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# **Machine learning approaches prevent posttreatment resistance-gaining bacterial recurrences**

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## **Keywords**

Machine-learning; Antimicrobial resistance; Infection recurrences; Whole genome sequencing

## **Abstract**

Despite susceptibility testing, recurrent infections are common and associated with resistance. Using whole-genome sequencing, Stracy *et al.* demonstrated that recurrence is often driven by a different strain than the original infection. By machine learning analysis, they developed an algorithm for patient-specific recommendations to minimize antimicrobial resistance at the individual-patient level.

The global death toll from antimicrobial resistance (AMR) has recently become ahead of other pathogens including AIDS and malaria, contributing to the deaths of almost five million people in 2019 including 1.27 million cases directly attributed to drug resistance [1]. Infections due to multidrug-resistant (MDR) bacteria are endemic across the world and their prevalence is expanding annually, representing a major therapeutic challenge, particularly when resistance to last-resort antibiotics such as colistin and carbapenem is found. Susceptibility testing can facilitate timely and adequate antibiotic treatment but does not avoid recurrent infections. Resistance trends are strongly associated with previous antibiotic exposure [2]. Recurrence rates in urinary and wound infections are high and usually associated with antibiotic resistance with a higher risk of complications.

Typical surveillance approaches of estimating statistical associations between phenotypic and genotypic resistance require separate analyses for each resistance phenotype [3,4]; thus, innovative artificial intelligence approaches are now increasingly used in the medical system promoting surveillance, antimicrobial stewardship programs, and contact tracing. Predictive algorithms have been developed to assess and monitor AMR as well as anticipate the onset of drug-resistant infections after patient hospitalization [4,5]. The best predictive indicators for AMR can be obtained by combining data from patient-specific demographics, previous resistance patterns, and drug consumption [6]. Undoubtedly, machine learning approaches are now representing a new paradigm to understand AMR trends, guide empirical treatment, and improve the judicious use of antibiotics [7]. Nevertheless, predicting the implication of drug-resistant strains is not always sufficiently discriminant to make recommendations for prescriptions at the individual-patient level.

Using whole-genome comparative sequencing and machine learning analysis of a large-scale longitudinal database of urinary and wound clinical isolates from same-patient recurrent infections, Stracy and coworkers [8] recently developed an antibiotic prescribing algorithm to

understand and predict the personal risk of treatment-induced gain of AMR and minimize the occurrence of early resistance recurrences of urinary and wound infections at the individual-patient level. This study was interested in early recurrences, which are defined as a second positive sample within four to 28 days after the first episode of urinary and wound infections initially successfully treated with a susceptibility-matched antibiotic. The average percentage of gained-resistance recurrences was relatively high among both urinary (30%) and wound (19%) infections, with the highest percentages were observed after treatment with ciprofloxacin or trimethoprim-sulfamethoxazole.

The choice of optimal antibiotic therapy is based on a balance between the probability to cure the current infection without relapse and the risk of the off-target effect of the drug, which has been the source of many debates for decades. The mutation rate of bacteria has been proposed to individualize the better antibiotic to choose with the idea that this mechanism mainly explains the risk of recurrence of an infection. Indeed, recurrent drug-resistant infections may result from the evolution of resistance through *de novo* evolution or reinfection with different resistant bacteria from the host's microbiota. By analyzing the genetic relatedness of *Escherichia coli* isolates, the main cause of urinary-tract infections, from 510 patients who experienced early recurrent urinary infections, current evidence deciphered that the gained-resistance recurrence was commonly conferred by the selection of different existing resistant strains which replace the original isolates responsible for the initial infections. Regarding antibiotics for which *E. coli* resistance is rare (e.g., nitrofurantoin, fosfomycin), 44% and 78% of gained-resistance recurrences in urinary and wound infections were caused by an entirely different species, respectively.

Interestingly, compared to treated patients, untreated cases showed an increased overall risk of urinary recurrent infections, but a much lower rate of gained-resistance recurrences associated with a few events of original strain replacement. These findings concurred with

other studies that highlighted the potential role of changing antimicrobial prescribing behavior and modulating the patient microbiota to prevent infections [9,10]. The authors underlined the ability to use the previous infection history to anticipate the emergence of resistance in recurrent infections at the individual-patient level, which also confirms the initial findings of the selection of existing resistant strains persisting in the microbiota. After accounting for personal demographics (gender, age) and infection history, multivariate logistic regression analysis demonstrated that patients with prior infections, dating up to four years before the current infection and resistant to a given antibiotic, were at much higher risk of recurring with gained resistance to the same antibiotic prescribed for the original infection than were patients whose past infections were sensitive. Moreover, age and gender are significantly associated with the risk of treatment-induced gain of resistance.

Using supervised machine-learning models for each antibiotic, the study emphasized the importance of adjusting antibiotic treatment to curb the emerging early recurrent infections resistant to the initially prescribed antibiotic agent (figure 1). The adopted models integrating data from patient demographics, potential risk factors (catheter use, pregnancy), and past infections allowed to successfully predict individual risks of gaining resistance to specific antibiotics, and consequently minimize the occurrence of early resistance recurrences by almost half compared with those of physicians' susceptibility-matched prescriptions (i.e., this method of analysis divided the patient-specific machine learning predictions for urinary infections into high- and low-risk treatments, equivalent to unrecommended and recommended treatments, respectively). The authors demonstrated that considering recommended treatments for each patient reduced the overall risk of emergence of resistance for urinary (70%) and wound (74%) infections when compared with the risk for physician-prescribed antibiotics.

In summary, this outstanding study highlighted that the emergence of AMR could be predicted in individual patients' infections. Unquestionably, combining genomic techniques and machine learning models can promote accurate antibiotic treatments by providing greater detail about drug resistance than standard antibiogram methods. In perspective, the resulting predictive models may be applied at the point of care to significantly improve current physician prescribing practices (e.g., personalized antibiotic treatments) and antimicrobial stewardship programs across the world. However, even though the importance of the current data-driven methods for healthcare, the clinical significance of the suggested algorithms should be further confirmed on actual patients through prospective longitudinal interdisciplinary investigations. Furthermore, there is a critical need to investigate other infections, particularly respiratory and bloodstream infections, as well as long-term resistance recurrences beyond the 28-day defined window.

**Figure 1:** Interest of a machine-learning system in preventing resistant recurrences after antimicrobial treatment and recovery

**Legend:**

For each individual patient, by considering demographic data, particular health status, invasive procedures, infection history and past resistance, the machine learning system allows to prescribe antibiotics with minimizing the occurrence of resistance recurrences.

## References

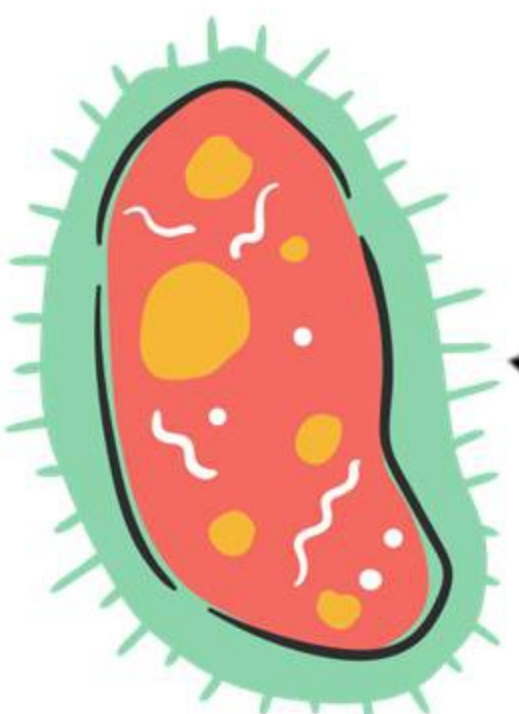
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Past infections

Current infection (Urinary or Wound)

Early gained-resistance recurrence (Yes/No)



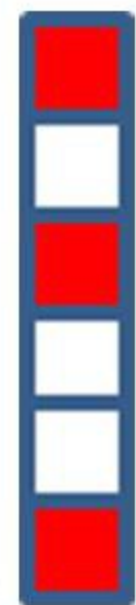
RECOVERY



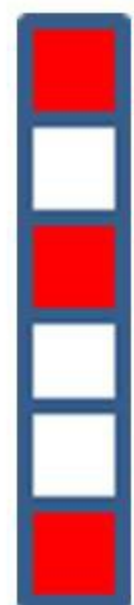
RECOVERY



Same species (different clone)



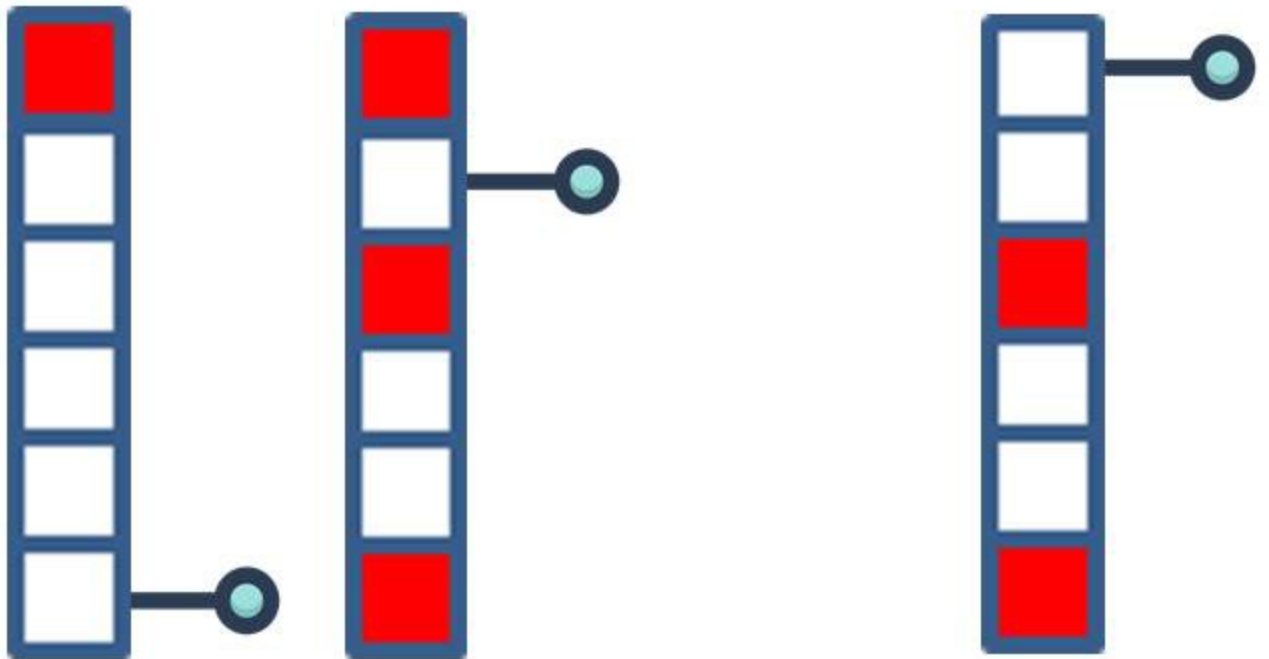
Different species



No infection

Average percentage: 30% (urinary infections) and 19% (wound infections)

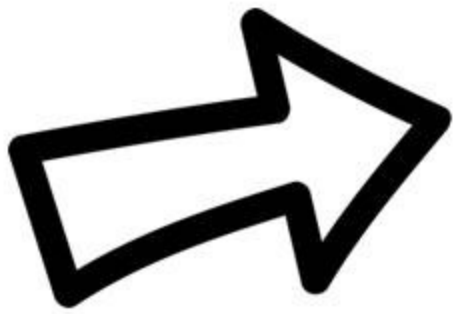
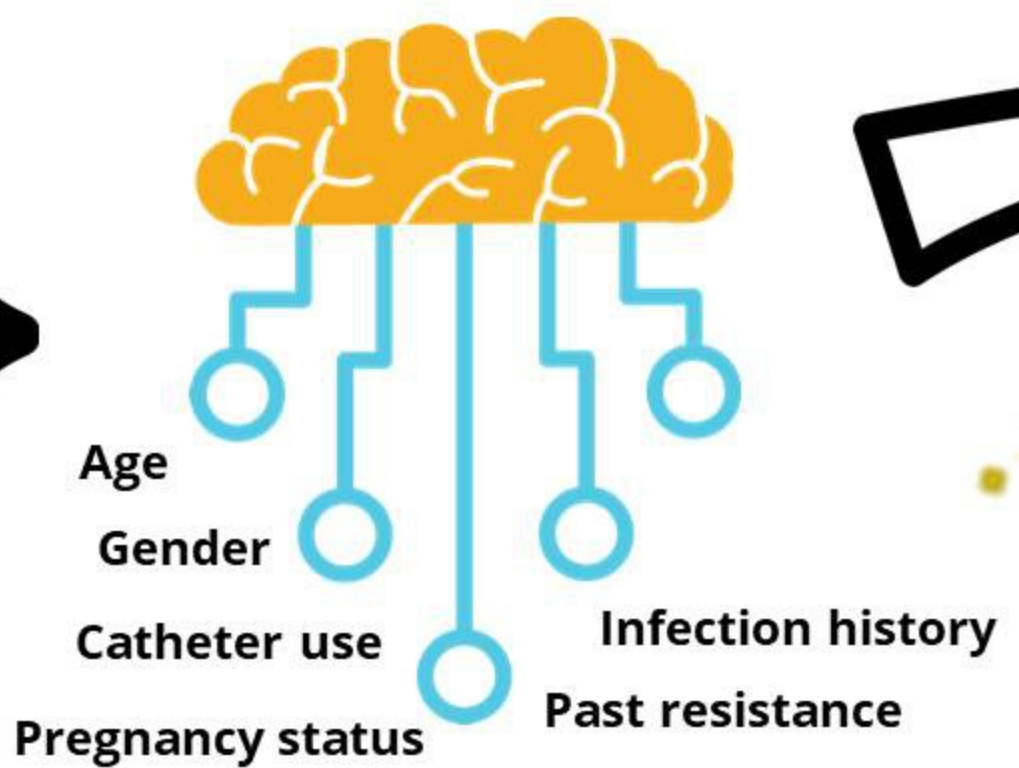
Susceptibility testing



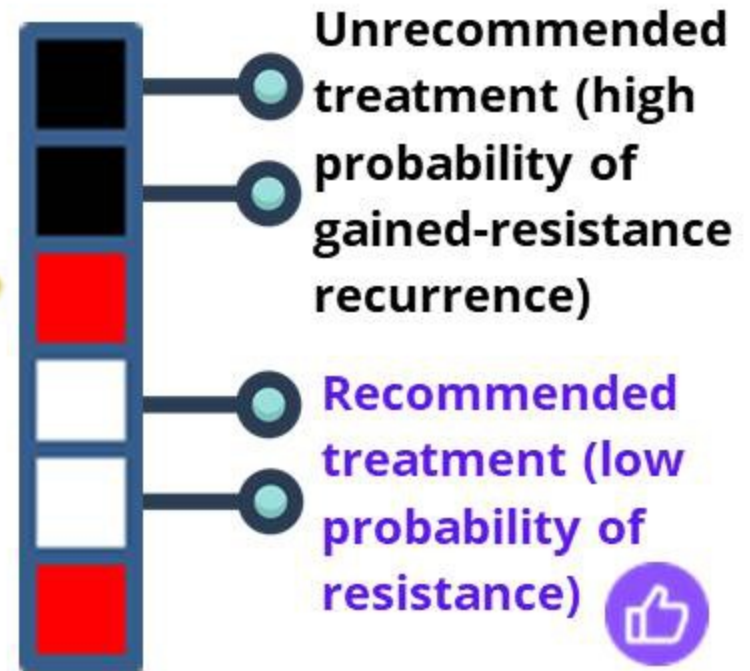
Appropriate treatment based on susceptibility-matched antibiotics

Resistant antibiotic (red square)  
Susceptible antibiotic (white square)

Supervised machine-learning models for each antibiotic



Antibiotic recommendation for current infection



Unrecommended treatment (high probability of gained-resistance recurrence)  
Recommended treatment (low probability of resistance)