



Breakpoints and expert rules for 3rd and 4th generation cephalosporins and aztreonam for Enterobacteriaceae with and without acquired beta-lactam resistance mechanisms.

The following revised proposals are for breakpoints and expert rules in relation to 3rd and 4th generation cephalosporins and aztreonam for Enterobacteriaceae with and without acquired beta-lactam resistance mechanisms.

The proposals are for discussion in the national breakpoint committees (BSAC, CA-SFM, CRG, DIN, NWGA, SRGA) and the Expert Rules Subcommittee. They are also distributed for consultation with the EUCAST General Committee, the EUCAST consultation networks and via the EUCAST website.

Comments should be sent to the EUCAST Scientific Secretary (derek.brown222@btinternet.com). The deadline for receiving comments from all groups is 1st March 2010.

Any data relating MICs of 3rd and 4th generation cephalosporins and aztreonam to clinical outcome would be particularly welcome.

Enterobacteriaceae and 3rd and 4th generation cephalosporins with and without beta-lactam resistance mechanisms

Over the last year there has been extensive discussion regarding breakpoints of 3rd and 4th generation cephalosporins for Enterobacteriaceae and expert rules for dealing with ESBL producers. There have essentially been two points of view: the first requires that all isolates displaying resistance to any 3rd and 4th generation cephalosporin are tested for ESBL production and, if positive, the isolates are reported resistant to all 3rd and 4th generation cephalosporins; the second contends that ESBL production is not always clinically significant and that if breakpoints are appropriate the susceptibility tests can be reported “as found” and without the need to test for ESBL production other than for epidemiological or infection control purposes.

Two alternative proposals attempting to reconcile these points of view were discussed by the national breakpoint committees and neither had sufficient consensus.

A further proposal, based on discussion of comments received by the Steering Committee, suggested retention of current breakpoints and reporting all 3rd and 4th generation cephalosporin results “as found”. This proposal was released, with supporting data, for wide consultation on 28th November 2009.

While most groups were happy to accept the proposal there was concern that reporting “as found” with an I/R breakpoint of 8 mg/L is too high as some references indicate poorer response for ESBL-producers with MICs of 8 mg/L.

Following further discussion by the Steering Committee it was felt reasonable to take a slightly more cautious approach and modify the I/R breakpoints slightly.

The existing intravenous 3rd and 4th generation cephalosporin and aztreonam breakpoints for Enterobacteriaceae are:

Cefotaxime	S≤1 / R>2 mg/L
Ceftriaxone	S≤1 / R>2 mg/L
Cefepime	S≤1 / R>8 mg/L
Ceftazidime	S≤1 / R>8 mg/L
Aztreonam	S≤1 / R>8 mg/L

Oral cephalosporin breakpoints for Enterobacteriaceae apply to UTI only and correspond to their respective epidemiological cut-off values (ECOFFs).

The current proposal made by the EUCAST Steering Committee (8-9 February, 2010) is as follows:

1. To retain current susceptible and resistant breakpoints for cefotaxime and ceftriaxone as follows.

Cefotaxime	S≤1 / R>2 mg/L
Ceftriaxone	S≤1 / R>2 mg/L

2. To reduce the I/R breakpoints for ceftazidime, cefepime and aztreonam from 8 mg/L to 4 mg/L.

Cefepime	S≤1 / R>4 mg/L
Ceftazidime	S≤1 / R>4 mg/L
Aztreonam	S≤1 / R>4 mg/L

As the pharmacokinetics and pharmacodynamics of these agents are similar it is appropriate to reduce the I/R breakpoints similarly.

3. To retain the non-species-related breakpoints for extended-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime and cefepime) and aztreonam.
4. To report all 3rd and 4th generation cephalosporin and aztreonam results “as found”.
5. To modify expert rules in accordance with Pk/Pd criteria and current clinical evidence (distributed previously).
6. To avoid recommendations on how to detect specific beta-lactamases in the expert rules as this is not needed for expert rules. Recommendations will be provided in the future as a separate document.

Implications for breakpoints

The I/R breakpoints for ceftazidime, cefepime and aztreonam are reduced from 8 mg/L to 4 mg/L.

Implications for expert rules:

Rule 9.1 changed to indicate that test results should be reported as found. There may, however, be strong arguments for testing for ESBLs or other resistance mechanisms for infection control or epidemiological surveillance reasons. Testing for ESBL production is not required for reporting results of routine antimicrobial susceptibility tests.