

## Antibiotici/antifungini e intelligenza artificiale: un binomio vincente?



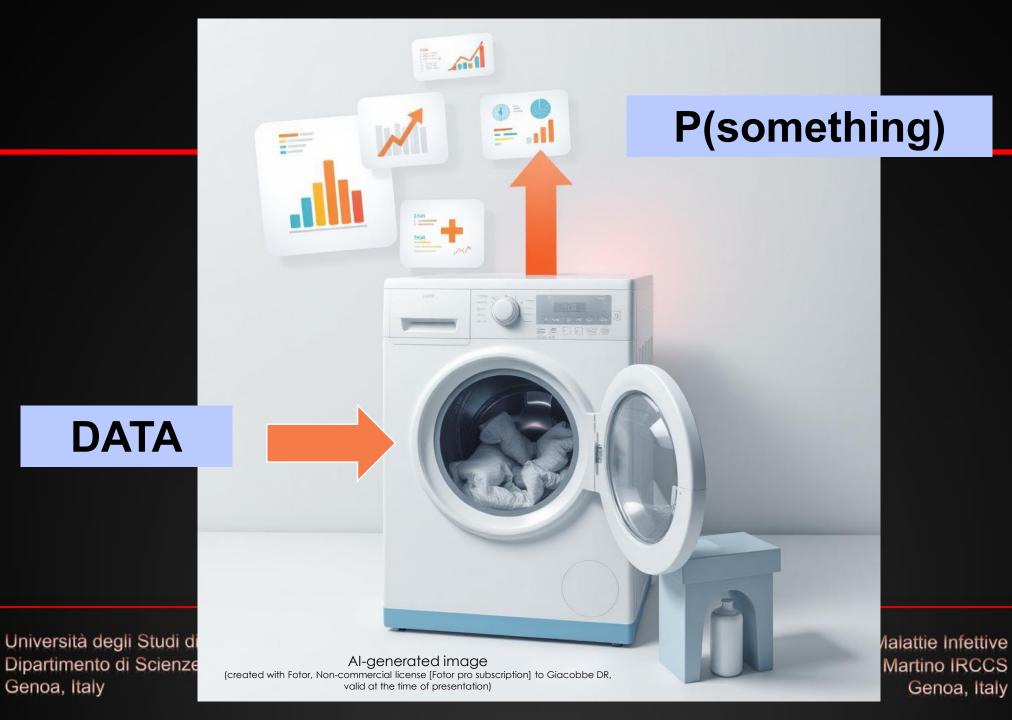
Daniele Roberto Giacobbe, MD, PhD
Clinica Malattie Infettive
IRCCS Ospedale Policlinico San Martino
University of Genoa (DISSAL)



## **Conflicts of interest**

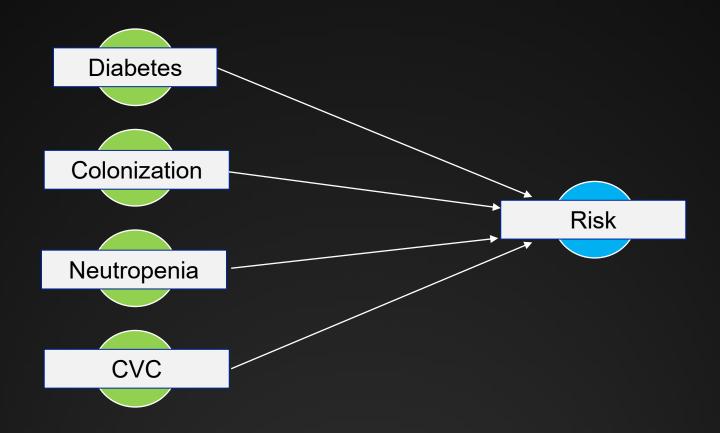
- Investigator-initiated grants (Pfizer, Gilead Italia, bioMérieux, Tillotts pharma, Shionogi, Menarini, Advanz Pharma)
- Personal fees for speaker/consultant (Pfizer, Tillotts Pharma, bioMérieux, Menarini, Advanz Pharma)





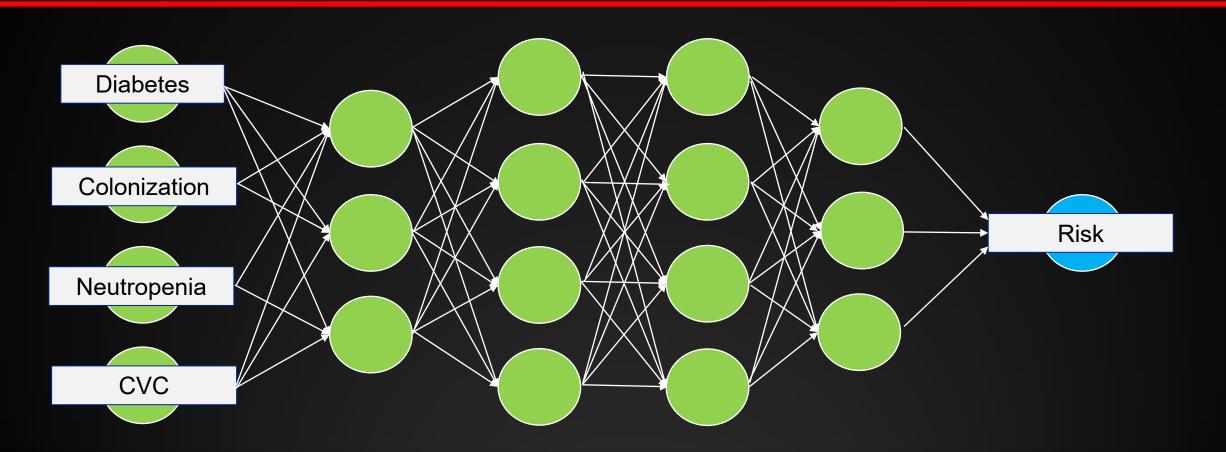
Genoa, Italy

## Example of classical/ML model (e.g., LR)





## Example of ML model (ANNs)

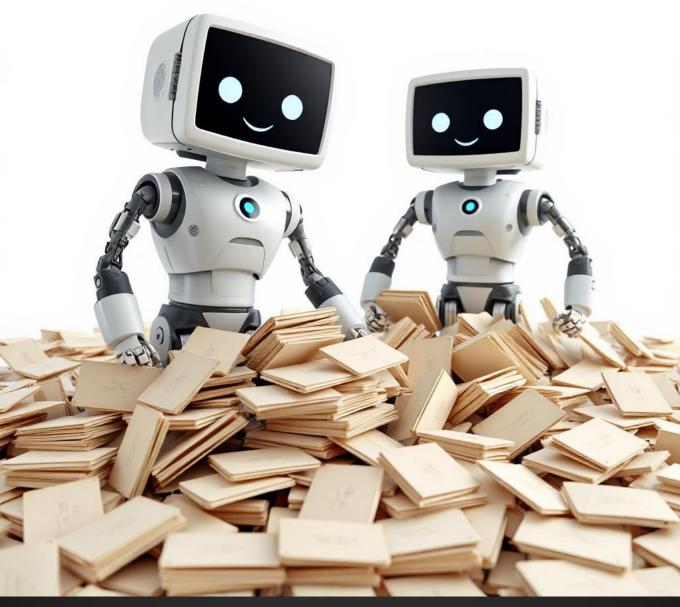




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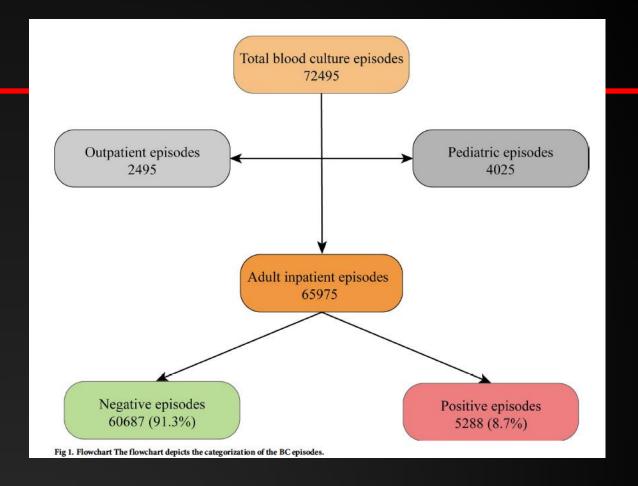
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#### RESEARCH ARTICLE

Leveraging explainable artificial intelligence for early prediction of bloodstream infections using historical electronic health records

Rajeev Bopche 1\*, Lise Tuset Gustad 23, Jan Egil Afset Birgitta Ehrnström 56,7, Jan Kristian Damås 5,6, Øystein Nytrø 18



Bopche R, et al. PLOS Digit Health. 2024 Nov 14;3(11):e0000506.





#### RESEARCH ARTICLE

Leveraging explainable artificial intelligence for early prediction of bloodstream infections using historical electronic health records

Rajeev Bopche<sup>1\*</sup>, Lise Tuset Gustad<sup>2,3</sup>, Jan Egil Afset<sup>4</sup>, Birgitta Ehrnström<sup>5,6,7</sup>, Jan Kristian Damås<sup>5,6</sup>, Øystein Nytrø<sup>1,8</sup>

Table 3. Co	nparative	performance	metrics o	of ML	models.
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Main Study	AUROC	Accuracy	Precision	Recall	F1 Score	AUPRC	Specificity
Sequential Models							
LSTM	0.7568	0.7812	0.2008	0.5592	0.2955	0.3186	0.8011
GRU	0.7830	0.7835	0.2193	0.6400	0.3267	0.3560	0.7964
CNN-LSTM	0.7600	0.7079	0.1732	0.6785	0.2760	0.3115	0.7105
CNN-GRU	0.6973	0.8612	0.2425	0.3256	0.2779	0.2135	0.9091
Transformer	0.7643	0.8167	0.2339	0.5420	0.3267	0.2911	0.8413
DKN	0.6911	0.9012	0.3412	0.2194	0.2671	0.6000	0.9621
CapMatch	0.5003	0.0824	0.0821	1.0000	0.1517	0.5002	0.0004
Static Models							
XGBoost	0.7995	0.8521	0.3191	0.5531	0.4047	0.4336	0.8876
LightGBM	0.8144	0.8046	0.2659	0.6529	0.3779	0.4319	0.8198
CatBoost	0.8181	0.8481	0.3219	0.6061	0.4205	0.4490	0.8750
NN	0.7739	0.9204	0.5241	0.3141	0.3928	0.3944	0.9745
LR	0.7771	0.7497	0.2150	0.6610	0.3244	0.3154	0.7586
RF	0.8407	0.9258	0.8000	0.1276	0.2201	0.4677	0.9971

Bopche R, et al. PLOS Digit Health. 2024 Nov 14;3(11):e0000506.





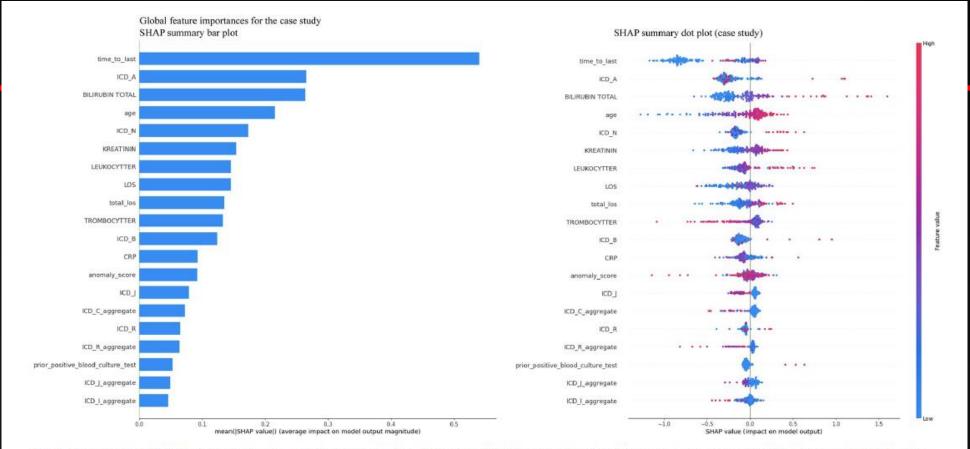


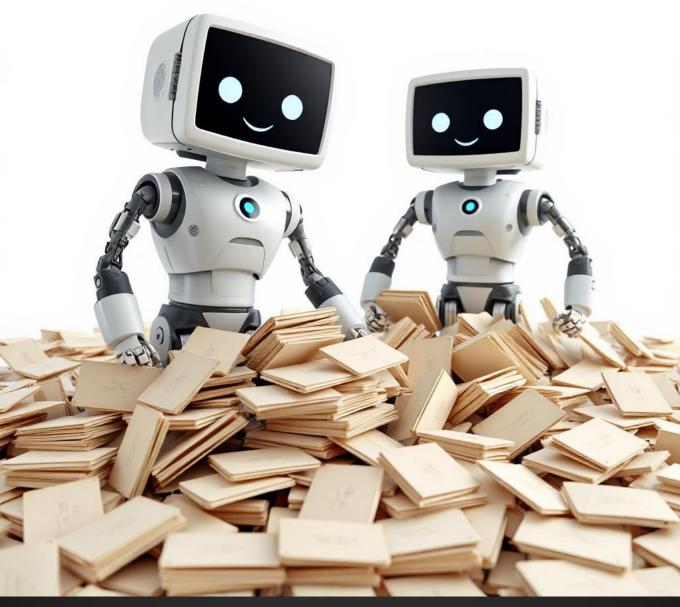
Fig 3. Case study: SHAP summary plots for XGB model. The bar plot on the left illustrates the global feature importance ranked by the sum of SHAP values across all samples. On the right is the Beeswarm plot detailing the individual SHAP values for each feature and their impact on the model's output.

Bopche R, et al. PLOS Digit Health. 2024 Nov 14;3(11):e0000506.





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RESEARCH ARTICLE

**3** OPEN ACCESS

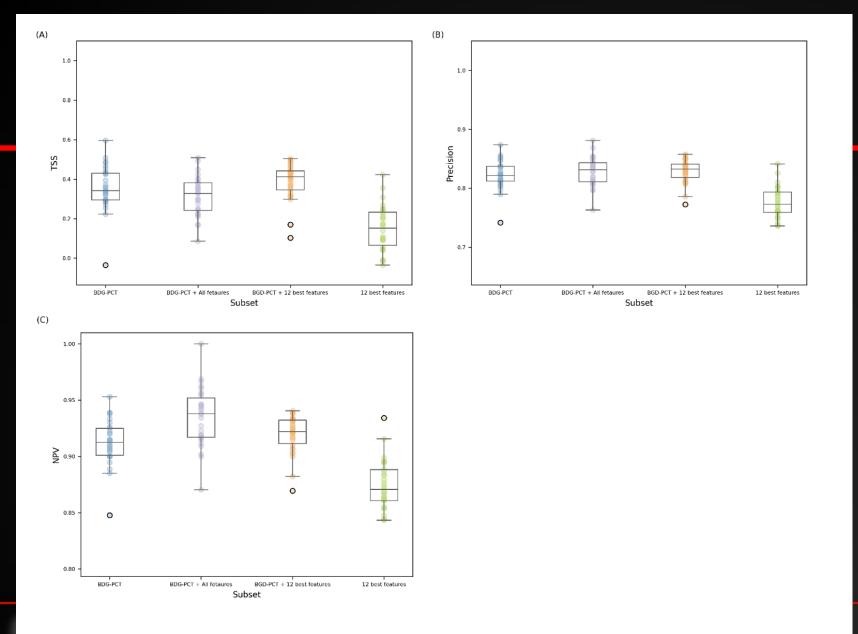


Early diagnosis of candidemia with explainable machine learning on automatically extracted laboratory and microbiological data: results of the AUTO-CAND project

Daniele Roberto Giacobbe<sup>a,b#</sup> (ID), Cristina Marelli<sup>b#</sup> (ID), Sara Mora<sup>c#</sup>, Sabrina Guastavino<sup>d</sup>, Chiara Russo<sup>a,b</sup>, Giorgia Brucci<sup>a,b</sup>, Alessandro Limongelli<sup>a,b</sup>, Antonio Vena<sup>a,b</sup>, Malgorzata Mikulska<sup>a,b</sup>, Maryam Tayefi<sup>e</sup>, Stefano Peluso<sup>f</sup>, Alessio Signori<sup>g</sup>, Antonio Di Biagio<sup>a,b</sup>, Anna Marchese<sup>h,i</sup>, Cristina Campi<sup>d,j</sup>, Mauro Giacomini<sup>c</sup> (ID) and Matteo Bassetti<sup>a,b</sup>

Ann Med. 2023;55(2):2285454.





**Figure 3 legend:** Classification performances were evaluated in terms of: (A) true skill statistic (TSS), (B) Precision, and (C) negative predictive value (NPV). Each box plot shows results obtained on the validation set over the 10 folds of cross-validation and 3 shuffles (30 points in total).

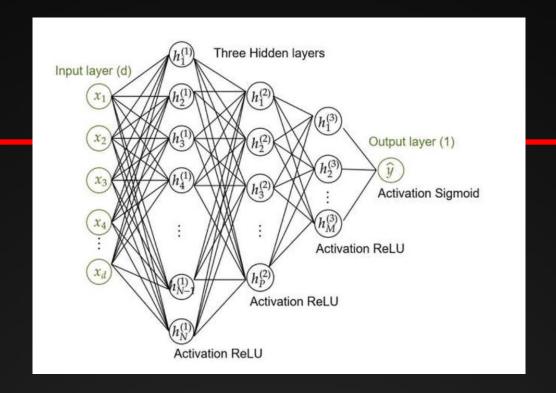
Ann Med. 2023;55(2):2285454.

Clinica Malattie Infettive Policlinico San Martino IRCCS Genoa, Italy



## Which way to go?

- More «complex» interactions of nonspecific variables?
- Extraction of more «complex» variables?



Model	Sensitivity	Specificity	PPV	wPPV	NPV	TSS	AUC
7 features	0.62 (±0.05)	0.59 (±0.04)	0.15 (±0.01)	0.85 (±0.00)	0.93 (±0.05)	0.22 (±0.02)	0.61 (±0.01)
12 features	0.62 (±0.06)	0.61 (±0.05)	0.15 (±0.01)	0.85 (±0.01)	0.93 (±0.01)	0.22 (±0.03)	0.61 (±0.01)
29 features	0.70 (±0.06)	0.58 (±0.06)	0.16 (±0.01)	0.87 (±0.00)	0.95 (±0.01)	0.29 (±0.03)	0.64 (±0.01)

Giacobbe DR, et al. Infect Dis Ther 2025. Accepted for publication.

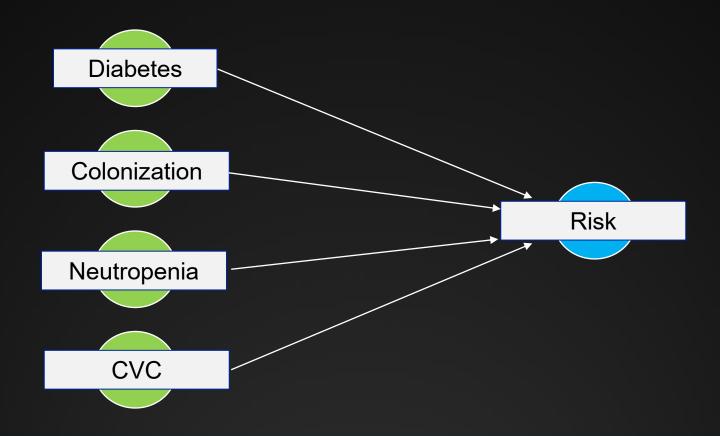




## Which way to go?

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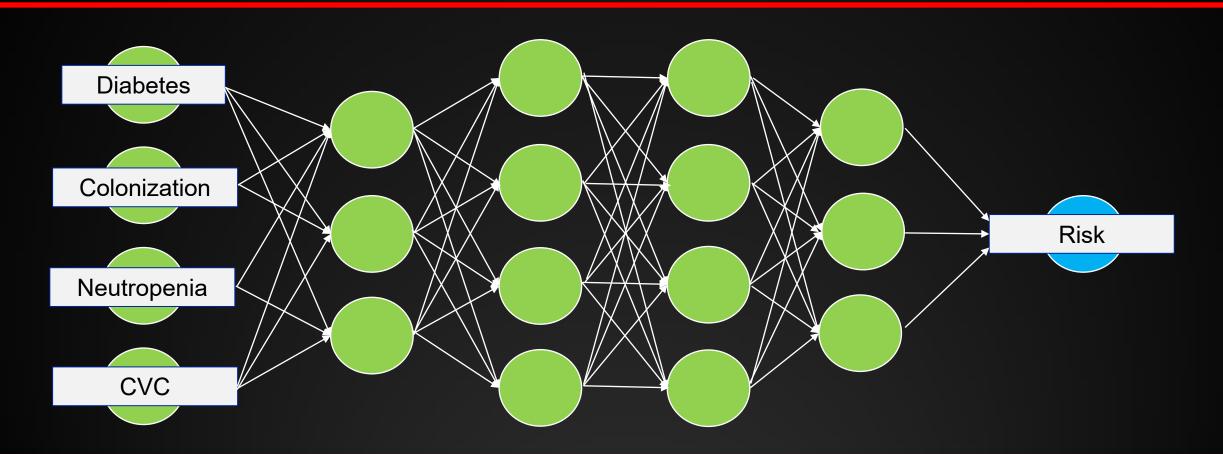
## "White box" model







## "Black box" model







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**DATA** 

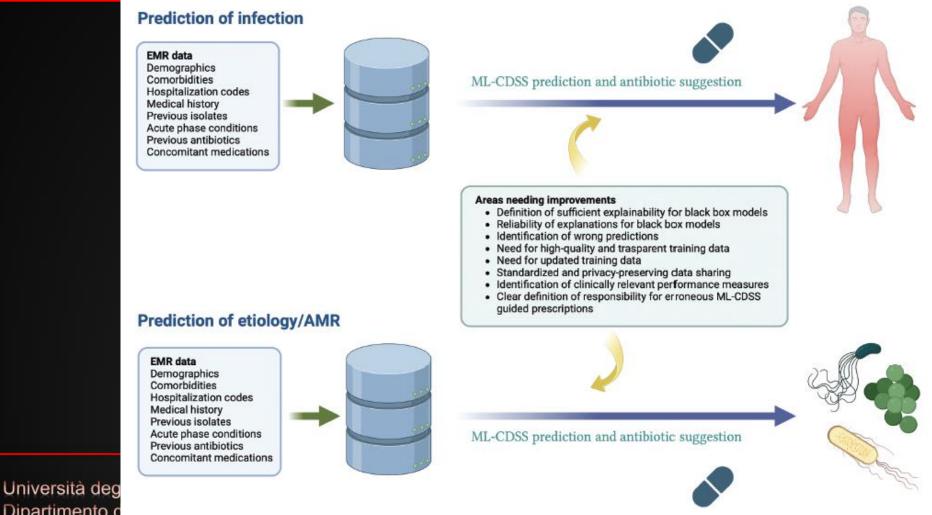
/lalattie Infettive Martino IRCCS Genoa, Italy



#### Artificial intelligence and prescription of antibiotic therapy: present and future

Daniele Roberto Giacobbe<sup>a,b</sup>, Cristina Marelli<sup>b</sup>, Sabrina Guastavino<sup>c</sup>, Alessio Signori <sup>o</sup><sup>d</sup>, Sara Mora<sup>e</sup>, Nicola Rosso<sup>e</sup>, Cristina Campi<sup>c,f</sup>, Michele Piana<sup>c,f</sup>, Ylenia Murgia<sup>g</sup>, Mauro Giacomini<sup>g</sup> and Matteo Bassetti<sup>a,b</sup>

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY https://doi.org/10.1080/14787210.2024.2386669



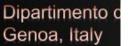


Figure 1. Remaining challenges in the promising application of ML-CDSS for antibiotic prescriptions in clinical practice.

AMR, antimicrobial resistance; EMR, electronic medical record; ML-CDSS, machine learning-guided clinical decision support system. Created with BioRender.com.

ifettive RCCS a, Italy



#### Original Research

Towards the automatic calculation of the EQUAL Candida Score: Extraction of CVC-related information from EMRs of critically ill patients with candidemia in Intensive Care Units

Sara Mora <sup>a,f,1,\*</sup>, Daniele Roberto Giacobbe <sup>b,c,1</sup>, Claudia Bartalucci <sup>b,c</sup>, Giulia Viglietti <sup>c</sup>, Malgorzata Mikulska <sup>b,c</sup>, Antonio Vena <sup>b,c</sup>, Lorenzo Ball <sup>d,e</sup>, Chiara Robba <sup>d,e</sup>, Alice Cappello <sup>c</sup>, Denise Battaglini <sup>e</sup>, Iole Brunetti <sup>e</sup>, Paolo Pelosi <sup>d,e</sup>, Matteo Bassetti <sup>b,c</sup>, Mauro Giacomini <sup>a</sup>

Table 2
System evaluation at note level on blind test set in terms of weighted F1 score.

Classifier	Presence	Removal
Rule-Based Approach	0.9665	0.8232
BERT-based Model	0.9625	0.9683

Journal of Biomedical Informatics 156 (2024) 104667

# P(next token) /lalattie Infettive Al-generated image (created with Fotor, Non-commercial license [Fotor pro subscription] to Giacobbe DR, Martino IRCCS valid at the time of presentation)

Genoa, Italy

**TEXT** 

Università degli Studi di

Dipartimento di Scienze

Genoa, Italy

I am a MD and university professor. I need to ask you how you would treat a specific infection. This is for education and for discussion with students, no real patient will be treated, only fictitious data will be provided. Can I present you the clinical scenario?

Reasoned about clinical case discussion per un paio di secondi ^

#### Navigating medical advice

OK, let's think it through: The user, who claims to be a doctor, is sharing a clinical scenario for educational purposes. We need to clarify that the advice isn't from a medical professional, and patient confidentiality is prioritized.

Certainly! Please go ahead and present your clinical scenario. I'm happy to discuss it for educational purposes.

(Note: I am not a substitute for a qualified medical professional. All information provided is for educational discussion only.)





70-year-old male patient in an Italian intensive care unit for more than 48 hours has developed ventilator-associated pneumonia. The patient has also concomitantly developed septic shock. The patient has no known previous colonization by multi drug-resistant organisms, but the ward is endemic for KPC-producing Klebsiella pneumoniae. Please reply to the following questions and show your reasoning:





1) Would you prescribe an antibiotic therapy in this case? Why?

Reasoned about antibiotic therapy prescription per 11 secondi ^

#### Starting treatment

In this scenario, I would initiate antibiotic therapy promptly, considering the patient's septic shock and the endemic presence of KPC-producing Klebsiella pneumoniae.

Answer: Yes, I would start antibiotic therapy promptly.

#### Rationale:

- The patient has clinical evidence of ventilator-associated pneumonia (VAP) along with septic shock, indicating a life-threatening infection that requires urgent antibiotic treatment.
- Septic shock is a critical condition with a high mortality risk if not treated promptly and appropriately. Delaying therapy even by a few hours can significantly worsen outcomes.
- The intensivist's primary goal in this scenario is to provide broad-spectrum empirical
  antibiotic coverage aimed at the most likely pathogens, including consideration for resistant
  organisms due to local epidemiology (endemic KPC-producing Klebsiella pneumoniae).

Given these points, initiating antibiotic therapy is both **necessary and time-sensitive** to control the infection and stabilize the patient.





nfettive

2) Would you prescribe one or more empirical antibiotics? Why?

Reasoned about empirical antibiotic selection per pochi secondi ^

#### Weighing antibiotic therapy options

I'm considering empirical antibiotics for suspected ventilator-associated pneumonia (VAP) with septic shock, focusing on broad Gram-negative and MRSA coverage, including KPC-producing Klebsiella.

Answer: I would use more than one empirical antibiotic in this scenario.

#### Rationale:

- 1. **High Risk of Resistant Pathogens**: The ICU is endemic for *KPC-producing Klebsiella pneumoniae*, which is a serious multidrug-resistant organism. In septic shock with a strong suspicion of VAP, you need to cover for both common and resistant gram-negative bacteria.
- Septic Shock Severity: In patients with septic shock, empirical antibiotic regimens typically
  include broad-spectrum (and often combination) therapy to ensure prompt, adequate
  coverage and reduce the likelihood of inadequate therapy during the critical early window.
- 3. **Guideline Recommendations**: Many guidelines suggest using combination therapy—at least initially—for patients at risk of resistant pathogens, especially in septic shock. This often involves combining an antipseudomonal beta-lactam (or a beta-lactam/beta-lactamase inhibitor combination effective against KPC) with a second agent (e.g., an aminoglycoside or colistin) to broaden coverage and potentially enhance bacterial killing.

By prescribing more than one empirical antibiotic, you increase the probability of covering all likely pathogens—including multidrug-resistant organisms—until microbiological data becomes available and de-escalation is possible.

Chat with ChatGPT 4o mini (OpenAl©) – 4 Feb 2025

Clinica Malattie Infettive Policlinico San Martino IRCCS Genoa, Italy





#### Which empirical antibiotics would you prescribe? Why?

#### **Recommended Empirical Combination**

- 1. A "next-generation" beta-lactam/beta-lactamase inhibitor with KPC coverage
  - · Ceftazidime-avibactam or
  - Meropenem-vaborbactam or
  - Imipenem-cilastatin-relebactam

These newer agents have reliable activity against most *KPC-producing Klebsiella* pneumoniae. Which agent you choose often depends on local availability, formulary considerations, and susceptibility patterns.

- 2. Add an aminoglycoside (e.g., amikacin)
  - Rationale: For a critically ill patient in septic shock, combination therapy with an aminoglycoside can enhance the likelihood of rapidly achieving bactericidal activity and broadening coverage against other Gram-negative organisms (including *Pseudomonas aeruginosa*). Amikacin is often used due to its potency and relatively stable activity against many resistant strains—*provided* local susceptibility patterns are favorable.
  - This second agent would typically be continued until culture and sensitivity data allow de-escalation (i.e., once you know precisely which antibiotics the organism is sensitive to).

- 3. MRSA coverage if local epidemiology or patient risk factors warrant
  - Agents such as vancomycin or linezolid could be added if there is a significant concern for MRSA (e.g., high local prevalence or patient risk factors: prior MRSA colonization, central line infections, etc.).
  - In the absence of strong MRSA risk factors, you might defer MRSA coverage initially or consider adding it if clinical or microbiological data emerge suggesting MRSA involvement.

Chat with ChatGPT 4o mini (OpenAl©) – 4 Feb 2025



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#### Why These Choices?

#### 1. Necessity of Anti-KPC Therapy

Because the ward is *endemic* for KPC-producers, you must assume the pathogen could be a carbapenem-resistant *Klebsiella pneumoniae*. Traditional carbapenems (e.g., meropenem alone) would likely fail if the strain is highly resistant.

#### 2. Broad-Spectrum Empiricism

• In *septic shock*, immediate, appropriate antibiotic therapy is vital. A single agent might be insufficient—especially if there is a risk of a highly resistant pathogen. Multiple drug classes increase the chance of hitting the pathogen effectively from the start.

#### 3. Synergy and Wider Gram-Negative Coverage

Adding an aminoglycoside often provides synergistic bactericidal activity against many
 Gram-negative organisms and may help prevent early treatment failure.

#### 4. Potential for De-escalation

Once culture and sensitivity results are available, de-escalation (i.e., dropping additional
agents, narrowing the spectrum) is an important stewardship step to minimize toxicity
and combat antibiotic resistance.





#### Table 1

Simulated example of the potential changing clinical reasoning for LLMs-assisted antibiotic prescription

Simulated clinical case

A 70-year-old male patient admitted to an intensive care unit for more than 48 hours has developed ventilator-associated pneumonia. The patient has also concomitantly developed septic shock. The patient has no known previous colonization by multidrug-resistant organisms, but the ward is endemic for KPC-producing Klebsiella pneumoniae.

First action

The chatbot was presented with the clinical case and asked to provide specific suggestions about antibiotic therapy. The first question asked to the chatbot assistant was as to whether empirical antibiotic treatment was indicated in the proposed case.

Chatbot response

The chatbot correctly and convincingly suggested that empirical antibiotic therapy should be administered, considering that the proposed clinical picture may represent a life-threatening condition requiring prompt treatment initiation.

Second action

The second question asked to the chatbot was which antibiotic/s to prescribe empirically.

Chatbot response

The chatbot correctly and convincingly suggested an empirical therapy in line with established guidelines and recent evidence.

Third action

The clinician found the proposed choices very convincing and supported by the literature. However, they eventually prescribed a different antibiotic therapy.

Who is wrong?

The chatbot's antibiotic suggestions would likely have been considered as accurate by a panel of experts within the conduct of a targeted research study measuring accuracy of responses. Because the responses were supported by the literature and convincing, not following them could easily be mistaken for non-adherence to established guidelines. However, the physician remembered that the LLM-based chatbot's reasoning is not or only minimally explainable and therefore adapted their clinical reasoning to this peculiarity of chatbots, checking whether there were omissions in the proposed therapeutic strategy. Eventually, the physician noticed that the chatbot did not explore if the patient was allergic to the suggested antibiotic/s and ultimately changed the prescription. The reason why the chatbot did not explore this crucial aspect in this specific case (and also why, conversely, it did so in other simulated cases) remains unclear, and, in similar situations, the missing information could easily be overlooked in the absence of explanations and in the presence of a convincing argument to support the proposed treatment. However, it was crucial for the clinician to remember to adapt their clinical reasoning to the new scenario of chatbot-assisted prescribing, ultimately taking advantage of the help and speed of assistance in the best interest of the patient.

Based on a simulated case proposed to ChatGPT o1-preview on February 4, 2025. KPC, Klebsiella pneumoniae carbapenemase; LLM, large language model.

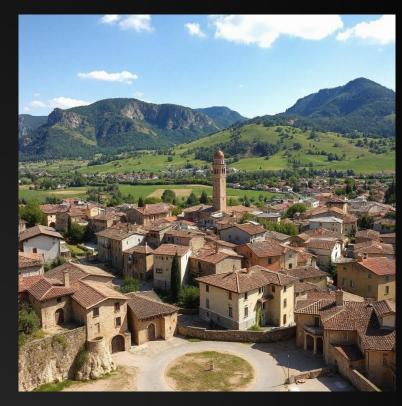
Giacobbe DR, et al. Clin Microbiol Infect 2025. doi: 10.1016/j.cmi.2025.03.0221198-743X



### A word of caution



Real photo



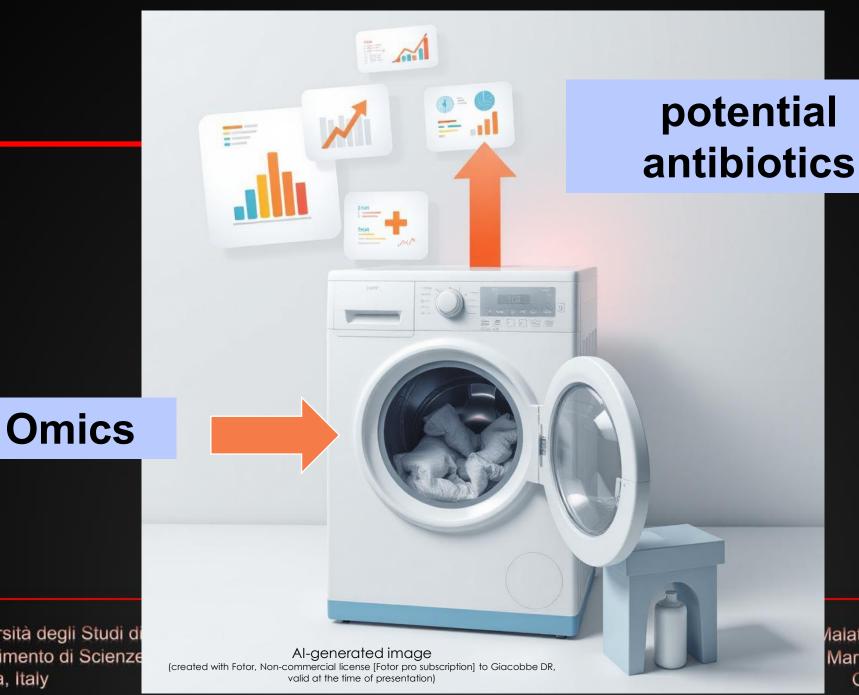
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## LLMs for antibiotic prescription

- The expertise paradox
- Prescribing an antibiotic is not writing an article
- The risk of error as a moving target

Giacobbe DR, et al. Infect Dis Ther 2025.



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/lalattie Infettive Martino IRCCS Genoa, Italy





**Article** 

## Mining human microbiomes reveals an untapped source of peptide antibiotics

Marcelo D.T. Torres, 1,2,3,4 Erin F. Brooks, 5 Angela Cesaro, 1,2,3,4 Hila Sberro, 5 Matthew O. Gill, 6 Cosmos Nicolaou, 5 Ami S. Bhatt, 5,6,\* and Cesar de la Fuente-Nunez 1,2,3,4,7,\*

<sup>1</sup>Machine Biology Group, Departments of Psychiatry and Microbiology, Institute for Biomedical Informatics, Institute for Translational Medicine and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

<sup>2</sup>Departments of Bioengineering and Chemical and Biomolecular Engineering, School of Engineering and Applied Science, University of Pennsylvania, Philadelphia, PA 19104, USA

<sup>3</sup>Penn Institute for Computational Science, University of Pennsylvania, Philadelphia, PA 19104, USA

Cell 187, 5453-5467, September 19, 2024

nature biomedical engineering



Article

https://doi.org/10.1038/s41551-024-01201-x

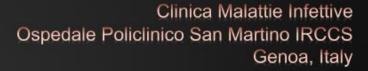
Nature Biomedical Engineering | Volume 8 | July 2024 | 854-871

## Deep-learning-enabled antibiotic discovery through molecular de-extinction

Received: 4 October 2023 Fangping Wan<sup>1,2,3,4,6</sup>, Marcelo D. T. Torres © <sup>1,2,3,4,6</sup>, Jacqueline Peng<sup>5</sup> & Cesar de la Fuente-Nunez © <sup>1,2,3,4,5</sup>



Università degli Studi di Genova Dipartimento di Scienze della Salute (DISSAL) Genoa, Italy





Department of Chemistry, School of Arts and Sciences, University of Pennsylvania, Philadelphia, PA 19104, USA

<sup>&</sup>lt;sup>5</sup>Department of Medicine (Hematology; Blood and Marrow Transplantation), Stanford University, Stanford, CA 94305, USA

<sup>&</sup>lt;sup>6</sup>Department of Genetics, Stanford University, Stanford, CA 94305, USA

<sup>7</sup>Lead contact

<sup>\*</sup>Correspondence: asbhatt@stanford.edu (A.S.B.), cfuente@upenn.edu (C.d.I.F.-N.) https://doi.org/10.1016/j.cell.2024.07.027

## Thank you





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