Appendix A Intrinsic, implied and default resistance

Magiorakos et al. [1] and CLSI [2] are our primary sources of information on intrinsic resistance. Sanford et al. [3] and Gilbert et al. [4] have been used to fill in missing susceptibilities, but do not distinguish between acquired and instrinsic resistance. In cases where Sanford et al. [3] and Gilbert et al. [4] indicate resistance we therefore rely on other sources to distinguish between intrinsic and acquired resistance. These sources are explicitly acknowledged in the following notes, as are instances of disagreement among our primary sources:

- Amoxicillin and penicillin: Amoxicillin is similar to ampicillin [5], and penicillin does not cover Gram-negative bacilli [6].

- Enterobacteriacea: We assume that all Enterobacteriaceae resistant to ceftriaxone, cefazolin or cefotaxime produce ESBLs, AmpC beta-lactamases, or KPCs, and are therefore resistant to flouroquinolones, trimethaprim-sulfamethoxazole, penicillins, cephalosporins, cephamycins, and β-lactam/lactamase inhibitor combinations [4, 7, 8]. We assume that all Enterobacteriaceae resistant to carbapenems produce KPCs, and are therefore also resistant to chloramphenicol [4, 8]. CLSI [2] provides breakpoints for Polymyxin B, and FDA drug labels indicate susceptibility among *E. coli, Enterobacter aerogenes, and Klebsiella pneumoniae* strains. We assume that resistance to cephalexin among *Enterobacter spp.* and *Serratia marcescens* strains [3, 4] is intrinsic, and that all strains are intrinsically resistant to oxacillin and cloxacillin [5].

- *Pseudomonas aeruginosa*: CLSI [2] suggests that *P. aeruginosa* is intrinsically resistant to fosfomycin, but Magiorakos et al. [1] does not. We follow Magiorakos et al. [1]. FDA labels and Sanford et al. [3] suggest that some strains were once susceptible to ceftriaxone, but we follow CLSI [2] and assume intrinsic resistance. We also assume that resistance to the following drugs [3, 4] is intrinsic: nitrofurantoin, tigecycline, ampicillin, cefotaxime, cephalexin, oxacillin, cloxacillin and ceftaroline.

- *Acinetobacter* spp: Given potential susceptibility to extended-spectrum cephalosporins, we assume susceptibility to ceftaroline.

- Coagulase-negative Staphylococci (CoNS): According to FDA labels nitrofurantoin, clindamycin and ampicillin have in vitro activity against at least some strains of CoNS, so we assume susceptibility. CLSI [2] give breakpoints for doxycycline and minocycline, and our data show some susceptibility to doxycycline, so we assume former susceptibility.

- *Enterococcus*: CLSI [2] claims intrinsic resistance to all cephalosporins, but Gilbert et al. [4] claims that *E. faecalis* is susceptible to ceftaroline. We assume susceptibility. Sanford et al. [3] and Gilbert et al. [4] also claim resistance to erythromycin and tetracycline but CLSI [2] provides breakpoints so we assume that at least some strains are susceptible. Gilbert et al. [4] claims partial susceptibility of *E. faecium* to imipenem, but Magiorakos et al. [1] suggests intrinsic resistance, so we assume resistance. We assume that resistance to the following drugs [3, 4] is intrinsic: rifampin (*E. faecium*), ciprofloxacin (*E. faecium*), levofloxacin (*E. faecium*), cefotetan, cefoxitin, cloxacillin and oxacillin.

We used understanding of common multi-drug resistant strains (table 3) to fill gaps in our example antibiogram. We also used the following general knowledge of resistance patterns, assuming 100% susceptibility or resistance in cases where testing was not done:

- Enterobacteriaceae are generally susceptible to carbapenems [2] and generally resistant to ampicillin [4].

- *A. baumanii* strains are generally susceptible to polymixins [2].

- Staphylococci are generally susceptible to daptomycin, linezolid, quinupristin-dalfopristin, and vancomycin [2], and generally resistant to ampicillin [4].

- CoNS strains are generally resistant to chloramphenicol, tetracyclines, amoxicillin-clavulanic acid, and aminoglycosides [4].

- Enterococci are gnerally susceptible to linezolid and daptomycin [2] and generally resistant to erythromycin and tetracyclines [4]. *E. faecalis* strains are generally susceptible to ampicillin [7], and generally resistant to ciprofloxacin and moxifloxacin [4].

Finally, we considered the potential impact of two new drugs:

- ceftazidime-avibactam (caz-avi): Caz-avi was active against 99.8% of clinical Enterobacteriacea isolates from US medical centres in 2012-2013, 95.6% of *P. aeruginosa* isolates, and 26.4% of *A. baumanii* isolates [9]. We assume that staphylococci resistant to cefazolin are also resistant to caz-avi, and that enterococci at intrinsically resistant. Caz-avi remains active against carbapenemase (KPC)-producing Enterobacteriacea [9]. According to these numbers, caz-avi would cover 95% of Gram-negative CLABSIs in our basket (similar to tobramycin). Coverage of Gram-negative CAUTIs would be 98% (similar to amikacin), and Gram-negative VAP coverage would be 90% (similar to gentamicin).

- ceftolozane-tazobactam (cef-tazo): Assuming a breakpoint of $\leq$ 8mg/L [10] cef-tazo provided the following coverage of bacteria associated with healthcare associated UTIs in US and European hospitals in 2012: 99.9% of *E. coli*, 95.2% of *Enterobacter*, 90.9% of *Klebsiella*, 100% of *Serratia* and *Proteus*, *40%* of *A. baumanii* and 93.4% of *P. aeruginosa* [11]. Susceptibility among pneumonia isolates was similar [12]. We assume that staphylococci resistant to cefazolin are also resistant to cef-tazo, and that enterococci at intrinsically resistant. Cef-tazo is not active against carbapenemase (KPC)-producing Enterobacteriacea [11]. According to these numbers, cef-tazo would cover 90% of Gram-negative CLABSIs in our basket (similar to gentamicin). Coverage of Gram-negative CAUTIs would be 96% (similar to meropenem), and Gram-negative VAP coverage would be 88% (similar to gentamicin).

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