



Letter to the Editor

Amoxicillin dosing recommendations are very different in European countries: a cross-sectional survey

Dear Sir,

National antibiotic stewardship programmes recommend monitoring antibiotic consumption and benchmarking. The WHO recommend the Anatomic Therapeutic Chemical classification and respective Defined Daily Doses (DDD) for drug utilization research [1]. This is the most frequently used unit of measure within the European Union (EU). Wide variations in antibiotic consumption exist between EU countries in the outpatient setting, ranging in 2012 from 11.3 (the Netherlands) to 31.9 DDD per 1000 inhabitants and per day (Greece) [2].

Penicillins are the most consumed antibacterial agents in the community in all EU countries. Amoxicillin and amoxicillin/clavulanate are the two most widely prescribed penicillins, except in Denmark, Norway and Sweden where penicillin V and other very narrow-spectrum penicillins are used preferentially [2].

For amoxicillin, one WHO-DDD corresponds to 1 g/day [1]. Following informal contacts with European colleagues, our hypothesis was that wide variations exist between European countries in

dosing recommendations for amoxicillin, and that these variations may partly explain the differences in total antibiotic consumption between EU countries, as measured in DDD. Differences in antibiotic consumption measured in DDD also depend on the mode of dispensing of antibiotics (unit dispensing versus packages), and on the DDD per package, which has increased over the last years in some European countries [3].

We therefore conducted an exploratory cross-sectional survey among a convenience sample of national representatives from 16 European countries, chosen among ESCMID Study Group for Antibiotic Policies (ESGAP) members or personal contacts. Each national representative received a short questionnaire by e-mail, asking for the total daily dose (in g/day) of amoxicillin recommended in their national guidelines for seven common clinical situations (six in the outpatient setting, and one in the inpatient setting). Amoxicillin dosing was reported for an 80-kg adult patient with normal renal function, either as empirical or targeted treatment, and as first or second choice treatment. If national guidelines were not available, local or regional guidelines could be used

Table 1
Total daily dose (in grams/day) of amoxicillin recommended in guidelines in 16 European countries (for an 80-kg adult patient with normal renal function, either as empirical or targeted treatment, and as first or second choice treatment)

Clinical indication	1	1.5	2	2.25	3	4	4.5	6	8	12	16
Patients treated orally with amoxicillin in the outpatient setting											
Streptococcal pharyngitis			FR, IT, LU	CH							
Otitis media	EL	ES EN, ES, HR SI		CH, NL	BE, DE, FR, IT, LU						
Bacterial maxillary sinusitis		EN, HR, MT, NO SI		CH, NL	PL BE, DE, FR, IT, LU						
Pneumococcal pneumonia		EN, HR, NL, NO SI		CH	PL BE, DE, ES, FR, IT, LU, PL					EL	
Cystitis (in a woman)		CH, EN, ES, MT	PL		FR, LU						
Uncomplicated streptococcal cellulitis (erysipela)			IT	CH	LU, MT IT						FR
Patients treated intravenously in the inpatient setting											
Uncomplicated <i>Enterococcus faecalis</i> bacteraemia (no endocarditis)										NL	CH
										SI	DE, FR, IT
											BE

When a country is not listed, it means that either no local, regional or national guidelines exist for this specific clinical indication, or that amoxicillin is not recommended for this indication in guidelines.

Abbreviations: BE, Belgium; CH, Switzerland; DE, Germany; EL, Greece; EN, England; ES, Spain; FR, France; HR, Croatia; IT, Italy; LU, Luxembourg; MT, Malta; NL, The Netherlands; NO, Norway; PL, Poland; SE, Sweden; SI, Slovenia.

instead. Each national representative provided links or documents for their guidelines (see [Supplementary material, Table S1](#)), so the lead author (CP) double-checked the collected data.

All 16 contacts participated in the survey, and the results are presented in [Table 1](#). Wide variations in amoxicillin dosing recommendations were found (two- to three-fold variation in the outpatient setting, and four-fold variation for the enterococcal bacteraemia treated in hospital). Some countries had quite consistent dosing patterns for amoxicillin across the different clinical situations: Croatia, England, the Netherlands and Norway recommended low doses, whereas France, Germany and Italy recommended high doses. In other countries, such as Greece or Spain, doses could either be in the lower or upper range depending on the clinical situation. Interestingly, in many countries, amoxicillin is not recommended for common infections such as streptococcal pharyngitis, erysipelas and cystitis. Our exploratory work includes a limited number of countries and clinical situations, and deserves further investigation.

Our findings are consistent with a study published in 2008, comparing antibiotic consumption in the United Kingdom (England, Northern Ireland, Scotland and Wales) and in Belgium. The authors found that differences between all four UK administrations and Belgium were much less marked for number of prescriptions per 1000 inhabitants per day than for DDD per 1000 inhabitants per day, suggesting that there are important differences in dosing and/or duration of antibiotic treatments between the two countries [4].

The variations in dosing recommendations that we noted for amoxicillin probably apply to amoxicillin/clavulanate, and this should be investigated further. Also, we need to understand better how much total antibiotic use variation in DDD is explained by these variations in dosing of penicillins. Adding another unit of measure, such as days of therapy, might be helpful to meaningfully interpret data on the impact of antibiotic use, as the effects on the microbiota might depend more on total duration of treatment than on total daily dose. It is also important to have two complementary units of measure to monitor antibiotic consumption in children, as DDD are not valid in the paediatric population. Using two different quantity metrics to monitor antibiotic consumption was indeed recommended in the DRIVE-AB project, based on a systematic literature review and a consensus procedure [5]. Finally, we must assess which consumption measures correlate best with antimicrobial resistance.

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Appendix A. Supplementary material

Supplementary material related to this article can be found at <http://dx.doi.org/10.1016/j.cmi.2016.11.013>.

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