EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

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Consultation on: Breakpoints for Temocillin Date: 11 October

Comment from (name, contact details)	Comments	EUCAST Responses
	EUCAST statement about the usage of temocillin "*Temocillin is used principally to treat more serious infections caused by Enterobacterales producing extended-spectrum and AmpC type beta-lactamases.*" This statement does not fit with the clinical practices in Belgium a country in which there has been extensive experience with this antimicrobial agent for more than 30 years not only for the treatment of resistant (ESBL/AmpC producing) Enterobacterales but also as empiric first line treatment of complicated urinary tract infections without risk factors for resistant bacteria (current recommendation of the Belgian Society of Infectious Diseases and Clinical Microbiology (http://organesdeconcertation.sante.belgique.be/fr/documents/recommandations-de-traitements-anti-infectieux-en-milieu-hospitalier-2017-integral) A large number of hospitals, temocillin is used as first line treatment for complicated UTI (including urosepsis) in patients infected by resistant bacteria or not. This has been confirmed through recent point prevalence surveys on antimicrobial use and resistance performed in Belgium in 2015 and 2017 (http://consultativebodies.health.belgium.be/sites/default/files/documents/18nov2015_k.magerman-pps.pdf; Versporten A. et al, P2045, ECCMID 2019) which in both cases highlighted that temocillin accounted as the third most frequently prescribed antibiotics in the treatment of urinary tract infections in Belgian hospitals.	
	Proposed breakpoint tables by EUCAST which applies only in the setting of maximum dosing (2g /8h iv) will be very difficult to implement in Belgium as the current standard practice dosage (which has always been the same since 1986) is 2g /12h iv) for isolates with MICs ≤16 mg/L). EUCAST should clarify whether the mentioned breakpoint (as apparently stated in the table refers to UTIs only) or whether it applies to systemic infections (or to both) ? The high urinary concentrations of temocillin (+/-75% of temocillin excreted as active drug in urine with concentrations as high as 268+/-149 mg/L 12h after a 2g iv injection (Staniforth DH et al, Int J Clin Pharmacol Ther Toxicol. 1990;28(7):286-91) provides sufficient concentrations to cover infections due to organisms with MIC to 16 mg/L (and	

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	even with CMI up to 32 mg/L (as proposed by BSAC for the UTI breakpoint). No single data are provided on this matter by EUCAST in the pharmacokinetics table and in the setting of the proposed urinary breakpoint (UTI only) we feel that it is necessary to include the available pharmacokinetic data on urinary concentrations.	
	Concerning the laboratory practices in Belgium, the majority of the laboratories currently use the BSAC breakpoints for Enterobacterales (systemic 8/8, UTI 32/32), but a substantial number still rely on the clinical breakpoint of S≤16 mg/L (Fuchs PC. et al., Eur J Clin Microbiol. 1985;4(1):30-3). Also, a large number of laboratories still use disk diffusion testing and again rely for this on the criteria proposed by Vanstone et al. (J Antimicrob Chemotherapy 2013) or those from Fuchs (cf. above reference). The Vanstone study previously validated the disk diameter zones with MICs (S ≥ 20 mm for MICs ≤8 mg/L for the systemic breakpoint and S ≥ 12 mm for MIC ≤ 32 mg/L for the UTI only breakpoint). While it is understandable that EUCAST may wish to perform their own validation on temocillin disk diffusion zone size criteria, we feel that these should be included together and be available in the proposal submitted for consultation and not be added in a second step. Data collected by the Belgian Nation reference laboratory for monitoring antimicrobial resistance in gram-negative (CHU UCL Namur, Mont-Godinne, Belgium) on large collections of ESBL/AmpC producing Enterobacterales isolates have shown that there is no shift/trend towards increased resistance or selection of resistant isolates over time with MIC_{50}/MIC_{90} remaining constant at 8/16 mg/L over the last 20 years (data of NRC on file). Also the most recent data from EARS-Net susceptibility data in 2018 (collected by Belgian laboratories in the setting of the EARS-Net annual surveys) mostly using the proposed BSAC breakpoints showed very low resistance rates in blood culture and in urine isolates of 3.7% (131/3524) / 2.9% (2771/95196) respectively for *E. coli*, and of 5.8% (42/721)/ 2.8% (356/12483) for *K. pneumoniae*. These low resistance rates (which remain stable over the years) support the recommendation in Belgium to use temocillin as first line agent for empiric treatment of complicated urinary tract infection. There may be some concerns about the fact that data presented by EUCAST in the appendix do contain a very limited number strains (WT susceptible or with different resistance mechanisms) and only from one source. Also the figure Concerning ESBL-producing *K. pneumoniae* (19 isolates only from international collections) is very surprising and strongly suggests that the observed MIC distributions (especially for the very high MIC values at 256 or above) would strongly suggest the presence of additional resistance mechanisms than just ESBLs only.	

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	It is not stated why and at variance with other penicillins, a PK/PD target has been set specifically at higher threshold of 40-50% for temocillin (while for other penicillins (amoxicillin, mecillinam, piperacillin-tazobactam) in Enterobacterales these are set at 30-35%). From the Monte-Carlo simulations and PK/PD breakpoints presented from the study of the de Jongh (JAC 2016) which used a 2 x 2 g dosage the median 50% T>MIC (for a MIC of 8 mg/L) is at 79.70% and the probability to achieve (PTA) this target is very close to 95% even data are not reported. It is thus difficult to understand the reasons why the higher dosage of 2g x 3 would be recommended for isolates with MIC of ≤8 mg/L.	
	Based on the extensive clinical experience in our country (not to mention the UK), the use of previous breakpoint (Fuchs et al. 1985 and more recently the BSAC UTI/Systemic breakpoints S≤8 mg/L / R>16mg/L) and the elevated urinary concentrations of temocillin, the proposal of EUCAST seems excessively cautious and the Belgian NAC would like to suggest the following proposals to EUCAST for consideration: a) S≤8 mg/L / R>16mg/L (which would allow to continue the usage of the standard regimen 2g bid iv for infection caused by Enterobacterial isolates with MIC ≤ 8 mg/L) or as an alternative: b) S≤16 mg/L / R>16 mg/L (which would be in line with the high urinary concentrations and the clinical experience in Belgium and also in the UK). Such proposal would also be supportive of the former breakpoints set by both the BSAC (uUTI S≤32g/L mg/L/R>32mg/L and systemic S≤8 mg/L/R>8mg/L) and the CA-SFM (S≤8 mg/L/R>8mg/L) and will remain in line with the actual use of the drug. It should again be reemphasized that temocillin has been extensively used in Belgian hospitals in daily practice for the last 30 years (with an increased usage over the last two decades with the upsurge of resistant isolates (ESBL/AmpC)) mostly for treating various types of complicated urinary tract, urosepsis and bloodstream infections at the standard dosage of 2gx2. This has not resulted in any particular concern of emergence/selection of resistance nor in decreased clinical efficacy. As a general comment, the new definition developed by EUCAST relative to the report of 'I' as Susceptible increase exposure is still at its early infancy and is currently not known or known but not yet translated into application by many physicians. We acknowledge that this is the task of the NAC and of scientific societies (e.g. clinical microbiology, infectious disease) to inform and to educate physicians so that they would modify their habits.	

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	In Belgium (like elsewhere we presume), we (the NAC and the Belgian Society of t Microbiology and Infectious Diseases) are extremely concerned and have already initiated several actions during workshops and meetings to inform microbiologist colleagues and hospital practitioners. Yet it has to be realized that this is a complex and lengthy process which will require time before it is accepted and widely implemented in daily practice. This means that during a transition period which may last for a while, many physicians will continue to adopt their former attitude favouring the use of antimicrobials reported as S (susceptible, standard dose) rather than using a drug for which a I (susceptible, increased exposure) is reported. We anticipate that this current recommendation which implies the systematic usage of higher dosage of temocillin for every situation may have a major impact on its use (the more so that temocillin would be (besides cefuroxime) the only beta-lactam agent for which new suceptibilty breakpoint categories will apply among Enterobacterales. Thus, we fear that these breakpoints changes may lead to major consequences counteracting our antimicrobial stewardship strategies which aim to limit the use of broad-spectrum antibiotics (i.e. the use of temocillin as one of the few carbapenem-sparing option for the treatment of ESBL infections).	
	In summary, the Belgian NAC and the Belgian Society for Infectious Diseases and Clinical Microbiology data cannot endorse the proposal on temocillin in its current form which will imply the use a higher dosage (2g x3) in all patients since there is currently very little evidence of clinical ineffectiveness (and also only scarce data highlighting the superiority of the higher dosage over the current 2g bid dosage in non-critically ill patients). Further, the EUCAST current proposition on temocillin will clearly impact and endanger the antimicrobial stewardship strategies developed in Belgium which aim to preserve the usage of carbapenems as last line therapy in case of infections due to resistant Enterobacterales (ESBL/AmpC) where temocillin has been used successfully in the daily practice for more than 30 years in hospitals. For all the above mentioned reasons we would gently ask EUCAST to reconsider their proposal.	