Supplementary Tables

Supplementary Table 1: Experimental Evidence for Treatment Strength

Note: This table was created by performing a systematic search on PubMed using the terms "Evolution of Resistance Dose", "Evolution of Resistance Chemotherapy", "Resistance Emergence Dose", "Low Dose Treatment Resistance." Several other studies not found using these terms are included as well. Note that the column "General Direction of Evidence" always refers to the direction of evidence (more moderate or more aggressive) relative to the baseline treatment chosen in the source.

Pathogen	Treatment range	Outcome	Source	General Direction of Evidence
***In vivo* evidence (human)**				
S. aureus, S. pneumonia, H. influenza	Long-term, low-dose azithromycin (in CF patients)	Reduction of colonization by all pathogens tested, but increased macrolide resistance in S. aureus (clinically insignificant)	[1]	Not long-term, low dose although evidence weak. Short-term/high-dose not tested, so evidence could go either direction.
S. pneumoniae	Low daily dose and long duration of oral β -lactam	Dosing strategy was associated with carriage of penicillin-resistant S. pneumoniae	[2]	Mixed evidence: both low dose and long duration were associated with resistance
Community-Acquired Pneumonia *(S. pneumonia, H. influenza,* etc.)	High-dose, short-course levofloxacin vs. longer duration, lower dose (Fluoroquinolones)	High-dose, short course just as effective as long duration lower dose, and may prevent resistance emergence better due to hastened bacterial demise	[3]	Aggressive Treatment (high dose, short course)
Ventilator-Associated pneumonia *(P. aeruginosa, A. baumannii, E. coli,* etc.)	8 day vs. 15 day duration of regimen decided by physician	Similar clinical efficacy for both durations. Shorter treatment had higher infection recurrence, but recurrent infections less likely to be resistant.	[4]	Moderate Treatment (shorter duration better in terms of resistance)
Oral strepto-coccus	3-day vs. 7-day treatment with amoxicillin	3-day and 7-day treatment courses yielded similar clinical efficacy and induced similar selection of reduced-susceptibility streptococci, suggesting selection can happen over very short durations	[5]	Mixed evidence
Hepatitis C	Varying doses of IFN	Patients administered higher doses of IFN had	[6]	Aggressive Treatment (high

		reduced the diversity of quasi-species present, though persistent strains survived in all patients		dose)
HIV	Once Daily and Twice Daily doses of daily lopinavir/ritonavir in combination with NRTIs	No difference in resistance evolution between treatment groups, with better adherence and no other adverse outcomes among once-daily dosed individuals	[7]	Neutral (although adherence advantage to moderate treatment)
Bacteriuria	Oxolinic Acid in 1g and 2g per day doses in a previous study, showed 1 ineffective and 2 difficult to tolerate due to side effects so tried 1.5g.day	Limited clearance plus resistance emergence and side effects, so not recommended to lower dose below 2g	[8]	Aggressive Treatment (high dose)
HIV	Lopinavir/ritonavir combination therapy once daily vs. twice daily	Similar low emergence of resistance with both treatments, better adherence with once daily	[9]	Neutral (although adherence advantage to moderate treatment)
HIV	Different adherence levels to HAART	Worse adherence was associated with worse outcome and emergence of drug resistance	[10]	Aggressive Treatment (here equivalent to good adherence)
HIV	A number of predictors of resistance mutations	High but imperfect adherence and perfect adherence, but low drug concentration were associated with development of resistance	[11]	Aggressive Treatment if perfect, otherwise low/no treatment
HIV	Different levels of adherence to HAART	High but imperfect adherence associated with resistance acquisition	[12]	Aggressive Treatment if perfect, otherwise low/no treatment
TB	Meta-analysis of different durations and intermittency of rifampin treatment	Regimes that used rifampin for a short duration (1-2 vs. 5-7 months) had higher rates of resistance acquisition; non-significant increase observed for higher durations (8+ months)	[13]	Mixed evidence
In vivo evidence (animal model)				
Salmonella spp., E. coli	low-level continuous, pulse, and no antimicrobial	Cephalothin-resistant E. coli under pulse strategy with chlortetracycline, Otherwise no difference between regimens	[14]	Mixed Evidence

Plasmodium chabaudi	Weak and Strong drug pressure, Pyrimethamine curative chemotherapy	Weaker drug pressure reduced competitive release of resistant strains, resistance remained under positive selection for longer than expected given drug half-life	[15–17]	Moderate treatment (lower dose)
S. pneumoniae	Wide range of time that drug concentration >MIC	Insufficient treatments selected for more resistant strains	[18]	Aggressive Treatment (high dose)
P. aeruginosa	Range of dosing regimens, beta-lactams	Resistance only emerged when T>MIC greater than 50% of dosing interval	[19]*	Moderate Treatment (shorter duration above MIC)
P. aeruginosa	Range of dosing regimens of aminoglycosides	Suboptimal dosing may lead to resistance through reduced uptake of drug by bacteria	[20,21]*	Aggressive Treatment (high dose)
Bacteroides fragilis, Enterobacter cloacae	Range of dosing with ceftizoxime (beta-lactam)	No increased resistance in B. fragilis with differing dosage, fAUC-to-MIC ratio is the pharmacodynamic index best correlated to emergence of resistance in E. cloacae, and ratio of 1000 needed to prevent emergence of resistance	[22]	Mixed evidence
S. aureus	Various doses of levofloxacin	Bacteria lost susceptibility when drug concentrations at the site of infection were in mutant selection window	[23]	Aggressive Treatment (high dose)
Plasmodium Chabaudi	Virulent and avirulent strains treated for short or long duration	Sub-optimal treatment may select for virulent strains	[24]	Aggressive Treatment (high dose)
Plasmodium Chabaudi	Treatment or no treatment	Treating mice coinfected with sensitive and resistant strains allowed transmission of resistance	[25]	Moderate Treatment (lower dose)
Enterobacteriaceae	Ciprofloxacin, placebo, 1.5 or 15 mg per kg body weight/day for 5 days	Higher doses were associated with more resistant strains found in fecal samples	[26]	Moderate Treatment (lower dose)
Enterococcus faecalis	3 different doses of linezolid over different durations	Resistance increased with decreasing dose but increasing duration	[27]	Aggressive Treatment (higher dose, shorter duration)
Enterobacter cloacae	Differing doses of ceftazidime at frequencies of 6, 12 or 24 hrs for 18 days	Moderate doses administered frequently were most correlated with resistance emergence	[28]	Aggressive Treatment (high dose)
S. aureus, E. faecium	Four doses of Linezolid over 72 hrs	Resistance development potentially highest when a	[29]	Aggressive Treatment (high

		constant concentration near the MIC maintained		dose)
S. Aureus	Varying concentrations of vancomycin *in vitro* and *in vivo* (rabbit model)	Both experiments confirmed that the only way to maintain vancomycin susceptibility was to keep concentrations above the MPC	[30]	Aggressive Treatment (high dose)
E. coli	Varying concentrations of cefotaxime	Peak resistance at low concentration, second peak at higher concentrations	[31]	Mixed evidence
Klebsiella pneumonia & Enterobacteriaceae	Low and high doses of cefquinome (targeting Klebsiella)	Both high and low doses cured Klebsiella, but high doses resulted in amplification of resistance Enterobacteriaceae	[32]	Moderate Treatment (lower dose)
Malaria	Varying doses of an artemisinin derivative	Aggressive treatment of mixed infections provided advantage to resistant mutants without benefit to host	[33]	Evidence against aggressive treatment
***In vitro* evidence**				
P. aeruginosa[a,b], *Klebsiella pneumoniae*[a], *E. coli*[a], *and S.aureus*[a,b], *S. pneumoniae*[c]	Fluoroquinolones	High doses of Fluoroquinolones are good for minimizing the development of resistant strains	[34–36]*	Aggressive Treatment (high dose)
E. coli	Ciprofloxacin	Neither time with dose > MPC nor maximum concentration were singly correlated with preventing resistance emergence. For wild-type strains, AUC/MPC ratio ≥22 was predictive of prevention of resistant mutant emergence	[37]	Aggressive Treatment (higher AUC/MPC ratio)
K. 4neumonia, S. aureus	Range of doses of garenoxin, ciprofloxacin	Peak of resistant populations at intermediate drug doses: inverted "U-shaped" curve	[38]	Aggressive Treatment (high dose)
C. albicans	Fluconazole	Frequent dosing prevented *de novo* resistance emergence, while prolonged sub-MIC doses gave rise to resistant strains	[39]	Aggressive Treatment (frequent dosing above a certain level)
Mycobacteria	Azithromycin	Subtherapeutic treatment for more than 3 days led to many-fold increase in expression of mutation that codes for efflux pump	[40]	Aggressive Treatment (high dose)
E. coli and S.	Sub-MIC dose of	Reduced rate of growth of	[41]	Aggressive

enterica	tetracyclin	susceptible strain markedly with no effect on resistant strain		Treatment (high dose)
E. coli	Cefotaxime	Emergence of resistance not only increased dependent on time spent in mutant selection window, but also on previous antibiotic concentrations (post-antibiotic effect)	[42]	Aggressive Treatment (dose to get out of mutant selection window but also dependent on previous exposure)
C. albicans	Fluconazole	Emergence of resistance correlates with time below MIC, more frequent dosing prevents resistance	[39]	Aggressive Treatment (higher and more frequent dosing)
M. tuberculosis	Rifampicin	Higher doses prevent emergence of resistance	[43]	Aggressive Treatment (high dose)
P. Aeruginosa, A. baumannii	Various doses/times of doripenem	Low-dose, short duration yielded the most resistance mutants, though repeated doses somewhat alleviated this effect.	[44]	Aggressive Treatment (high dose, longer duration)
P. aeruginosa	Colistin Methanesulphonate in 8,12,24 hr dosage intervals	All intervals yielded the same killing rate, but the 8hr was best at minimizing resistance	[45]	Aggressive Treatment (more frequent dosing)
P. aeruginosa	Varying C(min):MIC ratios of meropenem	Higher ratios associated with less resistance	[46]	Aggressive Treatment (high dose)
S. pneumoniae	Moxifloxacin below MIC, between MIC and MPC, above MPC	Samples treated with concentrations between MIC and MPC developed most resistance	[47]	Aggressive Treatment (high dose)
S. pneumoniae	Benzylpenicillin at various concentrations leading to different T>MICs in a mixed solution of susceptible, intermediate and resistant strains	Doses targeted at susceptible strains yielded more resistance	[48]	Aggressive Treatment (high dose)
TB	Varying levels of adherence with in vitro susceptible, rifampin- and isoniazid- resistant strains, and *in silico* simulations	Treatment failure only occurred when non-adherence was greater than 60%. *In silico* simulations predicted that resistance would emerge due to pharmacokinetic variability	[49]	Mixed evidence
Bacteria	Range of evidence	First dose exposure determines outcome of infection, therapy should be	[50] and references	Aggressive Treatment (high dose but short

		initiated as soon as possible and for as short a duration as possible, avoid suboptimal dosing	therein	duration)
S. Pneumoniae	Range of concentrations of amoxicillin, cefixime, cefuroxime, and cefotaxime	Antibiotics at lower levels select for low level resistance, at intermediate levels potentially for high-level resistance, and at high enough levels may preclude resistance	[51]	Aggressive Treatment, if aggressive enough

*Reviewed in Roberts et al. [52]

Supplementary Table 2: Theoretical Models of Resistance Emergence

Theoretical/mathematical models			***Source***	***Direction of Evidence***
Bacteria	Short Duration	Immunity is an important mediating factor in determining duration of treatment	[53]	Neutral (immunity important)
Influenza	Adaptive strategy beginning with conservative treatment followed by scale-up	Final size of pandemic minimized and outbreaks of resistant infections prevented	[54]	Moderate Treatment scaled up over time
HIV	ARVs	High selection pressure expected during antiretroviral therapy can cause recombination to favor evolution of resistance under a wide range of population sizes.	[55]	Neutral (resistance always possible)
Any – direct and vector-borne	Spatial distribution of treatment	Critical patch sizes of treated areas can be found that minimize the spread of resistance	[56]	Neutral (patch-size dependent)
HIV	Transient monotherapy	Even transient increases in subpopulations of common mutants are associated with accelerated appearance of further rarer mutations, and can be caused by fluctuating treatment	[57]	Aggressive Treatment (consistent – no fluctuation)
Malaria	Model of low to high doses of Mefloquine	Model predicts lower dose leads to more rapid resistance evolution	[58]	Aggressive Treatment (high dose)
Helminths	Model of a range of dosing strategies	Under-dosing can promote or impede	[59]	Either

		resistance under different circumstances		
TB	Monte Carlo simulations of moxifloxacin doses	Highest dose best for wiping out drug resistance, tolerability unknown,	[60]	Aggressive Treatment (high dose)
Bacterial infections	Proportion of population uses antibiotics, antibiotic use discouraged when resistance levels are high	Niche-forming can occur, maintaining polymorphism in situations when it would not be expected	[61]	Moderate (avoid AB use when resistance is high)
HIV	Structured treatment interruptions	Interruption strategies w short-term suppression do not guarantee long-term clinical benefit	[62]	Interrupted Treatment not beneficial
P. aeruginosa	Range of dosing regimens of fluoroquinolones	Highest dose most effective in reducing both total bacterial load and resistant subpopulation	[63]	Aggressive Treatment (high dose)
Bacteria	Time course of antibiotic concentration (e.g. patient adherence)	*S.* Emergence of resistance is maximal at an intermediate rate of antibiotic-mediated killing II) Large, infrequent doses can be advantageous if the first dose kills intermediately resistant subpopulation.	[64]	Aggressive Treatment (high dose)
S. pneumoniae	Dose distribution of beta-lactams in population of patients	Limiting beta-lactam use while increasing the doses reduces the prevalence of resistance, but selects for higher levels of resistance	[65]	Aggressive Treatment (high dose)
TB	Prophylaxis with isoniazid	Antibiotic prophylaxis gives resistant strains exclusive access to hosts and therefore strongly selects for resistance	[66]	Moderate (prophylaxis can be dangerous)
Bacteria	Varying dosages and durations	High-dose, full-term antimicrobial chemotherapy maximizes cure rate and minimizes de novo resistance acquisition	[67]	Aggressive Treatment (high dose, long duration)

Malaria	Varying drug efficacy and duration of treatment (model based on absolute fitness)	High efficacy and long duration of drug treatment delays the emergence of drug resistance	[68]	Aggressive Treatment (high dose, long duration)

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