LETTERS TO THE EDITOR

An unexpected isolate of Hafnia alvei with reduced susceptibility to cefoxitin

Dear Editor,

Hafnia alvei is a member of the family Enterobacteriaceae, which has been recognized as a cause of sporadic gastroenteritis and nosocomial systemic infections. The organism is usually susceptible to broad-spectrum cephalosporins, aztreonam, carbapenems, chloramphenicol, quinolones, aminoglycosides, and cotrimoxazole, but often shows resistance to penicillin, aminopenicillins, amoxicillin-clavulanate, aminopenicillins, and narrow-spectrum cephalosporins. H. alvei commonly possesses a naturally occurring inducible chromosome-encoded Bush group 1 beta-lactamase (Ambler Class C), conferring resistance to aminopenicillins and restricted-spectrum cephalosporins. This activity never confers resistance to cefoxitin, interestingly, and is associated with the expression of a high-level constitutive cephalosporinase (ceftazidime-resistant), or to production of a low-level inducible cephalosporinase (ceftazidime-susceptible). Also, a peculiar naturally occurring AmpC beta-lactamase, which was cloned from H. alvei by Girlich et al., is responsible for ceftazidime- and cefotaxime-resistance, and for an uncommon reduced susceptibility to cepiprome.2

A Gram negative organism collected from feaces of a hospitalized patient was identified as H. alvei, with 99% certainty, both by Vitek2 and miniAPI system (instruments provided by bioMérieux). The strain was named as HAS, according to the collection reference number. Susceptibilities were documented by a disk diffusion test (disks provided by Liofilchem, Roseto degli Abruzzi, Italy). Also, MICs were obtained by performing a broth microdilution assay, and are listed in Table 1. Sensitivity data provided by the agar and broth methods were interpreted according to the CLSI (NCCLS, previously) guidelines.6,7 H. alvei resistance to ampicillin, ampicillin/sulbactam, and amoxicillin/clavulanate was considered as common, due to the well known naturally occurring cephalosporinase. Instead, intermediate susceptibility to cefoxitin was not expected, as cefoxitin-resistant H. alvei strains have never been reported; in fact, cefoxitin cannot be hydrolyzed by the above mentioned Ambler Class C enzymes, which are commonly found in this species. We supposed the presence of an inducible AmpC-type enzyme, given that cefoxitin is notoriously resistant to both common cephalosporinas and extended-spectrum beta-lactamases (ESBLs), but not to AmpC hydrodases. We performed a disk approximation test (D-test), based on the assays previously described by other authors,1,5 by using imipenem/cefazidime, imipenem/ceftaxime, imipenem/piperacillin-tazobactam, and imipenem/cefoxitin as inducer/substrate combinations. Inducer/substrate disks were placed at a distance of 25 mm (center to center). After 24 h of incubation, inhibition zones were measured on both the induced (towards the inducer disk) and the uninduced side of the substrate disk, from disk edge to zone edge. The test gave positive results, as inhibition zone on the induced side of each substrate disk was reduced by > 3 mm. Interestingly, reduction of cefoxitin inhibition zone towards the inducer was not expected. Porin-mediated and efflux mechanisms have been excluded, as reduction of cefoxitin zone was documented to be imipenem-induced. Further, reduced susceptibility to this compound due to efflux pumps or reduced permeability of the bacterial cell wall has been described only in Escherichia coli and Klebsiella spp., so far.8 Hence, we suggest that an inducible AmpC-type enzyme is expressed by the isolate, and is responsible for reduction of cefoxitin-susceptibility. We considered then the strain as potentially resistant to piperacillin-, piperacil- lin-tazobactam, and third generation cephalosporins, despite Vitek2 and disk diffusion test results.

Production of inducible AmpC cephalosporinasinases has gained increasing importance in the recent years. These are usually chromosom-encoded enzymes, which are responsible for resistance to oxymino-cephalosporins, sulbactam, clavulanate, tazobactam, and cefoxitin (whilst the latter is resistant to ESBL activity). They have been commonly found in E. coli, Klebsiella pneumoniae, Enterobacter spp., Citrobacter freundii, Proteus mirabilis, Morganella morganii, Providencia spp., Serratia spp., Pseudomonas aeruginosa, and Salmonella spp. Betalactam/beta-lactamase inhibitor combination and third generation cephalosporins weakly induce AmpC-hydrolases expression, whilst carbapenems act as strong inducers. Mutations can occur in the regulatory components of AmpC, bringing to stable (no more inducible) enzyme over-expression, and concomitant loss of drug efficacy; organisms involved are called derepressed mutants, and can be selected in a single patient during beta-lactam treatment. Sporadic plasmid-encoded AmpC variants have recently been reported in E. coli and Klebsiella spp.3 The routine clinical microbiology laboratories should employ simple tests to screen inducible AmpC-type hydrolases producer strains, as these organisms may lead to
therapeutic dead ends. To our knowledge, intermediate susceptibility to cefoxitin has never been described in H. alvei, previously. Though the role of this uncommon species as an agent of human infections is partly unclear, development of antibiotic-resistance in H. alvei is emerging and will surely represent a serious concern in the field of nosocomial infections in the future years.

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References


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Time for a change in the definition of fever of unknown origin

In 1961, Petersdorf and Beeson defined “fever of unknown origin” (FUO) as a fever lasting for three or more weeks with temperatures ≥38.3 °C which remained undiagnosed after one week off intensive hospital work-up. 1 Currently, many infectious disease physicians, after making minor revisions to the original definition, define FUO as temperatures ≥38.3 °C lasting for three or more weeks which remained undiagnosed after three days of n-hospital work-up or during two or more outpatient visits. 2

In all these definitions, it seems that the major concern was on defining fever as a temperature of ≥38.3 °C, and on

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S, susceptible; R, resistant; I, intermediate. FOX, cefoxitin; AMP, ampicillin; PRL, piperacillin; AUG, amoxicillin/clavulanate; AMS, ampicillin/sulbactam; TZP, piperacillin/tazobactam; CTX, cefotaxime; CAZ, ceftazidime; FEP, cefepime; IMI, imipenem; MRP, meropenem; AK, amikacin; TM/SMX, trimethoprim/sulfamethoxazole; TE, tetracycline.
CORRIGENDUM

Corrigendum to “Letter to the Editor e An unexpected isolate of Hafnia alvei with reduced susceptibility to cefoxitin” [Journal of Infection 57 (2008) 165 e 166]

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It is regretted that the author name Domenico D’Antonio was incorrect. The correct name is now shown.