

Aminopenicillin breakpoints for *Enterobacterales*

General Consultation

November 30, 2021 to January 14, 2022

Comments to the EUCAST Scientific Secretary at jturnidge@gmail.com by **January 14, 2022**.

Background

Enterobacterales breakpoints for aminopenicillins (ampicillin ± sulbactam, amoxicillin ± clavulanic acid) have historically been somewhat similar and did not account for differences in mode of delivery or site of infection. It has always been recognised that members of this order which naturally encode inducible/de-repressible chromosomal AmpC are poor targets for these agents. These species almost always test as “R” to aminopenicillins alone and combined with a beta-lactamase inhibitor.

Some years ago, EUCAST developed breakpoints for amoxicillin ± clavulanic acid in uncomplicated UTI but left breakpoints for the other aminopenicillins alone. Very recently, EUCAST developed breakpoints for iv ampicillin and amoxicillin for the treatment of bacterial meningitis based on the use of high dosages specific to that condition.

EUCAST has now undertaken a review of aminopenicillins to account of the

- mode of delivery (oral versus iv) and
- site of infection (uncomplicated UTI, complicated UTI ± associated bacteraemia, and other systemic infection sites).
Meningitis has already been reviewed.

MIC distributions and ECOFFs

MIC distributions have recently been re-assessed for acceptability using the new Standard Operating Procedure SOP 10.2, and ECOFFs have been reviewed and revised where appropriate.

Currently Agreed Dosages

Aminopenicillin	Route of administration	Standard dosage	High dosage	Uncomplicated UTI	Meningitis
Ampicillin	iv	2 g x 3	2 g x 4		2 g x 6
Ampicillin	oral	Not listed	Not listed		
Ampicillin-sulbactam	iv	(2 g + 1 g) x 3	(2 g + 1 g) x 4		
Ampicillin-sulbactam	oral	Not listed	Not listed		
Amoxicillin	iv	1 g x 3-4	2 g x 6		2 g x 6
Amoxicillin	oral	0.5 g x 3	0.75-1 g x 3	0.5 g x 3	
Amoxicillin-clavulanic acid	iv	1 g + 0.2 g x 3-4	(2 g + 0.2 g) x 3		
Amoxicillin-clavulanic acid	oral	(0.5 g + 0.125 g) x 3	(0.875 g + 0.125 g) x 3	(0.5 g + 0.125 g) x 3	

Currently Listed Breakpoints

Penicillin	MIC breakpoints (mg/l)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Ampicillin	8	8		10	14	14	
Ampicillin-sulbactam	8	8		10-10	14	14	
Amoxicillin	8	8		-	Note ^B	Note ^B	
Amoxicillin-clavulanic acid	8	8		20-10	19	19	19-20
Amoxicillin-clavulanic acid (uncomplicated UTI only)	32	32		20-10	16	16	

Note B: Susceptibility inferred from ampicillin

Pharmacokinetics and pharmacodynamics

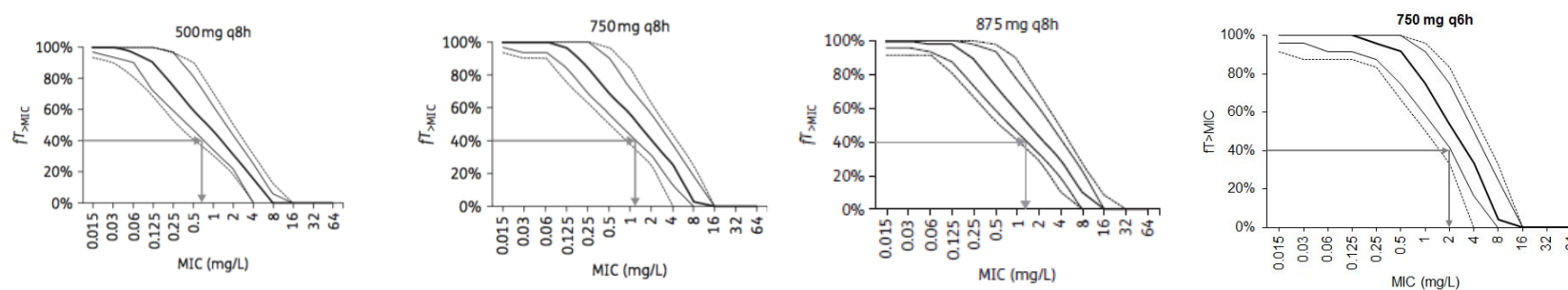
Oral amoxicillin ± clavulanic acid

For oral amoxicillin and amoxicillin-clavulanic acid data were presented in a previous consultation on *Streptococcus pneumoniae* and *Haemophilus influenzae*.

The standard dosing regimens used for oral amoxicillin varies between 750 and 3000 mg/day, divided into two to four doses. For amoxicillin-clavulanic acid, the standard dosing regimens are 500/125 mg x 3 or 875/125 mg x 2-3. The target for Monte Carlo simulations was set at 40% $fT > MIC$ [1,2]. This target is derived from clinical studies on children with acute otitis media or sinusitis, and support a PK-PD relationship for not only *S. pneumoniae* but also *H. influenzae*, indicating that the latter can act as a true pathogen. It is assumed, based on the observation that *Escherichia coli* has similar responses to amoxicillin in vitro (kill rates, no post-antibiotic effect), that the same targets apply to *Enterobacterales*.

Data from de Velde et al. [3] presented the results of Monte Carlo simulations for some of the most used dosing regimens of amoxicillin (Figure 3). In order to achieve a target of 40% $fT > MIC$, patients infected by isolates with an MIC of ≤ 0.5 mg/L would need to be treated with a dosing regimen of 500 mg x 3 while patients infected by isolates with an MIC of ≤ 1 mg/L would need a dosage of 750 mg x 3.

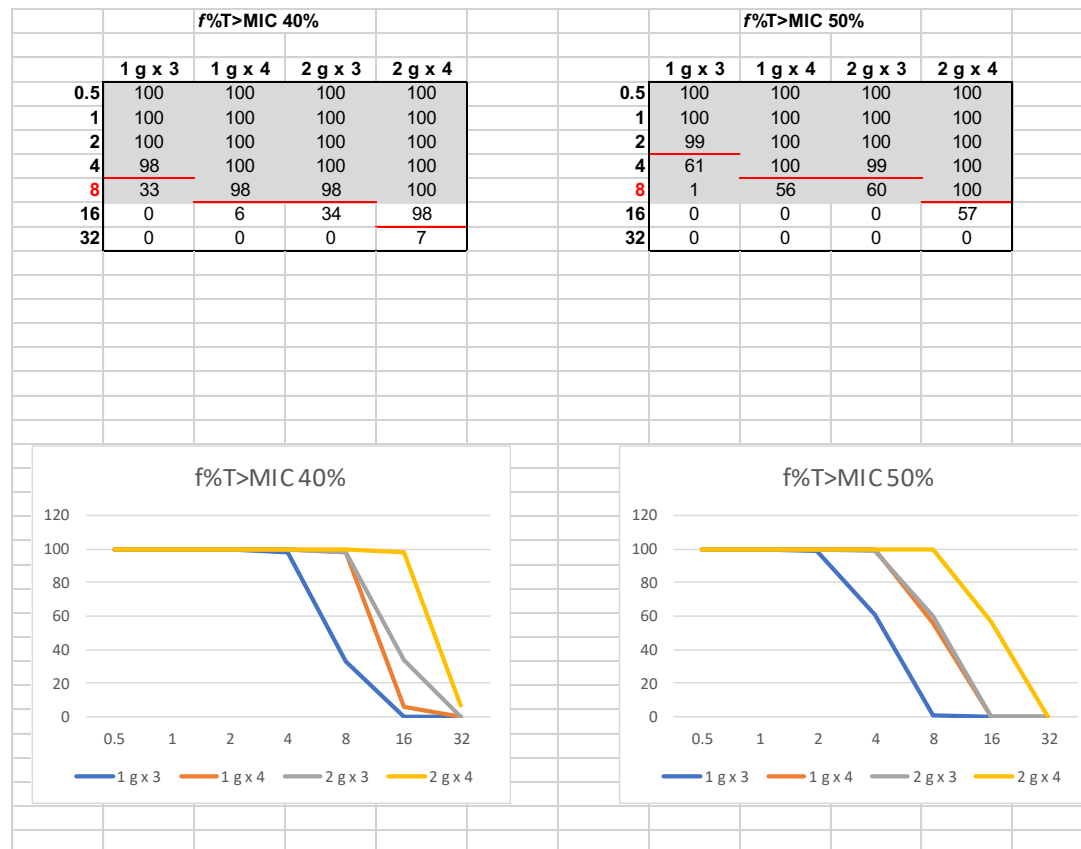
Figure 1: Monte Carlo simulations for different oral doses of amoxicillin [3]



For amoxicillin-clavulanic acid, the situation is further complicated by the variable absorption of clavulanic acid [4].

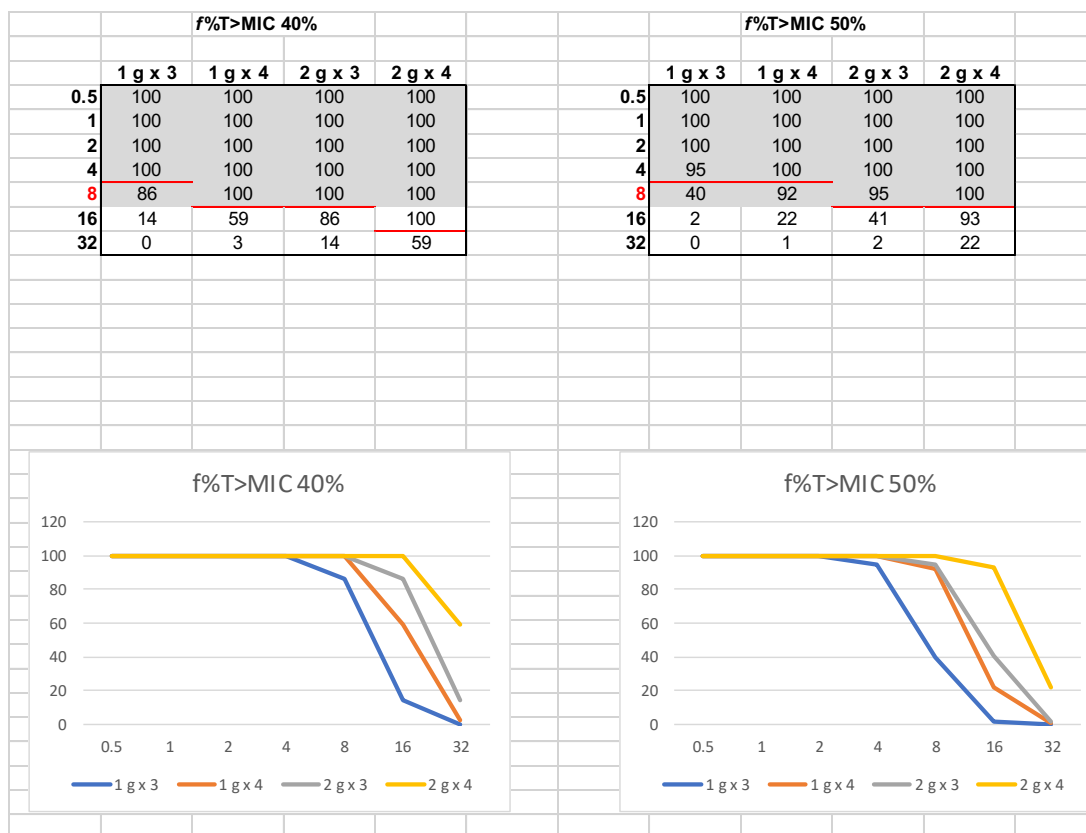
Intravenous amoxicillin ± clavulanic acid

For amoxicillin ± clavulanic acid administered intravenously, data from Zarowny et al. [5] were used to conduct Monte Carlo simulations of 4 different dosing regimens and two $fT > MIC$ targets of 40 and 50%. For the 40% target, three of the regimens (1 g x 4, 2 g x 3 and 2 g x 4) were adequate to cover the wild type of *E. coli*. For the 50% target, only 2 g x 4 was adequate. Because the intravenous formulation of amoxicillin-clavulanic acid comes as the two separate components, the findings of amoxicillin alone are applicable.



Intravenous ampicillin

For ampicillin administered intravenously, data from Lewis et al. [6] we used to conduct Monte Carlo simulations of 4 different dosing regimens and two $fT > MIC$ targets of 40 and 50%. For the 40% target, three of the regimens (1 g x 4, 2 g x 3 and 2 g x 4) were adequate to cover the wild type of *E. coli* (ECOFF 8 mg/l). For the 50% target, only 2 g x 3 and 2 g x 4 were adequate. Because the intravenous formulation of ampicillin-sulbactam comes as the two separate components (unlike the oral formulation), the findings of ampicillin alone are applicable.



Clinical data

The tables below were kindly provided by the CLSI Aminopenicillin Working Group who undertook the literature search and gave permission to EUCAST to use the material for the consultation.

Amoxicillin oral

Summaries of oral amoxicillin in UTI clinical trials

Infection type	Design	Outcome measure	Results	Interpretation
uUTI/prostatitis ¹	50 pts with UTI/prostatitis ; PO Amox 250mg po TID	Microbiologic and clinical	Eradication of original bug 94% ; 76% cure rate overall. Bugs: E.coli, P, mirabilis, enterococci, staphylococci	250mg po TID is a good dosing strategy for uUTI
uCystitis (1 pyelo) ²	Pts w/ UTI randomly assigned to PO Amox (250 mg q 8 hrs) or PO Amp (750 mg q 8 hrs)	Microbiologic and clinical	10 pts got amp – 100% bacteriologic cure 21 pts got amox – 76% bacteriologic cure (3 reinfections) Mean serum conc. (1hr) : 3 µ g/mL (amp) and 4.7 µ g/mL (amox); were the same at 7 hrs Bugs: E.coli, P, mirabilis, enterococci, staphylococci, 1 Kleb	250 mg amox equally effective to 750 mg amp Amox reinfections due to host factors
uUTI ³	31 Pts assigned to PO Amox (250 mg q 6 hrs or 500mg TID) x 10-14 days	Microbiologic and clinical	Eradication 87%; 84% clinical cure	Amox effective and comparable to amp
Recurrent UTI ⁴	34 pts w/ recurrent UTI and urologic abnormalities; half got PO Amox (250 mg q 8 hrs) and half got 500mg TID ;	Microbiologic and clinical	20 E. coli isolated; Eradication in 25 pts (73%)	250mg po TID is a good dosing strategy for uUTI

	treatment X 1-6 weeks (25 pts 3 wks or less)			
UTI (incl recurrence) ⁵	38 pts w/ bacteriuria; 22 single episode; 16 recurrence; 6 structural anomalies. PO Amox : 250 mg /day TID X 10 d	Microbiologic and clinical	32 pts w/ E. coli: 90% 'cure' – urine sterile but only 69% free from bacteriuria on f/u weeks later 4 pts w/ P. mirabilis: 2 persistent infection despite in vitro 'S'	Amox as effective as other UTI drugs
Chronic UTI - kids ⁶	20 Pts w/ UTI grouped by anatomic abnormality (Grps 2 and 3) vs none (Group 1 - uUTI). Treated for 3 wks (grps 1 and 2) and 6 wks (grp 3). Amox PO 25 mg/kg/day TID	Microbiologic and clinical	Eradication >80% in 48 hrs; reinfections or new infections common 3 weeks later (Fig)	Amox suitable for prolonged use (fewer side effects) and good for eradication but may be problematic b/c of development of resistance (vs reinfection - likelier) in such pts
Clinical isolates, cancer pts ⁷ ; III. 22 UTI (14 pyelo), 7 SSTI, 6 Resp (2 LRTI, 4 URI)	I. 126 GPC and 250 GNB clinical isolates for AST II. 11 adult volunteers for PK/PD: gor PO amox 125, 250, 500mg X1. Blood and urine taken hours later. III. 35 pts w/ cancer, good ANC, and nonbacteremic infections; amox po 500 mg 3-4x/day	Microbiologic, pharmacologic, clinical	I. P. mirabilis : 76% S to <=1.56 ug/mL amox; 20% R to 12.5 ug/mL. E.coli: 57% S to <=6.25 ug/mL, rest R to 50 ug/mL. II. Peak serum :1-2 hrs	Amox adequate for S organisms in cancer pts with good ANC (maybe not resp infections)

1. Cox CE. JID 1974. 129:S 235-6, 2. Gilbert DN. JID 1974. 129:S231-234, 3. Miller GB. JID 1974. 129:S237-240; 4. Pow-Sang J et al. JID 1974. 129:S246-247; 5. Turck et al. JID 1974. 129: S 248-; 6. Mongeau and Mahfoud. JID 1974. 129: S243-245; 7. Rodriguez and Bodey. JID 1974. 129:S209-212

Outside the urinary tract, amoxicillin efficacy data are limited. Rodriguez and Bodey examined efficacy in 13 cancer patients treated with oral amoxicillin and showed some efficacy against *Proteus mirabilis* and to a lesser extent, *E. coli*.

Table 2. Response of infections to treatment with amoxicillin.

Organism	Cure rate*
Soft tissue infections	
β -hemolytic <i>Streptococcus</i>	1/1
Microaerophilic α - <i>Streptococcus</i>	1/1
<i>Escherichia coli</i>	1/1
<i>Enterobacter</i>	1/1
<i>Pseudomonas</i>	0/2
Mixed gram-negative	0/1
Total	4/7 (57%)
Urinary tract infections	
Enterococcus	3/3
<i>E. coli</i>	8/12
<i>Proteus mirabilis</i>	2/2
<i>Enterobacter</i>	0/1
<i>E. coli</i> + <i>Proteus vulgaris</i>	1/1
<i>E. coli</i> + enterococcus	1/1
<i>P. mirabilis</i> + <i>Klebsiella</i>	0/1
Enterococcus + <i>Citrobacter</i>	0/1
Total	15/22 (68%)
Respiratory infections	
β - <i>Streptococcus</i>	1/1
<i>Haemophilus influenzae</i>	0/1
<i>Klebsiella</i>	0/1
<i>Klebsiella</i> + <i>E. coli</i>	0/1
<i>Proteus</i> + <i>Klebsiella</i>	0/1
<i>E. coli</i> + <i>Enterobacter</i>	0/1
Total	1/6 (17%)

* Number of cures/number of infections treated.

Summaries of oral amoxicillin in skin and skin structure infections

Infection type	Design	Outcome measure	Results	Interp
SSTI ¹	45 outpts with SSTI. 250mg TID X 10 d. 1 child: 250mg BID and 125 mg TID X 10 d	Clinical and microbiologic	78% cure rates overall: 69% <i>S. aureus</i> , 100% beta strep. Susceptible <i>P. mirabilis</i> failed therapy (fistula)	Amox PO is effective for beta strep
Surgical site and Miscellaneous infections ²	30 surgical pts w/ organisms S to amp treated with amox po 250 or 500 mg TID.	Clinical and microbiologic	Repeat cultures up to 1 week post. 100% cure rate by 9 days (In Results they say 1 pt with Strep was not cleared after 7 days but details are not otherwise clear about that case). Authors also don't list all organisms identified.	Amox PO is effective

1. Pankey JID 1974. 129:S202-206; 2. Rocko and Timmes JID 1974. 129:S198-199

Amoxicillin-clavulanic acid

Summaries of oral amoxicillin-clavulanic acid in non-UTI clinical trials

Infection type	Design	Outcome measure	Results	Interpretation
Drained dental abscess ¹	A/C + MTZ IV x 1-2 doses, then A/C 500 q 8 alone or combined with oral MTZ	Clinical cure	12/30 A/C patients had regimen changed b/c poor response; 6 MTZ added, 6 A/C changed to another drug	A/C alone failures
Drained/resected CIAI ²	IV Pip/tazo vs. IV moxiflox x 3-5 d; followed by oral A/C 800q12 vs moxiflox x 5-14 d	Clinical and microbiologic	Overall no difference 80-90% cured. Moxi superior for HAI, in elderly and those with mild-mod illness. 656 patients	Unclear if A/C beneficial b/c initial IV Rx for 3-5 d (duration current guidelines)
Anaerobic lung abscess ³	A/C 2g IV q8 x ~10 d, then oral A/C 875-1 g q8 x ~30 d	clinical	All 35 patients had good outcomes. No Enterobacteriaceae. No MICs reported.	Possible role oral A/C at high dose after prolonged IV therapy
SSTI ⁴	A/C 1g IV q8 x ~3d, then oral A/C 500 q8 x 7-21d vs. Moxi IV x 3d, then oral moxi	Clinical @ 2 wks	No differences ~80% cured. A/C arm 27 E. coli, 12 P. mirab, 5 E. cloacae, 8 P. aerug, 3 K. pneum. Most infect S. aureus. 210 each arm. No MICs reported	Possible role high dose A/C after IV therapy. Duration guidelines ~5 d . Assess not using current FDA guidance
Outpatient SSTI ⁵	A/C 500 q8 vs. A/C 250 q8 vs. cefaclor 5-10 d	Clinical at EOT	No differences ~70% cured. Most S aureus 12 GNRs – all suscept; treatment arm unstated. 80 total pts. No MICs	A/C suitable outpatient cellulitis.

1. Br J Oral Max Fac Surg 53:18, 2. Ann Surg 244:204, 3. EJCMID 22:185, 4. Infect 37:407, 5. AAC 24:856

Summaries of oral amoxicillin-clavulanic acid in UTI clinical trials

Infection type	Design	Outcome measure	Results	Interpretation
Cystitis, mainly E. coli, half amox R ¹	A/C 250,500 q8	Clinical & microbiologic	250 – 30% success 500 - 70% success amox S, 30% amox R E coli modal MICs 8 (amox S) >32 amox R	A/C 500 q 8 works if MIC<=8
Pyelonephritis kids ²	Oral A/C 50mpk q8 x 10d vs. ceftriaxone 50mpk x 3 d, then A/C	Clinical, micro & renal scars at 1 yr.	95% E. coli. 99% cure both arms, no diff scar%. 6% resist A/C. MICs not reported, breakpoint criteria not stated	A/C at slightly higher than 25-40 q8 FDA dose effective for pyelonephritis
Cystitis ³	Oral A/C 875 q12 x 10 d	Clinical, micro	87% cured D10, 61% D30. E. coli, Klebs, Proteus. 94% "S"	A/C effective for cystitis ? Up to MIC 8
Pyelo ⁴	875 bid vs 500 q8	Micro	No diff, ~70% clinical success, no MICs or suscept	A/C 875 bid as effective as 500 tid, both reasonably effective
UTI ⁴	Misc uncontrolled 875/125 bid	Micro	No MICs, ~70-80% micro responses	A/C 875 bid apparently effective UTIs

1. Lancet 1980;I:620, 2. BMJ 2007 online, 3. 16th ICC , 4. GSK FDA submission via Dr. Reddy's

Proposed Breakpoints

The table below is based on the following observations:

- Oral amoxicillin ± clavulanic acid dosages are inadequate to cover the wild type of any species of *Enterobacterales*. However, in the case of urinary tract focus, high exposure therapy is considered adequate, for which reason the wild type has been placed in the I-group
- Oral ampicillin gives about half the exposure in vivo compared to oral amoxicillin, and therefore oral breakpoints are not listed.
- In general, and based on PK/PD analyses, the required minimum dose is 2 g x 3 (aminopenicillin-component) for all aminopenicillins, with or without inhibitor. This dosing regimen is required to cover the wild type of “susceptible” species. The dosing tab will be updated accordingly to reflect that this should be considered the standard dose.

Penicillin	MIC breakpoints (mg/l)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Ampicillin iv	8	8		10	14	14	
Ampicillin oral, uncomplicated UTI only	8	8			14	14	
Ampicillin-sulbactam iv	8	8		10-10	14	14	
Ampicillin-sulbactam oral, uncomplicated UTI only	8	8			14	14	
Amoxicillin iv	8	8		-	Note ^B	Note ^B	
Amoxicillin oral, complicated UTI	<0.001	8			Note ^B	Note ^B	
Amoxicillin oral, uncomplicated UTI only	8	8			Note ^B	Note ^B	
Amoxicillin oral, other indications	(8) ¹	(8) ¹			Note ^{A B}	Note ^{A B}	
Amoxicillin-clavulanic acid iv	8	8		20-10	19	19	19-20
Amoxicillin-clavulanic acid oral, complicated UTI	<0.001	8			19	19	
Amoxicillin-clavulanic acid oral, (uncomplicated UTI only)	32	32		20-10	16	16	
Amoxicillin-clavulanic acid oral, other indications	(8)	(8)			16	16	

Note 1/A: Breakpoints in brackets distinguish between isolates without and with phenotypically detectable resistance mechanisms. Clinical evidence for their use in monotherapy is lacking but for a specific indication or in combination with another agent or measure they serve to exclude isolates with resistance mechanisms. The latter can be reported R (resistant) but S and I should be avoided in reports

Note B: susceptibility inferred from ampicillin

References

1. Craig, Andes. *Pharmacokinetics and pharmacodynamics of antibiotics in otitis media*. *Pediatr Infect Dis J* 1996; 15(3):255-9
2. Craig WA. Pharmacodynamics of antimicrobials: general concepts and applications. In: CH Nightingale, T. Murakawa, PG Ambrose, eds. *Antimicrobial pharmacodynamics in theory and clinical practice*. New York: Marcel Dekker, 2002:1-22
3. de Velde D, de Winter BC, Koch BCP et al. Non-linear absorption pharmacokinetics of amoxicillin: consequences for dosing regimens and clinical breakpoints. *J Antimicrob Chemother* 2016; 71:2909-17
4. de Velde D, de Winter BC, Koch BCP et al. Highly variable absorption of clavulanic acid during the day: a population pharmacokinetic study. *J Antimicrob Chemother* 2018; 73:469-76
5. Zarowny D, Ogilvie R, Tamblyn D et al. Pharmacokinetics of amoxicillin. *Clin Pharmacol Ther* 1974; 16:1045-51
6. Lewis CP, Jusko WJ. Pharmacokinetics of ampicillin in cirrhosis. *Clin Pharmacol Ther* 1975; 18:475-84