AST breakpoints: a case of not aging gracefully

Karen Titus

April 2020—When Romney Humphries, PhD, D(ABMM), was section chief for clinical microbiology at UCLA Medical Center, it wasn't unusual for her to take calls from worried clinicians who were concerned about patients who'd been transferred to the hospital for a higher level of care. The accompanying laboratory reports would indicate the presence of an isolate that was susceptible to a particular drug. But when Dr. Humphries' lab did its own testing, the results were strikingly different: The isolate was drug resistant.

When Dr. Humphries would call the first lab, the reason for the discrepancy became clear. "Sure enough, they were using old breakpoints," says Dr. Humphries, who is now chief scientific officer, Accelerate Diagnostics, and professor of pathology, University of Arizona.

Dr. Romney Humphries and others are working to draw attention to obsolete breakpoints and urge labs and manufacturers to adopt current breakpoints. "It sends the wrong message about susceptibility testing," she says, "if things are being misinterpreted with breakpoints that are incorrect." (Photo: Troy Hollar)

Unlike Bordeaux, antimicrobial susceptibility test breakpoints do not age well. Over time, they might no longer be clinically useful, even as they continue to be used clinically.

Dr. Humphries' anecdote is, of course, just that—an anecdote. But the problem is hardly unique to Los Angeles. How about the whole state of California?

Here, too, Dr. Humphries has something to say. As part of a survey done in that state (Humphries RM, et al. *Clin Infect Dis.* 2018; 66[7]:1061–1067), "We phoned every single clinical lab in the state of California to find out what breakpoints they were using," she says. The answer: Some 30 percent were using obsolete breakpoints.

The study did not address the number of beds served. "When we went back and looked, some of the biggest labs in the state were using obsolete breakpoints," says Dr. Humphries, a member of the CAP Microbiology Committee.

“Just because it was only 30 percent, that doesn’t mean it’s not the majority of patients being tested.”

More recently, data collected through CAP proficiency testing raised further concerns about the use of obsolete breakpoints. Dr. Humphries declines to offer specifics, pending publication, but says, “It’s pretty striking.”

Undoubtedly she doesn’t mean “striking” in a good way.

That’s why Dr. Humphries and others are amping up efforts to draw attention to obsolete breakpoints and urge laboratories and manufacturers of antimicrobial susceptibility testing devices to adopt current breakpoints.

Their work has gained more urgency recently with updates of several breakpoints in 2019 and 2020: ciprofloxacin, levofloxacin (Enterobacterales, *Pseudomonas aeruginosa*); daptomycin (*Enterococcus* spp.); ceftaroline (*Staphylococcus aureus)*; and colistin (*P. aeruginosa, Acinetobacter* spp.).

Dr. Simner

Trish Simner, PhD, D(ABMM), minces no words when she explains the importance of keeping up to date. Breakpoints are revised to ensure patient care and safety, and to limit and reduce the spread of antimicrobial resistance, says Dr. Simner, director of the medical bacteriology laboratory, Johns Hopkins University School of Medicine, and associate professor, Department of Pathology. Case in point: A study in Southern California (Bartsch SM, et al. *J Clin Microbiol.* 2016;54[11]:2757–2762) found that for each year laboratories delayed updating their carbapenem breakpoints for Enterobacterales, an additional 6,000 patients were predicted to become colonized by carbapenem-resistant Enterobacterales.

The gravity of the situation is hardly news to labs, which have long been concerned about drug-resistant organisms. “The big problem is that many labs, and even institutional management, don’t understand that revisions to breakpoints have occurred,” says Dr. Simner, who is a member of the Clinical and Laboratory Standards Institute’s AST subcommittee as well as the CAP Microbiology Committee.

The other challenge is figuring out what to do once a breakpoint has been revised. “You can’t simply start using the updated breakpoint without validating or verifying that your current” AST device accurately uses a new breakpoint interpretation, says Dr. Simner.

Breakpoint revisions don’t happen overnight, though it may seem that way to those who are grappling with making the changes.

Dig a little deeper and it soon becomes evident that nearly every aspect of breakpoint revisions involves multiple steps that unfold over time. In the best of circumstances, that can mean thoughtful change. In other cases, it gives way to confusion and what might pass for torpor when it comes to updates. Who, exactly, is responsible for doing what?

Breakpoints in the United States are set by CLSI and FDA’s Center for Drug Evaluation and Research. When CLSI (which began publishing breakpoints in 1972) revises a breakpoint, it creates a rationale document to explain its reasoning. CLSI submits the document to the FDA, which reviews it and responds (usually within six months). “In general, they tend to agree,” says Dr. Simner. But not always. When the agency does agree, the new breakpoint is recognized on the FDA’s susceptibility testing interpretive criteria, or STIC, website (www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria).

Once a breakpoint is revised by CLSI, FDA, or both, commercial AST device manufacturers decide how to respond.

Changing breakpoints isn't a simple task for manufacturers, any more than it is for laboratories, and some react more swiftly than others. In the best-case scenario, this can be a yearlong process.

In others, it's been a decade.

"We know this based on our experience with the cephalosporin breakpoints that were changed in 2010 for the Enterobacterales," says Dr. Simner. "There are still some commercial [AST] systems out there that have not updated to the current breakpoints."

It may, in fact, surprise some to know that manufacturers aren't required to update their breakpoints after their devices have received FDA clearance, says Dr. Simner, nor is there a push from an accreditation standpoint to ensure labs are using current breakpoints.

"The challenge we still face," says Dr. Humphries, "is companies *still* haven't updated all of their breakpoints. And we know there's a huge, *huge* misunderstanding among clinical labs, where they think, *If my test is FDA cleared, that must mean it's using the most up-to-date breakpoints.*"

That places the onus on labs to do verification and validation studies to update breakpoints manually on their devices, Dr. Humphries says. Whether that's the best use of a lab's resources is also open to discussion, she says. "They should be spending their time doing patient testing," she argues.

But that might mean labs are using obsolete breakpoints. "We see time and time again in our proficiency testing Surveys, where it comes up as a challenge," Dr. Humphries says. "It really sends the wrong message about susceptibility testing if things are being interpreted with breakpoints that are incorrect."

Assumptions, like rumors, float easily in all directions. Just as labs might be taking it on faith that their AST devices use current breakpoints, clinicians are apt to make suppositions about test results. "A lot of our clinical colleagues rely on the lab to keep up to date with this," says Dr. Simner, and for AST results "to reflect the updated breakpoints in the interpretations we apply in our reports."

All of which "just creates the perfect storm," Dr. Simner says. "Here we are 10 years after the carbapenem breakpoints were lowered, and a lot of labs still haven't implemented those changes."

Updating breakpoints might be laboratory medicine's equivalent of sorting through one's basement. Yes, it needs to be done. Someone needs to start, but who? And how? As Dr. Simner puts it, "There's really no one pushing from any direction to make sure this happens."

So where to begin? Each lab's starting line might be different.

"You need to make sure you know what breakpoints you're applying," Dr. Simner says. While that may sound obvious, she acknowledges, "I can guarantee there are many labs that don't. There are a lot of assumptions by laboratories at all levels," says Dr. Simner, "from small community hospitals to large academic centers, that the breakpoints that their automated systems are applying are the most up to date."

Finding that information may also sound straightforward, she continues, but that's not always the case. "A lot of the time that information is hidden within the automated system and the expert rules." Labs can either try to figure it out on their own system, Dr. Simner says, or call their commercial vendor.

Once the labs have that information, they should turn to the most recent CLSI M100 document (the 30th edition was released in February), which is available online, and free (https://j.mp/2UEHgtj). That wasn't always the case, Dr. Simner says, "but now there should be no barrier to having the most up-to-date document."

Labs should also look at the FDA's STIC website. The most up-to-date breakpoint would be one that is recognized by both CLSI and FDA, says Dr. Simner. In most cases, CLSI leads the charge. Last year, she notes, CLSI updated the fluoroquinolone breakpoints for Enterobacteriaceae and *Pseudomonas aeruginosa* about six months before FDA did. That's not to say a laboratory needs to wait until a breakpoint appears on both sites. "For the most part, larger

clinical labs will follow the M100 documents as they become available," Dr. Simner says.

CLSI updates the M100 document annually, with changes listed at the beginning, and offers webinars to explain key revisions. The M100 document also provides additional information about media, incubation times, etc., Dr. Simner notes, while the FDA site simply provides interpretive criteria based on its evaluations of the new breakpoints.

If they're not already doing so, labs should check the CLSI and FDA breakpoints annually "to help them prioritize what they might want to implement," Dr. Simner recommends.

Once they've figured out the breakpoints they're using, some labs may find they're lagging a bit, to put it delicately. "These might be labs that haven't done this since 2010," Dr. Simner says.

"If they're one of those labs," she continues, "they need to work with institutional leadership and some of their clinical colleagues," such as the antimicrobial stewardship team, infection disease specialists, pharmacists, or some other clinical champion to help them make the changes.

That's key, she says, "because if labs have not kept up to date with this, the amount of work needed to update this could be quite overwhelming." (The longer you've been avoiding those boxes in the basement . . . .)

Regardless of an institution's size or breakpoint savvy, working with clinical colleagues is crucial. At Johns Hopkins, says Dr. Simner, she and her lab colleagues work with the infection control team as well as the antimicrobial stewardship team, among others. "It's a close-knit group."

In fact, she says, "Each lab should know or get to know their antimicrobial stewardship lead and have these conversations with them," if they haven't already. (The Joint Commission has mandated new antimicrobial stewardship standards in recent years.)

It's helpful, she says, for labs to talk to their clinician and pharmacist colleagues and understand the importance of a particular breakpoint change. She says she speaks with her pharmacy colleagues regularly, updating them on upcoming breakpoint revisions and discussing how to implement them. The updated fluoroquinolone breakpoints were a high priority for her pharmacists, she says. Because hers is a large, high-volume lab, they decided it would be too resource-intensive to set up a disk or gradient diffusion method as an interim step; instead, they waited to obtain a commercial AST panel with updated breakpoints. "There's always open communication between the two teams, prioritizing the changes and how to make them happen—what works for both pharmacy and the lab in terms of workflow and resources."

Dr. Simner has also found it critical to let institutional leadership know that breakpoints are a patient safety issue, as a way to garner resources. Labs "can be stuck in a situation where it isn't a high priority unless something big happens. Make them understand the implications of not using the proper breakpoints." No one wants carbapenem-resistant gram-negative organisms to spread undetected within a facility.

The work involved in updating breakpoints is real but not insurmountable. The basic steps—knowing what breakpoints the lab is currently using, and then putting together a strategy for doing updates as needed—is half the battle, observers say. After that, resources are available, especially for labs that may not have a PhD or MD laboratory director to help guide the process.

As Isabella Martin, MD, puts it, "We're trying to lower the activation energy required to implement these changes."

The CDC offers an excellent resource in the free isolates, which can be ordered online through the CDC and FDA Antibiotic Resistance Isolate Bank (www.cdc.gov/drugresistance/resistance-bank/index.html; ARbank@cdc.gov). The California Department of Public Health website (www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/Antibiotics.aspx) also offers resources, developed by Janet Hindler, MCLS, MT(ASCP), which include step-by-step instructions, worksheets, and troubleshooting instructions on how to perform a validation study. While designed for carbapenems and the Enterobacterales, the suite of tools can be further adapted for other breakpoint validations,

says Dr. Simner.

In addition to the previously characterized CDC isolates, “You also want to make sure that you’re testing a good variety of isolates from your own local patient population, and know you’re comparing your new method with lower breakpoints to another reference platform,” says Dr. Martin, medical director of microbiology, Dartmouth-Hitchcock Medical Center, and assistant professor of pathology, Geisel School of Medicine, Dartmouth College.

Labs might find the work worrisome, Dr. Simner acknowledges. To validate a modified breakpoint on a system that’s used every day requires a minimum of 30 isolates and staggering the breakpoints. “You’re really looking at categorical agreement,” she says. For a new system, 30 isolates is again the minimum; it also requires spanning breakpoints, as well as looking at both categorical and essential agreements. Bringing in a new disk for disk diffusions, or a new gradient diffusion strip, requires less-intense verification.

“There are some nuances to validation and verification studies,” Dr. Simner says, and the guidance isn’t always clear. The CLSI M52 document is helpful, but some labs might find its open-endedness disconcerting. “That’s why we’re creating more resources—to remove the question marks and tell labs: Here’s the FDA isolate panel bank you should order; here’s how you need to approach your scenario; here’s what your results should look like; here is the exact validation outline you should pursue.”

Dr. Humphries promises more webinars, as well as feedback through PT write-ups, which highlight every suspected use of an obsolete breakpoint. CLSI webinars and newsletters, both current and past, are another useful source of information, she says.

Smaller labs may feel like they’re at a disadvantage when it comes to updating breakpoints, says Dr. Martin, who is a member of the CAP Microbiology Committee. That might be especially true for community hospitals, she says, “where you don’t have a dedicated microbiologist or even a dedicated microbiology supervisor. You have people who are more a Jack- and Jill-of-all-trades, who are very good at what they do, but it becomes a little more challenging to keep up with some of these nuances.”

‘If we’re lowering breakpoints for the carbapenems, we start to have more isolates that test as carbapenem resistant.’ Isabella Martin, MD

Nevertheless, “It can be broken down into manageable pieces,” she says, offering her own experiences at Dartmouth as evidence.

She and her lab colleagues recognized that their breakpoints weren’t current, but they, like many labs, faced chronic staff shortages as well as competing priorities within the lab. Little wonder updating breakpoints kept

getting moved to the back burner.

In 2016–2017, the lab selected new panels to validate for new carbapenem and cephalosporin breakpoints. “It took us a year to do the validation and get everything built into our LIS,” says Dr. Martin.

At the same time, the laboratory was adopting MALDI-TOF, so it wasn’t until 2019 that the lab went live with its new panel and lower breakpoints.

Unfortunately, that wasn’t the end of the story. That same year the breakpoints for fluoroquinolones were lowered. “As it turned out, our new panels did not have dilutions that were low enough for the new breakpoints,” Dr. Martin says.

That’s why the lab has yet to adopt those breakpoints. For now, Dr. Martin says, the lab will use the old breakpoints but report results with a comment to inform clinicians that ciprofloxacin and levofloxacin should be used with caution in critically ill patients.

That approach isn’t foolproof. “That’s always the worry with adopting a ‘solution’ where you’re depending on a clinician to read a comment,” Dr. Martin says. “I think there’s a lot of misunderstanding about susceptibility testing on the part of many clinicians.” She considers her lab to be fortunate, since their infectious disease colleagues at Dartmouth-Hitchcock are well versed in the nuances of testing and actively seek out discussions with her. “But for the broader population of clinical providers, there’s a need to educate.”

One unintended consequence of changing breakpoints: In changing the panels, “we lost a drug or two from our old panels,” says Dr. Martin, a change that was especially concerning to urologist colleagues. “We hadn’t anticipated all the ramifications of what the new panels would mean, even though we had vetted those panels with our antimicrobial stewardship and infectious disease colleagues.”

She also points to another consideration: “If we’re lowering breakpoints for the carbapenems, we start to have more isolates that test as carbapenem resistant,” Dr. Martin says. That requires follow-up, “which means an increased volume of tests for carbapenemase production.” They’re in a low-prevalence area, so they currently send those to their state public health laboratory for further evaluation.

Updating breakpoints, clearly, is necessary, doable, yet complicated. Dr. Humphries is sympathetic to those who feel intimidated and offers this bit of reassurance: “Susceptibility testing is not a chemistry test,” she says. “You’re dealing with living organisms, and like any living organism, the bacteria can misbehave a little bit sometimes.

“One of the biggest things I hear—and I continue to hear it—is people expect perfect when they do these transitions, and that’s just not the reality,” Dr. Humphries continues. “So labs need to be thoughtful about understanding what are the most important drugs being used at your institution.” In short, that means “just using some common sense, and discussing with the clinicians and pharmacy how these tests are being used.”

“If we expect perfect performance,” she says,” it’s never going to happen.”

Given that no one actually embraces the use of obsolete breakpoints, curious minds might wonder: Why has it been so hard to spur change? Why does every action seem to trigger an equal and opposite inaction, to misquote Newton?

As is so often the case, a little history is instructive.

In late 2016, president Barack Obama signed the 21st Century Cures Act into law, which allowed the FDA to be more nimble in updating breakpoints, explains Dr. Humphries.

Prior to that, the FDA didn’t have a mechanism to recognize CLSI breakpoints, says Dr. Humphries, who works with CLSI staff to write rationale documents. Breakpoints were included in the drug prescribing information, and whenever CLSI updated a breakpoint, the FDA had to do its own due diligence, research, and evaluation to see if the drug sponsor would be willing to update the breakpoint. The Act removed breakpoints from the drug labeling

and put them on the FDA website, which allowed the FDA to do a couple of things, says Dr. Humphries.

“First, it allowed them to not be so beholden to the pharmaceutical companies when they make updates,” she says.

Second, the FDA could now distinguish between a drug’s approval for treatment, “and what makes sense for susceptibility testing. That distinction is important because many drugs are used off-label,” says Dr. Humphries, yet still have CLSI breakpoints.

Another historical chapter involves the pace of breakpoint revisions. In addition to the changes in 2019 and 2020, there’s been an uptick since 2010. For many antimicrobials still in use, the first breakpoints were published in the 1980s and 1990s, Dr. Martin says. Matters were fairly quiet in the early aughts, as she puts it, and then since 2010 there have been “tweaks to various breakpoints every year or two.”

In some cases, revisions occur when a new antimicrobial mechanism is recognized. Prior to 2010, says Dr. Simner, there were very few carbapenem-resistant Enterobacterales. When that began to change, the previous breakpoints were set quite high and thus could not identify some carbapenemase producers. “It would look like you had a carbapenem-susceptible organism, despite it having a carbapenemase enzyme.”

In other cases, breakpoints are revised when new pharmacokinetic and pharmacodynamic data indicate a current breakpoint is too high or too low. That’s what happened in 2019, when the breakpoints for the fluoroquinolones needed to be lowered.

The data used to inform a change in breakpoints send a sobering message about drug resistance, Dr. Humphries notes. “The whole reason the breakpoints are updated is because of a very high mortality signal” associated with older breakpoints. “If you have an isolate that has an MIC of, let’s say, 4, to a carbapenem, that would be susceptible by the old breakpoints and resistant by the new breakpoints. The mortality for that patient is in the 80s,” compared to an MIC of 1—the new susceptible breakpoint—where the mortality drops down to the 20s, Dr. Humphries says.

While the gaps between CLSI and FDA have slowly narrowed, some remain frustrated by the gaps that can still occur between laboratories and commercial AST manufacturers.

To be clear, Dr. Humphries says, some manufacturers “have stepped up to the plate—some are totally up to date with everything.”

And companies are in a tough position, Dr. Humphries says, even as she and others continue to press for updated breakpoints. “They’re in a difficult situation,” she says. On the one hand, they want to update breakpoints—it is, after all, the right thing to do for patient care.

On the other hand, manufacturers have competing priorities, just like labs do. Resources need to be aimed at developing new, cutting-edge tests, as well as updating tests already on the market.

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Jean Patel, PhD, D(ABMM), has seen firsthand the pressures on both labs and manufacturers. Formerly with the CDC’s Antimicrobial Resistance Laboratory Network and the Office of Antimicrobial Resistance, she also formerly chaired the CLSI AST subcommittee. The refrain was familiar—those who updated breakpoints wanted them implemented ASAP, given that patient safety was at stake, and didn’t understand why it took so long.

Her move to Beckman Coulter, where she is principal scientist, gave her “a whole new perspective on how challenging it is for AST device manufacturers to translate a decision made by CLSI or FDA or EUCAST [European Committee on Antimicrobial Susceptibility Testing] into a product.” Manufacturers are always watching the breakpoint-setting process, she says. Once an update occurs, “The clock starts ticking. There’s an expectation that as soon as that decision’s made, we’ll have a product for customers. And that’s unrealistic.”

“It takes a lot of time. It takes a lot of planning,” she says, as well as “a lot of money.”

When manufacturers know a new breakpoint will be recommended, they typically conduct a clinical trial to collect data. “It’s not something we can do on the fly,” Dr. Patel says. Planning and conducting the study takes about a year; the data then need to be analyzed and submitted to the FDA, tacking on several more months.

Once the FDA responds, manufacturers have to implement the data into their product. Sometimes—but not always—that means designing new panels, Dr. Patel says. It also requires software updates to implement the new breakpoint.

She’d like to see the standards development organizations lay out multiyear agendas for updating breakpoints. “That helps us in industry plan.”

“For a long time we talked at CLSI about having a plan to solicit information from outside groups,” she says, to anticipate concerns about breakpoints, new drugs, and the need for new drug point classifications. Such transparency would help “harvest all the issues and then prioritize them,” she says.

It’s helpful, Dr. Patel notes, that industry representatives are allowed to participate in CLSI meetings (including as a voting member of the subcommittee), which enables manufacturers “to anticipate what changes are coming, to some extent.” EUCAST, on the other hand, bars industry from participating in its meetings. “We get surprised a lot by EUCAST decisions.”

Like labs, manufacturers are faced with decisions of whether to respond to a breakpoint that’s supported by either CLSI or FDA but not both. The stakes are higher for industry, Dr. Patel says. “It’s a huge challenge from a business perspective—it does not make sense to start developing toward a CLSI breakpoint for the U.S. market unless you’re pretty sure the FDA is going to take it up.” Even though the gap between CLSI and FDA breakpoints has narrowed, she says, “industry is unable to predict when FDA will adopt a breakpoint.”

Dr. Patel also echoes others in noting the difficulties labs face in updating breakpoints even when all the other pieces are in place. “One place where we’ve seen a little bit of a struggle is customers who don’t want to switch to a new panel with a new breakpoint. It’s a lot of work. They have to go through a validation process. It takes time.”

In those cases, manufacturers do have a lever they can pull: They can start to obsolete the breakpoints, removing panels from the inventory. It’s a step they take gradually, she says, “because that is a lot of upheaval for the customer.”

Still, says Dr. Patel, a more severe upheaval appears to lie in wait. “Antimicrobial resistance is a health problem that’s going to get worse before it gets better,” she predicts. The likely source of trouble: carbapenem-resistant Enterobacteriaceae and other gram-negatives in which metallo-beta-lactamases occur.

“Almost all of the new drugs coming to market for treating those infections aren’t active against bacteria that carry those metallo-beta-lactamases,” Dr. Patel warns. “And the number of bacteria that are carrying those enzymes is increasing—they’re actually the most common type of CRE worldwide.”

Unfortunately, she continues, the drug pipeline is not robust. Nothing is happening quickly enough “to predict a savior drug,” she says. In fact, there’s only one effective drug on the near horizon that covers all CRE infections. “And having only one drug that’s effective in treating an infection is a bad plan.”

A bad plan is the last thing the world needs. “We’re worried about bacteria spreading faster than drugs are being developed,” she says. “That does not bode well for the general public.” Already such infections are spreading inside hospitals. “And that’s bad,” Dr. Patel says. “But what’s worse is when they start causing community-associated infections.”

Detecting resistance is key. That’s the simple, hard truth—she barely needs to draw a parallel to COVID-19. “If you can’t detect it, you can’t prevent it,” she says. “And breakpoints are how you detect it.”

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