**Belfast User Group Day – 8 November 2007**

**Questions and Answers**

**Shift to European (EUCAST) breakpoints – the impact on BSAC recommendations**
**Derek brown**

**Q** Why are EUCAST and CLSI not harmonising breakpoints together?

**DB** EUCAST offered to work jointly with CLSI but officially they were not receptive to the idea. It is difficult partly because CLSI sell all their documents whereas EUCAST provides all information freely. Also they do not have the same arrangement with FDA (who license antibiotics in the USA) as EUCAST has with EMEA (who license antibiotics in Europe). EUCAST officially set breakpoints for EMEA whereas FDA set legal breakpoints in the USA and specifically state that CLSI do not. After our initial attempts to get CLSI involved in harmonising breakpoints, we felt that we should just get on with doing it in Europe. It obviously makes sense to have one set of breakpoints internationally and hopefully this will happen to some extent through the scientific process of setting breakpoints being more defined. With new agents the USA is coming to similar conclusions that we are in Europe. If they go back and apply similar methods to their old breakpoints, as EUCAST has, they will find that many of the old breakpoints should be revised.

**DL** I wish I could believe that was correct. With tigecycline, FDA breakpoints are higher than ours and as I recall also for daptomycin FDA are recognising enterococci as a target whereas we are not. I think that maybe the academics, professional infectious disease doctors and microbiologists within CLSI are actually moving very close to the EUCAST position, seeking lower breakpoints. I don't see that movement within the FDA who, as you rightly said, have asserted their position as the arbiters of breakpoints within the USA.

**DB** FDA tigecycline breakpoints for Enterobacteriaceae are one dilution step higher than EUCAST for the susceptible category, others are not higher. Whether a breakpoint is set of not depends on the licensing by EMEA and FDA – for daptomycin, FDA accepted enterococci as a target group, EMEA did not. I think the way the FDA works on breakpoints is to convene a group to set the breakpoints for each antibiotic that comes through.

**DL** Rightly or wrongly my impression is that FDA's decision making process is very much predicated on the clinical outcome in relation to MICs seen in the clinical trials. They put much less weight than we do on either pharmacodynamics or on MIC distributions.

**DB** That may be true, but clinical outcome data are often not available or very limited for isolates with higher MICs, so this should not push breakpoints higher.

**Q** If a Microbiology Laboratory is using CLSI breakpoints and they want to test an agent, for example tigecycline, which CLSI don't provide, what are they to do in practical terms to get a breakpoint – do they use the FDA breakpoints?

**DB** They can use the FDA breakpoints. The FDA used to set disc diffusion breakpoints but I'm not sure they do this now. I think you will find that the pharmaceutical company concerned will give you the disc diffusion breakpoints as well as MIC breakpoints.

**Q** Are those breakpoints using CLSI methods?

**DB** They are almost certainly with CLSI methods if related to FDA breakpoints.

**Q** I was interested in your MIC distributions for vancomycin with *S. aureus*, because you've got a wild sensitive population with MICs up to 2 mg/L. There were several presentations at ICAAC this year which said if the MIC was 2 mg/L it is possible that these wouldn't respond clinically – do you agree?

**DB** Sometimes you get strains with resistance mechanisms that remain within the MIC range of the wild susceptible population -you don't always get a clear increase in MIC when organisms have a resistance mechanism. For vancomycin with *S. aureus,* MICs for h-VISA isolates are commonly in the susceptible range. There have indeed been reports that infections with isolates with vancomycin MICs of 2 mg/L do not respond so well clinically as isolates with lower MICs. It is not clear whether those that do not respond involve h-VISA. Goldstein has suggested that vancomycin treatment failures involving h-VISA infections are related to inadequate dosing, but with current treatment practices it does appear that vancomycin treatment may be less effective when vancomycin MICs are 2 mg/L.

**Detection of ESBLs and AmpC beta-lactamase**
**David Livermore**
~~David Livermore Q&A Belfast~~

**Q** You went through all the methods we can use in the lab to screen routinely for the various types of resistances. My lab has, for some time now, been backing this up with automated sensitivity system using the Vitek 2 with two particular types of cards. What's your view on that?

**DL** We validated the Advanced Expert system on the Vitek - this that was published in JAC in 2001/2 - against the ESBL producers that were circulating then, sensitivity and specificity were good. Subsequent to that there has been the spread ~~spell~~ of CTX-M-15. We collaborated with Helen Jones and her colleagues in Wolverhampton and put through quite a number of CTX-M-15 producing *E. coli* and, again detection was good. However one pitfall is that some users customise the cards for the Vitek and change the antibiotics that are on them. In this case they may get substantially poorer performance than with the standardised card that we tested. Likewise, any updated card from bioMerieux themselves needs to be tho~~u~~roughly evaluated.

~~Comment – from whom?~~
~~Q~~**Comment** Most of the UK use the same standardised cards.

**Q** In most laboratories where we don't have access to this new the Cica β-Test, are we saying that, if we have screen results indicating the possible presence of ESBL, we really can't ~~say so~~give a result until we speciate the organism? Do we have to delay giving sensitivities back to the wards until we have finally speciated the organisms?

**DL** I think that any multi-resistant organisms should be identified to species level. However, ~~I~~if you have done a direct sensitivity and at day one ~~and~~ you know the isolate ~~that~~ is resistant to cefpodoxime, I do think you should contact the clinician and tell him that the organism looks like it's highly resistant. If it is a severe infection, the patient should be on a carbapenem early~~;~~ or, if it is an uncomplicated UTI and we are looking at oral treatment, perhaps they should be on nitrofurantoin rather than trimethoprim, ciprofloxacin or a cephalosporin;~~. B~~but properly interpreting what is going on in an organism requires knowing the species. There are good chromogenic agars now available which allow you very quickly to pull apart the *E. coli* from the *Enterobacter, Klebsiella* group etc. We really have to move away from this habit of booking everything as coliform unless it is from blood.

**Q** In the meantime, while results are pending, we would have to apply caution?

**DL** Yes, on the principle of getting the most useful data to the clinician as quickly as possible. Ultimately you need the species and the antibiogram to make sense of what is going on.

**Q** If you are using the combination disc method looking for ESBLs and you are happy that they are an *E. coli* or a *Klebsiella*, but you only have synergy in only one set of combined discs – cefotaxime or ceftazidime, not both, does that give rise to any confusion?

**DL** In general, synergy with either disc pair means the isolate has an ESBL. Some enzymes like TEM-10 or TEM-26 give much clearer resistance and synergy with ceftazidime than cefotaxime; whilst CTX-M-9 or 14 give you much clearer resistance synergy with cefotaxime. The only real exception is where you get very, very weak synergy with the cefotaxime disc pair and none with the ceftazidime pair for a *K. oxytoca*. That is likely to signify high-level K1, not an ESBL.

**BSAC recommendations for interpreting the susceptibility of urinary tract isolates**
**Jenny Andrews**

**Q** Will the literature review looking at the treatment of enterococci with trimethoprim be published as a leading article?
**JA**. Gunnar Kahlmeter would like it to be published; he is trying to encourage the registrar to write it up. It would be very useful for microbiologists to see the conclusions of this work before making a decision on treatment.

**Comment from the audience**. We reported trimethoprim with a cautionary comment 3 years ago, and then stopped reporting it; there wasn't a great rebellion from GPs.
**DB**. This question has been asked many times before and we always come to same conclusion, we don't know the answer.

**General discussion on questions related to the BSAC recommendations (Selected questions sent to the BSAC and questions from the audience)**

**Q**. Many people have asked if they need to test for ESBLs in organisms that have AmpC such as *Enterobacter* spp. Apart from an epidemiological point of view, would it make any difference to the treatment of the patient?
**DL.** What they are saying is "is there a need to test with a fourth generation cephalosporin to see if the organism has an ESBL?"
For surveillance from a Public Health point of view we do need to know. If for example an Enterobacter has just AmpC present then cefpirome and cefepime are clinically usable antibiotics; when you have an ESBL present they should not be used. Cefepime is used widely worldwide, but has never been marketed in the UK. For cefpirome, it has a marketing authorisation in the UK, but is not widely used if at all. From a clinical treatment point of view, because of the fourth generation cephalosporins are hardly used, knowing that an ESBL is present doesn't matter so much.

**Q.** Another question we have been asked frequently is the efficacy of temocillin against ESBL producers. Do you know its availability in the UK and have there been any patient studies using temocillin to treat ESBL infections?

**DL**. It is available in the UK, it keeps just about complete activity against both ESBL producers and AmpC derepressed organisms. However serum levels are not high, so the mode of the MIC distribution is actually quite close to the pharmacodynamic breakpoint. Small studies from Belgium, where it has been used extensively for a long time~~;~~, do suggest that it is active in urinary infections and even in urosepsis and mild infections caused by ESBL producers. The manufacturer, Eumedica, is in the process of trying to set up a clinical trial treating urinary infections caused by ESBL producers. Temocillin may be an alternative to the carbapenems.

**Q**. David, what is your opinion on the use of mecillinam to treat urinary tract infections caused by ESBL and AmpC producers?

**DL.** My impression is that there are few clinical trials that have been done against ESBL producers. There was a trial which was presented as a poster at ECCMID a few years ago that showed that mecillinam was equally active against ampicillin resistant and ampicillin susceptible isolates. Mecillinam MICs for ESBL producers are only a dilution or so higher than for the Tem penicillinase producers. If you have a patient with ~~got~~ a lower UTI caused by an ESBL producer mecillinam is potentially an alternative option to nitrofurantoin; it is also more palatable than fosfomycin. If you've got a straightforward UTI caused by an ESBL-producing *E. coli* cefixime or cefpodoxime can be given, perhaps combined with augmentin where the clavulanic acid will protect the cephalosporin.

**JA**. I would like to comment that when ~~MIC~~ testing mecillinam MICs~~,~~ with Klebsiellae there is often a trailing end~~-~~point that is not seen with *E. coli*. I don't know what impact this inoculum effect would have on the activity of mecillinam if there was a high concentration of organisms in the urine.

**Q.** Is there a possibility that a European disc diffusion method will be available in the future?

**DB.** We have been told by people in Europe using CLSI disc diffusion methodology that it would be easier for them to switch to EUCAST MIC ~~BP~~breakpoints if they could use ~~CLSI~~the same methodology, but interpret susceptibility using EUCAST ~~BP~~breakpoints. This would mean developing a European standardized method. There is no evidence that CLSI methodology is any better than BSAC as a standardised technique or vice versa. It is the breakpoints that are different and as long as there is a standardised method with calibration data relating MICs to zone sizes you c~~an~~ould apply different breakpoints. We~~We have talked to CLSI who~~ have ~~provided some~~talked to sources in the USA who have basic data for the CLSI method and asked them to provide data they used with MIC versus zone distributions so that we could apply EUCAST breakpoints. If we are going to have a European method it would be easier to develop it based on the CLSI technique because Iso-Sensitest agar is not widely used in Europe. The development of a European method will probably take at least 2-3 years.

**Q.** From the veterinary world~~. W~~we take part in NEQAS which is organised in Denmark. The laboratories that take part either use BSAC or CLSI methodology and generally speaking there is no good correlation of the disc diffusion between the laboratories taking part. For the most recent NEQAS distribution Salmonellae were included and EUCAST breakpoints were quoted, not CLSI as had happened previously. Using EUCAST breakpoints might be the way to get over the differences in methodology.

**DB**. There have been a lot of discussions about veterinary recommendations and t~~. T~~here are lots of issues to discuss in particular the treatment of animals. The clinical breakpoints we use for humans might be totally irrelevant and ideally there should be a range of different breakpoints for different animal species, but this is ~~probably impossible~~unlikely to be achieved. Another approach by some of the veterinary groups in Europe has been to use ~~-~~epidemiological breakpoints when ~~you do not know~~ there is no other MIC breakpoint . It doesn't matter whether~~re the~~ organisms ~~is~~are isolated from humans or animals as the "wild type" distributions are the same. If you have the MIC distributions you can apply different breakpoints.

**JA** This approach has also been used by veterinary groups in the UK.

**JA** We have had lots of requests from laboratories asking for acceptable ranges for the controls mentioned in the HPA document on the detection of ESBLs.

**DB** ~~We~~BSAC is ~~are~~ currently undertaking a study with diagnostic laboratories in the UK to establish acceptable ranges for these controls.

**JA** David, do you know how many isolates of *N. gonorrhoeae* there have been in the UK that are susceptible to nalidixic acid yet ciprofloxacin?

**DL** I don’t know exact numbers, but they are still uncommon. The proportion of ciprofloxacin resistance ~~of~~in gonococci is now up to about 25%~~;~~. ~~–t~~There is a high prevalence of 35-40% in men and usually a much lower prevalence of 5-6% in women. There has been a general move away from the use of ciprofloxacin to treat gonorrhoea.

**JA** Have you seen any resistance to azithromycin?

**DL** I haven’t seen any cephalosporin or azithromycin reduced susceptibility. There are reports from the Far East of isolates with reduced susceptibility to cefixime and ceftriaxone.