



Worldwide Overview of Antimicrobial Resistance

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Penicillin was discovered in 1929 and came into wide usage early in the 1940s, and was initially widely effective against many common pathogenic bacteria, especially staphylococci and streptococci. During this decade sulfonamides were discovered and streptomycin followed closely. Within a few years the first signs of resistance began to be reported in *Staphylococcus aureus* to penicillin and in *Mycobacterium tuberculosis* to streptomycin.^{1,2} In the 1960s and 1970s antibiotic resistance started to increase, becoming a serious and increasing problem for clinicians within the last two decades. Bacterial resistance to antimicrobial agents is mediated by a variety of mechanisms, with resistance occurring both intrinsically and being acquired by the bacteria. The susceptibility of any isolate to an agent used clinically depends of the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the agent and the dosing regimen used. Since breakpoints are established to facilitate treatment of patients, it is best to use breakpoints based on PK/PD parameters to predict whether the drug will be efficacious in treating illness.^{3,5}

Resistance in Common Bacterial Species

***Staphylococcus aureus*.** Most isolates of *S. aureus* are resistant to penicillins due to production of β -lactamases, and many have also acquired resistance to oxacillin, which confers resistance to all currently available β -lactams. Additional acquired resistance to macrolides, quinolones, trimethoprim/sulfamethoxazole, tetracyclines, and aminoglycosides has also occurred. Thus far, vancomycin remains very effective, though four strains have thus far been identified with high-level acquired resistance to this agent.⁶ Oxacillin resistance in *S. aureus* varies around the world, from a low of 5.7% in Canada to 46% in the western Pacific.⁷ Ciprofloxacin resistance of 22.7%, 37% and 42.9% were reported in Mexico, Asia, and North America, respectively.

Enterococci. Enterococcal species such as *E. faecalis* and *E. faecium*, have intrinsic resistance to trimethoprim/sulfamethoxazole, tetracyclines, clindamycin, cephalosporins, and aminoglycosides. The intrinsic resistance to aminoglycosides is low level, but high-level resistance can be acquired. Other acquired resistance found in these species includes penicillins, vancomycin (especially *E. faecium*), macrolides, and quinolones.

***Streptococcus pneumoniae*.** Wild-type *S. pneumoniae* initially were highly susceptible to most antimicrobials, except for low-level intrinsic aminoglycoside resistance. However, this species readily

acquires foreign DNA by transformation. While resistance to trimethoprim/sulfamethoxazole is common worldwide, little resistance to quinolone agents has developed to date. Worldwide surveillance indicates a prevalence of penicillin resistance of approximately 20%, ranging from under 10% in Africa to nearly 40% in Asia.^{4,5} Amoxicillin, with the prevalence of non-susceptible strains being well below 10% in most regions, remains an effective agent for treatment of infections caused by *S. pneumoniae*, as does ceftriaxone (except for Asia where 13.8% of strains are non-susceptible) and all of the quinolones except for ciprofloxacin.^{4,5}

Streptococcus pyogenes. There has yet to be a penicillin-resistant *S. pyogenes* strain identified. Macrolide resistance varies throughout the world with very high rates being reported from Taiwan (78% in 2001).⁸

Escherichia coli. There was initially little intrinsic resistance found in wild type *E. coli*. Acquired resistance, however, to ampicillin, piperacillin, ticarcillin, and ceftazidime due to TEM-type β -lactamases is now common. In addition, more recent mutations of TEM-type β -lactamases has resulted in the development of extended spectrum β -lactamases (ESBL), conferring resistance to third generation cephalosporins. In addition, resistance to quinolones, tetracycline, trimethoprim/sulfamethoxazole, and aminoglycosides has been acquired.⁹⁻¹³

Klebsiella spp. Species within the *Klebsiella* genus have intrinsic resistance to β -lactam agents through a chromosomal TEM-like SHV β -lactamase. The genus is susceptible to β -lactam/ β -lactamase inhibitor combination agents. Acquired resistance develops through ESBL forms of SHV- or TEM-type β -lactamases. In addition, quinolone, tetracycline, trimethoprim/sulfamethoxazole, and aminoglycoside resistance can all be acquired.⁹⁻¹³

Enterobacter spp., Serratia spp., Citrobacter freundii, Morganella spp. These genera are all intrinsically resistant to ampicillin, ticarcillin, piperacillin, β -lactam/ β -lactamase inhibitor combinations, and ceftazidime due to a chromosomal broad-spectrum β -lactamase. This β -lactamase is usually produced in low amounts, but high-level production can readily be induced during therapy with β -lactams, conferring resistance to all available cephalosporins except ceftazidime. Resistance to quinolones, tetracycline, trimethoprim/sulfamethoxazole, and aminoglycosides can all be acquired.^{9,10}

Proteus mirabilis. This species is intrinsically resistant to nitrofurantoin and tetracyclines. Resistance can be acquired to ampicillin, trimethoprim/sulfamethoxazole, first- and second-generation cephalosporins and quinolones.¹⁰ ESBL-producing strains have been reported from Europe and Korea.^{14,15}

Pseudomonas aeruginosa. This species is intrinsically resistant to trimethoprim/sulfamethoxazole, tetracyclines, ampicillin, including combination with currently available β -lactamase inhibitors, first- and second-generation cephalosporins, as well as ceftazidime and ceftazidime. Resistance to β -lactams is mediated via a similar chromosomal broad spectrum β -lactamase to those found in *Enterobacter spp.*, *Serratia spp.*, *Citrobacter freundii* and *Morganella spp.*: The only cephalosporins to which *P. aeruginosa* is susceptible are ceftazidime and ceftazidime. Resistance through derepressed chromosomal β -lactamase results in resistance to ceftazidime, piperacillin, piperacillin/tazobactam, aztreonam and, in some instances, to ceftazidime as well. Aminoglycoside, quinolone, and, occasionally, carbapenem resistance can also be acquired, with carbapenem resistance usually due to cell membrane porin mutations.^{9,10}

Acinetobacter spp. *Acinetobacter* spp. are intrinsically resistant to trimethoprim/sulfamethoxazole, ampicillin, and first- and second-generation cephalosporins. This genus can acquire resistance to penicillins, quinolones, aminoglycosides, third- and fourth-generation cephalosporins, and carbapenems.^{16,17} This genus has a high prevalence of resistance to most agents tested, with imipenem and meropenem being the most active agents.

Stenotrophomonas maltophilia. *S. maltophilia* isolates produce an intrinsic metallo- β -lactamase which confers resistance to all β -lactam agents, and they are also intrinsically resistant to aminoglycosides. Gatifloxacin and trimethoprim/sulfamethoxazole were active against the *S. maltophilia* strains tested, although this species has acquired resistance to quinolones.¹⁷

H. influenzae. *H. influenzae* is intrinsically resistant to some oral cephalosporins, including cefaclor and cefprozil, as well as to macrolides due to intrinsic efflux pumps.⁵ The species can acquire β -lactamases leading to ampicillin resistance, which can be overcome with the addition of β -lactamase inhibitor agents. Non- β -lactamase mediated ampicillin resistance, due to altered penicillin-binding proteins, can also occur, and is not reversed by the addition of β -lactamase inhibitors; this mechanism is common in some Asian countries, accounting for one-third of ampicillin resistant strains.^{4, 5, 18} Most isolates tested were macrolide resistant (97.4-100%) and also had moderately high rates of doxycycline (52.4-81.6%) and cefprozil (54.8-90.6%) resistance. Quinolones, ceftriaxone, cefixime, and chloramphenicol are all highly active against recently isolated *H. influenzae* strains.^{4, 5, 18}

Conclusions

In an era of rapidly increasing resistance to entire classes of drugs, it is apparent that further work needs to be done in development of novel drugs and treatment strategies. In the absence of new wonder drugs on the horizon, work must turn to the mundane yet important aspects of rational drug use. Clinicians need to assure that the drug chosen is the one most appropriate to the condition being treated. In many cases, antibiotics are entirely unnecessary, as many infections - especially upper respiratory infections - resolve spontaneously without antimicrobial treatment. In addition to better prescribing practices, the patient must be educated to understand the uses and misuses of antimicrobial treatment so that adherence can be assured. In addition, drug dosing needs to be optimized.

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