Orally Administered Amoxicillin/Clavulanate: Current Role in Outpatient Therapy

Balaji Veeraraghavan · Yamuna Devi Bakthavatchalam · Rani Diana Sahni

Received: September 22, 2020 / Accepted: November 19, 2020 / Published online: December 11, 2020 © The Author(s) 2020

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 cefitubutene 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
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

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13259639

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.
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 %f T > 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 f T > MIC of 30–35% for Enterobacteriales, 25–35% for S. pneumoniae and H. influenzae as PK/PD targets for these pathogens [10]. However, this rationale document for f T > MIC attainments is based on PK of intravenously administered (IV) amoxicillin. Employing the PK/PD target for Enterobacteriales (f T > 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% f T > 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) Enterobacteriales 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
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 1 Mean amoxicillin and clavulanate potassium pharmacokinetic parameters [7]

| Dose and regimen       | Amoxicillin AUC_0–24 (mcg h/mL) | Clavulanate AUC_0–24 (mcg h/mL) |
|------------------------|---------------------------------|---------------------------------|
|                        | Amoxicillin (± SD)              | Clavulanate (± SD)              |
| 250/125 mg q8h         | 26.7 ± 4.56                     | 12.6 ± 3.25                     |
| 500/125 mg q12h        | 33.4 ± 6.76                     | 8.6 ± 1.95                      |
| 500/125 mg q8h         | 53.4 ± 8.87                     | 15.7 ± 3.86                     |
| 875/125 mg q12h        | 53.5 ± 12.31                    | 10.2 ± 3.04                     |

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

\[\triangle\text{Adis}\]
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].

**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]. 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].

**ORAL AMOXICILLIN/CLAVULANATE FOR RESPIRATORY AND OTHER INFECTIONS**

With regards to community respiratory infections, since penicillin resistance in *S. pneumoniæ* 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** | **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 |
| **Dosage** | Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis |
| Neonates and infants aged < 12 weeks (3 months) | Bone and joint infections, in particular osteomyelitis |
| Based on the amoxicillin component, 30 mg/kg/day divided q12h (125 mg/5 mL suspension is recommended) | |
| Paediatric patients 12 weeks (3 months) and older | 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 | Based on the amoxicillin component, 20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses |
| Based on the amoxicillin component, 25 mg/kg/day q12h or 20 mg/kg/day q8h for less severe infections | Adults and children ≥ 40 kg |
| Paediatric patients weighing 40 kg and more | 500/125 mg, q8h |
| Should be dosed with adult dose regimens | 875/125 mg, q12h |
| Adults | 875/125 mg, q8h (higher dose for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infection) |
| 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 | |
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 blaTEM or blaAmpC 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...
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

---

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]       |
| UTI                       | France              | 2014–2017                  | *E. coli* (16,630)                   | EUCAST                           | 20                              | [21]       |
|                           |                     |                            | *Klebsiella spp.* (84)               |                                  |                                 |            |
|                           |                     |                            | *K. pneumoniae* (1724)               |                                  |                                 |            |

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         |
| Disk diffusion (zone size in mm) | 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

---

△ Adis
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
Enterobacteriales.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was
received for this study or publication of this
article.

Authorship. All named authors meet the
International Committee of Medical Journal
Editors (ICMJE) criteria for authorship for this
take responsibility for the integrity of
the work as a whole, and have given their
approval for this version to be published.

Disclosures. Balaji Veeraraghavan, Yamuna
Devi Bakthavatchalam and Rani Diana Sahni
have nothing to declare.

Compliance with Ethics Guidelines. 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.

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

Open Access. This article is licensed under a
Creative Commons Attribution-Non-Commercial 4.0 International License, which
permits any non-commercial use, sharing,
adaptation, distribution and reproduction in
any medium or format, as long as you give
appropriate credit to the original author(s) and
the source, provide a link to the Creative
Commons licence, and indicate if changes were
made. The images or other third party material
in this article are included in the article’s
Creative Commons licence, unless indicated
otherwise in a credit line to the material. If
material is not included in the article’s Creative
Commons licence and your intended use is not
permitted by statutory regulation or exceeds the
permitted use, you will need to obtain permis-
sion directly from the copyright holder. To view
a copy of this licence, visit http://
creativecommons.org/licenses/by-nc/4.0/.

REFERENCES

1. Geddes AM, Klugman KP, Rolinson GN. Introduc-
tion: 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 com-
munity-acquired respiratory tract infection: a
review of the continuing development of an inno-
vative antimicrobial agent. J Antimicrob Che-
mother. 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 Augmenetin. 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-clavulante
combination against extended-spectrum-β-lacta-
masse-producing enterobacteriaceae in the murine
thigh infection model. Antimicrob Agents Che-
mother. 2019;63(7):e00145-e219.

9. Gustafsson I, Löwdin E, Odenholt I, et al. Pharma-
cokinetic 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. Sabih 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, Cepea 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-Urdes 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. Leffon-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. Diez-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, Muijlwijk 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.