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Tracking the implementation of NCCLS M100-S12 expanded-spectrum cephalosporin MIC breakpoints for nonmeningeal isolates of *Streptococcus pneumoniae* by clinical laboratories in the United States during 2002 and 2003

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Abstract

Background: The Performance Standards for Antimicrobial Susceptibility Testing, Twelfth Informational Supplement, M100-S12, published by the National Committee for Clinical Laboratory Standards (NCCLS) in January 2002 introduced distinct minimum inhibitory concentration (MIC) interpretative breakpoints for ceftriaxone, cefotaxime, and cefepime for nonmeningeal isolates of *Streptococcus pneumoniae*. Previously, a single set of interpretative breakpoints was used for both meningeal and nonmeningeal isolates.

Methods: To estimate the rate of adoption of the M100-S12 interpretive breakpoints by clinical laboratories, antimicrobial susceptibility test results for ceftriaxone and cefotaxime from nonmeningeal *S. pneumoniae* isolates were studied using data collected from January 2002 to June 2003 by The Surveillance Network® Database – USA (TSN®), an electronic surveillance database.

Results: Of the 262 laboratories that provided data that could be evaluated, 67.6% had adopted the M100-S12 breakpoints one and one-half years after they were published.

Conclusions: The NCCLS M100-S12 recommendation to interpret MICs to expanded-spectrum cephalosporins using two distinct sets of breakpoints for meningeal and nonmeningeal isolates of *S. pneumoniae* was steadily implemented by clinical microbiology laboratories in the United States following their initial publication in January 2002. The use of these new breakpoints more accurately reflects the clinical activities of expanded-spectrum cephalosporins than did the single set of interpretative breakpoints previously used for both meningeal and nonmeningeal isolates.

Background

Ceftriaxone, cefotaxime, and cefepime minimum inhibitory concentration (MIC) interpretive breakpoints for meningeal and nonmeningeal isolates of *Streptococcus pneumoniae* were published in January 2002 by the National Committee for Clinical Laboratory Standards (NCCLS) in their M100-S12 document [1]. Previously, a single set of breakpoints was used to interpret ceftriaxone,

cefotaxime, and cefepime MICs for both meningeal and nonmeningeal *S. pneumoniae* isolates [2]. These breakpoints were initially published in 1996 and remained unchanged through December 2001. For ceftriaxone and cefotaxime, the M100-S12 guidelines advise laboratories to report both meningeal and nonmeningeal interpretations for pneumococcal isolates recovered from body sites other than cerebrospinal fluid. Ceftriaxone and cefotaxime MICs for isolates from cerebrospinal fluid should be reported with meningitis interpretative criteria only. Since cefepime does not have an approved indication for meningitis in the U.S., the recommendation is to report only the nonmeningitis interpretations for this agent [1]. A previous study based on historical data showed the M100-S12 ceftriaxone and cefotaxime interpretive breakpoints for nonmeningeal isolates decreased the number of *S. pneumoniae* isolates interpreted as intermediate by 10% and as resistant by 3 to 4% [3]. A second study, by Jones and colleagues, showed a 9.1 to 13.0% increase in susceptibility to cefotaxime, ceftriaxone, and cefepime using the M100-S12 nonmeningeal interpretive criteria [4]. The current study was conducted to determine the rate at which a set of clinical laboratories in the United States adopted the M100-S12 interpretive breakpoint changes from January 2002 to June 2003.

Methods

The Surveillance Network Database – USA (TSN), an electronic database that collects MICs, MIC categorical interpretation data, and other microbiology laboratory data from 326 U.S. clinical microbiology laboratories, was used as the source of antimicrobial susceptibility test data [5]. Nonmeningeal isolates of *S. pneumoniae* were limited to those isolated from blood and respiratory tract sources. Respiratory tract isolates included those from both the upper and lower respiratory tracts. Ceftriaxone and cefotaxime MICs and corresponding susceptible, intermediate, and resistant interpretations were cross-referenced to determine if laboratories used the M100-S11 [2] or the M100-S12 [1] nonmeningeal *S. pneumoniae* MIC interpretive breakpoints to interpret the MICs they generated. Cefepime was not included in this analysis as only 16 laboratories reported results (n = 572) for this agent. Sixty-four TSN laboratories did not report assessable data for ceftriaxone or cefotaxime during the time period of the study. Laboratories were not assessable if they did not test cefotaxime or ceftriaxone against *S. pneumoniae* or did not report MIC values of 1 or 2 μg/ml. The breakpoint standard used could only be inferred when MIC values of 1 or 2 μg/ml were obtained.

In addition, a questionnaire was sent to laboratories in September 2002, inquiring if the M100-S12 nonmeningeal breakpoints were in use at their laboratory. Laboratories that had not adopted the new breakpoints were asked why the changes had not been implemented, if they would be implemented, and when they would be implemented. Only laboratories that had assessable MIC data and returned a completed questionnaire were included in the analysis of the questionnaire data set.

To determine the effect of not adopting the new interpretations, MICs from 12,827 nonmeningeal isolates of *S. pneumoniae* tested against ceftriaxone and cefotaxime from January 2002 to June 2003 were evaluated and susceptible, intermediate, and resistant interpretation rates for ceftriaxone and cefotaxime were calculated using both the M100-S11 and M100-S12 breakpoints.

Results

Two hundred sixty-two TSN laboratories were included in the overall analysis. One hundred and seventy-four laboratories were included in the analysis for ceftriaxone and 200 laboratories were included for cefotaxime. Table 1 compares the number of laboratories with interpretable data that were using the M100-S11 or M100-S12 criteria by quarter from January 2002 to June 2003. Cross-referencing quantitative (MICs) and qualitative (susceptible, intermediate, resistant) data showed that at the end of January 2002, 13.1% (11/84) of laboratories reporting ceftriaxone results and 17.4% (22/126) of laboratories reporting cefotaxime results used the new M100-S12 breakpoints (data not shown). The proportion of laboratories using the M100-S12 breakpoints for ceftriaxone and cefotaxime increased an average of 3% per month from January 2002 to June 2003. By September 2002, 36% (90/250) of laboratories reporting results for expanded-spectrum cephalosporins used the M100-S12 breakpoints.

One hundred seventy-three of 262 laboratories (66.0%) responded to the questionnaire sent in September 2002. Among the laboratories responding to the questionnaire, 53.2% (92/173) stated they were using the M100-S12 breakpoints and 46.8% (81/173) of laboratories had not yet adopted the new breakpoints. Of the respondents that were not using the M100-S12 breakpoints, nearly one-half attributed this to difficulty in modifying their laboratory information system (LIS) or to not having information systems staff available to make the necessary changes. Thirty-six percent (29/81) of the responding laboratories that stated they were not currently using the new breakpoints reported that they planned to adopt the new breakpoints by the end of 2002.

By the end of 2002, 42.6% (109/256) of laboratories with data that could be evaluated had adopted the M100-S12 nonmeningeal *S. pneumoniae* cefotaxime or ceftriaxone interpretive breakpoints and 57.4% (147/256) of laboratories continued to use the M100-S11 breakpoints. The laboratories that adopted the M100-S12 breakpoints

Table 1: Implementation of NCCLS M100-S12 MIC breakpoints for expanded-spectrum cephalosporins tested against nonmeningeal isolates of *S. pneumoniae* by US clinical laboratories from January 2002 to June 2003

Antimicrobial agent(s)	Quarter of 2002 and 2003	Total No. of laboratories with assessable data	Number of laboratories (%) using the following breakpoints:			
			M100-S11		M100-S12	
			no.	(%)	no.	(%)
Ceftriaxone and/or cefotaxime	January-March 2002	216	168	(77.8)	48	(22.2)
	April-June 2002	231	157	(68.0)	74	(32.0)
	July-September 2002	250	160	(64.0)	90	(36.0)
	October-December 2002	256	147	(57.4)	109	(42.6)
	January-March 2003	260	135	(51.9)	125	(48.1)
	April-June 2003	262	85	(32.4)	177	(67.6)
Ceftriaxone	January-March 2002	119	93	(78.2)	26	(21.8)
	April-June 2002	135	82	(60.7)	53	(39.3)
	July-September 2002	163	94	(57.7)	69	(42.3)
	October-December 2002	166	92	(55.4)	74	(44.6)
	January-March 2003	172	78	(45.3)	94	(54.7)
	April-June 2003	174	82	(47.1)	92	(52.9)
Cefotaxime	January-March 2002	158	142	(89.9)	16	(10.1)
	April-June 2002	168	143	(85.1)	25	(14.9)
	July-September 2002	186	159	(85.5)	27	(14.5)
	October-December 2002	196	141	(71.9)	55	(28.1)
	January-March 2003	200	137	(68.5)	63	(31.5)
	April-June 2003	200	96	(48.0)	104	(52.0)

included 44.6% (74/166) of laboratories reporting ceftriaxone and 28.1% (55/196) of laboratories reporting cefotaxime. By June 2003, 67.6% (177/262) of laboratories with data that could be evaluated had adopted the M100-S12 nonmeningeal *S. pneumoniae* cefotaxime or ceftriaxone interpretive breakpoints and 32.4% (85/262) of laboratories continued to use the M100-S11 breakpoints. The laboratories that adopted the M100-S12 breakpoints included 52.9% (92/174) of laboratories reporting ceftriaxone and 52.0% (104/200) of laboratories reporting cefotaxime. One hundred and twelve of 262 laboratories tested both ceftriaxone and cefotaxime, 88 laboratories tested only cefotaxime, and 62 laboratories tested only ceftriaxone in April-June 2003.

Ceftriaxone (n = 7,940) and cefotaxime (n = 4,887) MICs for nonmeningeal *S. pneumoniae* isolates were interpreted by applying both the M100-S11 and the M100-S12 interpretive criteria (Table 2). The proportion of isolates interpreted as susceptible increased by 9.9% for ceftriaxone and 13.5% for cefotaxime when interpreted using M100-S12 nonmeningeal breakpoints. The proportion of isolates interpreted as intermediate decreased by 7.6% and 10.9% and the proportion of isolates interpreted as resistant decreased by 2.2% and 2.6% for ceftriaxone and cefotaxime, respectively, when interpreted using M100-S12 nonmeningeal breakpoints.

Table 2: Susceptibility of nonmeningeal isolates of *S. pneumoniae* recovered from January 2002 to June 2003 to expanded-spectrum cephalosporins using both M100-S11 and M100-S12 NCCLS standards

Antimicrobial agent	Total no. of isolates	NCCLS standard	% Susceptible	% Intermediate	% Resistant
Ceftriaxone	7,940	M100-S11	86.9	9.9	3.2
		M100-S12	96.8	2.3	1.0
Cefotaxime	4,887	M100-S11	82.4	13.5	4.1
		M100-S12	95.9	2.6	1.5

Conclusions

Based on MIC and MIC interpretation data submitted by participating TSN laboratories, we conclude that 67.6% of all laboratories with interpretable data for *S. pneumoniae* tested against expanded-spectrum cephalosporins had implemented the M100-S12 breakpoints by June 2003. Approximately one-half (52.9%) of the laboratories with interpretable data for *S. pneumoniae* and ceftriaxone and 52.0% of laboratories reporting cefotaxime had implemented the M100-S12 breakpoints by June 2003. The adoption of the M100-S12 breakpoints is more difficult for laboratories to implement than previous NCCLS interpretive breakpoints as laboratory information systems were not designed to accommodate reporting multiple breakpoints for a single organism-antimicrobial agent combination. Also, as this is the first instance of multiple specimen source-specific interpretive breakpoints for a single organism-antimicrobial agent combination, education of laboratory staff and clinicians was required, likely further complicating the implementation of the new criteria. Continued use of the M100-S11 breakpoints for expanded-spectrum cephalosporins may lead to the reporting of false in vitro non-susceptibility of nonmeningeal *S. pneumoniae* isolates. Application of the new interpretative criteria, with higher breakpoints for nonmeningeal isolates, will result in an increase in the number of *S. pneumoniae* isolates reported as susceptible to cefotaxime and ceftriaxone (Table 2) [2,4]. Based on analysis of data from January 2002 to June 2003, approximately 10–15% more nonmeningeal isolates will be reported as susceptible when the M100-S12 breakpoints are used. The publication and use of the M100-S12 breakpoints to interpret meningeal and nonmeningeal isolates of *S. pneumoniae* will more accurately reflect the clinical activities of these agents where the use of an expanded-spectrum cephalosporin is indicated.

Authors' contributions

RNM, DCD, MEJ, CT, DFS, and JAK each contributed to the study design, collection and analysis of data, and manuscript writing.

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