Comparison of Staphylococcal sensitivity data using EUCAST vs CLSI

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Introduction

Laboratories across Europe are being encouraged to move across to the harmonised European antimicrobial sensitivity testing breakpoints published by the European Committee on Antimicrobial Sensitivity Testing (EUCAST). This will facilitate comparisons of resistance rates throughout Europe. Scottish laboratories moved mainly from Clinical Laboratory Standards Institute (CLSI) breakpoints over the course of a year. It is anticipated that changing the breakpoints will have an impact on local resistance rates which has previously been described for Gram negative isolates (Hombach, 2012) and *Streptococcus pneumoniae* (Goossens, 2013). We aim to compare our historical minimum inhibitory concentration (MIC) data for *Staphylococcus aureus* with CLSI and EUCAST breakpoints in order to anticipate likely changes to resistance patterns that may emerge as we adopt the EUCAST breakpoints in Scotland.

Methods

We extracted 20481 non duplicate isolates (1 per quarter) of *S. aureus* from blood cultures from April 1996 to September 2013. Prior to 2008 the data is extracted from the Scottish MRSA reference lab database and subsequently the data comprises all isolates submitted to the Electronic Communication of Surveillance in Scotland (ECOSS) database. These isolates comprise 13211 isolates of methicillin sensitive *S. aureus* and 7270 isolates of methicillin resistant *S. aureus*. Initial sensitivity testing had been carried out using combinations of Stokes methodology followed up by E-testing for some antibiotics. In April 2004 the Vitek (Biomerieux) was introduced and then in November 2008 this was changed to the Vitek 2 (Biomerieux) system. The Gram positive sensitivity card for the Vitek 2 was changed in December 2011 to include daptomycin.
Due to the way the data had been recorded there were some isolates for which it was not possible to interpret the data compared with either or both of the published breakpoint systems. E.g. if an isolate is recorded as having an MIC of ≤4 and the breakpoint is 2 it is not clear where this minimum inhibitory concentration (MIC) actually lies with regards the breakpoint. In this situation the data point was excluded from both the numerator and denominator for the purposes of calculating resistance rates. For some antibiotics such as teicoplanin due to the number of datapoints that would have to be excluded the analysis would not be valid.
Table 1 illustrates the breakpoints used by the two systems.

Table 1 – comparison of CLSI and EUCAST breakpoints

Drug	MIC breakpoints µg/ml				
	CLSI 2013			EUCAST 2013	
	S	I	R	S	R
Benzyl penicillin	≤0.12	-	≥0.25	≤0.12	>0.12
Oxacillin	≤2	-	≥4	≤2	>2
Vancomycin	≤2	4-8	≥16	≤2	>2
Teicoplanin	≤8	16	≥32	≤2	>2
Daptomycin	≤1	-	-	≤1	>1
Gentamicin	≤4	8	≥16	≤1	>1
Erythromycin	≤0.5	1-4	≥8	≤1	>2
Tetracycline	≤4	8	≥16	≤1	>2
Ciprofloxacin	≤1	2	≥4	≤1	>1
Moxifloxacin	≤0.5	1	≥2	≤0.5	>1
Nitrofurantoin	≤32	64	≥128	≤64	>64
Clindamycin	≤0.5	1-2	≥4	≤0.25	>0.5
Trimethoprim	≤8	-	≥16	≤2	>4
Chloramphenicol	≤8	16	≥32	≤8	>8
Rifampicin	≤1	2	≥4	≤0.06	>0.5
Quinupristin-Dalfopristin	≤1	2	≥4	≤1	>2
Linezolid	≤4	-	≥8	≤4	>4

Results

The percentage resistances to each drug compared against the two breakpoint systems are shown in Table 2. There is no change to the rate of resistance to penicillin with application of the EUCAST breakpoints. The findings are similar for oxacillin. Detection of MecA remains the definitive method of determining when an organism is an MRSA but a significant change in the breakpoint may result in an increase in erroneous reporting from individual laboratories before confirmation by the reference laboratory.
As expected there was no change to the interpretation of resistance rates to vancomycin. It was not possible to look at the effect of changing the teicoplanin breakpoint due to the way the historical data was stored. There was no information available for daptomycin for this time period.
There were no changes to resistance rates for ciprofloxacin when EUCAST breakpoints were compared with CLSI breakpoints. Using the EUCAST breakpoints 26.6% of Staphylococcal isolates are moxifloxacin resistant compared with 21.6% under CLSI. This difference is most marked for the MRSA isolates, where 79.2% of the isolates are resistant to moxifloxacin using EUCAST compared with 46.7% are resistant using CLSI .
No change to resistance rates for quinupristin-dalfpristin was seen when changing from CLSI to EUCAST.
For gentamicin some of the historical data points had to be excluded as it was not possible to interpret them in terms of the EUCAST breakpoints. Using the datapoints that it was possible to interpret there seemed to be an increase in gentamicin resistance when the EUCAST breakpoints are applied. Due to the way the historical data is recorded it was not really possible to interpret the tobramycin resistance with the EUCAST breakpoints .
No MIC data was available for mupirocin.
3.8% of isolates are resistant to trimethoprim using CLSI breakpoints. Using the EUCAST breakpoints 4.31% isolates are resistant. There was no MIC data available for septrin.
No fusidic acid breakpoints are given in the CLSI guidance.
Table 3 shows the same analysis just for the MRSA isolates. The most significant increases in resistance changing from CLSI to EUCAST amongst MRSA isolates occurred for gentamicin and moxifloxacin. The other antibiotic for which an apparent increase in resistance was seen were as per all isolates i.e. clindamycin, chloramphenicol and rifampicin.

Discussion and learning points

• Potential drawbacks to this analysis lie in the duration of the dataset. There have been several **method changes** during this time with the introduction of the VITEK then the VITEK 2 systems. For some antibiotics such as daptomycin these method changes have resulted in changes to the MIC of an antibiotic which may span a breakpoint.

• Repeating the analysis on just the data from last 5 years (2009 onwards), where the method should have stayed fairly constant results in no significant change in gentamicin, clindamycin and rifampicin resistance rates. Repeating the chloramphenicol analysis showed an increase in resistance rates from 0.11% to 0.16%. Changing resistance rates over the time period and a smaller amount of data may be explanations for this effect.

•It is also important to be aware that prior to the start of mandatory referral of all *S. aureus* isolates from blood cultures to the Scottish MRSA reference laboratory in 2005 the isolates may not be a true reflection of all blood culture isolates in Scotland.

• As discussed in the methods a further problem has been the **recording of the MIC data** where the figure given does not give an indication as to whether the true MIC is above or below the new breakpoint. In this situation the datapoints that it was not possible to evaluate were exluded. Antibiotics where this kind of problem particularly arose were gentamicin and tobramycin, teicoplanin, trimethoprim. For tobramycin and teicoplanin this problem meant it was not possible to interpret the data.

• Despite these possible problems the data still usefully illustrate the possible changes in resistance patterns that we are likely to encounter as we move to adopt the EUCAST guidelines.

Table 2 - % resistances for all Staphylococcal isolates

Drug	% of those tested which are resistant using CLSI breakpoints	% of those tested which are resistant using EUCAST breakpoints	Change
Benzyl-penicillin	97.22	97.22	No change
Oxacillin	34.37	34.37	No change
Vancomycin	0	0	No change
Teicoplanin	0	Analysis not possible due to the way historical data is stored	
Gentamicin	2.96	5.71	Apparent increase in resistance
Erythromycin	27.71	27.71	No change
Tetracycline	6.51	6.51	No change
Ciprofloxacin	32.42	32.42	No change
Moxifloxacin	21.61	26.63	Apparent increase in resistance
Nitrofurantoin	0.17	0.17	No change
Clindamycin	9.13	51.84 (after removal of ≤0.5mmol/L datapoints 15.94)	Apparent increase in resistance
Trimethoprim	3.8	4.31	Apparent increase in resistance
Chloramphenicol	0.08	0.23	Apparent increase in resistance
Rifampicin	0.85	1.67	Apparent increase in resistance
Quinupristin-Dalfopristin	0	0	No change
Linezolid	0.02	0.02	No change

Conclusions

As countries across Europe move to the new EUCAST breakpoints **we would encourage a look back at local data** in order to anticipate the effect that the change in breakpoints will have on local resistance rates. **While the increase in resistance rates with the adoption of new guidelines is largely anticipated the scale of this for *S. aureus* in Scotland was not clear prior to this analysis.** As resistance data is important for use in developing empirical antibiotic policies **it will be interesting to see if this change has a wider impact.**

Disclosure

Nil to disclose.

Table 3 - % resistances for MRSA isolates only

Drug	% of those tested which are resistant using CLSI breakpoints	% of those tested which are resistant using EUCAST breakpoints	Change
Vancomycin	0	0	No change
Teicoplanin	0	Analysis not possible due to the way historical data is stored	
Gentamicin	8.54	24.27	Apparent increase in resistance
Erythromycin	75.05	75.05	No change
Tetracycline	7.32	7.32	No change
Ciprofloxacin	96.96	96.96	No change
Moxifloxacin	46.66	79.17	Apparent increase in resistance
Nitrofurantoin	0.84	0.84	No change
Clindamycin	29.43	56.05	Apparent increase in resistance
Trimethoprim	8.27	9.71	Apparent increase in resistance
Chloramphenicol	0.13	0.42	Apparent increase in resistance
Rifampicin	2.36	7.41	Apparent increase in resistance
Quinupristin-Dalfopristin	0	0	No change
Linezolid	0	0	No change

References

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