Invited narrative review

Oral amoxicillin and amoxicillin-clavulanate: properties, indications, and usage

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Abstract

Background: Amoxicillin has been in use since the 1970s; it is the most widely used penicillin both alone and in combination with the beta-lactamase clavulanic acid.

Objectives: In this narrative review, we re-examine the properties of oral amoxicillin and clavulanic acid and provide guidance on their use, with emphasis on the preferred use of amoxicillin alone.

Sources: Published medical literature (MEDLINE database via Pubmed)

Content: While amoxicillin and clavulanic acid have similar half-lives, clavulanic acid is more protein-bound and even less heat-stable than amoxicillin, with primarily hepatic metabolism. It is also more strongly associated with gastrointestinal side effects, including *Clostridium difficile* infection, and thus, in oral combination formulations, limits the maximum daily dose of amoxicillin that can be given. The first ratio for an amoxicillin-clavulanic acid combination was set at 4:1 due to clavulanic acid's high affinity for beta-lactamases; ratios of 2:1, 7:1, 14:1 and 16:1 are currently available in various regions. Comparative effectiveness data for the different ratios are scarce. Amoxicillin-clavulanic acid is often used as empiric therapy for many of the World Health Organisation's Priority Infectious Syndromes in adults and children, leading to extensive consumption, when some of these syndromes could be handled with a delayed-antibiotic-prescription approach or amoxicillin alone.

Implications: Using available epidemiologic and pharmacokinetic data, we provide guidance on indications for amoxicillin versus amoxicillin-clavulanic acid and on optimal oral administration, including choice of combination ratio. More data are needed, particularly on heat stability, pharmacodynamic effects and emergence of resistance in "real-world" clinical settings.

Introduction

Amoxicillin is a semisynthetic penicillin in use since the 1970s. Alone and in combination with the beta-lactamase inhibitor clavulanic acid, it is the most widely used penicillin in Europe [1] and elsewhere, and is a WHO-designated "core access antibiotic" [2]. This document outlines the key properties of amoxicillin and clavulanic acid, describes current oral formulations and clinical experience with them, and provides recommendations for appropriate use of oral amoxicillin alone versus amoxicillin with clavulanic acid.

History of amoxicillin and clavulanic acid

Penicillin's narrow spectrum led to a search for derivative agents with bactericidal activity against both Gram-positive and Gram-negative organisms. The first clinically relevant derivative was ampicillin, discovered by Beecham Laboratory scientists in the United Kingdom and released in 1961. Amoxicillin was then built from ampicillin: in 1972, Beecham released the novel, semisynthetic penicillin, which differs structurally from ampicillin only by the addition of a hydroxyl group on the benzene ring [3].

Clavulanic acid, sometimes referred to as clavulanate, its salt form in solution, was also developed by Beecham scientists, who isolated this beta-lactamase inhibitor (BLI) from *Streptomyces clavuligerus* [4] in 1974. Despite also possessing a beta-lactam ring, clavulanic acid has little efficacy by itself as an antibiotic [5]; it works as a "suicide inhibitor", irreversibly binding to and thus preventing bacterial beta-lactamase enzymes from hydrolysing amoxicillin and other penicillins. Currently, clavulanic acid is commercially available only in combination with either amoxicillin or ticarcillin.

Properties of amoxicillin and clavulanic acid alone and in combination

Amoxicillin

Amoxicillin binds to penicillin-binding protein (PBP) 1A, an enzyme essential for bacterial cell wall synthesis. Amoxicillin's beta-lactam ring opens to acylate the transpeptidase C-terminal domain of PBP 1A. This irreversible binding inactivates PBP 1A, without which peptidoglycan, an integral

bacterial cell wall component, cannot be synthesized; cell wall elongation and permeability follow, leading ultimately to cell lysis and death [6].

The hydroxyl group creating amoxicillin from ampicillin results in a drug that is more lipid-soluble and thus has increased bioavailability and duration of action and, in some pharmacodynamic studies, heightened bactericidal activity [3, 7]. In healthy volunteers, amoxicillin's half-life is roughly one hour, its volume of distribution approximately 20 L, and its protein binding up to 20% in serum [8]. Most amoxicillin is excreted unchanged in urine; hepatic metabolism accounts for little of the biotransformation of most penicillins.

Amoxicillin is rapidly absorbed after oral administration; early studies in young, healthy male volunteers reported bioavailability of 77% to 93% [8, 9]. While bioavailability appears to be improved when amoxicillin is taken fasting [10], clinical trials in which oral amoxicillin was administered without regard to meals have demonstrated efficacy [11]. Data on penetration into various tissues are somewhat complex, as many studies were performed with outdated techniques rather than microdialysis. It is traditionally reported that amoxicillin distributes well into liver, lungs, prostate, muscle, middle ear effusions, maxillary sinus secretions, bone, gallbladder, bile, and into ascitic and synovial fluids [12] but has poor penetration into cerebrospinal fluid [13]. Yet effective distribution depends, of course, on the targeted micro-organism's MIC (*e.g.*, penetration may be sufficient for a streptococcus but insufficient for an enterococcus). Meanwhile, bioavailability of oral amoxicillin, which appears to have high inter-individual variability, will greatly affect the medicine's distribution. Bioavailability in healthy volunteers is reported to be roughly 70% [14, 15]; recent data on bioavailability in ill, comorbid, or elderly patients are lacking. A recent study shows that amoxicillin's absorption rate appears to be saturable, with more frequent doses increasing the probability of pharmacokinetic/pharmacodynamic (PK/PD) target attainment [16]. In this study, no beneficial effect of doses higher than 750 mg per administration was observed. The drug is often administered to pregnant women; no teratogenic effects have been observed in non-human studies (US FDA category B).

More information on stability is available for intravenous solutions of amoxicillin than for oral preparations. The recommended storage temperature for amoxicillin sodium solution is 2-8°C. It is

stable at higher temperatures for only short periods of time and dependent on several conditions (container, solvent, light exposure); in sodium chloride or water for injection, stability at 25°C may reach 8 or 3 hours, respectively [17]. There are few data (with robust reporting allowing for reproducibility) on stability at higher temperatures.

While an early report indicated strong stability of reconstituted oral amoxicillin at 25°C and even 40°C, with conservation of at least 90% in prepared unit dose syringes for 78 and 10 days, respectively [18], recent studies have demonstrated more rapid degradation in similar conditions. Mehta et al. observed 90% conservation of reconstituted oral amoxicillin at 20°C for only 7 days [19], while Peace et al. report only 79% conservation at 7 days at a temperature of 27-29°C [20]. Currently there are few data on the stability of oral amoxicillin tablets.

Clavulanic acid

Clavulanic acid achieves its effect as a suicide inhibitor by covalently binding to a serine residue in the active site of the beta-lactamase, which results in its own restructuring. Clavulanic acid then becomes more active, attacking another amino acid at the beta-lactamase's active site, permanently inactivating it.

While clavulanic acid and amoxicillin have similar distribution patterns and a half-life of roughly one hour, the BLI differs with respect to other pharmacokinetic properties [21]. Its metabolism is primarily hepatic, with only 30-40% excreted unchanged in the urine, and up to 30% is bound to serum proteins. A recent study confirms that the absorption of clavulanic acid in healthy volunteers is highly variable and suggests that it decreases through the course of the day [22]. Importantly, oral clavulanic acid appears to cause increased gastrointestinal side effects, particularly diarrhea, in comparison to those experienced in relation to amoxicillin alone. Thus the addition of the beta-lactamase inhibitor significantly limits the maximal daily dose of amoxicillin that can be given orally [23, 24], as the maximum recommended daily dose of clavulanic acid is 500 mg [14].

Importantly, clavulanic acid is even less heat stable than amoxicillin in either intravenous or reconstituted oral suspension form. Its stability in aqueous solutions has been poorly characterized, though one recent study noted that in sodium chloride, stability was maintained for 8 hours at 4°C

and for only 4 hours at 20°C. Reconstituted oral suspensions appear to be somewhat more stable; at 8°C, clavulanic acid maintains at least 90% of its initial concentration for 7 days, though at 20°C only 60% is maintained in the same time period [19], and at 27-29°C, only 55% [20].

Amoxicillin-clavulanic acid combinations

The first ratio for an amoxicillin-clavulanic acid combination was set by Beecham pharmacists at 4:1; relatively little clavulanic acid was needed to inhibit beta-lactamases because of its high affinity for them [4]. Later, a 7:1 ratio was introduced, largely to avoid clavulanic acid-related toxicity. Currently ratios of up to 14:1 and 16:1 are available in some areas.

Data on both clinical and microbiologic comparative effectiveness of the varying ratios are scarce. One US trial compared a 16:1 formulation of amoxicillin (2 g, extended release) combined with 125 mg of clavulanic acid (traditional formulation) to the 7:1 formulation of 875/125 mg for clinical efficacy in a randomized trial of nearly 900 patients with chronic bronchitis exacerbations [25]; clinical non-inferiority was demonstrated at 14-21 days. Bacterial infections were few, however, with only 30% of sputum samples positive for potential bacterial pathogens; bacteriologic success rates for beta-lactamase-positive organisms—even fewer in this large study—were similar in both groups (22/24, 92% versus 21/25, 84%). Further, recent evidence that the absorption of oral-table amoxicillin is saturable [16] might also contribute to the lack of difference in clinical outcomes, given the limited uptake of the 2 g dose. The adverse event profiles of both formulations were similar, with diarrhoea reported by 14% and 17% of patients in the 16:1 and 7:1 arms, respectively.

Microbiologic spectra and indications for the addition of clavulanic acid

Classification of beta-lactamases

Beta-lactamases have been classified via different systems; the best known is that of Ambler [26], which currently categorizes the enzymes into four classes, A through D, based upon their amino acid sequences. Initially there were only classes A and B, composed of active-site serine beta-lactamases and metallo-beta-lactamases, respectively. Thereafter a new class of serine beta-lactamases was

identified; this group of cephalosporinases had little sequence similarity to class A enzymes and was thus designated class C; its members are also known as *AmpC* beta-lactamases [27]. Finally, another group of serine beta-lactamases, familiarly known as the OXA beta-lactamases, was identified and given its own class D [28]. Though differences in sequence structure are significant enough to warrant separate classes, the three serine classes are descendants of a common ancestor [29].

The penicillinases responsible for inactivating amoxicillin belong to class A. Some organisms express these beta-lactamases intrinsically, *i.e.*, they carry chromosomal genes coding for the enzymes. For example, all *Klebsiella* species and *Citrobacter koseri* are intrinsically resistant to amoxicillin given their chromosomal coding for class A penicillinases.

Organisms may also acquire the ability to express beta-lactamases, either through chromosomal mutations or through horizontal transfers of mobile genetic elements, most notably via plasmids. Unfortunately plasmids often carry multiple resistance determinants, so that a single conjugation event may confer multidrug resistance to a bacterial strain [30]. The expression of penicillinases leading to amoxicillin resistance is both intrinsic and acquired. Clavulanic acid effectively "blocks" only class A beta-lactamases. Most extended-spectrum beta-lactamases (ESBLs) derive from this class, however, indicating that clavulanic acid is stable against these enzymes, which is why it is commonly used for *in vitro* detection of ESBL-producing bacteria.

Susceptibility to amoxicillin versus amoxicillin-clavulanic acid: a rough overview of organisms and their resistance prevalence

In Table 1, we list clinical syndromes that may precipitate use of amoxicillin or amoxicillin-clavulanic acid, the organisms that are most often causative of these syndromes, and their respective resistances by geographic region. The clinical syndromes align with World Health Organisation's "priority infectious syndromes" in adults and children; syndromes for which empiric therapy with amoxicillin alone or in combination with clavulanic acid is either inappropriate or unlikely to be effective have not been included here. For some syndromes, intravenous antibiotics may be more appropriate at least during the initial treatment phase. We have included them here, however, for settings in which access to intravenous antibiotics is limited. Also of note, the prevalences cited here

are general and not necessarily population-specific, and though we list bacterial pathogens only, some of these syndromes are more commonly caused by viruses (*e.g.*, pneumonia, otitis media, etc.).

Testing for susceptibility to amoxicillin-clavulanic acid

To test susceptibility to amoxicillin-clavulanic acid, most laboratories follow guidelines and breakpoints from the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the United States Committee on Antimicrobial Susceptibility Testing (USCAST), or the Clinical & Laboratory Standards Institute (CLSI). Current testing is not always an exact science: disc contents vary among different committees and bacterial species, and for many species, such as viridans and Groups A, B, C and G streptococci, amoxicillin susceptibility is inferred from the susceptibility of other antibiotics such as benzylpenicillin or ampicillin.

The concentration of clavulanic acid used varies by testing method. The EUCAST method uses a fixed concentration of 2 mg/L of clavulanic acid, whereas USCAST recommends the use of a fixed ratio between the amoxicillin and clavulanic acid concentrations of 2:1 mg/L. These different strategies provide different test results, and there is no consensus among committees as to which strategy should be used. Nonetheless, there is evidence that inhibitor-resistant TEM beta-lactamases, which represent a potential threat to the use of amoxicillin-clavulanic acid, are more likely detected when fixed concentrations of clavulanic acid are used [31].

Current post-market use

Despite the plethora of bacterial strains listed above that are not beta-lactamase producers, amoxicillin-clavulanic acid use far outstrips that of amoxicillin alone in some regions and populations. Figure 1 below shows the comparative use in various countries of aminopenicillins, chiefly amoxicillin, and penicillin-beta-lactamase-inhibitor combinations, chiefly amoxicillin-clavulanic acid. Many countries consume twice as much of the latter. In some countries, consumption of the combination amoxicillin-clavulanic acid is increasing steadily and not entirely within proportion to the increase of beta-lactamase-producing strains (Figure 2).

Recommendations and conclusions

Advantage and disadvantages of amoxicillin combined with clavulanic acid

The advantage of prescribing the amoxicillin-clavulanic acid combination has been clear for decades: with little effort and minimal reflection, the physician's patient is better "covered" for all clinical eventualities. Yet this short-term, non-collective approach has quickly—in the space of just decades—brought this and all patients to a new reality in which adequate antibiotic options for the next infection are increasingly jeopardized.

The major disadvantage of using the combination instead of amoxicillin alone is thus the unavoidable fact that antibiotic overuse is the main accelerator of emergence of resistance. The current increase in consumption of amoxicillin-clavulanic acid will further select for organisms resistant to both the beta-lactam and its BLI, and by extension for increased consumption of "downstream" antibiotics such as cephalosporins, fluoroquinolones, and carbapenems.

The other disadvantages of adding clavulanic acid are very immediate: clavulanic acid is associated with more side effects, particularly diarrhoea that can be disabling [24]; *Clostridium difficile* infection is more associated with amoxicillin-clavulanic acid than with amoxicillin alone [32]. In turn, the addition of clavulanic acid significantly limits the maximal daily dose of amoxicillin that can be given orally [23, 24].

Recommendations for use of oral amoxicillin versus amoxicillin-clavulanic acid

Because amoxicillin with or without clavulanic acid is often used empirically when, by definition, pathogen identity and resistance profiles are not available, we provide recommendations that are syndrome-based rather than pathogen-based. The severity of illness at the time of presentation should also play a role in clinical decision-making: patients with mild disease do not need immediate coverage for all possible scenarios, no matter how unlikely. In addition, the level of access to healthcare should be considered: the consequences of missing a beta-lactam-resistant strain with initial therapy are unlikely to be serious in a patient with mild symptoms and an ability to return easily for re-evaluation in case of non-improvement or worsening. Finally, certain clinical syndromes do not warrant any antibiotic therapy given that their aetiologies are likely to be viral or even non-

infectious. In Table 2, we thus list four possible therapeutic approaches to the clinical syndromes for which amoxicillin with or without clavulanic acid may be relevant as empiric therapy:

(1) "Delayed antibiotic therapy" with amoxicillin alone only after symptomatic therapy and the passage of time have failed to improve clinical symptoms
(2) Delayed therapy with amoxicillin-clavulanic acid as the delayed antibiotic
(3) Treatment with amoxicillin alone
(4) Treatment with amoxicillin-clavulanic acid

Of course, as much as is possible, "empiric" therapy should be avoided: culturing and other diagnostic work-up should be performed whenever possible. Finally, though it is not the main topic of this document, it should be remembered that antibiotic durations should be shortened wherever possible. There are few data for the long courses of one and two weeks often given for many of the clinical syndromes covered here, and durations are being increasingly re-examined in randomized trials [33, 34].

Recommendations regarding the different ratios of amoxicillin to clavulanic acid

The availability of different combination ratios varies by geographic region, and more data are generally needed to inform the choice of such ratios. In broad strokes, two rules can be followed. First, to achieve sufficient amoxicillin and high clavulanic acid exposure, the optimal regimen is to administer narrower ratio amoxicillin-clavulanic acid (typically 4:1, as the 2:1 combination is not available in many regions) in a three-times daily regimen. If the physician wishes to decrease the patient's medication burden by prescribing only twice daily amoxicillin-clavulanic acid (rather than three or four times daily), then a broader ratio (e.g., 7:1) can be employed in order to increase amoxicillin exposure (to improve efficacy) and limit clavulanic acid exposure (to reduce toxicity). Such twice-daily regimens are commonly recommended in the treatment of acute otitis media or community-acquired pneumonia during childhood.

Second, Gram-negative organisms require higher and more sustained levels of both amoxicillin as well as the clavulanic-acid component for optimal therapy [35]; thus for clinical syndromes in which Gram-negative pathogens are causative (e.g., urinary tract infection), a narrower ratio (e.g., 4:1) with more frequent dosing (three or four rather than two times daily) is needed for efficacy. For Gram-positive pathogens, which appear to have a higher affinity for clavulanic acid and are also susceptible to lower amoxicillin concentrations, combinations with a wider ratio (e.g., 7:1) appear to be sufficient in terms of clavulanic acid exposure. In general, extreme ratios of 14:1 or 16:1 should be used with caution until more data are available.

In conclusion, amoxicillin-clavulanic acid is used more frequently than amoxicillin alone in many countries, although in some clinical scenarios and geographical regions, it is needed much less frequently. The use of either agent should be questioned for most clinical syndromes: thorough microbiologic work-up should be performed wherever possible and delayed prescription attempted in patients with non-severe presentations of clinical syndromes that are likely to be of viral origin or represent only mucosal infection (e.g., lower urinary tract infection). Amoxicillin without clavulanic acid has fewer side effects and can be prescribed in higher oral doses. When using the combination, a narrow ratio of amoxicillin to clavulanic acid (e.g., 4:1) should be used when the medication will be taken in fewer daily doses and when targeting Gram-negative organisms, which require higher and more sustained concentrations of both amoxicillin and clavulanic acid for optimal therapy.

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Conflict of interest

All authors declare no conflict of interest.

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Table 1. Clinical syndromes that may precipitate use of oral amoxicillin or amoxicillin-clavulanic acid, the organisms that are most often causative of these syndromes, and the approximate fraction of amoxicillin-clavulanic acid-susceptible strains by geographic region that are susceptible to amoxicillin alone. Neither the list of syndromes nor that of causative pathogens is exhaustive, and proportions presented here cannot be considered fully representative: recent data allowing comparisons between these two compounds are scarce and may come from relatively small datasets.

Clinical syndrome	**Most common causative bacterial pathogens**		
	Organism	**Geographic region**	**Approximate fraction of amoxicillin-clavulanic-acid-susceptible strains that are susceptible to amoxicillin alone**
Community-acquired pneumonia [36]	*Streptococcus pneumoniae**	All regions	100%
	Haemophilus influenzae	North America	70% [37]
		South America	82% [37]
		Europe	86% [37]
		Asia	60 - 98% [37-39]
		Africa	94% [37]
	*Staphylococcus aureus***	North America	13-50% [40]
		South America	12-50% [40]
		Europe	20-50% [40, 41]
		Asia	1 - 50% [40, 42]
		Africa	3 - 50% [43, 44]
	Mycoplasma pneumoniae	NA	NA
	Legionella pneumophila	NA	NA
Pharyngitis [45]	*Streptococcus pyogenes**	All	100%
	S. pneumoniae	As above	100%
	Corynebacterium diphtheriae	North America	>99% [46]
		South America	100% [46]
		Europe	100% [47]
		Asia	100% [48]
		Africa	100% [49]
	Fusobacterium spp.***	North America	23 - 60% [50]
		South America	33% [51]
		Europe	50% [52]
		Asia	100% [51]
		Africa	No data
	Moraxella catarrhalis	North America	<5% [53]
		South America	5-10% [37]
		Europe	5-10% [37]
		Asia	5-10% [37]
		Africa	5-10% [37]
	M. pneumoniae	NA	NA
	Chlamydophila pneumoniae	NA	NA
	Bordetella pertussis	NA	NA
	Neisseria gonorrhoeae	NA	NA
Sinusitis [54]	*S. pneumoniae*	All regions	100%
	H. influenzae	As above	As above

Clinical syndrome	Most common causative bacterial pathogens		
	Organism	**Geographic region**	**Approximate fraction of amoxicillin-clavulanic-acid-susceptible strains that are <u>susceptible to amoxicillin alone</u>**
	Moraxella catarrhalis	As above	As above
	S. aureus	As above	As above
	S. pyogenes	All regions	100%
Otitis media [55]	*S. pneumoniae*	All regions	100%
	H. influenzae	As above	As above
	M. catarrhalis	As above	As above
	S. aureus	As above	As above
	S. pyogenes	All regions	100%
Urinary tract infection§ [56]	*Escherichia coli*	North America	55 - 71% [57, 58]
		South America	50% [59]
		Europe	68% [60]
		Asia	0 - 47% [61-63]
		Africa	30 - 70% [64, 65]
	Klebsiella spp.	All regions	0%
	Proteus spp.***	North America	32% [66]
		South America	5 - 70% [67, 68]
		Europe	33% [69]
		Asia	46% [70]
		Africa	34 – 90% [65]
	Group B *Streptococci**	All	100%
	Enterobacter spp.	NA	NA
	*Enterococcus faecalis**	All regions	100%
Complicated intra-abdominal infections [71]	*E. coli*	As above	As above
	Bacteroides spp.***	North America	0-35% [50]
		South America	2% [72]
		Europe	1 - 2% [73]
		Asia	2- 30% [70, 74, 75]
		Africa	<30% [76]
	Enterobacter spp.	NA	NA
	Klebsiella spp.	As above	0%
	Enterococcus faecalis	All regions	100%
	Clostridium spp.***	North America	<10% [77]
		South America	<2% [78]
		Europe	2% [79]
		Asia	10 – 30% [75]
		Africa	No recent comparative data
Wound, skin and soft-tissue infections, including erysipelas§§ [80]	*S. aureus*	As above	As above
	Coagulase-negative Staphylococci***	North America	30-75% [81]
		South America	30-75% [81]
		Europe	30-75% [81]
		Asia	37% [82]
		Africa	28% [83]
	S. pyogenes	All regions	100%
	*Streptococcus agalactiae**	All regions	100%
	E. coli	As above	As above
Surgical site infections [84]	*S. aureus*	As above	As above
	Coagulase-negative *Staphylococci*	As above	As above
	Enterococcus faecalis	All regions	100%
	E. coli		55%
Cellulitis [85]	*S. aureus*	As above	As above

Clinical syndrome	Most common causative bacterial pathogens		
	Organism	**Geographic region**	**Approximate fraction of amoxicillin-clavulanic-acid-susceptible strains that are susceptible to amoxicillin alone**
	*Streptococcus dysgalactiae**	All regions	100%
	S. pyogenes	All regions	100%
	*S. agalactiae**	All regions	100%
Acute infectious diarrhoea [86]	*E. coli*	As above	As above
	Campylobacter spp.***	North America	0-50% [87, 88]
		South America	88% [89]
		Europe[+]	0-98% [90]
		Asia[+]	20% [91]
		Africa	20% [92]
	Salmonella spp.***	North America[+]	0-70% [93]
		South America	No recent comparative data
		Europe	70% [94]
		Asia	0% [95]
		Africa	40% [96]
	Shigella spp.	North America	27% [97]
		Asia	30% [98]
		Africa	37-40% [96, 99]
		Other regions	No recent comparative data
	Yersinia enterocolitica	NA	NA
	Vibrio cholera	NA	NA
Exacerbations of chronic obstructive pulmonary disease [100]	*H. influenzae*	As above	As above
	M. catarrhalis	As above	As above
	S. pneumoniae	All regions	100%
	P. aeruginosa	NA	NA
	Haemophilus parainfluenzae	North America	30% [101]
		Europe	70% [101]
		Other regions	No recent data
	S. aureus	As above	As above
Bone and joint infections [102]	*S. aureus*	As above	As above
	Coagulase-negative *Staphylococci*	As above	As above
	S. pyogenes	All regions	100%
	Enterococcus faecalis	All regions	100%
	Enterobacter spp.	NA	NA

* These organisms are not known to possess beta-lactam enzymes and thus are essentially always susceptible to amoxicillin alone.

**Efficacy of amoxicillin in oral formulations remains uncertain (refer to EUCAST breakpoints; www.eucast.org).

***There is considerable variability in resistance among different species of this genus; local patterns should be reviewed.

[§]Amoxicillin and amoxicillin-clavulanic acid are not first-line agents for urinary tract infection.

[§§]Erysipelas is most commonly caused by Streptococci and can be treated with amoxicillin alone.

[+]Isolates are from poultry on dairy farms; no recent comparative data from human clinical specimens identified.

Table 2. Recommended approaches to empiric therapy for clinical syndromes for which amoxicillin with or without clavulanic acid may be warranted, and only where oral therapy is considered sufficient, or intravenous antibiotic therapy cannot be accessed.

Empiric therapeutic approach	**Clinical syndrome**	**Comments**
Delayed prescription, with amoxicillin alone as the delayed therapy	Pharyngitis	Usually of viral origin
	Sinusitis	
	Otitis media	
	Mild COPD exacerbation	Often no pathogen detected or of viral origin
Delayed prescription, with amoxicillin-clavulanic acid as the delayed therapy	Lower, uncomplicated UTI	Nitrofurantoin and fosfomycin should be used as first-line agents and amoxicillin-clavulanic acid only second-line
	Acute infectious diarrhoea	Antibiotics are generally not recommended
	Wound, skin and soft-tissue infections	Try to avoid any antibiotic therapy, with local wound care, debridement and drainage as first-line strategies
Amoxicillin alone	Mild or moderate community-acquired pneumonia in patients with good/rapid access to healthcare structures	Other aetiologies (viral, atypical bacteria) should be ruled out according to the clinical presentation and corresponding therapy considered
Amoxicillin-clavulanic acid	• Severe community-acquired pneumonia • Community-acquired pneumonia of any severity in patients with little/no access to healthcare structures	In all cases, narrow the spectrum once microbiologic data available
	Severe COPD exacerbation	
	Surgical site infection	
	Complicated intra-abdominal infection	
	Cellulitis	
	Bone and joint infections	

UTI: urinary tract infection; COPD: chronic obstructive pulmonary disease

Figure 1. Consumption of aminopenicillins (chiefly amoxicillin) and penicillin-beta-lactamase-inhibitor combinations (chiefly amoxicillin-clavulanic-acid) in various European countries in 2017. Data are from the European Centres for Disease Prevention and Control (www.ecdc.eu).

Figure 2. Increasing use over time of amoxicillin-clavulanic acid in Germany (www.ecdc.eu).