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COMMENTARY

Orally Administered Amoxicillin/Clavulanate: Current Role in Outpatient Therapy

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ABSTRACT

Oral amoxicillin/clavulanate is a community workhorse antibiotic, routinely prescribed for respiratory tract infections, skin infections as well as urinary tract infections (UTIs). Multiple adult and paediatric dose formulations of amoxicillin/clavulanate are available in different parts of the world. In adult formulations, clavulanic acid dose is restricted to 125 mg because of tolerability issues. Despite its popular use for 40 years, few pharmacokinetic/pharmacodynamic (PK/PD) studies were undertaken to justify the doses and breakpoints currently in use for various infections. Clavulanate has a minimal role in the combination's use for respiratory infections. In the context of rising extended spectrum beta-lactamase (ESBL) prevalence globally, empirical and overuse of orally administered amoxicillin/clavulanate may select resistance in Gram-negative pathogens. The susceptibility test methods and interpretive criteria differ between the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST). Third-generation oral cephalosporins such as ceftibuten or cefpodoxime can be combined with amoxicillin/clavulanate to tackle UTIs involving ESBL producing *Escherichia coli* and *Klebsiella* spp. Clinicians who routinely prescribe amoxicillin/clavulanate in outpatient settings should be aware of potential benefits and limitations of this combination.

Keywords: Amoxicillin/clavulanate; Outpatient; Pneumonia; UTI

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Key Summary Points

Various dosing regimens of amoxicillin/clavulanate such as 250/125 mg q8h, 500/125 or 750/125 or 1000/125 mg are available for the management of infections. However, few PK/PD studies were undertaken to justify its doses and breakpoints.

Oral amoxicillin/clavulanate is often prescribed for community respiratory tract infections as well as urinary tract infections (UTIs).

In the context of rising ESBL prevalence globally, empirical use of orally administered amoxicillin/clavulanate in UTI is questionable.

Third-generation oral cephalosporins such as ceftibuten or cefpodoxime can be combined with amoxicillin/clavulanate to tackle UTIs involving ESBL producing *Escherichia coli* and *Klebsiella* spp.

DIGITAL FEATURES

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INTRODUCTION

Until 1960, the entire β-lactam family comprised only two narrow spectrum, Gram-positive bacteria-active antibiotics—penicillin G and penicillin V. Beecham Research Laboratories (BRL) synthesized ampicillin in 1961 and amoxicillin in 1970 from the precursor, 6-aminopenicillanic acid. Both showed relatively broad-spectrum activity that encompassed the common community respiratory pathogens *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and *Moraxella catarrhalis* as well as the common urinary tract pathogen *Escherichia coli*. Amoxicillin showed superior oral absorption leading to a plasma exposure approximately two times that of ampicillin [1]. Subsequently, amoxicillin was also combined with clavulanate (the first-ever β-lactamase inhibitor introduced in to clinics) by BRL in 1981 (Augmentin tablets) to tackle the emerging challenge from β-lactamase-harbouring *S. aureus*, *H. influenzae*, *M. catarrhalis*, *E. coli*, *Klebsiella* spp. and *Bacteroides fragilis* [2].

The initially approved amoxicillin/clavulanate dose for adults was a 250/125 mg, q8h regimen. Later, for the management of more severe infections and/or convenience of a q12h regimen, the amoxicillin dose was increased to 500 or 750 or 1000 mg while the clavulanate dose was retained at 125 mg. Doubling the clavulanate dose to 250 mg resulted in higher incidences of nausea with no additional benefit in clinical efficacy [3]. Later a high dose amoxicillin 2000 mg plus clavulanate 125 mg had also been introduced but in extended release form. In the case of paediatric formulations, initial strengths were 20/5 or 40/10 mg/kg/day in three divided doses. Now, the standard paediatric regimen for mild to moderate infections is 25/3.6 mg/kg/day in two divided doses and for severe infections, 45/6.4 mg/kg/day or 90/6.4 mg/kg/day (in two divided doses) is recommended [2]. Even after 40 years since its introduction, amoxicillin/ clavulanate is among the largest prescribed antibiotics. In this review, we analyse the current role of amoxicillin/clavulanate amidst growing antibiotic resistance rates and better insights into the pharmacokinetic/pharmacodynamic (PK/PD) features of this combination. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

PK/PD OF AMOXICILLIN/CLAVULANATE

Both amoxicillin and clavulanate show good oral absorption (about 60% oral bioavailability) [4]. Moreover, there is no pharmacokinetic interaction between amoxicillin and clavulanate. The fasted or fed state has minimal effect on the absorption and pharmacokinetics of amoxicillin. However, absorption of clavulanate in the fed state is greater relative to the fasted state.

Mean amoxicillin and clavulanate potassium pharmacokinetic parameters are shown in the Table 1. The half-life of amoxicillin and clavulanate after oral administration is 1.3 and 1 h, respectively. Both amoxicillin and clavulanate are low serum protein-bound drugs; 18% for amoxicillin and 25% for clavulanate. In general, amoxicillin and clavulanate are well distributed in body tissues. The mean concentrations in tracheal mucosa were 200% and 118% of the corresponding serum levels for amoxicillin and clavulanate respectively [5]. Unlike macrolides, fluoroquinolones and tetracyclines, amoxicillin and clavulanate do not attain high exposures in epithelial lining fluid (ELF) (ELF: unbound plasma exposure 0.35 for amoxicillin) [6]. Amoxicillin does not undergo appreciable metabolism and 50–85% of the drug is excreted in the urine as intact, 6 h after an oral dose. However, clavulanate is metabolized to a significant extent and approximately 25–40% of intact drug is excreted in urine after an oral dose [2, 7].

Being a β-lactam, the $\%fT >$ minimum inhibitory concentration (MIC) (proportion of time during which plasma unbound concentration exceeds MIC) is the PK/PD index driving the efficacy of amoxicillin. However, the PK/PD index of clavulanate in the presence of amoxicillin has not been yet studied. Since the PK/PD of β-lactamase inhibitors has been a subject of investigation in recent times (only after such investigations were undertaken for avibactam), it is therefore not surprising that no PK/PD information is available for clavulanate in the presence of amoxicillin. However, the PK/PD driver of clavulanate in the presence of another partner, ceftibuten, has been described. A 20.59% free $T > 0.5$ mg/L was found to be linked with a static effect in a neutropenic mice thigh infection model [8].

The PK/PD targets of stand-alone amoxicillin have been described but in limited studies. In an in-vitro kinetic model, a $T > 50\%$ was required for amoxicillin to exert maximal killing of penicillin-susceptible and penicillin-intermediate *S. pneumoniae* [9]. The EUCAST rationale document provides $fT >$ MIC of 30–35% for Enterobacterales, 25–35% for *S. pneumoniae* and *H. influenzae* as PK/PD targets for these pathogens [10]. However, this rationale document for $fT >$ MIC attainments is based on PK of intravenously administered (IV) amoxicillin. Employing the PK/PD target for Enterobacterales ($fT >$ MIC of 30%), the Monte Carlo simulation of amoxicillin showed greater than 90% probability of target attainment (PTA) in plasma for MICs up to 2 mg/L in the 500 mg, q8h, IV dose regimen which worryingly drops to a mere 8% at the CLSI and the US Committee on Antimicrobial Susceptibility Testing (USCAST) susceptibility breakpoint of 8/4 (2:1 ratio MIC) mg/L (Table 2). Since the bioavailability of orally administered amoxicillin is approximately 60%, the PTA is expected to be even lower for orally administered amoxicillin. Cattrall et al. showed that even an oral dose of 1000 mg, q8h did not attain 90% PTA (target 32.5% $fT >$ MIC) at 8 mg/L [11]. Considering these observations, the clinical utility of orally administered amoxicillin/clavulanate in treating serious infections such as pyelonephritis caused by Enterobacterales with MICs around 8 mg/L is questionable.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) Enterobacterales susceptibility breakpoint of 32 mg/L for orally administered amoxicillin/clavulanate (standard dose 500/125 mg, q8h) is applicable only for uncomplicated urinary tract infections (UTIs). It should be noted that EUCAST MIC breakpoints are based on amoxicillin MICs determined in the presence of fixed 2 mg/L.

In the case of lower respiratory infections, where *S. pneumoniae* is the primary causative pathogen, the efficacy is driven by the antibiotic concentrations in the epithelial lining

Table 1 Mean amoxicillin and clavulanate potassium pharmacokinetic parameters [7]

Dose† and regimen	AUC_{0-24} (mcg h/mL)		C_{max} (mcg/mL)	
Amoxicillin/clavulanate potassium	Amoxicillin (± SD)	Clavulanate potassium (± SD)	Amoxicillin (± SD)	Clavulanate potassium (± SD)
250/125 mg q8h	26.7 ± 4.56	12.6 ± 3.25	3.3 ± 1.12	1.5 ± 0.70
500/125 mg q12h	33.4 ± 6.76	8.6 ± 1.95	6.5 ± 1.41	1.8 ± 0.61
500/125 mg q8h	53.4 ± 8.87	15.7 ± 3.86	7.2 ± 2.26	2.4 ± 0.83
875/125 mg q12h	53.5 ± 12.31	10.2 ± 3.04	11.6 ± 2.78	2.2 ± 0.99

Mean values of 14 normal volunteers (n = 15 for clavulanate potassium in the low-dose regimens). Peak concentrations occurred approximately 1.5 h after the dose

mcg microgram, *SD* standard deviation

† Administered at the start of a light meal

fluid. Therefore, the PTA based on plasma exposures is not an appropriate method to judge the clinical potential. Nevertheless, multiple prospective or retrospectively collected clinical data established the clinical utility of amoxicillin/clavulanate for mild to moderate respiratory tract infections [12]. Moreover, unlike in the case of Enterobacterales, resistance to penicillins and other β-lactams remained very low in *S. pneumoniae*. Since β-lactamase-mediated resistance is not found with *S. pneumoniae*, clavulanate does not play a role in efficacy in pneumococcal infections.

AMOXICILLIN/CLAVULANATE ORAL DOSING REGIMENS

The rationality behind the dose selection for a β-lactam/β-lactamase inhibitor depends on the tolerability vs the PK/PD requirement to achieve efficacy. In the case of amoxicillin/clavulanate, rather than PK/PD, clinical experience and dosing convenience guided the selection of dose regimens. As mentioned earlier, initially, the combination of amoxicillin/clavulanate was introduced as a 250/125 mg, q8h dosing regimen. To align with the standard amoxicillin dosage, the amoxicillin/clavulanate regimen of 500/125 mg, q8h was registered in Europe (in 1982) and the USA (in 1986) [2]. Over the years, the ratio of amoxicillin to clavulanate has varied to reflect prescribing needs, to improve convenience and to treat more severe infections or those caused by resistant organisms. Rather than the PK/PD, the reason to prescribe a twice-a-day regimen (q12h) instead of a thrice-a-day regimen (q8h) is given by the outcomes of the clinical studies which show satisfactory efficacy and safety with a twice-a-day regimen. The highest recommended dose, 875/125 mg, q12h is well tolerated albeit with diarrhoea being the common adverse reaction.

Table 3 shows the prescribing information (indication and usage and dose regimens) of amoxicillin/clavulanate as per the US Food and Drug Administration (FDA) and European Medicines Agency summary of product characteristics (SmPC).

ORAL AMOXICILLIN/CLAVULANATE FOR COMMUNITY UTIS

In the case of uncomplicated and moderate urinary tract infections in the community, the empirical oral antibiotics nitrofurantoin, trimethoprim/sulfamethoxazole, fosfomycin, pivmecillinam, fluoroquinolones (levofloxacin, ofloxacin and ciprofloxacin) as well as amoxicillin/clavulanate and oral cephalosporins are prescribed. A susceptibility study for 2017 SENTRY surveillance of *E. coli* isolates collected from US patients with UTI showed 77.9%

Table 2 Clinical breakpoints of amoxicillin/clavulanate recommended by CLSI, EUCAST and USCAST guidelines

	Guidelines (MIC, mg/L)						
	CLSI, 2020			EUCAST, 2020		USCAST, 2020	
	S	I	R	S	R	S	R
S. pneumoniae (non-meningitis)	≤ 2	4	≥ 8	≤ 0.5	> 1	NA	NA
H. influenzae	≤ 4	–	≥ 8	≤ 0.001	> 2	≤ 2	≥ 4
Enterobacterales	≤ 8	16	≥ 32	≤ 32	> 32	≤ 8	≥ 16
M. catarrhalis	NA	NA	NA	≤ 1	> 1	NA	NA

S susceptible, *I* intermediate, *R* resistant, *NA* not available

susceptibility to amoxicillin/clavulanate [13]. More published studies also point towards contemporary UTI-causing Enterobacterales showing reduced susceptibility to amoxicillin/clavulanate (Table 4). This phenomenon is part of the larger trend of rising prevalence of extended spectrum beta-lactamases (ESBLs) coupled with OXA-1. Moreover, TEM-1 hyperproduction has also been implicated in resistance to amoxicillin/clavulanate [22]. It should be also noted that, as a result of systemic metabolism, urinary concentrations of clavulanate could be low at the recommended oral dose of 125 mg. Furthermore, no PK/PD data is available to support that the detected urinary levels of clavulanate are adequate to restore the amoxicillin activity against ESBL isolates. All these observations need to be considered regarding the current utility of orally administered amoxicillin/clavulanate for the treatment of community UTI infections that do not require hospitalization [23–28].

ORAL AMOXICILLIN/CLAVULANATE FOR RESPIRATORY AND OTHER INFECTIONS

With regards to community respiratory infections, since penicillin resistance in *S. pneumoniae* and β-lactamase-negative, ampicillin-resistant (BLNAR) in *H. influenzae* is very low, amoxicillin/clavulanate continues to be a promising choice. Moreover, the benefit of adding clavulanate to amoxicillin is only limited to BLPAR *H. influenzae* and β-lactamase-positive *M. catarrhalis*. There are also published (but limited) animal PK/PD data supporting the efficacy of amoxicillin/clavulanate for these pathogens. The American Thoracic Society and Infectious Diseases Society of America recommend use of amoxicillin/clavulanate in combination with a macrolide or doxycycline for outpatient treatment of community-acquired bacterial pneumonia in adults with comorbidities [29]. It should be noted that amoxicillin/clavulanate is not active against cell-wall-lacking atypical pathogens which are involved in community-acquired bacterial pneumonia.

Amoxicillin/clavulanate is active against *Bacteroides* spp. including *B. fragilis* that express β-lactamases. It is also active against β-lactamase-expressing *Fusobacterium* spp. Further, the standalone amoxicillin covers *Peptostreptococcus* spp. However, there is no formal approval for use of amoxicillin/clavulanate for intra-abdominal infections on the FDA label [7].

S. aureus is the leading causative pathogen implicated in skin and structure infections. The β-lactamase-producing *S. aureus* are susceptible to amoxicillin/clavulanate while methicillin-resistant *S. aureus* (MRSA) are resistant. Therefore, amoxicillin/clavulanate can be used for the treatment of skin and skin structure infections caused by β-lactamase-producing strains of *S. aureus* [7].

Table 3 Indication and dosage of amoxicillin/clavulanate recommended by the US Food and Drug Administration (FDA) and European Medicines Agency summary of product characteristics (SmPC)

	US FDA	EMA SmPC
Indications	Treatment of following indications caused by susceptible pathogens	Treatment of following indications
	Lower respiratory tract Infections caused by β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*	Acute bacterial sinusitis (adequately diagnosed)
	Otitis media caused by β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*	Acute otitis media
	Sinusitis caused by β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*	Acute exacerbations of chronic bronchitis (adequately diagnosed)
	Skin and skin structure Infections caused by β-lactamase-producing strains of *S. aureus*, *E. coli* and *Klebsiella* spp.	Community-acquired pneumonia
	Urinary tract infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.	Cystitis
	In the case of *S. pneumoniae* in these indications, amoxicillin alone is sufficient	Pyelonephritis
		Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis
		Bone and joint infections, in particular osteomyelitis
Dosage	Neonates and infants aged < 12 weeks (3 months)	Children < 40 kg
	Based on the amoxicillin component, 30 mg/kg/day divided q12h (125 mg/5 mL suspension is recommended)	Based on the amoxicillin component, 20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses
	Paediatric patients 12 weeks (3 months) and older	Adults and children ≥ 40 kg
	Based on the amoxicillin component, 45 mg/kg/day q12h or 40 mg/kg/day q8h for otitis media, sinusitis, lower respiratory tract infections and more severe infections	500/125 mg, q8h
		875/125 mg, q12h
	Based on the amoxicillin component, 25 mg/kg/day q12h or 20 mg/kg/day q8h for less severe infections	875/125 mg, q8h (higher dose for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infection)
	Paediatric patients weighing 40 kg and more	
	Should be dosed with adult dose regimens	
	Adults	
	Based on the amoxicillin component, 500 mg, q12h or 250 mg, q8h and for more severe respiratory infections 875 mg, q12h or 500 mg, q8h	

Table 3 continued

	US FDA	EMA SmPC
Available formulations	Oral suspensions	Oral suspensions
	125/31.25 mg/5 mL	600/42.9 mg/5 mL
	200/28.5 mg/5 mL	400/57 mg/5 mL
	250/62.5 mg/5 mL	There are no clinical data for 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made
	400/57 mg/5 mL	
	Chewable tablets	Tablets
	125/31.25 mg	500/125 mg
	200/28.5 mg	875/125 mg
	250/62.5 mg	
	400/57 mg	
	Tablets	
	250/125 mg	
	500/125 mg	
	875/125 mg	

INTERPRETING SUSCEPTIBILITIES OF GRAM-NEGATIVES TO AMOXICILLIN/CLAVULANATE: CLSI VS EUCAST DICHOTOMY

There is a difference between CLSI and EUCAST methods in determining the MICs for amoxicillin/clavulanate. The CLSI recommends a 2:1 ratio method while EUCAST recommends use of fixed 2 mg/L clavulanate. As a result, for a given bacterial strain, amoxicillin/clavulanate MICs could be discordant between these two methods. Furthermore, as shown in the Table 5, the interpretive criteria differ between CLSI and EUCAST. Studies showed that the EUCAST method of determining MICs had better correlation with clinical outcome [30, 31]. While appropriateness of these methods is still debatable, until harmonization is established, clinicians should interpret the susceptibility test results on the basis of the method used to determine the MICs.

Another important aspect that requires consideration is that resistance to amoxicillin/clavulanate depends not only on the presence of β-lactamases genes in the organism but even the expression levels of these β-lactamases could affect the amoxicillin/clavulanate MICs [32]. The clinical implication of this phenomenon is that the organism might underexpress the β-lactamases in susceptibility testing and thus turns out to be susceptible but in patients it could hyperproduce the β-lactamases (as a result of increase in bla_{TEM} or bla_{AmpC} copy numbers) during therapy leading to clinical failure [32]. Such discrepancies should be borne in mind for organisms that show MICs within ± 1 doubling dilution of the susceptible breakpoint.

ALTERNATIVE CHOICES: PRESENT AND FUTURE

Compared to amoxicillin, oral cephalosporins such as cefixime, cefpodoxime and ceftibuten

Table 4 Susceptibility of pathogens to amoxicillin/clavulanate

Syndrome/clinical isolates	Geographic location	Duration of isolate studied	Most common bacterial pathogen (*n*)	Guidelines used for interpretation	Percentage of susceptibility (%)	References
UTI	Singapore	2015–2016	*E. coli* (231)	CLSI	89	[14]
UTI	France	2012–2014	*E. coli* (733)	ACFMS	18.6	[15]
UTI	Switzerland	2012–2015	*E. coli* (5241)	NA	84.5	[16]
UTI	India	NA	*E. coli* (321)	CLSI	24.9	[17]
UTI	UAE	2008	*E. coli* (101)	CLSI	89.6	[18]
UTI	UK	2010–2012	*E. coli* (5436)	EUCAST	81	[19]
UTI	Europe	2018–2019	*E. coli* (311)	EUCAST	74	[20]
			Klebsiella spp. (84)		42	
UTI	France	2014–2017	*E. coli* (16,630)	EUCAST	20	[21]
			K. pneumoniae (1724)		12.7	

ACFMS Antibiogram Committee of the French Microbiology Society, *NA* not available

Table 5 Amoxicillin/clavulanate interpretative breakpoints recommended by CLSI and EUCAST guidelines for Enterobacterales

	Disk diffusion (zone size in mm)					Minimum inhibitory concentration (μg/mL)				
	CLSI			EUCAST		CLSI			EUCAST	
	S	I	R	S	R	S	I	R	S	R
Systemic infection	≥ 18	14–17	≤ 13	≥ 19	< 19	≤ 8/4	16/8	≥ 32/16	≤ 8	> 8
Uncomplicated UTI				≥ 16	< 16				≤ 32	> 32

S susceptible, *I* intermediate, *R* resistant

are less vulnerable to ESBLs and stable to OXA-1; therefore, they are promising options in combination with clavulanate for the treatment of UTIs [33]. Such combinations are not approved in the USA and Europe, but are available in India [16]. In-vitro studies showed that MICs of these oral cephalosporins in the presence of clavulanate against ESBL isolates were below their respective susceptibility breakpoints [8, 15, 34]. Another potentially clinically beneficial approach is to combine amoxicillin/clavulanate with cefpodoxime or ceftibuten (both show high urinary concentrations) [34, 35]. However, the benefit of clavulanate plus oral cephalosporin is limited to *E. coli* and *K. pneumoniae* since clavulanate is an inducer of chromosomal AmpC enzyme present in pathogens such as *Enterobacter* spp. and *Citrobacter* spp. [16].

CONCLUSION

Clinicians who routinely prescribe amoxicillin/clavulanate in outpatient setting should be aware of potential benefits and limitations of this combination. While the combination is

better placed for treatment of mild to moderate community respiratory infections, it could be combined with cefpodoxime or ceftibuten in treating uncomplicated UTI caused by ESBL Enterobacterales.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

REFERENCES

1. Geddes AM, Klugman KP, Rolinson GN. Introduction: historical perspective and development of amoxicillin/clavulanate. Int J Antimicrob Agents. 2007;30(Suppl 2):S109–12.

2. White AR, Kaye C, Poupard J, et al. Augmentin (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent. J Antimicrob Chemother. 2004;53(Suppl 1):i3-20.

3. Ball AP, Geddes AM, Davey PG, Farrell ID, Brookes GR. Clavulanic acid and amoxycillin: a clinical, bacteriological, and pharmacological study. Lancet. 1980;1(8169):620–3.

4. MacGregor RR, Graziani AL. Oral administration of antibiotics: a rational alternative to the parenteral route. Clin Infect Dis. 1997;24(3):457–67.

5. Gould IM, Harvey G, Golder D, et al. Penetration of amoxycillin/clavulanic acid into bronchial mucosa with different dosing regimens. Thorax. 1994;49(10):999–1001.

6. Kiem S, Schentag JJ. Interpretation of antibiotic concentration ratios measured in epithelial lining fluid. Antimicrob Agents Chemother. 2008;52(1):24–36.

7. The United States Food and Drug Administration. Prescribing information for Augmnetin. GSK. 2006. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050564s051lbl.pdf. Accessed 11 Sept 2020.

8. Abdelraouf K, Stainton SM, Nicolau DP. In vivo pharmacodynamic profile of ceftibuten-clavulanate combination against extended-spectrum-β-lactamase-producing enterobacteriaceae in the murine thigh infection model. Antimicrob Agents Chemother. 2019;63(7):e00145-e219.

9. Gustafsson I, Löwdin E, Odenholt I, et al. Pharmacokinetic and pharmacodynamic parameters for antimicrobial effects of cefotaxime and amoxicillin in an in vitro kinetic model. Antimicrob Agents Chemother. 2001;45(9):2436–40.

10. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Amoxicillin. Rationale for the EUCAST clinical breakpoints, version 1.0. 2010. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Amoxicillin_rationale_Nov2010_v_1.0.pdf. Accessed 17 Sept 2020.

11. Cattrall JWS, Asín-Prieto E, Freeman J, et al. A pharmacokinetic-pharmacodynamic assessment of oral antibiotics for pyelonephritis. Eur J Clin Microbiol Infect Dis. 2019;38(12):2311–21.

12. Wong DM, Blumberg DA, Lowe LG. Guidelines for the use of antibiotics in acute upper respiratory tract infections. Am Fam Phys. 2006;74(6):956–66.

13. Critchley IA, Cotroneo N, Pucci MJ, et al. The burden of antimicrobial resistance among urinary tract isolates of *Escherichia coli* in the United States in 2017. PLoS One. 2019;14(12):e0220265.

14. Ho HJ, Tan MX, Chen MI, et al. Interaction between antibiotic resistance, resistance genes, and treatment response for urinary tract infections in primary care. J Clin Microbiol. 2019;57(9):e00143-e219.

15. Guyomard-Rabenirina S, Malespine J, Ducat C, et al. Temporal trends and risks factors for antimicrobial resistant *Enterobacteriaceae* urinary isolates from outpatients in Guadeloupe. BMC Microbiol. 2016;16(1):121.

16. Erb S, Frei R, Tschudin Sutter S, et al. Basic patient characteristics predict antimicrobial resistance in *E. coli* from urinary tract specimens: a retrospective cohort analysis of 5246 urine samples. Swiss Med Wkly. 2018;148:e14660.

17. Sabir S, Ahmad Anjum A, Ijaz T, et al. Isolation and antibiotic susceptibility of *E. coli* from urinary tract infections in a tertiary care hospital. Pak J Med Sci. 2014;30(2):389–92.

18. Alanazi MQ. An evaluation of community-acquired urinary tract infection and appropriateness of treatment in an emergency department in Saudi Arabia. Ther Clin Risk Manag. 2018;14:2363–73.

19. Horner CS, Abberley N, Denton M, et al. Surveillance of antibiotic susceptibility of Enterobacteriaceae isolated from urine samples collected from community patients in a large metropolitan area, 2010–2012. Epidemiol Infect. 2014;142(2):399–403.

20. De Lorenzis E, Alba AB, Cepeda M, et al. Bacterial spectrum and antibiotic resistance of urinary tract infections in patients treated for upper urinary tract calculi: a multicenter analysis. Eur J Clin Microbiol Infect Dis. 2020;39(10):1971–81.

21. Pulcini C, Clerc-Urmes I, Attinsounon CA, et al. Antibiotic resistance of Enterobacteriaceae causing urinary tract infections in elderly patients living in the community and in the nursing home: a retrospective observational study. J Antimicrob Chemother. 2019;74(3):775–81.

22. Wu PJ, Shannon K, Phillips I. Effect of hyperproduction of TEM-1 beta-lactamase on in vitro susceptibility of *Escherichia coli* to beta-lactam antibiotics. Antimicrob Agents Chemother. 1994;38(3):494–8.

23. Knottnerus BJ, Grigoryan L, Geerlings SE, et al. Comparative effectiveness of antibiotics for uncomplicated urinary tract infections: network meta-analysis of randomized trials. Fam Pract. 2012;29(6):659–70.

24. Leflon-Guibout V, Ternat G, Heym B, et al. Exposure to co-amoxiclav as a risk factor for co-amoxiclav-resistant *Escherichia coli* urinary tract infection. J Antimicrob Chemother. 2002;49(2):367–71.

25. Vihta KD, Stoesser N, Llewelyn MJ, et al. Trends over time in *Escherichia coli* bloodstream infections, urinary tract infections, and antibiotic susceptibilities in Oxfordshire, UK, 1998–2016: a study of electronic health records. Lancet Infect Dis. 2018;18(10):1138–49.

26. Lancet T. Balancing treatment with resistance in UTIs. Lancet. 2018;391(10134):1966.

27. Beytur A, Yakupogullari Y, Oguz F, et al. Oral amoxicillin-clavulanic acid treatment in urinary tract infections caused by extended-spectrum beta-lactamase-producing organisms. Jundishapur J Microbiol. 2014;8(1):e13792.

28. Pallett A, Hand K. Complicated urinary tract infections: practical solutions for the treatment of multiresistant Gram-negative bacteria. J Antimicrob Chemother. 2010;65(Suppl 3):iii25-33.

29. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45–67.

30. Díez-Aguilar M, Morosini MI, López-Cerero L, et al. Performance of EUCAST and CLSI approaches for co-amoxiclav susceptibility testing conditions for clinical categorization of a collection of Escherichia coli isolates with characterized resistance phenotypes. J Antimicrob Chemother. 2015;70(8):2306–10.

31. Leverstein-van Hall MA, Waar K, Muilwijk J, et al. Consequences of switching from a fixed 2:1 ratio of

amoxicillin/clavulanate (CLSI) to a fixed concentration of clavulanate (EUCAST) for susceptibility testing of *Escherichia coli*. J Antimicrob Chemother. 2013;68(11):2636–40.

32. Davies TJ, Stoesser N, Sheppard AE, et al. Reconciling the potentially irreconcilable? Genotypic and phenotypic amoxicillin-clavulanate resistance in *Escherichia coli*. Antimicrob Agents Chemother. 2020;64(6):e02026-e2119.

33. Cohen Stuart J, Leverstein-Van Hall M, Kortmann W, et al. Ceftibuten plus amoxicillin-clavulanic acid for oral treatment of urinary tract infections with ESBL producing *E. coli* and *K. pneumoniae*: a retrospective observational case-series. Eur J Clin Microbiol Infect Dis. 2018;37(10):2021–5.

34. Al-Tamimi M, Abu-Raideh J, Albalawi H, et al. Effective oral combination treatment for extended-spectrum beta-lactamase-producing *Escherichia coli*. Microb Drug Resist. 2019;25(8):1132–41.

35. Stewart AG, Harris PNA, Henderson A, et al. Oral cephalosporin and β-lactamase inhibitor combinations for ESBL-producing Enterobacteriaceae urinary tract infections. J Antimicrob Chemother. 2020;75(9):2384–93.