In two recently published articles, Wachino et al. designated a novel ceftazidime-hydrolyzing class B extended-spectrum β-lactamase (ESBL) (GES-a) as GES-3 (4), and a new cephalosporin-hydrolyzing and inhibitor-resistant class A ESBL (GES-b) as GES-4 (5). In actuality, their articles are fraught with misleading nomenclature of GES-type ESBLs and contradictory conclusions on the relationship between β-lactamase inhibitor resistance and an amino acid substitution in the center of the Ω-loop region.

Before Wachino and colleagues submitted their sequences for GES-a and GES-b genes to the GenBank nucleotide database (release dates, 25 May 2004 and 28 July 2004, respectively), sequences for GES-3 and GES-4 genes had already been released by Vourli et al. (3), the release date of which was 12 May 2004. As shown in Table 1, GES-a and GES-b genes are completely different from GES-3 and GES-4 genes. GES-3 and GES-4 were capable of hydrolyzing imipenem (3), while GES-a and GES-b could not hydrolyze imipenem and GES-b had a substrate profile extended to cephamycins as well as imipenem (4, 5). Presently, the different GES-type ESBLs have been designated by identical names. On the basis of priority of nomenclature, GES-a and GES-b genes should be renamed as GES-5 and GES-6 genes, respectively.

In their efforts to persuade readers that GES-b has a strong inhibitor-resistant nature like IRT enzymes and that it maintains the capacity to hydrolyze cephamycins and imipenem as a result of a single substitution at position 170, the center of the Ω-loop region, Wachino et al. (5) stated: “In comparison with GES-1, GES-2 [containing a single substitution at position 170] showed an extended substrate specificity for imipenem and a lower affinity for β-lactamase inhibitors (1), as was seen with GES-4 (GES-b).” However, Poirel et al. (1) stated: “Inhibition studies as measured by IC_{50} with benzylpenicillin as a substrate showed that GES-2 activity was inhibited by clavulanic acid and tazobactam more than GES-1 is.” The IC_{50} (inhibitory concentrations) of clavulanic acid and tazobactam for GES-a (5 and 2.5 M, respectively) were higher than those for GES-1 (1 and 0.5 M, respectively), and GES-a (1.5 and 0.19 M, respectively). Two GES-type ESBLs (GES-2 and GES-b) containing a single substitution at position 170 showed a different inhibition profile. Although GES-b has a strong inhibitor-resistant nature like IRT enzymes, the conclusion that the G170S substitution found in the GES-b affected inhibitor resistance could not be supported by the data as presented.

The renaming of GES-a and GES-b can help some authors to correctly designate new GES-type ESBLs, such as the novel enzymes identified from our nationwide survey supported by the Korea Research Foundation (KRF-2004-042-E00117).

REFERENCES


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Authors’ Reply 1

Unfortunately confusions in the nomenclature or the numbering of antibiotic resistance genes have occurred in various papers to date. In fact, several duplicate gene names have been sometimes assigned to the same resistance gene. In addition, dissimilar resistance genes possessing different nucleotide sequences have been assigned the same gene number. To solve these problems and resolve ambiguity, some useful suggestions have been made and discussed so far (1).

The dates of data submission to the GenBank/EMBL/DDBJ and data release as well as the review and publication periods were involved in the confusion that has occurred in the designated nomenclature of GES-3 and GES-4 β-lactamas (4–6). For example, as shown in Table 2, we submitted our sequence data for GES-3 and GES-4 to the GenBank/EMBL/DDBJ earlier than S. Vourli et al. Moreover, our manuscripts have also been submitted to the American Society for Microbiology earlier than theirs. Thus, we are persuaded that the priority of gene names should depend solely on the deposition

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**TABLE 1. Amino acid substitutions of GES-type ESBLs**

<table>
<thead>
<tr>
<th>β-Lactamase</th>
<th>Residue (coding triplet) at amino acid position:</th>
<th>Reference GenBank accession no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GES-1</td>
<td>Met (ATG) Glu (GAA) Gly (GGC)</td>
<td>2 AF156486</td>
</tr>
<tr>
<td>GES-2</td>
<td>Asn (AAC) Ser (AGC)</td>
<td>1 AF326355</td>
</tr>
<tr>
<td>GES-3</td>
<td>Ser (AGC)</td>
<td>3 AY494717</td>
</tr>
<tr>
<td>GES-4</td>
<td>Lys (AAA) Ser (AGC)</td>
<td>3 AY494718</td>
</tr>
<tr>
<td>GES-3b</td>
<td>Thr (ACG) Lys (AAA)</td>
<td>4 AB113580</td>
</tr>
<tr>
<td>GES-4b</td>
<td>Thr (ACG) Lys (AAA)</td>
<td>5 AB116260</td>
</tr>
</tbody>
</table>

*Ambler’s position.

b Temporarily named as GES-a and should be newly designated GES-5.

c Temporarily named as GES-b and should be newly designated GES-6.
date of the DNA sequence to the database and the submission date of the manuscripts to the relevant publication offices. For their part, Drs. Hall, Partridge, et al. recommended that the gene name assignment should depend, rather, on the date of data release by the GenBank/EMBL/DDJB database (1). At any rate, it would seem that this kind of confusion is unavoidable under the current systems employed for data deposition, data release, manuscript review, and publication. As a possible solution to this kind of confusion, the assignment of all antibiotic resistance gene names should be controlled through a web site such as http://www.lahey.org/studies/webt.htm, as was proposed by Hall et al. (1). Moreover, to resolve the confusion among GES-3 and GES-4 beta-lactamases, we would like to propose here a practical modification in the naming of GES-3 and GES-4 enzymes (Table 2).

In our previous article (5), we stated as follows: “In comparison with GES-1, GES-2 showed an extended substrate specificity for imipenem and a lower affinity for beta-lactamase inhibitors, as was seen with GES-4.” As was suggested by Drs. Lee and Jeong, this sentence might indeed cause some misunderstanding about the properties of GES-type enzymes against beta-lactamase inhibitors. However, since the IC50 of clavulanic acid for various TEM-derived ESBLs are usually lower than 0.2 μM/ml, our actual meaning could be further clarified by adding the following: “Among class A enzymes, GES-2 generally demonstrate lower affinities for beta-lactamase inhibitors.”

The above investigators mentioned that the G170S substitution found in GES-4J could not sufficiently explain the inhibitor-resistant nature of GES-4J. In our article (5), we compared the inhibition properties under the same experimental conditions between our GES-3 and those of GES-4J possessing a single G170S substitution. Although the IC50 of clavulanic acid for GES-2 (which has a single G170N substitution compared with GES-1 [2]) was lower than that for GES-1 (3), the G170S substitution found in GES-4J apparently served to raise the resistance level against beta-lactamase inhibitors (5). The differences observed in the substrate specificities and inhibition properties among GES-1, GES-2, GES-3G, GES-4G, GES-3I, and GES-4J enzymes must be attributable to the amino acid substitution at position 170 as well as those at positions 62 or 104. In any event, it is probable that the amino acid substitution at position 170 plays a key role in the expansion of substrate specificity among GES-type beta-lactamases, as has been demonstrated in the cases of GES-2 and GES-4J. Further enzymological analyses of GES-3G and GES-4G will reinforce our speculation, since both enzymes have a G170S substitution like the one in GES-4J. Molecular modeling analysis as well as a detailed X-ray crystallographic analysis will well explain the role of the amino acid substitution at position 170 in GES-type beta-lactamases. Both analyses will be undertaken in our forthcoming study.

### Table 2. Submission dates of DNA data and manuscripts

<table>
<thead>
<tr>
<th>Article (reference no.)</th>
<th>β-Lactamase (accession no.)</th>
<th>Modified name</th>
<th>Date (mo-day-yr) of GenBank/EMBL/DDJB</th>
<th>Date (mo-day-yr) of manuscript</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vourli et al., 2004 (4)</td>
<td>GES-3 (AY497177) GES-4 (AY497418)</td>
<td>GES-3G GES-4G</td>
<td>Submission 12-3-03 Release 5-12-04</td>
<td>Submission 12-1-03 Return for modification 1-16-04 Revision 3-19-04 Acceptance 4-5-04</td>
</tr>
<tr>
<td>Wachino et al., 2004 (5)</td>
<td>GES-3 (AB113580) GES-4 (AB116260)</td>
<td>GES-3J GES-4J</td>
<td>Submission 6-30-03 Release 5-25-04</td>
<td>Submission 8-8-03 Return for modification 11-16-03 Revision 12-12-03 Acceptance 11-19-03</td>
</tr>
</tbody>
</table>

### References

**Authors' Reply 2**

This comment is an attempt to rectify several mistakes in the nomenclature of GES-type enzymes and some false comments written in recently published papers on the subject. This initiative is relevant since it is true that some confusion has appeared in that field and, worse, that some false information has been reported. It is noteworthy that this enzyme (originally detected in a Klebsiella pneumoniae isolate from French Guiana and thus named GES for Guiana-Extended-Spectrum β-lactamase) is widespread in view of the recently published studies. β-Lactamase GES-1 and variants have been identified in Europe (France, Portugal, Greece) and also in South Africa, Brazil, and Japan in several species, including spp. of Enterobacteriaceae and Pseudomonas aeruginosa. The origin of these β-lactamase genes remains unknown. It is correct to underline that GES-2, the first described ESBL with such a capacity to hydrolyze imipenem, is well inhibited by β-lactamase inhibitors. In terms of nomenclature, an update is required, since identical names have been given for different enzymes which possess different hydrolytic properties. However, the authors did not include in their update the IBC-1 and IBC-2 enzymes...
which are also just point mutant analogues of the GES enzymes. To clarify the situation, we propose to maintain the current denomination concerning the fully characterized GES-3 and GES-4 enzymes published by Wachino et al. (references 4 and 5 of the comment letter above) and to rename the variants published by Vourli et al. as GES-5 and GES-6 (for GES-3 and GES-4, respectively). Therefore, the IBC-1 and IBC-2 variants identified in Greece (1, 2) should be renamed GES-7 and GES-8, respectively.

REFERENCES


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