EDITORIAL
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Macrolide combination therapy for hospitalised CAP patients? An individualised approach supported by machine learning

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The article by König and co-workers paves the way for the selection of a subset of patients with CAP in whom combination initial therapy including macrolides could improve outcomes using a new and interesting mathematical approach http://bit.ly/2p8RdCD

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The use of macrolides in combination with betalactams to improve outcomes in patients with community-acquired pneumonia (CAP) remains a topic of controversy, mainly because most of the evidence comes from observational studies rather than from randomised clinical trials (RCTs). Some recent studies have suggested that macrolides are effective in patients with *Streptococcus pneumoniae* infection plus a high systemic inflammatory response [1]. However, macrolides can be harmful [2] and there is a clear need to identify CAP phenotypes that would benefit from macrolides without suffering negative effects. We are unlikely to solve this question using conventional study designs; rather, we need to explore new technologies, among them the use of models obtained with machine learning methodology.

In an interesting paper, König *et al.* [3] used new statistical tools, combining propensity matching score with tree decision models (not specified) using non-supervised machine learning (also not specified) to identify patients in whom macrolide use would be beneficial. They found that a simple decision tree of pneumonia patients' characteristics, comprising chronic cardiovascular and chronic respiratory co-morbidities and leukocyte counts in the respiratory secretion at admission, was able to identify the ones who would achieve better outcomes with the addition of macrolide treatment. The results are important and open up new perspectives for conducting optimised, randomised trials to demonstrate the beneficial role of macrolides in patients with CAP.

But probably one of the most interesting features of this paper is the incorporation of new statistical tools in medical research. The machine learning approach involves the study of algorithms used by computer systems to perform a specific task, most of them associated with predictions, without using explicit instructions that rely on patterns. Machine learning builds a mathematical model based on training data in order to make predictions in a test dataset. It includes a heterogeneous range of approaches, such as

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regression models, neural networks and/or deep-learning. The aim is to detect a generalisable predictive pattern, independent of any causal relationships. In the coming years it is conceivable that machine learning will become the basis of a high number data analyses to help in the difficult task of personalising medicine.

Another advantage of this methodology is that it can produce models with variables which clinicians were unaware of or simply had never explored. In this study, for example, the number of leukocytes in sputum was one of the variables associated with a greater macrolide benefit.

However, physicians are still a long way from understanding how machine learning, neural networks or, most importantly, artificial intelligence (AI) tools can further current medical practice. Six studies have recently been published [4–9] using AI approaches to support pneumonia diagnosis and empirical antibiotic decision-making processes. Most of the research has been conducted in the field of pneumonia diagnosis through the study of chest radiographs. In contrast to the single image available to clinicians when analysing a chest radiograph, image processing performed by AI tools can break down an image's architecture into millions of pixels and provide far more accurate computerised discrimination. Therefore, the computer's ability to perform optimal pneumonia diagnosis based on chest radiograph analysis is much greater than that of a human [5].

However, when using machine learning, neural networks and deep learning, the quality of the clinical data is an issue of vital importance. In the study reported by König *et al.* [3], the data were from the prospective manual capture from the CAPNETZ cohort, and were thus of good quality. However, the handling of the missing data is a concern, and represents one of the greatest challenges facing analysts. It is even more complex in the medical setting, where a misinterpretation of the missing values might seriously distort the results.

This is a key point in this paper, in view of the author's comment that 60% of their patients had missing values in one of the significant variables (leukocyte counts in the respiratory secretion) and that those patients were assigned to the low leukocyte group. In a subanalysis, they showed how different management of these missing values changes their results.

We finish with a reflection on what machine learning can contribute to a single unconnected database when outputs are restricted to a limited set of values. Machine learning techniques try to predict the future given the past, and so a reinforcement learning giving feedback from updated data retrieved from a dynamic environment, for example data retrieved directly from electronic health records, seems an optimal methodology for applying AI algorithms in healthcare computer systems in order to support clinical decision-making processes around the clock [6].

In conclusion, the paper by König *et al.* [3] paves the way for the selection of a subset of patients with CAP in whom combination initial therapy including macrolides could improve outcomes. The authors use a new and very interesting mathematical approach to predict the subset of patients in whom macrolides will be useful. This approach should be considered as a useful additional tool at the service of clinicians and researchers.

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