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Resistance in gram-negative bacteria; the saga renews

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In the 1980s it seemed that gram-negative opportunists might be beaten. The huge majority of isolates were susceptible to oxyimino cephalosporins, carbapenems and fluroquinolones, all then recently introduced to the clinic.

Yet gram-negative bacteria have fought back, aided by their membrane organisation, which promotes the exclusion and efflux of antibiotics, and by a remarkable propensity to recruit, transfer and adapt resistance genes, including those for extended-spectrum β-lactamases, metallo and non-metallo-carbapenemases, aminoglycoside-blocking 16S rRNA methylases and even a quinolone-modifying variant of an aminoglycoside-modifying enzyme.

The result is that it is now commonplace to encounter gram-negative isolates –both fermenters and non-fermenters– susceptible only to colistin and, more variably, to fosfomycin and tigecycline, all of which have significant limitations as antibiotics and which also are vulnerable to resistance. Some β-lactamase genes have become associated with bacterial lineages that have great epidemic potential, thus disseminating across counties and continents. Examples include *Escherichia coli* ST131 with CTX-M-15 β-lactamase encoded by IncFII plasmids and *Klebsiella pneumoniae* ST258 with KPC-2 or -3 enzymes. In other cases, notably NDM carbapenemase, the gene is often carried by highly promiscuous plasmids that transfer among strains and species.

The prevalence of resistance varies with locale and species, but typically is highest in newly prosperous countries in East and South Asia, also Latin America and the Middle East –which collectively account for much of the world's population. Here, the growth in the availability of sophisticated medicine often outstrips weakly enforced infection control and prescribing regulation, providing a fertile soil for growth of resistance. In extreme cases, weak sanitation

infrastructure allows cycling of resistant Enterobacteriaceae outside of hospitals and in the urban environment. Resistance is then further spread by human travel and migration. Unless such public health issues are addressed, and unless antibiotic development is reinvigorated, there is a real prospect that gram-negative opportunists will spell the end of antibiotic revolution upon which so much of modern medicine depends.