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Inability to Adequately Control Antimicrobial Agents on AutoMicrobic System Gram-Positive and Gram-Negative Susceptibility Cards

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The Vitek Gram-Positive Susceptibility Card (GPS) and Gram-Negative General Susceptibility Plus Card (GSC Plus) were tested on the AutoMicrobic System (AMS) 50 times each with the recommended control organisms. Only 1 drug (chloramphenicol) of 11 on the GPS and 1 (gentamicin) of 10 on the GSC Plus could be adequately controlled, leaving unsubstantiated the results obtained with patient isolates on the remaining 19 antimicrobial agents.

The National Committee for Clinical Laboratory Standards has consistently indicated, as they have in their most recent standard (3), that for each antimicrobial agent tested to determine a MIC endpoint, at least one control strain should provide on-scale endpoints, plus or minus one twofold dilution from the known modal value. The ideal control strain should have MIC endpoints near the middle of the range of drug concentrations tested. For each antimicrobial agent, 95% of the MICs obtained should be within ± one dilution of the modal MIC (1). Batches of test panels in which the control MIC responses fall outside of the expected ranges are to be rejected after confirmation of the problem (1, 3). The stated objectives of efficient control procedures are to monitor the precision and accuracy of the test procedure, the performance of reagents, and the performance of individuals involved with the technology (3).

(This work was presented in part at the 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., 6 to 10 October 1984 [J. A. Kellogg, Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 1984, 1202, p. 303].)

In Vitek (Hazelwood, Mo.) package inserts, both the GPS and the GSC Plus have been described as ". . . a miniaturized and abbreviated version of the doubling dilution technique for the MIC by the microdilution method." During an evaluation of these two susceptibility cards, it was noticed that many of the drugs could not be adequately controlled by using the procedures and strains mentioned in the product inserts. To document the extent of the problem, the control data accumulated during the period of evaluation were analyzed.

The control strains used in the study (*Streptococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 29213 for the GPS and *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 for the GSC Plus) were those indicated in the Vitek product inserts. Each control strain was inoculated to 50 susceptibility cards over the 15-month period of study, by the procedures outlined in the instructions of the manufacturer. Eight lots of each type of card were used. The cards were incubated, read, and interpreted within the AMS (Vitek Inc.). Results were finalized and automatically printed after 3 to 10 h.

An antimicrobial agent response of a control strain was considered acceptable if it fell within a Vitek-predicted range that consisted of no more than three consecutive twofold dilutions. A control response was considered unacceptable if it fell outside of a Vitek-predicted range or if the Vitek-predicted range was less than or equal to the lowest drug concentration reported (an imprecise endpoint), greater than the highest concentration reported, or more than three consecutive twofold dilutions.

Only one antimicrobial agent (chloramphenicol [Table 1]) on the GPS and one antimicrobial agent (gentamicin [Table 2]) on the GSC Plus could be controlled 95% of the time or more. The remaining 10 drugs on the GPS could not be controlled on any day tested, whereas the other 9 drugs on the GSC Plus resulted in acceptable on-scale endpoints less than 95% of the time.

The use of two control strains with the 11 GPS antimicrobial agents provided 22 drug response endpoints. Of these, only two (those for chloramphenicol) included a range of three consecutive, on-scale doubling dilutions (Table 1), as specified by the National Committee for Clinical Laboratory Standards. The remaining responses consisted of AMS category calls (very susceptible, moderately susceptible, moderately resistant, and very resistant) made up of unacceptable MIC ranges or endpoints. For ampicillin and penicillin, the *Streptococcus faecalis* control responses covered a range of six and nine twofold dilutions, respectively, whereas the *Staphylococcus aureus* responses were off-scale high. With cephalothin, clindamycin, gentamicin, tetracycline, and vancomycin, the *Streptococcus faecalis* control responses also covered too broad a range of twofold dilutions, whereas the *Staphylococcus aureus* responses were less than or equal to the lowest concentration reported (cephalothin, clindamycin, and tetracycline) or covered too broad a range (gentamicin and vancomycin). For erythromycin, nitrofurantoin, and oxacillin, the *Staphylococcus aureus* responses were each less than or equal to the lowest concentration reported, whereas *Streptococcus faecalis* responses covered too broad a range (erythromycin), were at the low end of the range (nitrofurantoin), or were not supplied by Vitek in the GPS instructions (oxacillin).

The use of two control strains on the 10 GSC Plus antimicrobial agents provided 20 drug response endpoints. Of these, only four (*E. coli* versus ampicillin, cephalothin, and chloramphenicol; *P. aeruginosa* versus gentamicin) included a range of three consecutive, on-scale twofold dilutions (Table 2). Eight Vitek-predicted endpoint ranges were provided as two or three twofold dilutions, the lowest

TABLE 1. Responses of control strains to AMS GPS drugs

Drug	Range of drug interpretations (μg/ml)	MIC endpoints (μg/ml)					
		Streptococcus faecalis ATCC 29212			*Staphylococcus aureus* ATCC 29213		
		Vitek predicted		Result sought[b] (observed)[c]	Vitek predicted		Result sought[b] (observed)[c]
		Category[a]	Range		Category[a]	Range	
Ampicillin	≤0.25–>128	MS	0.5–16	CC	VR	>128	CC
Cephalothin	≤2–>256	MS-MR	4–256	CC	VS	≤2	CC
Chloramphenicol	≤1–>16	MS	2–8	2–8 (98)	MS	2–8	2–8 (100)
Clindamycin	≤0.5–>32	MS-MR	1–32	CC	VS	≤0.5	CC
Erythromycin	≤0.5–>32	VS-MS	≤0.5–4	CC	VS	≤0.5	CC
Gentamicin	≤0.5–>16	MS-MR	1–16	CC	VS-MS	≤0.5–4	CC
Nitrofurantoin	≤32–>128	VS	≤32	CC	VS	≤32	CC
Oxacillin	≤2–>2	NA	NA		VS	≤2	CC
Penicillin	≤0.03–>256	MS	0.06–16	CC	VR	>256	CC
Tetracycline	≤1–>64	MS-MR	2–64	CC	VS	≤1	CC
Vancomycin	≤0.5–>64	MS	1–16	CC	VS-MS	≤0.5–16	CC

[a] VS, Very susceptible; MS, moderately susceptible; MR, moderately resistant; VR, very resistant. NA, Not applicable; response not supplied by Vitek.
[b] MIC numbers or ranges sought were only those which, when obtained, would provide evidence of acceptable performance according to the guidelines of the National Committee for Clinical Laboratory Standards. CC, Could not control due to lack of any on-scale endpoints or too broad a range of Vitek-predicted endpoints.
[c] Numbers within parentheses indicate the percentage of 50 days tested that acceptable, on-scale results were obtained.

concentration of which was also the lowest concentration reported for the drug and therefore not a precise endpoint. For ampicillin, cefamandole, cefoxitin, cephalothin, chloramphenicol, and tetracycline, the Vitek-predicted GSC Plus responses for the *P. aeruginosa* control strain were off-scale high, whereas the desired responses indicating on-scale, within-range endpoints for *E. coli* were achieved less than 95% of the time (ampicillin, cefoxitin, cephalothin, chloramphenicol, and tetracycline), or the *E. coli* response was less than or equal to the lowest concentration reported (cefamandole). For amikacin, carbenicillin, and tobramycin, acceptable responses for *P. aeruginosa* were achieved less than 95% of the time (although they were very close with tobramycin), whereas those for *E. coli* were never achieved (amikacin), were less than or equal to the lowest concentration reported (carbenicillin), or also were obtained less than 95% of the time (tobramycin).

The GPS card currently available has been improved to the point that there are on-scale endpoints (± one dilution) with at least one control organism for 5 of the 11 drugs. The Gram-Negative Susceptibility Card which replaced the GSC Plus Card used in this study has control deficiencies identical to those reported here. In addition, the control endpoints for trimethoprim-sulfa (which has been added to the Gram-Negative Susceptibility Card) as listed in the product insert are too low (*E. coli*) or high (*P. aeruginosa*) to provide interpretable data.

An evaluation of any new antimicrobial agent response test system should include, among other considerations, the investigation of the ability of the individual laboratory to periodically and cost-effectively control the performance of each drug in the new system. Even if the system performs well during a parallel study with a reference method, the accuracy of the ongoing performance with clinical isolates cannot be assured without periodic, effective controls. The inability to control antimicrobial agent responses is not a problem confined solely to the AMS. To create room for an increasing number of new antibiotics, manufacturers of other drug response test panels are supplying the antimicrobial agents in such a limited number of test concentrations that effective control of the drugs is often difficult or impossible (2). A review of the product insert for the Autobac MIC disks (General Diagnostics, Warner-Lambert Co., Morris Plains, N.J.) and the manual for the Advantage (Abbott Laboratories, Irving, Tex.) indicates control deficiencies in these automated systems similar to those of the AMS. There is a distinct question as to whether any of the commercially available MIC test systems which cannot be adequately

TABLE 2. Responses of control strains to AMS GSC Plus drugs

Drug	Range of drug interpretations (μg/ml)	MIC endpoints (μg/ml)			
		Escherichia coli ATCC 25922		*Pseudomonas aeruginosa* ATCC 27853	
		Vitek-predicted range	Result sought[a] (observed)[b]	Vitek-predicted range	Result sought[a] (observed)[b]
Amikacin	≤2–>16	≤2–4	4 (0)	≤2–8	4–8 (68)
Ampicillin	≤0.25–>16	2–8	2–8 (86)	>16	CC
Carbenicillin	≤32–>128	≤32	CC	≤32–64	64 (22)
Cefamandole	≤2–>16	≤2	CC	>16	CC
Cefoxitin	≤2–>16	≤2–4	4 (74)	>16	CC
Cephalothin	≤2–>16	4–16	4–16 (92)	>16	CC
Chloramphenicol	≤1–>8	2–8	2–8 (82)	>8	CC
Gentamicin	≤0.5–>4	≤0.5–1	1 (0)	1–4	1–4 (96)
Tetracycline	≤1–>8	≤1–4	2–4 (26)	>8	CC
Tobramycin	≤0.5–>4	≤0.5–2	1–2 (82)	≤0.5–2	1–2 (94)

[a] MIC numbers or ranges sought were only those which, when obtained, would provide evidence of acceptable performance according to the guidelines of the National Committee for Clinical Laboratory Standards. CC, Could not control due to lack of any on-scale endpoints.
[b] Numbers within parentheses indicate the percentage of 50 days tested that acceptable, on-scale results were obtained.

controlled are suitable for routine use in a clinical microbiology laboratory when the accuracy of results obtained with patient isolates cannot be substantiated.

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