

Introduction

In recent years, there has been an increasing use of azole and other anti-fungal agents. Combined with clearer therapeutic guidelines, this has led to an increased demand for drug monitoring (TDM) and a resultant need for external quality assurance.

The UK National External Quality Assurance Scheme for Antibiotic Assays is a major international provider of EQA services in antibacterial TDM. In April 2012, an EQA service for antifungal TDM was introduced with worldwide uptake. Here we report from the first two years of operation of this service identifying the main methods used in TDM and their relative performance.

Methods

Monthly, four individual samples are spiked with a) itraconazole and its metabolite hydroxyitraconazole, b) posaconazole, c) voriconazole and d) flucytosine. These samples are shipped to participating laboratories which have 21 days to return results by web entry.

Individual results that are more than 30% away from the consensus mean are classed as poor and laboratory performance is assessed on the basis of both accuracy and precision over a six month period.

Laboratories are rated as good if their mean+2SD error score over the 6 months is below 30%, borderline if their score is 30-50% and poor if their score is >50%. Data are shown for September 2012, September 2013 and March 2014.

Results

Twenty-eight laboratories currently participate in the antifungal EQA scheme; 17 in Europe (10 UK), 5 in North America and 6 in Australasia. However, not all laboratories measure the five drugs present in the samples and 21 return results for itraconazole, 15 for hydroxyitraconazole, 25 for posaconazole, 26 for voriconazole and 11 for flucytosine.

The methods used for the assay of each analyte are shown in Table 1, with chromatographic methods (either HPLC or LC-MS) the predominant technique used. *In some cases the method for flucytosine was not known.

Table 1. Methods used for the assay of antifungal agents

Analyte	N	HPLC	LC-MS	Bioassay
Itraconazole	19	53%	47%	0%
Posaconazole	24	50%	42%	8%
Voriconazole	24	46%	50%	4%
Flucytosine*	11	55%	17%	18%

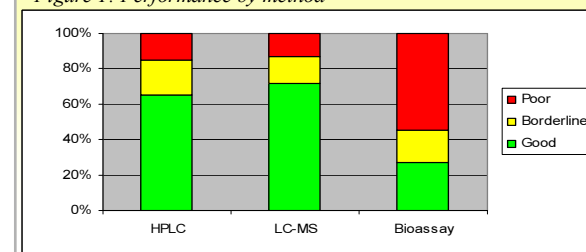
The overall performance of laboratories over the two years is shown in table 2, with most laboratories achieving good performance and little change over time.

Table 2. Performance by analyte

Analyte	Date	Labs N	Laboratory Performance (%)		
			Good	Borderline	Poor
Itraconazole	2012	14	71	8	21
	2013	18	44	44	12
	2014	19	58	10	32
Hydroxy-itraconazole	2012	10	90	10	0
	2013	13	69	16	15
	2014	14	78	14	8
Posaconazole	2012	19	57	22	21
	2013	23	61	21	18
	2014	24	75	8	17
Voriconazole	2012	17	47	36	17
	2013	22	55	23	22
	2014	24	79	12	9
Flucytosine	2012	no data			
	2013	8	87	0	13
	2014	7	100	0	0

The performance of laboratories returning results using the different methods is shown in figure 1, with significantly more laboratories using chromatographic methods achieving good performance than with bioassay. However, although there was a trend for better performance with LC-MS than HPLC, this was not statistically significant ($P > 0.05$; chi-square test)

Figure 1: Performance by method



Conclusions

Overall most laboratories offering antifungal TDM services use either HPLC or LC-MS techniques and achieve broadly equivalent performance, in contrast to those laboratories using bioassay which generally have poorer performance. Few laboratories have consistently poor performance for a given analyte and over the two years the performance of laboratories in the scheme has generally improved.

However, good performance for many analytes is still under 80% and suggesting that improvements in performance are possible and highlight the importance of continued participation in EQA.

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