**Table S1. Summary of Strategies for implementing Current Breakpoints:**

Based on instutional-level practices, for all breakpoint revisions laboratories should determine:

- the clinical use of the antimicrobial
- which testing options are available and most appropriate (for MIC tests, the concentrations encomposing lowered breakpoints must be available)
- which breakpoint(s) should be implemented

If the current breakpoints are not yet FDA-cleared on a cASTs, their use would be considered "off label" and a validation is required for implementation.

| Priority Level | Antimicrobial / Organism(s) | Noteworthy considerations for current breakpoint implementation | Questions to ask / issues to discuss with stakeholders at institional level to help determine laboratory testing and reporting strategy[1] |
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| 1 | Ertapenem, imipenem, meropenem / Enterobacteriaceae | - Highest priority for implementation; patient safety and public health risk unacceptable with use of obsolete breakpoints<br>- Carbapenems are first-line therapy for ESBL / AmpC producing isolates<br>- Carbapenemase testing **does not** substitute for use of current breakpoints, but can be done in tandem with use of current breakpoints, if desired<br>- If carbapenemase testing is needed, Modified Hodge Test is **no longer** an acceptable option due to sensitivity/specificity issues | - Which carbapenem(s) are on formulary / in use?<br>- Are different carbapenems used for different care services / patients (e.g., some institutions prefer meropenem over ertapenem for pediatrics)?<br>o Helps laboratory determine which panel of antimicrobial agents is best suited to institution, if multiple available for cASTs<br>o Helps laboratory determine which antimicrobials to focus on updating and which to supporess<br>o Helps laboratory determine which testing errors might not require pursuit if the agent will not be reported<br>- Would disk diffusion results (vs. MICs) suffice?<br>o Helps laboratory determine if manual testing is an option in some instances (e.g., species that do not perform reliably on cASTs with current BP, antimicrobial not validated, etc)<br>- Are carbapenemase tests needed for infection control or does a carbapenem "resistant" result suffice?<br>o Helps laboratory determine need to adopt/continue carbapenemase testing |

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| 1 | Cefotaxime, ceftriaxone, ceftazidime, ceftizoxime, cefepime, aztreonam / Enterobacteriaceae | - Highest priority for implementation; patient safety risk unacceptable with use of obsolete breakpoints<br>- Cephalosporins are first-line therapy for many indications (e.g., pneumonia)<br>- ESBL testing **does not** substitute for use of current breakpoints, but can be done in tandem with current breakpoints, if desired | - Which of these antimicrobials are on formulary / in use?<br>o Helps laboratory determine which panel of antimicrobial agents is best suited to institution if multiple available for cASTs<br>o Helps laboratory determine which antimicrobials to focus on updating<br>o Helps laboratory determine which testing errors might be acceptable because the agent need not be reported<br>- Are aztreonam results needed routinely? Or only in select cases? Would disk diffusion results (vs. MICs) suffice for these cases?<br>o Often only used in case of allergy; laboratory may not need to routinely test this antimicrobial<br>- Is there a preference for reporting cefepime results as "SDD" vs. "I" ?<br>o Helps laboratory determine extent to which they should pursue information technology resources to allow reporting of SDD interpretive category<br>- Should cefepime SDD results generate an ID consult to aid with dosing? Is dosing being optimized for cefepime?<br>o Some institutions continue to use 1g q12h dosing for cefepime, which many experts feel is suboptimal; implementation of current breakpoints is an opportunity for education on this issue<br>- Are ESBL tests needed for infection control or might ceftriaxone non-susceptibility suffice as a marker for ESBLs?<br>o Helps laboratory determine if ESBL testing needs to be continued or added |
| 1 | Ciprofloxacin, levofloxacin, | - Fluoroquinolones are first-line therapy for salmonellosis (including typhoid fever)<br>- Laboratories should test: | - Are there any special patient populations where non-typhoidal *Salmonella* isolates from stool should be tested? (e.g., elderly) |

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| | ofloxacin / *Salmonella* | - Non-typhoidal *Salmonella* from extra-intestinal sources<br>- *S*. Typhi / *S*. Paratyphi from all sources<br>- Disk diffusion testing is an option for ciprofloxacin, but no disk breakpoints for levofloxacin<br>- Levofloxacin and ciprofloxacin gradient diffusion perform well with current breakpoints; must validate<br>- **Do not** test nalidixic acid as it is unreliable<br>- One option is to suppress results if MIC by cASTs is:<br>o ciprofloxacin < 1 µg/ml<br>o levofloxacin/ofloxacin <2 µg/ml<br>o Sending isolate to a reference laboratory may be an option in these cases (note, unacceptable treatment delays may occur) | o Helps laboratory determine what testing protocols will minimize patient care delays<br>- Which fluoroquinolone is on formulary?<br>o Helps laboratory determine if performing ciprofloxacin disk diffusion is sufficient for testing, or if alternative method (e.g., gradient diffusion) is needed |
| 1 | Piperacillin-tazobactam / *P. aeruginosa* | - Piperacillin-tazobactam is a workhorse antimicrobial, used frequently for many patients / infections<br>- Patient safety risk unacceptable with use of obsolete breakpoints, especially for monotherapy | - Are appropriate doses of piperacillin-tazobactam used for *P. aeruginosa* infections?<br>o Many experts agree that 3.375g q8h with standard infusion is suboptimal, extended infusions have been adopted by many institutions<br>- Is piperacillin-tazobactam used as monotherapy for *P. aeruginosa*, or is combination therapy always used?<br>o If combination therapy is always used, laboratory may opt not to prioritize this breakpoint update immediately |
| 1 | Imipenem, meropenem / *P. aeruginosa, / Acinetobacter* | - Carbapenems are commonly used to treat infections caused by *P. aeruginosa* and *Acinetobacter* spp.<br>- Note: ertapenem is ineffective for *P. aeruginosa* and *Acinetobacter* spp. infections<br>- Patient safety risk unacceptable with use of obsolete breakpoints<br>- Carbapenemase producers increasing among non-fermenting Gram-negative bacteria | - How frequently are carbapenems used before AST results are available when an ID of *P. aerugionosa* or *Acinetobacter* spp. is reported?<br>o Helps laboratory determine whether carbapenem results should be reported for all *P. aeruginosa*/*Acinetobacter* isolated<br>- Are carbapenemase tests needed for infection control or does a carbapenem "resistant" result suffice?<br>o Helps laboratory with decision to adopt/continue carbapenemase testing<br>o Carbapenem resistance in *P. aeruginosa* and *A. baumannii* often due to non- |

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| | | | carbapenemase mechanisms or a combination of mechanisms |
| 2 | Cefazolin / *E. coli, K. pneumoniae, P. mirabilis* (non-urine) | - Is cefazolin used? Suppress cefazolin results for non-urine isolates if not used for systemic therapy<br>- Consider testing by disk diffusion or by gradient diffusion (with validation) for non-urine isolates with MICs ≤4 µg/mL<br>- If cefazolin results are suppressed, consider an alert for laboratory staff that if physician calls to request cefazolin result on isolate from non-urine source to perform alternative testing prior to reporting a "S" result | - Is IV cefazolin used routinely as de-escalation for *E. coli*, *Klebsiella* and *P. mirabilis* infections?<br>o Helps laboratory determine need to adopt current breakpoint<br>- Which dose of cefazolin is being used clinically? Would FDA vs. CLSI breakpoints be most appropriate?<br>o FDA breakpoints are for 1 g q 8 dose<br>o CLSI breakpoints are for 2g q8 dose.<br>o Decision on which breakpoint to validate depends on dose in routine use |
| 2 | Cefazolin / *E. coli, K. pneumoniae, P. mirabilis (*urine) | - Oral cephalosporin and IV cefazolin use for treatment of uncomplicated urinary tract infections (UTIs) is not common to all institutions<br>- If used, consider reporting as "oral cephalosporins" on patient report with footnote to indicate which formulary agents are available<br>- Consider adding a report comment that results are for uncomplicated UTIs only | - Are cefazolin (IV) and/or oral cephalosporins among the agents used routinely to treat uncomplicated UTIs?<br>o Helps laboratory determine if breakpoint adoption is needed<br>- Are oral cephalosporins used to treat uncomplicated UTIs for select patients/services? (e.g., the elderly, the emergency room)<br>o Helps laboratory determine if testing and application of current breakpoints are needed for only select patients – in which case, a manual method (e.g., disk diffusion) may be an option |
| 2 | Ciprofloxacin, levofloxacin / *Enterobacteriaceae, P. aeruginosa* | - Fluoroquinolones are workhorse antimicrobials in hospitals, in particular as an oral option for patient discharge<br>- Adoption of breakpoints will be a challenge for laboratories as most cASTs do not contain antimicrobial concentrations low enough to encompass current breakpoints<br>- Current breakpoints most significant for isolates associated with serious infections; less of an issue for isolates causing uncomplicated UTIs. | - Discuss data supporting breakpoint change with stakeholders<br>- Are fluoroquinolones used to treat uncomplicated UTIs?<br>o Helps laboratory determine if breakpoint needs to be adopted for urine isolates<br>- Are there institutional initiatives to reduce fluoroquinolone use?<br>o Helps laboratory determine if fluoroquinolones should be reported on all |

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| | | - Depending on the results of institutional discussions (see column at right), laboratories may opt to:<br>o delay adoption of current breakpoint until: 1) cASTs are available with indicated drug concentrations; and/or, 2) cASTs are FDA cleared with the current breakpoints<br>▪ consider addition of a warning comment to patient report (see last bullet to the right)<br>o adopt current breakpoint partially, by performing off-line testing by disk diffusion or gradient diffusion (must validate) for selected specimen types (e.g., blood) and/or patient populations (e.g., immunocompromised), if the result is "S" (MIC ≤1 µg/ml) by obsolete breakpoints<br>o adopt completely | isolates, or selectively, or on request only. If on request only, manual testing for isolates with "S" results by obsolete breakpoints may be an option.<br>- Are fluoroquinolones used as prophylaxis for immunocompromised patients?<br>o Helps laboratory determine if fluoroquinolone results should be reported for select patient populations and prioritize use of current breakpoints for those patients.<br>- If current breakpoints cannot be adopted, would adding a comment to the report, indicating that for critical cases, ciprofloxacin or levofloxacin may not be effective if reported as "S" with obsolete breakpoints be an option ?<br>o Helps laboratory determine the validity of this option |
| 2 | Daptomycin / *Enterococcus* spp. | - Current breakpoints most significant for *E. faecium* associated with serious infections (e.g., endocarditis); less of an issue for *E. facaelis* where there are typically other therapeutic options (e.g., ampicillin or vancomycin)<br>- Current breakpoints bisect the wild-type MIC distribution of *E. faecium* and a signficiant number of minor errors may be expected by any test methodology. This means it would not be uncommon for isolates to test SDD one day and "S" or "R" the next day. CLSI has addressed this issue in 2019, to further revise the current breakpoint.<br>- Until daptomycin breakpoints are finalized, laboratories may consider one or more of the following interim strategies:<br>o Suppress results if daptomycin not used at your institution for enterococcal infections<br>o Suppress daptomycin results on enterococcal isolates from specimens other than blood<br>▪ The majority of clinical data for daptomycin use is for treatment of endocarditis | - Inform stewardship team of the breakpoint deliberations at CLSI<br>o Physicians / pharmacists should consider use of high-dose daptomycin for all serious *E. faecium* infections due to clinical evidence of failures with 6 mg/kg/day<br>- Is daptomycin used for serious infections caused by *E. faecium* (e.g., endocarditis)?<br>o Some institutions prefer use of linezolid; if this is the case, then the laboratory should ensure linezolid is tested and reported<br>- What doses of daptomycin are used to treat enterococcal infections? (are off-label doses used?)<br>o Most experts agree the label-dose of 6 mg/kg/day for *S. aureus* bacteremia is not sufficient to treat *E. faecium* endocarditis; doses of 10 – 12 mg/kg/day (off label) are generally used<br>- Do clinicians understand SDD? Should daptomycin S-DD results generate an ID consult to aid with dosing? |

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| | | ○ Report as "R" if MIC >4 µg/mL. Suppress MIC result and any interpretation if ≤4 µg/mL (susceptible by obsolete breakpoints) and add a comment regarding need for high-dose daptomycin for *E. faecium* treatment<br>▪ No need to perform validation for this strategy | |
| 3 | Colistin / *P. aeruginosa* | - Colistin is proving to be a less efficacious therapeutic option than other newer antimicrobials, and its use should be limited.<br>- Institutions with low carbapenem resistance rates likely do not use colistin with frequency<br>- Note that inhaled colistin is used for certain patient populations (e.g., cystic fibrosis); current breakpoints may not predict outcomes for this route of administration<br>- The only CLSI-endorsed test for colistin is broth microdilution<br>- Laboratories may adopt research use only (RUO) labeled tests (if acceptable at institution) if colistin is used frequently<br>- If colistin not used frequently, refer isolate to a reference laboratory for testing; establish turnaround time with reference laboratory to avoid unnecessary delays. | - When is colistin used for *P. aeruginosa* infections?<br>○ Helps laboratory determine need for internal testing vs. reference laboratory testimg<br>○ Develop rules for reflexive AST of MDR isolates (which may include colistin) to limit delays in testing. Reflexive testing guidelines should be endorsed by the Medical Director prior to implementation. |
| 3 | Ceftaroline / *S. aureus* | - Consider use of obsolete breakpoints and add a comment to the report regarding the possibility of using higher doses for MICs of 2-4 µg/mL | - Discuss current breakpoints and option to use a higher dose than is currently FDA-approved.<br>- Are there circumstances where the new breakpoint would be helpful?<br>○ If so, is this use limited to certain providers (e.g., ID pharmacist) and perhaps reporting MIC alone (without any interpretation) is sufficient |

AS team, antibiotic stewardship team; cASTs, commercial antimicrobial susceptibility test system; ESBL, extended-spectrum beta-lactamase; I, intermediate; ID, infectious diseases; MDR, multidrug resistant; R, resistant; S, susceptible; SDD, susceptible dose dependent;

[1] stakeholders include antibiotic stewardship team, pharmacy, infectious diseases (ID), infection control and others, as appropriate