# Antibiotic Dosing for Children:
# Draft expert Recommendations for the 2017 Essential Medicines List for Children (EMLc)

## Purpose and Scope of Recommendations

Expert recommendations for antibiotic dosing in the EMLc have been developed to address the lack of harmony in currently available international formularies. In many instances, recommendations are historical practise-based and not strongly evidence-based. Limited evidence is available from studies of effectiveness and safety as well as all age pharmacokinetics for children. National preferences for weight-based (US), age-banded (UK) and weight-banded (WHO) dosing strategies have resulted in quite widely varying recommendations.

The rationale of this dosing guidance has been to provide simple recommendations which are feasible in the LMIC context. Dosing guidance has been given as a single total daily dose (mg/kg/day) with options for acceptable frequency of dosing which can be adapted to local context. A maximum upper dose has been provided, largely based on available adult dosing. These recommendations have been developed for children ages 2 months to 12 years.

In general, the aim was to produce a simple dosing guidance that covered all clinical infection syndromes, except severe infections such as meningitis, where significantly higher doses are recommended. Dosing recommendations have not been adjusted for children with renal or liver impairment. The recommendations have not accounted for global variation in rates of antimicrobial resistance. Using a single dose in this overall guidance does not reflect the range of doses that are actually required to translate the guidance into practical weight/age based formulations for children.

## Methods

For the development of these recommendations, the expert group comprised paediatricians, paediatric clinical pharmacologists and pharmacists based in the UK and Europe. Due to the predominance of low-quality and limited paediatric pharmacokinetic evidence, selection of doses was based on expert consensus after evaluation of available data.

Antibiotic recommendations for eleven clinical syndromes (Community Acquired Pneumonia, Pharyngitis, Sinusitis, Otitis Media, Urinary Tract Infections, Meningitis, Central Catheter Infections, Complicated Intra-abdominal Infections, Skin and Soft Tissue Infections, Acute Infectious Diarrhoea and Infections in Immunocompromised hosts) were compiled from international guidelines (BNFC, Blue Book, IDSA/PIDS). As there was very little available evidence for different dosing for specific syndromes, a single dose was selected which was suitable for most indications. A higher dose has been indicated in special circumstances of severe infection.

*The Manual of Childhood Infections: The Blue Book (4$^{th}$ Edition)* – endorsed by the Royal College of Paediatrics and Child Health (RCPCH) and European Society of Paediatric Infectious Diseases (ESPID) – was used as initial reference for dosing recommendations. This handbook's dosing guide, with an online publication of June 2016, was used as an up-to-date reference with grading of pharmacokinetic evidence within its development. Where available, a repository of pharmacokinetic studies for each antibiotic was consulted. Furthermore, the *Red Book: 2015 Report of the Committee on Infectious Diseases (30$^{th}$ Edition)* endorsed by the American Academy of Pediatrics Committee on Infectious Diseases and the 2017 British National Formulary for Children (BNFC) online (www.bnfc.org) was reviewed. Paediatric guidelines from the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) were retrieved by searching National Guideline Clearinghouse and PubMed. Furthermore, WHO Institutional Repository for Information Sharing (IRIS) and *Pocket book of hospital care for children (2013)* were searched for available recommendations.

The electronic Medicines Compendium (eMC) was also consulted to ensure that recommendations complied with available Summary of Product Characteristics documentation approved by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA).

## Limitations and Further Research

Further work is required to develop optimal paediatric dosing recommendations for the use of common antibiotics in the LMIC setting. Currently available pharmacokinetic data are limited, especially for the commonly used twice daily dosing. There is a clear need for a prioritisation exercise of the key knowledge gaps to be addressed. Furthermore, the availability and use of generic formulations needs to be more clearly determined to ensure the feasibility of compliance to the summary dosing guidance in the LMIC setting.

# Antibiotic Dosing for Children: Expert Recommendations

*For Children Ages 2 months to 12 years*

*Dosing Recommendations at a Glance*

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| **Amikacin** | 15 mg/kg/day IV given once daily |
| **Amoxicillin** | 100 mg/kg/day PO divided in 2 or 3 doses |
| **Amoxicillin / clavulanic acid** | Amoxicillin component PO or IV 100 mg/kg/day divided in 2 or 3 doses |
| **Ampicillin** | 100 mg/kg/day PO or IV divided in 2 or 4 doses<br>200 mg/kg/day PO or IV divided in 2 or 4 doses (in severe infection) |
| **Azithromycin** | 10 mg/kg/day PO given once daily |
| **Aztreonam** | 100 mg/kg/day IV divided in 2 or 3 doses |
| **Benzylpenicillin** | 100 mg/kg/day IV divided in 2 or 4 doses<br>200 mg/kg/day IV divided in 2 or 4 doses (in severe infection) |
| **Cefalexin** | 50 mg/kg/day PO divided in 2 or 4 doses |
| **Cefazolin** | 50 mg/kg/day IV divided in 2 or 3 doses |
| **Cefotaxime** | 150 mg/kg/day IV divided in 3 doses |
| **Ceftazidime** | 150 mg/kg/day IV divided in 3 doses |
| **Ceftriaxone** | 80 mg/kg/day IV given once daily |
| **Cefuroxime** | 30 mg/kg/day PO or 100 mg/kg/day IV divided in 2 doses |
| **Chloramphenicol** | 50 mg/kg/day IV divided in 2 or 4 doses |
| **Ciprofloxacin** | 30 mg/kg/day PO or IV divided in 2 doses |
| **Clarithromycin** | 15 mg/kg/day PO or IV divided in 2 doses |
| **Clindamycin** | 20 mg/kg/day PO or IV divided in 3 or 4 doses |
| **Cloxacillin, Flucloxacillin** | 100 mg/kg/day IV divided in 2 or 4 doses |
| **Doxycycline** | 5 mg/kg/day given once daily or in 2 doses |
| **Erythromycin** | 50 mg/kg/day PO or IV divided in 4 doses<br>100 mg/kg/day PO or IV in severe infections |
| **Gentamicin** | 7 mg/kg/day IV given once daily |
| **Imipenem** | 60 mg/kg/day divided in 3 or 4 doses |
| **Levofloxacin** | 20 mg/kg/day PO divided in 2 doses |
| **Linezolid** | 30 mg/kg/day PO or IV divided in 2 or 3 doses |
| **Meropenem** | 60 mg/kg/day IV divided in 3 doses<br>120 mg/kg/day IV divided in 3 doses (in severe infection) |
| **Metronidazole** | 20 mg/kg/day PO or IV divided in 2 or 3 doses |
| **Moxifloxacin** | 10 mg/kg/day PO given once daily |
| **Nitrofurantoin** | 4 mg/kg/day PO divided in 2 or 4 doses |
| **Phenoxymethylpenicillin** | 100 mg/kg/day PO divided in 2 or 4 doses<br>200 mg/kg/day PO divided in 2 or 4 doses in severe infection |
| **Piperacillin-tazobactam** | 300 mg/kg/day IV divided in 3 or 4 doses |
| **Trimethoprim** | 8 mg/kg/day PO divided in 2 doses |
| **Trimethoprim / sulfamethoxazole** | 50 mg/kg/day PO divided in 2 doses |
| **Vancomycin** | 50 mg/kg/day IV divided in 2 or 3 or 4 doses |

| * | Antibiotic | Blue Book Recommendations | WHO Expert Recommendations | Daily Maximum Dose | | Additional Comments |
|---|---|---|---|---|---|---|
| | | | | PO max. | IV max. | |
| C | Amikacin | **1 month to 18 years:** 15mg/kg/dose given 24-hourly | 15 mg/kg/day IV given once daily | | 1.5 g/day | |
| E | Amoxicillin | **1 month to 18 years, PO:** 15–30mg/kg/dose given three times daily (max 500mg/dose)<br>**1 month to 18 years, IV:** 30–60mg/kg/dose given 8-hourly | 100 mg/kg/day PO divided in 2 or 3 doses | 4 g/day | 4 g/day | |
| E | Amoxicillin / clavulanic acid | **1 month to 6 years, PO:** 0.25–0.5mL/kg/dose of 125/31 suspension three times daily<br>**6–12 years, PO:** 0.15–0.3mL/kg/dose of 250/62 suspension three times daily<br>**12–18 years, PO:** one 250/62 strength tablet three times daily; increased in severe infections to one 500/125 strength tablet three times daily<br>**1–3 months, IV:** 30mg/kg/dose given 8-hourly<br>**3 months to 18 years, IV:** 30mg/kg/dose given 6- to 8-hourly (max 1.2g/dose) | Amoxicillin component PO or IV 100 mg/kg/day divided in 2 or 3 doses | 1.5 g/day[2] | 1.5 g/day | |
| E | Ampicillin | **1 month to 18 years:** 15–30mg/kg/dose (max 500mg) given four times daily<br>**1 month to 18 years:** 25mg/kg/dose (max 1g) given 6-hourly; may be doubled in severe infection<br>For *Listeria* meningitis, increase the IV dose to 100mg/kg/dose (max 2g) given 4-hourly | 100 mg/kg/day PO or IV divided in 2 or 4 doses | 4 g/day[2] | 12 g/day[2] | **In severe infection, double dose:** 200 mg/kg/day PO or IV divided in 2 or 4 doses |
| E | Azithromycin | **<15kg:** 10mg/kg/dose given once daily (max 500mg/dose) for 3 days<br>**15–25kg:** 200mg once daily for 3 days<br>**26–35kg:** 300mg once daily for 3 days<br>**36–45kg:** 400mg once daily for 3 days<br>**>45kg:** 500mg once daily for 3 days | 10 mg/kg/day PO given once daily | 500 mg/day | | |
| | Aztreonam | **1 month to 2 years, IV :** 30mg/kg/dose given 6- to 8-hourly<br>**2–18 years, IV:** 30mg/kg/dose given 8-hourly (increase to 50mg/kg/dose 6-hourly in severe infection and cystic fibrosis. Max 2g/dose | 100 mg/kg/day IV divided in 2 or 3 doses | | 8 g/day | |
| E | Benzylpenicillin | **1 month to 18 years, IV:** 25mg/kg/dose given 6-hourly<br>Double dose in severe infection to 50mg/kg/dose up to 4- to 6-hourly | 100 mg/kg/day IV divided in 2 or 4 doses | | 4 g/day[1] | **In severe infection, double dose:** 200 mg/kg/day IV divided in 2 or 4 doses |
| E | Cefalexin | **1 month to 18 years:** 12.5–25mg/kg/dose given twice daily given four times daily | 50 mg/kg/day PO divided in 2 or 4 doses | 1.5 g | | |
| E | Cefazolin | [2]**Mild-Moderate Infection** 25-50 mg in 3 doses (max 3g), **Severe Infection** | 50 mg/kg/day IV divided in 2 or 3 doses | | 6 g/day[2] | |

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| | | 100-150 mg in 3 doses (max 4-6g) | | | | |
| C | Cefotaxime | **1 month to 18 years, IV:** 50mg/kg/dose given 6- to 8-hourly | 150 mg/kg/day IV divided in 3 doses | | 12 g/day | |
| C | Ceftazidime | **1 month to 18 years, IV:** 25–50mg/kg/dose (max 2g/dose) | 150 mg/kg/day IV divided in 3 doses | | 6 g/day | |
| E | Ceftriaxone | **1 month to 18 years, IV, IM:** 50–80mg/kg/dose given once daily | 80 mg/kg/day IV given once daily | | 4 g/day | |
| | Cefuroxime | **3 months to 18 years, PO:** 10–15mg/kg/dose given twice daily<br>**1 month to 18 years, IV:** 20–60mg/kg/dose given 6- to 8-hourly | 30 mg/kg/day PO or 100 mg/kg/day IV divided in 2 doses | 1 g/day | 3 g/day | |
| E | Chloramphenicol | **1 month to 18 years, IV:** 12.5–25mg/kg/dose given 6-hourly | 50 mg/kg/day IV divided in 2 or 4 doses | | 4g[2] | **In severe infection, double dose:**<br>100 mg/kg/day IV divided in 2 or 4 doses |
| E | Ciprofloxacin | **1 month to 18 years, PO:** 15mg/kg/dose given 12-hourly (max 750mg/dose)<br>**1 month to 18 years, IV:** 10mg/kg/dose 8- to 12-hourly (max 400mg/dose) | 30 mg/kg/day PO or IV divided in 2 doses | 750mg / dose | 400mg / dose | |
| | Clarithromycin | **1 month to 18 years, PO:**<br>7.5–15mg/kg/dose given twice daily<br>**1 month to 18 years, IV:** 7.5mg/kg/dose given 12-hourly | 15 mg/kg/day PO or IV divided in 2 doses | 1 g/day | 1 g/day | |
| C | Clindamycin | **1 month to 18 years, PO:** 6mg/kg/dose given four times daily (body weight under 10kg, minimum dose 37.5mg three times daily)<br>**1 month to 18 years, IV:** 6–10mg/kg/dose given 6-hourly | 20 mg/kg/day PO or IV divided in 3 or 4 doses | 1.8 g/day | 1.8 g/day | |
| E | Cloxacillin, Flucloxacillin | **1 month to 18 years, IV:** 25mg/kg/dose given four times daily; Severe infection: use 50mg/kg/dose<br>**1 month to 18 years, IV:** 25–50mg/kg/dose given 6-hourly | 100 mg/kg/day IV divided in 2 or 4 doses | | 8 g/day | **In severe infection, double dose:**<br>200 mg/kg/day IV divided in 2 or 4 doses |
| E | Doxycycline | **12–18 years:** 200mg loading dose, then 100mg/dose given twice daily | 5 mg/kg/day given once daily or in 2 doses | 200 mg/day[1] | | |
| E | Erythromycin | **1 month to 18 years, PO:** 12.5–25mg/kg/dose given four times daily<br>**1 month to 18 years, IV:** 12.5mg/kg/dose given 6-hourly | 50 mg/kg/day PO or IV divided in 4 doses | 2 g/day[1] | 4 g/day[1] | **In severe infection, double dose:**<br>100 mg/kg/day PO or IV divided in 4 doses |
| E | Gentamicin | **1 month to 18 years:** 7mg/kg/dose given once daily | 7 mg/kg/day IV given once daily | | | |
| C | Imipenem/cilastatin | **1–3 months:** 20mg/kg/dose given 8-hourly<br>**3 months to 18 years:** 15mg/kg/dose (max 500mg) given 6-hourly<br>In children >12 years, the dose may be doubled in severe infection to 1g. Where Pseudomonas suspected, 25mg/kg given 6-hourly | 60 mg/kg/day divided in 3 or 4 doses | | 4g/day | |

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| C | Levofloxacin | [2]**Severe Infections:**<br>16-20 mg in 2 doses (daily adult dose, 500-750 mg) | 20 mg/kg/day PO divided in 2 doses | 750 mg/day[2] | 750 mg/day[2] | |
| C | Linezolid | **1 month to 12 years, PO:** 10mg/kg/dose (max 600mg) given three times daily<br>**1 month to 12 years, IV:** 10mg/kg/dose (max 600mg) given 8-hourly | 30 mg/kg/day PO or IV divided in 2 or 3 doses | 1.2 g/day | 1.2 g/day | |
| C | Meropenem | **1 month to 12 years:** 10–40mg/kg/dose given 8-hourly | 60 mg/kg/day IV divided in 3 doses | | 1.5 g/day | **In severe infection, double dose:**<br>120 mg/kg/day IV divided in 3 doses |
| E | Metronidazole | **1 month to 18 years:** 7.5mg/kg/dose given three times daily | 20 mg/kg/day PO or IV divided in 2 or 3 doses | 1.2 g/day | 1.2 g/day | |
| C | Moxifloxacin | | 10 mg/kg/day PO given once daily | | | |
| E | Nitrofurantoin | **3 months to 18 years:** 1mg/kg/dose given four times daily | 4 mg/kg/day PO divided in 2 or 4 doses | 400 mg/day | | **Prophylaxis (3 months to 18 years):**<br>1mg/kg/dose (max 100mg) given once daily |
| E | Phenoxymethylpenicillin | **1 month to 18 years:** 25mg/kg/dose given 6-hourly<br>Double dose in severe infection to 50mg/kg/dose up to 4- to 6-hourly | 100 mg/kg/day PO divided in 2 or 4 doses | 4 g/day | | **In severe infection, double dose:**<br>200 mg/kg/day PO divided in 2 or 4 doses |
| | Piperacillin-tazobactam | **1 month to 18 years, IV:** 90mg/kg/dose given 6- to 8-hourly | 300 mg/kg/day IV divided in 3 or 4 doses | | 18 g/day | |
| E | Trimethoprim | **1 month to 18 years:** 4mg/kg/dose given twice daily | 8 mg/kg/day PO divided in 2 doses | 400 mg/day | | **Prophylaxis (1 months to 18 years):**<br>2mg/kg/dose (max 100mg) given at night |
| E | Trimethoprim / sulfamethoxazole | **6 weeks to 18 years:** 24mg/kg/dose given twice daily | 50 mg/kg/day PO divided in 2 doses | 960 mg/day of trimethoprim | | |
| C | Vancomycin | **1 month to 18 years:** 15mg/kg/dose given 8-hourly | 50 mg/kg/day IV divided in 2 or 3 or 4 doses | | 2 g/day | |

*** Category in Current WHO EMLc Model List April 2015 (E: Essential, C: Complementary); [1]adapted from BNFC: British National Formulary for Children; [2]adapted from Red Book: 2015 Report of the Committee on Infectious Diseases**

**Further Information**

WHO EMLc

http://www.who.int/medicines/publications/essentialmedicines/EMLc_2015_FINAL_amended_AUG2015.pdf?ua=1

BNFC: British National Formulary for Children

Paediatric Formulary Committee. BNF for Children (online). London: BMJ Group, Pharmaceutical Press, and RCPCH Publications

Blue Book: Manual of Childhood Infections

Sharland M, Butler K, Cant A, Dagan R, Davies G, de Groot R, Elliman D, Esposito S, Finn A, Galanakis M, Giaquinto C, editors. Manual of childhood infections: the blue book. Oxford University Press; 2016 Apr 7.

Red Book: 2015 Report of the Committee on Infectious Diseases

Kimberlin DW, Brady MT, Jackson MA, Long SS. Red Book, (2015). American Academy of Pediatrics; 2015 May 1.

IDSA/PIDS: Infectious Diseases Society of America and the Pediatric Infectious Diseases Society

Community Acquired Pneumonia

Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, Kaplan SL, Mace SE, McCracken GH, Moore MR, St Peter SD. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clinical Infectious Diseases. 2011 Aug 30:cir531.

Pharyngitis

Shulman ST, Bisno AL, Clegg HW, Gerber MA, Kaplan EL, Lee G, Martin JM, Van Beneden C. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2012 Sep 9:cis629.

Sinusitis

Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, Pankey GA, Seleznick M, Volturo G, Wald ER, File TM. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clinical Infectious Diseases. 2012 Mar 20:cir1043.

Meningitis

Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, Whitley RJ. Practice guidelines for the management of bacterial meningitis. Clinical infectious diseases. 2004 Nov 1;39(9):1267-84.

Intra-abdominal Infections

Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O'Neill PJ, Chow AW, Dellinger EP, Eachempati SR, Gorbach S. 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. Surgical infections. 2010 Feb 1;11(1):79-109.

Acute Infectious Diarrhea

Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, Slutsker L, Tauxe RV, Hennessy T, Griffin PM, DuPont H, Sack RB, Tarr P. Practice guidelines for the management of infectious diarrhea. Clinical infectious diseases. 2001 Feb 1;32(3):331-51.