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POINT-COUNTERPOINT

Point-Counterpoint: What's in a Name? Clinical Microbiology Laboratories Should Use Nomenclature Based on Current Taxonomy

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INTRODUCTION The mnemonic SPICE (*Serratia*, *Pseudomonas*, indole-positive *Proteus*, *Citrobacter*, and *Enterobacter*) has served as a reminder to consider when a Gram-negative organism may carry a chromosomal copy of bla_{ampC}, with the associated risk of developing resistance to first-, second-, and third-generation cephalosporins. However, in 2017, there was a well-founded proposal to rename *Enterobacter aerogenes* to *Klebsiella aerogenes*, based on whole-genome sequencing (WGS), and the SPICE mnemonic lost its relevance. With the increased use of WGS for taxonomy, it seems like bacteria and fungi are undergoing constant name changes. These changes create unique challenges for clinical microbiology laboratories, who would like to issue reports that are readily understood and that help clinicians determine empirical antibiotic therapy, interpret antimicrobial resistance, and understand clinical significance. In this Point-Counterpoint, Drs. Karen Carroll and Erik Munson discuss the pros of updating bacterial taxonomy and why clinical labs must continue to update reporting, while Drs. Susan Butler-Wu and Sheila Patrick argue for caution in adopting new names for microorganisms.

KEYWORDS taxonomy, phylogenomics, nomenclature, taxa, prokaryotes

POINT

Updating taxonomy is critical for clinical labs.

Controversy surrounding microbial nomenclature has existed for decades, perhaps even centuries. Initial attempts in the 1700s to ascribe taxonomic designations to discoveries within the emerging field of prokaryotic science implemented rules that were used for botanical species. Should one delve into this topic with some degree of detail, the taxon *Staphylococcus aureus*, originally published by Rosenbach in 1884 (1), may be encountered. Effective (in other words, properly described) synonyms of this taxon also described in 1884 included "*Staphylococcus pyogenes aureus*" (ascribed also by Rosenbach) and "Micrococcus aureus." Just 1 year later, the designation "Staphylococcus pyogenes citreus" was used by Passet. In 1896, Lehmann and Neumann reported findings relative to "Micrococcus pyogenes," which was later determined to be an additional synonym of *S. aureus*. For those of you scoring at home, that would be 12 years and five effectively published names—only one of which (obviously, the first one) is valid.

Now imagine a similar scenario potentially occurring with hundreds of newly discovered microbes (some of which are relevant to medical microbiology). It has been estimated that toward the latter stages of the 20th century, upwards of 30,000 taxa were available to describe various prokaryotes (2). A great proportion of these designations were likely redundant and/or the results of duplicated efforts. In 1973, the Plenary Session of the First Congress for Bacteriology convened to establish a

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contemporary approach for systemic nomenclature of bacteria. This resulted in the initial rendition of the *International Code of Nomenclature of Bacteria* (known to many as "the Code"), published in 1975 (3). The Code promulgated multiple reforms in prokaryotic taxonomy, one of which was the creation of the *Approved Lists of Bacterial Names*, which took effect in January 1980 (4). This standardization distilled the number of valid prokaryotic taxa to approximately 2,300, with all other names rejected from further use.

A second important reform emanating from the Code entailed the publication of (valid) novel or revised prokaryotic taxa in what is now entitled the *International Journal of Systematic and Evolutionary Microbiology* (IJSEM), either by primary publication or acceptance on an IJSEM validation list for taxa previously and effectively published in a non-IJSEM journal. In essence and in tandem with the Code, IJSEM is the clearinghouse or voice of the International Committee on Systematics of Prokaryotes (ICSP)—the ultimate authority on bacterial taxonomy. While the proverbial taxonomic buck stops with the ICSP, this group defines its role through the Code as "an instrument of scientific communication . . . [providing] the critical links between nomenclature, classification, and characterization; past, present and future" (5). That said, the responsibility of taxon discovery and revision remains in the hands of the microbiologist; perhaps more importantly, the responsibility for application and implementation of novel and revised taxonomy also resides with the (clinical) microbiologist.

Benefits of accurate nomenclature and taxonomic revisions. Newer molecular methods, such as whole-genome sequencing, provide greater clarity of taxonomic status and have both added to our understanding of prokaryotic taxonomic classifications and clarified prior ambiguous relationships within families and genera. For clinical microbiologists, these contributions support the cornerstone of our discipline, which is communication of accurate information to the users of our laboratories. As researchers, how we identify an organism has immense consequences for our understanding of pathogenesis, epidemiology, and the microbiome in health and disease. Researchers need to speak the same "language"; otherwise, development of novel diagnostics, such as metagenomic next-generation sequencing (mNGS), that depend upon curated and accurate databases may be negatively impacted (6).

In addition to creating an explosion of novel species with standing in nomenclature (now numbering 17,642) (7), modern molecular tools have enabled better understanding of disease pathogenesis. For example, in a study by Potter et al., the authors used several modalities of *in silico* analysis of 103 whole genomes of *Gardnerella* spp. to elucidate and better define species within this genus (8). Using tetranucleotide frequency analysis, the authors clarified that there are 9 genomospecies among the 103 *Gardnerella vaginalis* and *Gardnerella* sp. genomic deposits in the National Center for Biotechnology Information database. All of these genomospecies were isolated from patients with clinical bacterial vaginosis (BV), indicating that multiple *Gardnerella* species beyond *G. vaginalis* can contribute to this clinical entity (8). The authors verified the taxonomic status of *Gardnerella piotti* sp. nov. and proposed potential conflicts in the taxonomic status of *Gardnerella leopoldii* sp. nov. and *Gardnerella swidsinskii* sp. nov.; they appeared to be the same species (8). This work also explored, to a limited extent, putative virulence genes that are important in understanding the biology of BV and genetic differences between commensal and pathogenic species (8). The authors discussed how phylogenetic methods and the reassignment of species into new genera have delineated the biology of other organism groups, such as the cutaneous propionibacteria (now *Cutibacterium* spp. and other genera), which possess genes encoding various systems that allow adaptation to different skin niches (8, 9).

Improvements in taxonomic methods have clarified unusual phenotypes in clinical microbiology. *Corynebacterium diphtheriae*, an important human pathogen, was historically classified into four biovars based upon a variety of phenotypic characteristics (Gravis, Mitis, Intermedius, and Belfanti). Biovar Belfanti was unique among the biovars in that it lacked the *tox* gene, was nitrate negative, and was associated with chronic

nonspecific rhinitis and not the disease diphtheria (10, 11). *C. diphtheriae* biovar Belfanti was subsequently designated a new species, *Corynebacterium belfanti* sp. nov., and the biovar designations are no longer used (11). Subsequent genomic studies by Tagini and colleagues have clarified two clades of *C. diphtheriae* as subspecies *diphtheriae* and *lausannense* (12). Laboratories are unlikely to identify *C. diphtheriae* to the subspecies level; however, any identification of an isolate as *C. diphtheriae* should prompt confirmation by local public health laboratories.

Appropriate and accurate nomenclature can assist with enhancing epidemiological investigations. Several recent examples are highlighted here. In 2002, an outbreak of necrotizing enterocolitis in a hospital in Canada identified organisms recovered from the blood and stool of six ill neonates as *Clostridium clostridioforme* (13, 14). However, since this organism historically was not common among such cases in the institution, as well as uncommonly associated in the literature with enterocolitis, the isolate was sent to a reference laboratory for additional characterization (13, 14). After extensive evaluation and characterization by the reference laboratory, it was concluded that this organism was a novel species, subsequently named *Clostridium neonatale* sp. nov. (14). *Enterobacter bugandensis* originally came to attention as an unusual cause of neonatal sepsis among 17 infants in Tanzania (15). It was noteworthy for its multidrug resistance phenotype as a consequence of harboring the CTX-M-15 resistance determinant (15). Once characterized, this paved the way for additional detection among patients from other geographic locations and further ascertainment of this organism's enhanced virulence potential (10, 15–17). A final similar example of the impact of understanding disease associations and the epidemiology of infections lies within the genus *Elizabethkingia*. Prior to the discovery of *Elizabethkingia anophelis*, *E. meningoseptica* was believed to be the cause of a vast array of hospital-acquired infections, ranging from pneumonia and bacteremia in adults to meningitis in neonates. High morbidity and mortality were reported with these infections (18, 19). However, subsequent studies have determined that *E. anophelis* is the major cause of bacteremia and other infections and is likely the most virulent of the six known species of *Elizabethkingia* (18, 19).

The Clinical and Laboratory Standards Institute's guidance for appropriate antimicrobial susceptibility testing (AST) is increasingly based on accurate species detection. The various methods of testing for oxacillin resistance among species of coagulase-negative staphylococci provide one example of this point (20). In addition, if a laboratory has failed to embrace the revisions in taxonomic assignment of *Actinobacillus* spp. (specifically, *A. actinomycetemcomitans*) to the *Aggregatibacter* genus, then an incorrect method of susceptibility testing may be applied (21, 22). As more novel species are added to the order *Enterobacterales*, correct nomenclature assignments have implications for predicting antimicrobial resistance and possible expansion of testing for carbapenemase producers. For example, the newly recognized *Providencia huaxiensis* sp. nov. was discovered during routine surveillance for carbapenem-resistant *Enterobacterales* at a hospital in China (10, 23).

Many microbiologists and clinicians view nomenclature changes as a pain point for AST interpretation and subsequent clinical efficacy. The revision of *Enterobacter aerogenes* to *Klebsiella aerogenes* is often cited as an example of the potential dangers of embracing taxonomic changes. However, in our laboratory practice, we report both names and add an isolate comment just below the organism identification, as follows: "*Klebsiella aerogenes*, formerly *Enterobacter aerogenes*, may quickly develop resistance during therapy with third-generation cephalosporins (e.g., ceftriaxone, ceftazidime) due to production of AmpC beta-lactamases. This does not apply to cefepime." We have not received feedback from our stewardship team nor from our clinicians of potential harm related to this nomenclature change (K. C. Carroll, personal communication). Collaboration with antimicrobial stewardship and infectious disease services facilitated implementation and correct interpretation of this change.

With really no choice but to accommodate these revisions and additions to microbial taxonomy, it is fortunate that clinical microbiologists have access to resources that can assist with implementation of nomenclature changes into daily practice. As stated above, IJSEM represents the primary vehicle for communication from the ICSP. The microbiologist has the opportunity to assimilate this primary literature monthly or to peruse online resources, such as the List of Prokaryotic Names with Standing in Nomenclature (LPSN; www.bacterio.net), a website that is updated concomitant to valid IJSEM publication. Within the past 5 to 10 years, *Diagnostic Microbiology and Infectious Diseases* (24) and *Journal of Clinical Microbiology* (10) have committed to the publication of annual/biennial compendia that attempt to summarize medically relevant novel/revised taxonomy, largely on the basis of IJSEM primary literature or validation lists. In addition, a Clinical and Laboratory Standards Institute document is in progress to provide guidance to clinical and veterinary diagnostic laboratories relative to the implementation of novel/revised bacterial and fungal nomenclature into routine laboratory operations and the potential timing of these actions.

Progress in microbial taxonomy will continue. The clinical microbiologist must engage proactively in the assimilation of this progress, incorporate important tenets into laboratory practice, and succinctly (yet accurately) communicate changes to clinical partners and key stakeholders. Outcome studies may be warranted to provide tangible evidence of the impact of taxonomic revisions on clinical practice. The clinical microbiologist should eagerly participate in such endeavors.

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COUNTERPOINT

Microbial taxonomic reclassification: Just because something is correct doesn't make it right.

Changing microbial nomenclature is not a new phenomenon, nor is the discontent that invariably follows from some in the clinical microbiology and infectious disease communities. Clinicians and laboratorians alike have been grumbling about microbial name changes for decades (1). Over time, however, revised names have eventually been adopted, and the formerly used names become but a distant memory. Nevertheless, due to advances in sequencing methodologies and the resulting migration to genome-based microbial classification, the pace and frequency with which these changes have been occurring over the past decade is truly unprecedented. For instance, a total of 234 new names, combinations, and taxonomic opinions have been published in the last six issues of the *International Journal of Systematic and Evolutionary Microbiology* (IJSEM) alone (March to August 2022). And that is just for prokaryotes. The current scope and scale of taxonomic reclassification therefore represents a significant challenge for clinical microbiologists.

Some taxonomic changes are fairly benign, whereby the species name is unchanged, along with an accompanying relatively minor change to the genus name, e.g., *Clostridioides difficile*. Such changes are unlikely to lead to deleterious clinical consequences. In other cases, however, these changes have the potential to be harmful to patients if not appropriately communicated. A notable example is *Klebsiella aerogenes* (formerly *Enterobacter aerogenes*). As for *Enterobacter cloacae*, third-generation cephalosporin use should be avoided for the treatment of invasive infections caused by *K. aerogenes* due to the moderate to high risk for AmpC beta-lactamase expression and development of resistance (2). In contrast, third-generation cephalosporins are a mainstay of therapy for serious infections caused by other *Klebsiella* species. The risk of an unfamiliar name negatively impacting patient care is not merely theoretical. In a survey of 219 clinicians, 73% viewed a report including both original and new names (*Nakaseomyces glabrata* [formerly *Candida glabrata*]) as clinically significant, compared with only 38% when only a new name was reported (*Pichia kudriavzeveii*) (3).

To keep the clinical microbiology community abreast of nomenclature changes, this journal publishes biennial updates on newly described genera and species, as well as on taxonomic revisions of medically important microorganisms. Once published, commercial identification device manufacturers based in the United States typically consider the "revised name" accepted, and databases are subsequently updated accordingly. Though the College of American Pathologists (CAP) only requires clinical microbiology laboratories to incorporate those taxonomic changes that "potentially affect the choice of appropriate antimicrobials to report and/or the interpretive breakpoints to use" (MIC.11375), once identification databases make use of the revised nomenclature, clinical laboratories invariably will need to use it.

Proponents of adopting nomenclature changes correctly argue that these issues can easily be ameliorated through reporting of both the old name and the new name on a temporary basis. Though guidance for clinical laboratories on managing this issue is forthcoming from the Clinical and Laboratory Standards Institute (CLSI), a period of only 2 to 3 years to provide both names to clinicians has been suggested in several published articles (4), along with the need to provide appropriate clinician education. Critically, this assumes that all clinical microbiology laboratories have dedicated doctoral-level directors (they do not) (5) and that clinicians do a consistently excellent job of reading their emails (they do not).

For prokaryotes, all of the above is predicated on the premise of valid publication in IJSEM or in an IJSEM validation list. Validation is regulated by the International Code of Nomenclature of Prokaryotes, which expressly cannot "restrict the freedom of taxonomic thought or action" (6). In essence, taxonomy can be summed up with the immortal words of Jeffrey "The Dude" Lewbowski: "Yeah? Well, you know, that's, like, just your opinion, man." Any validated name, old or new, has standing in the nomenclature and can be used (7). The assumption is that in time, those affected by changes, which disproportionately impact practical microbiology (e.g., clinical, agricultural, food, or industrial), will coalesce around using one of the validly published names. Instead, we appear to be engaged in a lemming-like, self-flagellatory process of adopting these changes carte blanche.

Unlike the International Commission on the Taxonomy of Fungi and the International Committee on the Taxonomy of Viruses, there is no arbiter of taxonomic correctness for prokaryotic organisms. Arguably, the idea of an official taxonomic designation presents an issue, given the pace of change in the field (8). Critically, taxonomy based exclusively on evolutionary relationships can present challenges for microorganisms of clinical importance. Should we therefore simply shun names that are problematic? In the case of the reclassification of *Ochrobactrum* species as *Brucella* species (9, 10), the answer is an emphatic "yes." Genomic relatedness alone does not capture that the former genus is comprised of free-living environmental bacteria, whereas the latter consists of obligately intracellular pathogens. In other cases, the answer will be more nuanced and require more careful consideration. What is clear, however, is that there should be additional checks and balances in place before accepting and using newly published valid names.

We already have examples of where this has occurred. For instance, *Shigella* and *Escherichia* should be synonyms based on taxonomy, but *Shigella* has been maintained as a separate genus for clinical concerns (8, 11). The approach taken to address this issue more generally should be multipronged in nature. For instance, when new names are submitted for publication as valid, an additional vetting process to minimize the clinical impact could occur for organisms of clinical importance. An additional level of scrutiny should also be proposed for the names themselves to minimize the potential for harm; pragmatic name choices with a memorable link to the earlier name and the bacterium or disease could be advised. Finally, there represents enormous potential for professional societies such as the American Society for Microbiology and the Microbiology Society to come together to develop a framework for greater oversight of nomenclature changes, for not only microorganisms of clinical importance but those of commercial and environmental importance. That way, we can do what is right and not solely what is correct for the benefit of our patients.

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SUMMARY

Points of agreement

1. Clinical laboratories are faced with the significant challenge of communicating changes in taxonomy in a clear and transparent manner to reflect both the updated name and the former name for a period of time.
2. Taxonomic changes can be confusing to microbiologists and clinicians, potentially leading to flawed antimicrobial treatment.
3. Better means of communication of taxonomic changes between clinical laboratories and the clinicians they serve are badly needed.

Issues to be resolved

1. Changes in taxonomy published by the IJSEM should be immediately changed and not challenged.
2. There is a need for an arbiter of taxonomic changes between the clinical community and changes listed in IJSEM or included in the IJSEM validation list.

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