was detected, whilst 11 (8.7%) of 126 patients had renal scarring at 6 months. [10]

Pneumonia

A systematic review [11] of antibiotics for WHO defined non-severe community-acquired pneumonia in children included 29 trials with 14,188 children. None of the trials included infants <33 months of age. There was no difference in response or cure rates in comparing amoxicillin-clavulanic acid and azithromycin, cefpodoxime, penicillin and gentamycin, levofloxacin, and oxacillin and ceftriaxone. Amoxicillin-clavulanic acid was associated with an increased response rate compared to amoxicillin. Compared to azithromycin, amoxicillin-clavulanic acid was associated with an increase in side effects. In summary: Two trials with 276 infants >6 months age compared azithromycin versus amoxicillin-clavulanic acid 40 mg/kg/day for 10 days with meta-analysis finding no difference in failure rate [OR 1.21, 95% CI 0.42, 3.53] but more side effects with amoxicillin-clavulanic acid [OR 0.15, 95% CI 0.04, 0.61]. One trial in 100 infants ≥2 years age compared amoxicillin-clavulanic acid 250 mg + 62.5 mg or 500 + 125 mg tds) versus amoxicillin reported reduced poor or no response [OR 0.08, 95% CI 0.01, 0.67], increased cure rate OR 95% CI 10.44 [2.85, 38.21] and no difference in complications [OR 5.21, 95% CI 0.24, 111.24]. One trial with 278 infants aged ≥3 months compared cefpodoxime versus amoxicillin-clavulanic acid 6 to 13 mg/kg/day for 10 days and reported no difference in cure rate at end of treatment [OR 0.69, 95% CI 0.18, 2.60]. One trial with 71 infants aged 2 to 59 months compared penicillin and gentamycin versus amoxicillin-clavulanic acid 30 mg/kg IV q12 hourly for at least 3 days changed to oral when able to feed and reported no difference in failure rate [OR 0.86, 95% CI 0.05, 14.39]. One trial with 539 infants ≥6 months age compared levofloxacin versus amoxicillin-clavulanic acid 22.5 mg/kg/dose 12 hourly for 10 days and reported no difference in cure rate [OR 1.05, 95% CI 0.46, 2.42]. One trial with 104 infants ≥2 months age compared oxacillin and ceftriaxone versus amoxicillin-clavulanic acid 100 mg/kg/day every 8 hours for 10 days and reported no difference in failure rate OR 95% CI 0.98 [0.33, 2.92] but decreased time for improvement in tachypnoea [MD -1.0, 95% CI -0.11, -1.89] and decreased length of stay [MD -3.40, 95% CI -5.46, -1.34].

Acute otitis media

A systematic review of antibiotics for acute otitis media included 13 RCTs with 3401 children from high-income countries. [12] Early antibiotics compared had no early effect on pain, reduced pain in the days following, and reduced the number of children with tympanic perforations, contralateral otitis episodes and abnormal tympanometry findings at two to four weeks and at six to eight weeks compared with placebo. No serious complications occurred in either the antibiotic or the expectant observation group. Immediate antibiotics were associated with a substantial increased risk of vomiting, diarrhoea or rash (RR 1.71, 95% CI 1.24 to 2.36; NNTH 9). Three trials in 611 infants ≥6 months compared amoxicillin-clavulanic acid up to 90 + 6.8 mg/kg/day for 10 days to placebo and reported reduced pain, contralateral otitis media and abnormal tympanometry at 2 to 4 weeks, but increased vomiting, diarrhoea or rash. Conclusion: The benefits of antibiotics must be weighed against the possible harms: for every 14 children treated with antibiotics one child experienced an adverse event such as vomiting, diarrhoea or rash. Antibiotics are most useful in children under 2 years of age, with bilateral AOM, or with both AOM and otorrhoea. [LOE I GOR B]

Urinary tract infection

Two systematic reviews have assessed the effect of antibiotics for treating uncomplicated lower urinary tract infection in children [13,14]. The more recent included 16 RCTs in 1,116 children from 2 weeks to 18 years age [13]. The review found a long course (10-day) antibiotic treatment is more likely to eliminate bacteria from the urine than single-dose treatments, but there was no difference in rates of persistent bacteriuria, recurrence or reinfection. A single RCT in 48 children 1 to 13 years of 3 versus 10 days oral amoxicillin-clavulanate (20 + 5 mg/kg/d in 3 doses) reported no difference in bacteriuria at end of treatment (short 9/20 versus long 3/17; RR 2.55, 95% CI 0.82, 7.94) or UTI 1 to 15 months after treatment (2/20 versus 2/17; RR 0.85, 95% CI 0.13, 5.41). A single RCT in infants <4 months age comparing amoxicillin-clavulanate (dose not reported) in 7 infants to 4 other antibiotics for non-severe UTI that reported no difference in rate of resolution of bacteriuria. [15]

Another systematic review assessed the effect of antibiotics for treating acute pyelonephritis in children. The review included 27 RCTs in 4452 children >1 month of age and was biased towards

children who were less sick. [16] Oral antibiotics for 10 to 14 days were as effective as sequential IV therapy for 3 days followed by oral therapy for a total duration of 10 to 14 days, suggesting that children with acute pyelonephritis can be treated effectively with oral antibiotics. If IV antibiotic therapy is given, a short course of IV therapy given for two to four days followed by oral therapy with total therapy duration of 10 to 21 days was as effective as a longer duration of IV antibiotic therapy given for seven to 10 days with total duration of therapy of 10 to 21 days. [16] [LOE I GOR B for infants >1 month age] Four trials including 523 infants included IV or oral amoxicillin-clavulanate as a comparator to other antibiotics with no significant differences in outcomes reported in any. The dose of intravenous amoxicillin-clavulanate was 25mg/kg/dose 6 hourly, and oral amoxicillin-clavulanate ranged from 50 mg/kg/day to 50 mg/kg/dose 8 hourly.

Skin infection

One RCT, in 35 infants with impetigo, bullous impetigo, and impetigo complicated by cellulitis aged 6 months to 12 years, compared amoxicillin-clavulanate 25 mg/kg 8 hourly daily versus cefaclor 20 mg/kg 8 hourly. Clinical cure rates were similar: amoxicillin-clavulanate 18/21 (86%) versus cefaclor 18/20 (90%). Nine 9 (43%) of 21 on amoxicillin-clavulanate versus 1 (5%) of 20 taking cefaclor experienced an adverse reaction (diarrhoea in 9 and vomiting and diarrhoea in one).[17]

In another controlled clinical trial 200 infants, 10 months to 12 years ago with skin and soft tissue infections (impetigo, ecthyma, folliculitis, furunculosis and infected scabies), received amoxicillin-clavulanate 20mg/kg/dose 8 hourly for 10 days versus amoxicillin or erythromycin or co-trimoxazole. Mild to moderate infections were cleared by all regimens by the 2nd week, and the majority of severe infections cleared by all but co-trimoxazole. [18]

Safety

The most frequently reported adverse events in children were mild gastrointestinal disturbances (< 5%) with diarrhoea largely attributed to the clavulanate component. The incidence of diarrhoea was lower for 12 hourly than 8 hourly regimens (6.7 – 9.6% versus 10.3 – 26.7% respectively). A study on out-patient children showed an increased risk diarrhoea related to amoxicillin-clavulanate use compared with all other antibiotics combined (RR 2.43 CI 95%:1.40 – 4.21; p = 0.003) and was higher in children aged < 2 years. [19] No serious adverse events and a low total incidence of events (3.6%) were reported during post marketing surveillance of 3048 children aged ≤ 14 years with acute otitis media who received amoxicillin-clavulanate 300 – 450 mg/day in three divided doses. [19]

Liver toxicity (incidence ranging from 1 to 1.7 per 10,000) is strongly related to amoxicillin-clavulanate treatment, whereas amoxicillin is marginally implicated. Rare cases of Steven–Johnson Syndrome occur with amoxicillin-clavulanate, despite a higher incidence of skin reactions related to amoxicillin. 19]

Pharmacokinetics

There are 7 reported pharmacokinetic studies of amoxicillin in neonates (4 in children and 13 in adults). In summary statistics, the post menstrual age range of patients for amoxicillin ranged from 29 weeks to 82 years finding mean drug clearance for amoxicillin 10.9 (range 1.3–22.4) L/hour/70kg, and mean volume of distribution for amoxicillin 28.9 (10.7–53.5) L/70kg. There is a lower clearance and higher volume of distribution for amoxicillin in neonates. [20] The elimination half-life of amoxicillin in children averages 1 to 1.2 hours. [7]

There are no reported pharmacokinetic data for clavulanate in neonates. In summary statistics, the post menstrual age range for clavulanate ranged from 2.6 to 71 years finding mean drug clearance 13.9 (8.9–17.9) L/hour/70kg, and mean volume of distribution (all ages) (range) for clavulanate 23.9 (21.0–30.4) L/70kg. [20] The elimination half-life of clavulanate in children averages 1.0 hours. [7]

To achieve sufficient amoxicillin and high clavulanate exposure, the optimal regimen is to administer narrower ratio amoxicillin-clavulanate (typically 4:1) in a three times daily regimen. [8]

In adults and children, the oral bioavailability of amoxicillin is about 70 to 90% and maximum serum concentrations occur within 60 to 90 minutes of administration. Clavulanate has variable oral bioavailability of 31 to 99%. [7] However, neonates may have reduced bioavailability of oral amoxicillin. In a crossover study in 14 fasting newborn infants 6-13 days old given IM ampicillin or amoxicillin 50 mg/kg twice daily, the mean peak level was 58% (range 35-96%) for oral compared to parenteral dosing, and area under the time-concentration curve was 75% (range 60-101%). [21] There are no data for oral bioavailability of clavulanate in neonates.

To decrease the patient's medication burden by prescribing only twice daily amoxicillin-clavulanate, then a higher ratio (e.g. 7:1) can be employed in order to increase amoxicillin exposure (to improve efficacy) and limit clavulanate exposure (to reduce toxicity). Twice-daily regimens are commonly

	recommended in the treatment of acute otitis media or community-acquired pneumonia during childhood. [8] Gram-negative organisms require higher and more sustained levels of both amoxicillin as well as the clavulanic-acid component for optimal therapy. For clinical syndromes in which Gram-negative pathogens are causative (e.g. urinary tract infection), a narrower ratio (e.g. 4:1) with more frequent dosing (three or four rather than two times daily) is needed for efficacy. [8] For Gram-positive pathogens, which appear to have a higher affinity for clavulanate and are also susceptible to lower amoxicillin concentrations, combinations with a wider ratio (e.g. 7:1) appear to be sufficient in terms of clavulanate exposure. [8] Extreme ratios of 14:1 or 16:1 should be used with caution until more data are available.[8] Impaired renal function: Extra-renal elimination of clavulanate is much more rapid than that of amoxicillin. Whereas the elimination half-life of amoxicillin increases 6-fold in patients with severe renal failure, the corresponding increase for clavulanate is only 2.6-fold. [3] No dosage adjustments are required for patients with impaired hepatic function, but amoxicillin-clavulanic should be used with caution and hepatic function monitored. [3]
Practice points	The pharmacokinetics of clavulanate has not been evaluated in neonates. Further trials are needed to establish the safety and efficacy of iv-to-oral switch therapy in neonates although some efficacy data exist for infants >1 month age. [9] [LOE I GOR C] Amoxicillin-clavulanic acid should be considered a 2nd line agent for infants with WHO defined non-severe community-acquired pneumonia. There are no data for infants <3 months age. [LOE I, GOR B] Amoxicillin-clavulanate should be considered a 2nd line agent for infants with a urinary tract infection or for oral to IV switch therapy for pyelonephritis with a sensitive organism for infants >1 month age. [LOE I GOR B]
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VERSION/NUMBER	DATE
Original 1.0	22/06/2020
Version 1.1	2/07/2020
Version 1.2	16/07/2020
Version 1.3	16/11/2020
REVIEW	16/11/2025

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