Comment on: Redefining extended-spectrum \( \beta \)-lactamases: balancing science and clinical need


Keywords: carbapenemases, cephalosporinases, ESBLs, nomenclature

Sir,

The nomenclature of \( \beta \)-lactamases has been approached historically in one of two ways. The enzymes have been studied on the basis of molecular sequence or they have been grouped according to function. An attempt to align the two was made in 1995 and was based on an extensive analysis of existing biochemical and molecular data. As new \( \beta \)-lactamases have been identified, it has been relatively easy to assign a grouping of these new enzymes in either a clearly defined molecular or functional category. Over the past 20 years, various \( \beta \)-lactamase descriptions have commonly included the term extended-spectrum \( \beta \)-lactamase, or ESBL, to describe functional group 2b \( \beta \)-lactamases that hydrolyse extended-spectrum cephalosporins and monobactams, and are inhibited by clavulanic acid. Today, both microbiologists and clinicians understand the ramifications of the proper identification of strains expressing ESBLs and the subsequent appropriate antibiotic therapy.

Giske et al. recently proposed a new set of definitions in an attempt to provide a nomenclature that would be useful to those unfamiliar with the nuances of \( \beta \)-lactamase classification. In this proposal, the well-defined term ESBL is broadened to include the major plasmid-encoded \( \beta \)-lactamases of clinical importance, including both serine and metallo-\( \beta \)-lactamases with completely different hydrolytic and inhibitory mechanisms. The new classification uses subscripts to differentiate subclasses of enzymes with similar hydrolytic profiles or similar structural classes. There are indeed large numbers of \( \beta \)-lactamases that can be grouped in different ways. However, we argue that it is not a useful simplification to call all those enzymes that hydrolyse expanded-spectrum cephalosporins ESBLs. Furthermore, a system with multiple subscripts does not diminish or simplify the number of categories or the challenges to memory and typography.

The term ESBL has both a historical and an important clinical definition. Historically, ESBLs were named to differentiate them from their parental enzymes that did not hydrolyse extended-spectrum \( \beta \)-lactams. Clinically, ESBL-producing organisms are resistant to extended-spectrum cephalosporins and monobactams, but can be treated successfully with carbapenems. Thus, having a category ESBL\text{CARBA}, for organisms where carbapenems should not be used, is inherently unclear and potentially confusing to the practicing clinician. Furthermore, the easily understood term carbapenemase defines this functional category so that the designation ESBL\text{CARBA} is unnecessary.

Amp\(C\) \( \beta \)-lactamases, whether encoded on plasmids or the bacterial chromosome, confer resistance to a broader range of \( \beta \)-lactams than ESBLs as traditionally defined. It makes no sense scientifically to separate plasmid-encoded and chromosomal Amp\(C\) enzymes that have identical hydrolytic properties and homologous amino acid sequences. Although organisms producing Amp\(C\) \( \beta \)-lactamases can also generally be treated with carbapenems, they are more likely than those with traditional ESBLs to become resistant to carbapenems through the loss of outer membrane porin channels and enzyme overexpression; thus, these two classes should not be lumped together. The new designation of ESBL\text{M} for the plasmid-encoded Amp\(C\) enzymes is also confusing, as the M subscript can easily be mistaken to imply the mechanistically different class of metallo-\( \beta \)-lactamases that readily hydrolyse carbapenems.

Likewise, OXA-type ESBLs do not belong in the same functional or structural category as the traditional ESBLs: they are structurally diverse, currently geographically localized, relatively uncommon and do not require general consideration.

Important, the new classification ignores the diagnostic testing schemes in which traditional ESBLs should respond to the inhibitory effects of clavulanic acid, whereas other \( \beta \)-lactamases, such as the OXA-type ESBLs, Amp\(C\) cephalosporinases and metallo-\( \beta \)-lactamases, are not inhibited by the commercially available \( \beta \)-lactamase inhibitors. Hybrid \( \beta \)-lactamases, such as complex mutants of the TEM enzyme, with ESBL properties and...
Letters to the Editor

K. B. was an employee of Johnson & Johnson Pharmaceutical Research & Development; P. B. was an employee of Wyeth Research and is now an employee of Novartis Institutes for Biomedical Research Inc. No other contributing authors have an association that may be perceived to be a conflict of interest.

References


Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkp143
Advance Access publication 29 April 2009

Redefining extended-spectrum β-lactamases: balancing science and clinical need—authors’ response

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Keywords: ESBLs, AmpC, carbapenemases

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Sir,

Recently, we proposed a modified β-lactamase scheme for extended-spectrum β-lactamases (ESBLs) in recognition of the fact that this term is no longer sufficient to encapsulate accurately all β-lactamases possessing extended-spectrum activity and therefore requires refining.1 Our proposal was mainly based on a clinical perspective emphasizing the need for smooth communication between various groups of healthcare professionals. Accepting that such a proposal would be controversial, nonetheless we do not seek to polarize the ‘β-lactamase community’, but to stimulate dialogue on the merits of existing classifications and to explore necessary improvements. In reply to our proposal, Bush et al.2 raise a number of points that we wish to respond to:

1. Bush et al.2 claim that clinicians and microbiologists understand the concept of ESBL and how ESBLs should be treated. We do not believe that this is always the case. Several of the co-authors are clinical microbiologists with considerable international experience and we know from communication with infectious disease practitioners, other clinicians and infection control personnel, particularly in developing countries, that many people find the current terminology describing β-lactamases very complicated and that many of them do not have an a priori understanding of the concept ESBL. As Bush et al.2 point out in their comment, ESBLs were historically named to differentiate them from their parental enzymes that did not hydrolyse extended-spectrum β-lactams. This is not readily understandable beyond experts on β-lactamases, as carbapenemases are also considered to be extended-spectrum β-lactams.

2. Moreover, Bush et al.2 state that ESBL producers are resistant to cephalosporins and monobactams but can be treated with carbapenems, and that detection of β-lactamases is important for SIR-classification. This will not be true following the decided, but not yet implemented, CLSI extended-spectrum cephalosporin