ANTIBIOTIC RESISTANCE

Minimizing treatment-induced emergence of antibiotic resistance in bacterial infections

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Treatment of bacterial infections currently focuses on choosing an antibiotic that matches a pathogen's susceptibility, with less attention paid to the risk that even susceptibility-matched treatments can fail as a result of resistance emerging in response to treatment. Combining whole-genome sequencing of 1113 pre- and posttreatment bacterial isolates with machine-learning analysis of 140,349 urinary tract infections and 7365 wound infections, we found that treatment-induced emergence of resistance could be predicted and minimized at the individual-patient level. Emergence of resistance was common and driven not by de novo resistance evolution but by rapid reinfection with a different strain resistant to the prescribed antibiotic. As most infections are seeded from a patient's own microbiota, these resistance-gaining recurrences can be predicted using the patient's past infection history and minimized by machine learning–personalized antibiotic recommendations, offering a means to reduce the emergence and spread of resistant pathogens.

Urinary tract infections (UTIs) and wound infections are two of the most common conditions for which antibiotics are prescribed (*1*–*3*). These infections are frequently seeded from bacteria from a patient's own microbiota; uropathogens can persist for years in a patient's gut microbiota, which often acts as a reservoir for future infections (*4*–*6*). Wound infections are commonly caused by pathogens from a patient's skin microbiota, as well as pathogens from the gut flora (*7*). Both UTIs and wound infections can be treated by a range of antibiotics, but resistance is widespread among the causative pathogens, and considerable efforts are being made to develop strategies to minimize susceptibility mismatches, where an antibiotic is mistakenly prescribed to treat an infection resistant to it (*8*–*10*).

Yet even when an antibiotic is correctly prescribed to treat a pathogen sensitive to it (i.e., susceptibility-matched), treatment is a double-edged sword: It may clear the ongoing infection, but it may also select for resistant pathogens among a patient's resident microbial population, limiting current and future treatment efficacy (*11*, *12*). Indeed, prior antibiotic use is a strong risk factor for resistant UTIs and wound infections at the individual-patient level (*8*, *13*–*19*). This is especially problematic because these infections are often recurrent or chronic, with patients receiving multiple courses of antibiotics (*3*, *4*, *20*, *21*). Despite the importance of the emergence of resistance during or after treatment, we know very little about the mechanisms by which it occurs, and we lack strategies to prevent it (*22*). Currently, antibiotic choice focuses on avoiding antibiotics to which the ongoing infection is already resistant, however, it remains unknown if it is possible to select among the susceptibility-matched antibiotics in ways that minimize the risk of treatment-induced emergence of resistance at the individual-patient level.

To understand and predict personal risk of treatment-induced gain of resistance, we combined whole-genome sequencing of isolates from same-patient recurrent infections with analysis of a longitudinal dataset of UTIs and wound infections collected by Israel's Maccabi Healthcare Services (MHS) between June 2007 and January 2019. We identified 215,732 MHS patients with at least one record of a UTI (defined as a UTI diagnosis made by a physician followed within 7 days by a positive urine culture with a bacterial count of $>10^5$ colony-forming units per milliliter) (figs. S1 and S2) and 20,373 MHS patients with at least one record of a positive wound infection culture. For these patients, we collected clinical data including antibiotic susceptibilities and species identification from all positive cultures, antibiotic purchases, and patient demographics (age, gender, and pregnancy status). For UTI patients, we also collected potential comorbidities of chronic kidney disease and diabetes (*23*) and records of urinary catheterization (*24*) (tables S1 and S2). Randomly generated patient identifiers were used to link these different patient records. Resistance profiles were classified in accordance with the Clinical and Laboratory Standards Institute guidelines, with intermediate-level resistance grouped as sensitive. We identified 41,769 untreated UTI cases [defined as a UTI with no antibiotic purchases between 7 days before the sample was taken and the next positive sample or 28 days after the sample was taken (whichever comes first)] and 140,349 single-antibiotic treated cases [where, within 4 days of the sample being taken, one of the eight most frequently prescribed systemic antibiotics was purchased: combination trimethoprim/sulfamethoxazole (sulfa), ciprofloxacin, ofloxacin, combination amoxicillin/clavulanic acid (CA), cefuroxime axetil, cephalexin, nitrofurantoin, or fosfomycin] (table S3). Similarly, for wounds, we identified 7365 infections treated with one of the five most frequently prescribed oral systemic antibiotics (amoxicillin/CA, ciprofloxacin, cefuroxime axetil, cephalexin, and trimethoprim/sulfa). We further categorized these infections by their short-term clinical outcomes, indicating whether they resulted in an "early recurrence," defined as a second positive sample recorded within 4 to 28 days after the first positive sample (13,517 treated UTIs, 7933 untreated UTIs, and 442 treated wound infections).

Even for treatments correctly matching the susceptibility of the infection, early recurrence was common and was associated with infections gaining treatment-specific resistance. Cases were categorized into six groups on the basis of whether their initial infection was sensitive or resistant to the specified antibiotic (S→ and R→, respectively) and on the basis of their outcome: recurrence with a sensitive infection, recurrence with a resistant infection, or no recurrence (→S, →R, and →∅, respectively) (Fig. 1A). Although susceptibility-matched antibiotic treatments (S→) had a lower overall rate of recurrence than did mismatched treatments (R→), recurrences were still common (UTIs, 9.2%; wound infections, 5.1%) and frequently gained resistance to the prescribed antibiotic (S→R) (Fig. 1, B and G). Indeed, 30% of all UTI and 19% of all wound infection recurrences gained resistance after antibiotic treatment (S→R), with this fraction strongly varying by antibiotic, reaching as high as 59% (UTIs) and 27% (wounds) of recurrent infections after treatment with the first-line antibiotic ciprofloxacin (Fig. 1, C and H). These gained-resistance cases were strongly associated with treatment, with infections preferentially gaining resistance to the prescribed antibiotic class (Fig. 1, F and I) and temporally peaking soon after the last day of the antibiotic course (Fig. 1E and fig. S4). Compared with untreated cases, susceptibility-matched antibiotic treatment had two counteracting effects: It decreased the overall risk of UTI recurrence (the sum of S→S and S→R) but increased the risk of gained-resistance recurrence (S→R) (Fig. 1D and figs. S5 and S6).

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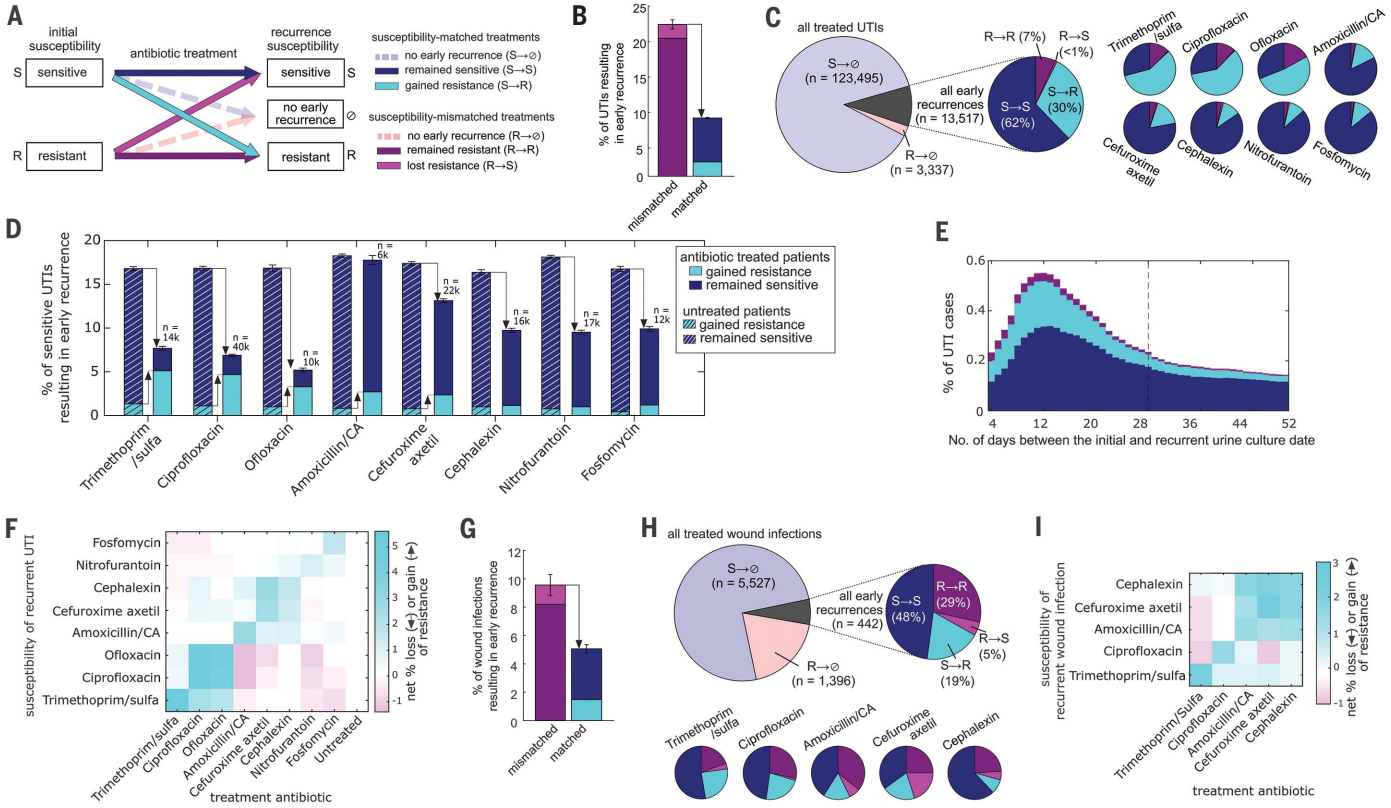

Fig. 1. Posttreatment recurrences are strongly associated with the infection gaining resistance specifically to the treatment antibiotic. (**A**) Each infection case was categorized into one of six possible groups on the basis of the susceptibility and treatment outcome. (**B** and **G**) The overall rate of recurrence for UTIs (B) and wound infections (G) after either susceptibility-matched or susceptibility-mismatched antibiotic treatments. (**C** and **H**) The percentage of all antibiotic-treated UTIs (C) and wound infections (H) resulting in early recurrence, and a breakdown of these early recurrences by their pre- and posttreatment susceptibility to the treatment antibiotic, for all treated cases and for each of the most frequently prescribed antibiotics. (**D**) The rate of early recurrence for UTIs initially sensitive to the specific antibiotic and either treated with this antibiotic (solid bars) or untreated (hashed bars). The cases are further categorized according to whether they recurred still sensitive to the specified antibiotic (dark blue) or recurred while gaining resistance to it (cyan). Susceptibility-matched treatment decreases the overall risk of early recurrences (down-pointing arrows) yet increases the risk of recurrence with gained resistance (up-pointing arrows). (**E**) The rate of UTI recurrences occurring on each day after antibiotic treatment (7-day moving average). Each recurrent case is categorized by pre- and posttreatment susceptibility to the prescribed antibiotic, as shown in (A). The dashed vertical line shows the 28-day threshold used to define early recurrences. (**F** and **I**) The net change in susceptibility of early recurrent UTIs (F) and wound infections (I). For infections treated with each antibiotic (*x* axis) or untreated (UTIs), the percentage of gain of resistance (cyan) minus loss of resistance (magenta) to each specified antibiotic is shown (*y* axis).

The large number of correctly treated infections that subsequently gained resistance could be caused by three possible mechanisms: evolution of resistance through mutations, through dedicated resistance genes, or through reinfection with a different strain resistant to the antibiotic (strain replacement) (Fig. 2A). To distinguish between these possibilities in UTIs, we collected 1113 isolates from 510 patients who experienced early UTI recurrence during a 4.5-month period (30 November 2017 to 16 April 2018). We focused on *Escherichia coli*, which accounts for 70 to 95% of all UTIs (table S4) (*4*, *22*, *25*). Sequencing these *E. coli* isolates, we analyzed the genetic relatedness among same-patient isolates collected before and after treatment and identified any differences in gene content or mutations in antibiotic target and resistance genes (see materials and methods in the supplementary materials).

The genomic analysis showed that while the same *E. coli* strain often persists in early UTI recurrences that do not gain resistance, resistance-gaining recurrences were caused by strain replacement. No cases were identified of resistance appearing through point mutations in the originally infecting strain. Analyzing strain relatedness, we found that while reinfection with a different strain was rare in recurrences that did not change resistance to the treatment (19% of S→S or R→R cases), it was the dominant mode in infections gaining resistance (93% of S→R cases; $P = 1 \times 10^{-27}$ compared with cases that did not gain resistance, Fisher test) (Fig. 2, B and C, and table S5). For example, despite the ability of *E. coli* to readily evolve resistance to ciprofloxacin through point mutations in the target enzymes DNA gyrase subunit A (*gyrA*) and DNA topoisomerase IV subunit A (*parC*) in lab conditions (*26*), we found that all UTI cases that gained resistance were caused by reinfection with a different strain carrying ciprofloxacin-resistant alleles of *gyrA* and *parC* (31 of 31 S→R cases were caused by a different strain compared with 6 of 25 S→S cases; $P = 4 \times 10^{-10}$, Fisher test) (fig. S7) (*27*). Similarly, while trimethoprim resistance can be acquired through point mutations in the target enzyme dihydrofolate reductase (DHRF) (*28*), posttreatment resistance was instead conferred by strain replacement (9 of 12 cases) or by the acquisition of a gene encoding a trimethoprim-resistant DHFR enzyme (3 of 12 cases; table S6) (*29*). Consistent with untreated cases having a much lower rate of gained-resistance recurrence, we found that strain replacement was rare in untreated cases (13%; Fig. 2, D and E). Furthermore, even for antibiotics for which *E. coli* resistance is rare, such as fosfomycin and nitrofurantoin (fig. S8),

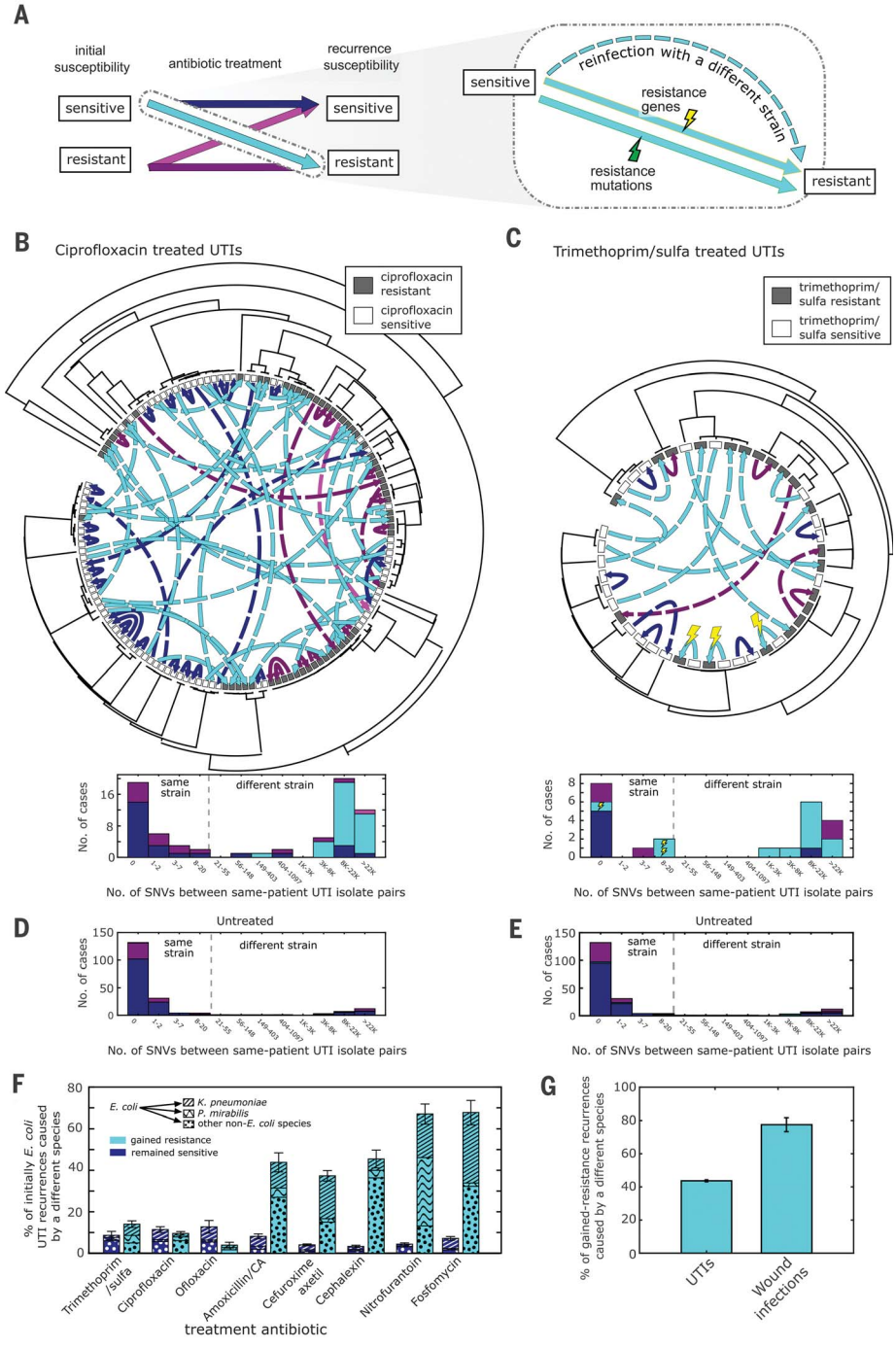

Fig. 2. Genomic analysis of infecting pathogens before and after antibiotic treatment. (**A**) Infections that recurred with gained resistance after treatment (cyan) could be a consequence of acquiring resistance-conferring mutations (green lightning bolt), resistance-conferring genes (yellow lightning bolt), or reinfection with a different strain resistant to the antibiotic (dashed arrow). (**B** and **C**) Phylogenetic trees of *E. coli* urine culture isolates collected from patients who experienced early recurrence after treatment with ciprofloxacin (B) or trimethoprim/sulfa (C), with isolate resistance and sensitivity to the prescribed antibiotic indicated by gray and white boxes, respectively. Same-patient isolates are connected with arrows whose color and style represent change in infection susceptibility and mechanism of gain of resistance [as defined in (A)]. Histograms show the genetic distance, in number of single-nucleotide variations (SNVs), between these same patient isolate pairs, again categorized by infection susceptibility and mechanism of gain of resistance [as defined in (A)]. Vertical dashed lines represent the threshold used to define same-strain versus different-strain recurrences. (**D** and **E**) Histograms of the genetic distance in SNVs between same-patient isolates in untreated cases categorized by infection susceptibility to ciprofloxacin (D) or trimethoprim/sulfa (E). (**F**) The percentage of *E. coli* infections treated with a susceptibility-matched antibiotic that resulted in early recurrence with different non–*E. coli* species (bar patterns), for recurrences that remained sensitive (dark blue) or gained resistance (cyan) to the prescribed antibiotic. (**G**) The percentage of gained-resistance recurrences in all UTIs and wound infections that were caused by reinfection with a different species.

early recurrence with gained resistance after treatment of an initially sensitive *E. coli* infection was strongly associated with reinfection with a different resistant strain, yet this time of an entirely different species (Fig. 2F). Overall, 44% of gained-resistance UTI recurrences were caused by a different species (Fig. 2G). A similar pattern was observed for wound infections: Although the rate of change of species was low among recurrent wound infections that remained sensitive to the treatment antibiotic (fig. S9), in most infections that gained resistance (78%), the species that caused the gain of resistance was not present in the original infection (Fig. 2G). Together, these results suggest that selection for existing resistant strains rather than de novo evolution is the predominant mechanism of treatment-induced emergence of resistance.

Given that posttreatment resistance was typically caused by strain or species replacement rather than by spontaneous, and therefore unpredictable, mutations, we wondered whether emergence of resistance may in fact be predicted at the individual-patient level. As strains are known to recur across same-patient infections even years apart (*6*), we hypothesized that patients with a history of infections with strains resistant to a given antibiotic are at higher risk of gained-resistance recurrence after susceptibility-matched treatment with that antibiotic (Fig. 3A). To test this hypothesis, we performed multivariate logistic regressions of the risk of recurrence with gained-resistance given patient demographics and past infection history among all infections treated with

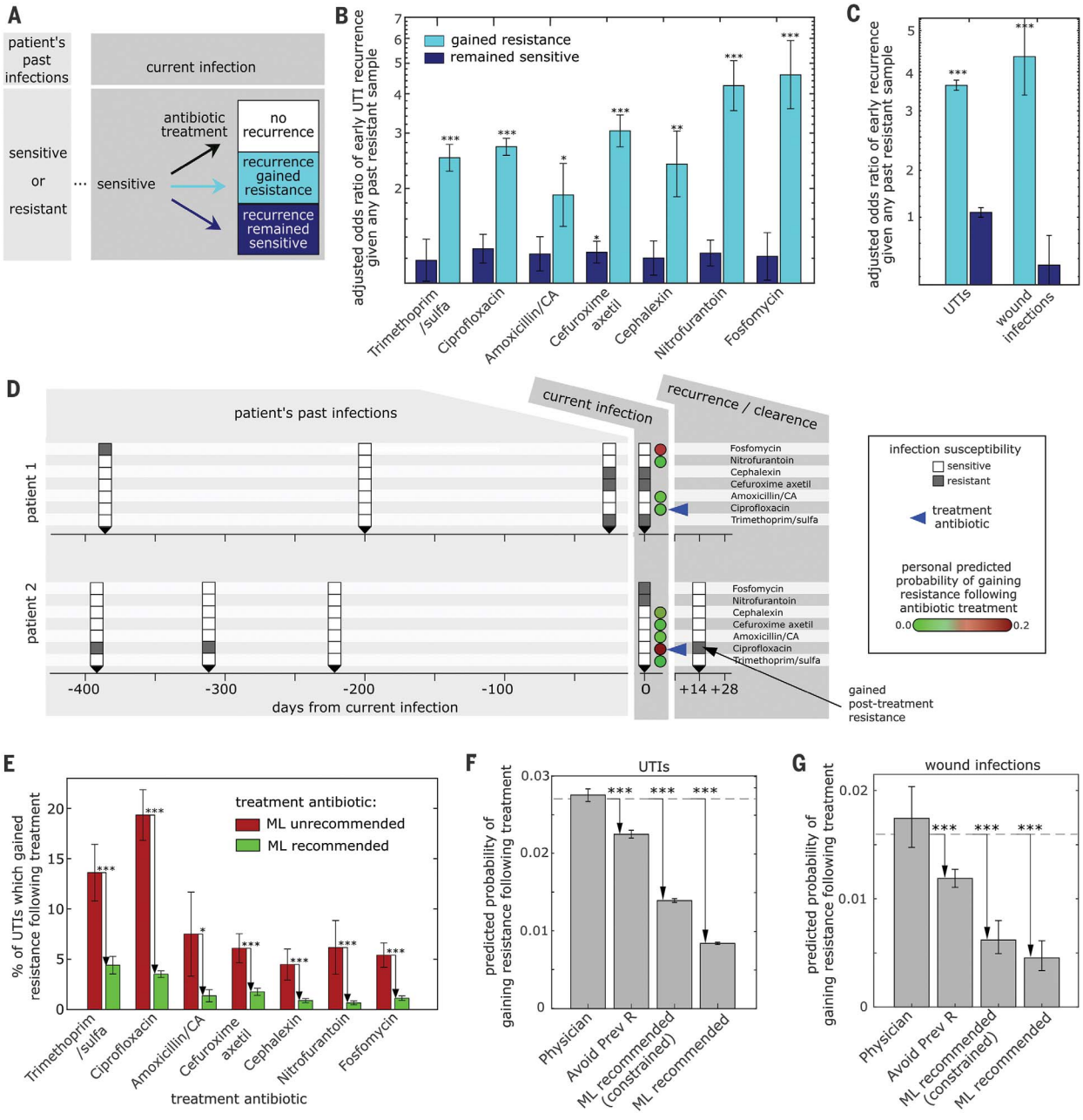

Fig. 3. Personalized, antibiotic-specific predictions of treatment-induced emergence of antibiotic resistance. (**A**) Schematic showing the possible outcomes of susceptibility-matched antibiotic treatment for patients with a recorded history of prior infection susceptibility to the currently prescribed antibiotic. (**B**) Odds ratio of risk of early recurrence that gained resistance (cyan) or remained sensitive (dark blue) given the patient's prior history of resistant infections (binary 1/0: any prior resistance to the prescribed antibiotic, or no prior resistance to the prescribed antibiotic). For each antibiotic, all susceptibility-matched treated cases for patients with any prior infections within the past 3 years are considered. Odds ratios are adjusted for demographics (age, gender) and potential risk factors (pregnancy, catheter use). (**C**) The adjusted odds ratio of early recurrence given the patient's prior history of resistant infections for all antibiotic treatments combined for both UTIs and wound infections. (**D**) Timeline of two example patients showing the susceptibilities of their current (t = 0) and prior (t < 0) infections for each antibiotic (white, sensitive; gray, resistant), as well as their ML-predicted probability of recurrence with gained resistance upon treatment of their current infection with each of the antibiotics (circles, green-to-red colormap). Despite both patients being treated with the same antibiotic to which their infection was sensitive, ciprofloxacin (blue arrow), they had very different ML personal predicted risk of gaining posttreatment ciprofloxacin resistance and indeed varied accordingly in their treatment outcome. (**E**) The percentage of UTIs within the 14-month test period that gained resistance after treatment for cases prescribed an antibiotic that was not recommended ("unrecommended," red, 15% highest predicted risk) or recommended (green, 85% lowest predicted risk) by the ML algorithm (these results are robust to the choice of grouping intermediate-level resistance with resistant, fig. S16). (**F** and **G**) The overall predicted probability of gaining resistance for all UTIs (F) and wound infections (G) during the test period for four different antibiotic prescription methods: (i) the actual antibiotic prescribed by the physician, (ii) an algorithm that randomly chooses an antibiotic but avoids antibiotics to which the patient had past resistance, and the ML recommendation either (iii) unconstrained or (iv) constrained such that each antibiotic is recommended at the exact same frequency as prescribed by the physicians. The dashed line represents the actual gained-resistance rate for the physician-prescribed antibiotics during the test period. *P < 0.05; **P < 0.005; ***P < 0.0005.

a susceptibility-matched antibiotic (136,047 UTIs and 5821 wound infections). Despite all of these cases being treated "correctly," that is, with a susceptibility-matched antibiotic, their risk of recurrence with gained resistance was not uniform: Patients with past infections resistant to the currently prescribed antibiotic were at much higher risk of recurring with gained resistance to the treatment than were patients whose previous infections were sensitive (Fig. 3, B and C; see tables S7 and S8 for regression coefficients). The association between the susceptibility of past infection and the risk of resistance emerging remained significant even for prior infections dating up to 4 years before the current UTI (fig. S10). In contrast, there was no or a much weaker association between past infection susceptibility and risk of early recurrence without gain of resistance, showing that this approach specifically predicts the emergence of resistance rather than merely the risk of early recurrence. A patient's past infection susceptibility was much more predictive than their past antibiotic purchases, which is consistent with within-host selection for strains persisting in the microbiota rather than de novo resistance evolution driving treatment-induced gain of resistance (fig. S11). Finally, beyond the important contribution of personal infection history, we also note the contribution of age and gender to risk of treatment-induced gain of resistance (tables S7 and S8).

Because some patients were at high risk of their infection gaining resistance to the treatment antibiotic, we asked whether the risk of such gained-resistance recurrences may be reduced with an alternative antibiotic. We developed machine learning (ML) algorithms for personalized antibiotic recommendations that minimize the predicted risk of treatment-associated emergence of resistance for both UTIs and wound infections (Fig. 3D). For each antibiotic, we trained a logistic regression model to predict the risk of acquiring resistance during or soon after treatment on the basis of patient demographics (age, gender), potential risk factors (pregnancy, catheter use for UTIs), and their record of prior infections, including the number of past sensitive and resistant isolates. Trained on an initial period and then tested on a temporally separated test period (UTIs: 14 months; wound infections: 30 months), the models predict the risk of resistance emergence well (the area under the curve ranged from 0.89 for nitrofurantoin to 0.62 for amoxicillin/CA in UTIs, and from 0.96 for amoxicillin/CA to 0.58 for cefuroxime in wound infections; ofloxacin was not included, because it was not routinely measured during the test period; fig. S12). More practically, binarizing the patient-specific ML predictions for UTIs into high-risk treatments ("unrecommended," 15% highest ML-predicted risk of gained-resistance recurrence) and lower-risk treatments ("recommended," all others), we found that for every antibiotic, patients for whom the prescribed antibiotic was classified as unrecommended by the ML algorithm acquired antibiotic resistance at a significantly higher rate than did those for whom the antibiotic was recommended, even though all of these cases were treated "correctly" with a susceptibility-matched antibiotic (Fig. 3E; the trends are robust with respect to the recommendation threshold; fig. S13).

Analyzing all susceptibility-matched treated cases in the test period, we found that in most cases there was an alternative susceptibility-matched antibiotic that had a lower patient-specific predicted risk of resistance emerging compared with the antibiotic prescribed by the physician (77% of UTIs and 76% of wound infections). Choosing for each patient the antibiotic with the lowest ML-predicted risk of emergence of resistance (ML recommended) reduces the overall risk of emergence of resistance by 70% for UTIs and 74% for wound infections compared with the risk for physician-prescribed treatments (Fig. 3, F and G). Given that many factors contribute to the rate at which physicians prescribe each antibiotic, such as antibiotic efficacy, cost, ease of use, and side effects, we also developed a constrained antibiotic recommendation model that minimizes the risk of emergence of resistance while preserving the same prescription frequency of each antibiotic as prescribed by physicians during the test period (fig. S14) (*14*). Even these constrained antibiotic recommendations, which merely permute the physician-prescribed antibiotics among patients, can reduce the risk of resistance emerging after treatment by 48% for both UTIs and wound infections compared with the physician-prescribed antibiotics (Fig. 3, F and G). To demonstrate that these constrained recommendations could be made on a case-by-case basis, we also show that the model remains effective when constrained to the physician prescription frequency during a temporally separated period before the final model evaluation period (fig. S14). We note that a simpler algorithm that randomly chooses an antibiotic but avoids antibiotics to which the patient had past resistance can still reduce the risk of resistance emerging after treatment, albeit at a lower frequency than either of the ML models, which is consistent with the contribution of other factors including age, gender, and the more quantitative representation of past infections (Fig. 3, F and G). Furthermore, analyzing the distribution of ML-recommended antibiotics for subsets of patients, such as those with past resistance to a specific antibiotic, may help guide treatment recommendations more broadly (fig. S15). Importantly, the constrained ML models also reduce overall predicted risk of early recurrence (the sum of S→S and S→R), showing that this personalized approach not only reduces gained-resistance recurrences but, by doing so, may also reduce the overall recurrence risk (fig. S17).

While much effort is being invested in methodologies for matching antibiotic treatment to infection susceptibility, susceptibility-matched treatments often fail, as they select for emergence of resistance by means of reinfection with different strains specifically resistant to treatment. The strong association between such treatment-induced selection for resistance and personal history of past resistant infections suggests a patient-specific strain reservoir. Given the known role that uropathogens and wound pathogens persisting in a patient's microbiota have in seeding new infections (*4*–*6*, *30*, *31*) and the collateral effect that antibiotics can have on a patient's microbiome (*32*–*34*), it will be interesting to see whether these emerging resistant strains can be detected in a patient's fecal or skin flora. Regardless of the exact source of these reinfecting resistant strains, our results show that a patient's past infection susceptibility data and patient demographics can be used to predict early recurrence with gained resistance after susceptibility-matched antibiotic treatment. We hope these results will serve as a basis for a personalized treatment approach that minimizes the selection and spread of resistant pathogens at both the individual-patient and population levels.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
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References (*36*–*38*)
MDAR Reproducibility Checklist
Data S1

View/request a protocol for this paper from *Bio-protocol*.

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Minimizing treatment-induced emergence of antibiotic resistance in bacterial infections

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Personal histories of past resistance

A serious infection may initially be diagnosed as antibiotic susceptible but subsequently become drug resistant—and life threatening. Rather than de novo resistance mutation occurring, it is more likely that a resistant strain or species persisting in the patient's gut or skin replaced the susceptible strain. From this starting point, Stracy *et al*. built machine-learning models that predict individual risks of gaining resistance to specific antibiotics using 8 years of records on more than 200,000 patients' microbiome profiles (see the Perspective by Lugagne and Dunlop). Data on antibiotic use for urinary tract and wound infections were used to train the algorithms and to develop personalized antibiotic treatment strategies. For most patients, there was an alternative susceptibility-matched antibiotic that had a lower predicted risk of resistance emerging compared with the antibiotic prescribed by the physician. —CA

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