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van der Werf, Tjip S.

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EDITORIAL COMMENTARY

Artificial Intelligence to Guide Empirical Antimicrobial Therapy–Ready for Prime Time?

Tjip S. van der Werf

Department of Internal Medicine, Division of Infectious Diseases, University Medical Center Groningen University of Groningen, Groningen, The Netherlands

(See the Major Article by Lewin-Epstein et al on pages e848–55.)

Nosocomial infections by drug-resistant gram-negative bacteria and *Staphylococcus aureus—especially* methicillin-resistant *S. aureus* (MRSA)—impose a huge public health threat [1]. Mortality increases if initial antimicrobial therapy is inappropriate [2]. Doctors are aware of this daunting perspective, and fueled by their fear to leave such organisms uncovered, they often feel seduced to prescribe excessive, and sometimes, even inappropriate antimicrobials [3]. The ensuing cumulative antimicrobial pressure has long been recognized as the main driver of drug resistance [4, 5]. A policy to use reserve antimicrobials in a cycling pattern, rather than in a random, mixed pattern, does not help to reduce bacterial resistance in the high-risk environment of Intensive Care Units (ICU) [6]. In Dutch ICUs, oral and intestinal nonresorbable antimicrobials—colistin, tobramycin and amphotericin—combined with systemic cefotaxime for 4 consecutive days—resulted in a small but significant survival advantage [7]. However, in ICUs with a high pressure of resistant bacteria, selective digestive decontamination did not reduce blood stream infections caused by these bacteria, compared to standard care, chlorhexidine mouth and skin treatment, or oral selective decontamination [8]. Education on the risks of antimicrobial pressure, with instructions on updated guidelines for the treatment and prevention of nosocomial infections do not invariably address the emotional component of prescribers.

"Antimicrobial Stewardship," a term that has been used for more than 2 decades now [3], has been designed to address both cognitive, or intellectual, and emotional factors, that make prescribers change their behavior [9]. Antibiotic Stewardship Programs (APS) that included a direct feedback to prescribing clinicians, with information on culture and susceptibility results, epidemiological information, and updated guideline information, seem to work best. Two days after starting empirical antimicrobial treatment, by the time culture and susceptibility testing are available, a team of hospital pharmacists, clinical microbiologists, and infectious disease specialists consult with prescribers [10].

APS have been shown to reduce antimicrobial use, both in terms of reducing duration and choice of reserve antimicrobials [11]. These programs appear safe and cost-effective [12], and importantly, help to reduce the burden of high-risk pathogens, including resistant (extended spectrum beta-lactamase, ESBL) gram-negative Enterobacteriaceae, and MRSA [13]. These programs might be supplemented by acute-phase assessments, (eg, procalcitonin- or C-reactive protein-driven decisions to stop antimicrobial therapy if response to therapy seems favorable). Using an algorithm with procalcitonin resulted in a significant reduction of treatment duration by 2 days in one multicenter trial in ICU patients [14].

In one study among mechanically ventilated ICU patients with suspected ventilator-associated pneumonia (VAP), undergoing bronchoscopic bronchoalveolar lavage (BAL), researchers hypothesized that IL-1β and IL-8 in BAL might be a good predictor of VAP; they advised stopping empirical antimicrobial treatment if biomarker levels were below a predefined threshold. This approach did not result in earlier discontinuation of antimicrobial treatment in the intervention group [15]; the authors suspected, that emotional factors driving antimicrobial use could not be addressed by this algorithm. The advice given was perhaps smart and safe, but prescribing behavior did not change; indeed, stopping a successful antimicrobial regimen ("never change a winning team") appears difficult. APS surely is an important approach to reduce antimicrobial pressure, and thereby, to fight ever-increasing antimicrobial resistance. Any time soon, we will be running out of antimicrobial options, with no novel antimicrobial products in the pipeline to salvage this problem [16]. A way to safely refrain from using reserve drugs in empirical antimicrobial treatment for our vulnerable patients is to use surveillance culture results in individual patients, collected earlier during hospital admission,

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Correspondence: Tjip S van der Werf, Department of Internal Medicine, Division of Infectious Diseases, PO box 30.001, 9700 RB Groningen, The Netherlands (t.s.van.der.werf@umcg.nl).

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or general information on surveillance data. Using this information, an educated guess of the offending micro-organism for the current febrile episode can be made, to select empirical antimicrobials [17–19]. Could we improve the quality of advice on empirical antimicrobial treatment using machine learning with artificial intelligence (AI) software? Computer-aided pattern recognition has become an integral part of our everyday life. Indeed, AI is involved in prioritizing our likes by analyzing our pattern of internet searching using search engines. Even when I check my smart phone, it opens by recognizing my face, all the result of AI software, that recognizes my face under different angles, even with light only produced by the screen, using machine learning that requires only seconds. AI was perhaps first introduced by space scientists [20], but has become an integral part of our everyday life. AI has entered medicine over 3 decades ago [21], and has impacted on a vast array of diagnostic and therapeutic decisions [22].

In this issue of the Journal, Ohad Lewin-Epstein et al. report a machine-learning model to predict antimicrobial resistance to 5 commonly used antimicrobial agents—Ceftazidime, Gentamicin, Imipenem-cilastin, Ofloxacin, and Cotrimoxazole [23]. To predict the presence of resistant bacteria causing infection to any of these drugs, they used a large database of culture and susceptibility testing from thousands of electronic in-patient records between May, 2013, and December, 2015, in the Rabin Medical Center in Israel. A large part of the data set was used to train the model; they next tested the model in a separate batch of medical records. Should the prediction models be perfect, the area under the receiver-operator curve (AUC) would be equal to 1. Unfortunately, the precision of their prediction model was less than what we need in the clinic; though better than usual care, AUC was only around 0.7. Using information of the typing of the offending organism, the AUC increased to 0.8, but using phenotypic culture-based data, this would result in a considerable delay to start effective treatment. The authors argue that this delay might be overcome using molecular tools to identify the offending organism within hours, but this was not part of their work flow. The study followed the code of conduct to develop this machine learning tool, with large datasets to train, and to validate the model; what should happen next, is testing it prospectively. Could the model be flawed by the time elapsed between the development and the final prospective testing? Should perhaps more data be entered into the model, including comorbid conditions, surveillance data, epidemiological data, genomic, metabolomic, or microbiome data? Is the model, developed for this single medical center, applicable to other locales and settings? Although many questions remain unanswered, this study represents a hallmark in this novel approach, and deserves to be followed by similar approaches with even more sophistication. Perhaps, other technologies might be added, such as breath analysis of volatile organic compounds using machine learning and neural networks [24], an approach that eventually might be developed as a point-of-care test, as has been explored to detect tuberculosis [25, 26]. This work shows, that machine learning—although not yet ready for prime time—will one day help guide initial antimicrobial selection in nosocomial infections. One problem that needs to be addressed, is that clinical decisions are only partly driven by cognition—emotions are equally important. AI-driven machine learning may one day provide overwhelming scientific, cognitive evidence, but prescribers should feel comfortable about it, or else, they would not follow the evidence-driven advice. To incorporate these novel tools, interactive training is required to overcome these emotional barriers, to improve antimicrobial prescription behavior.

Notes

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