# Predicting antimicrobial resistance in Gram-negative bacterial bloodstream infections through evaluation of dynamic host responses and deep learning

Vasin Vasikasin[1,2], Damien K Ming[1], Bernard Hernandez[1], Timothy M Rawson[1,2], James R Price[3], Alison H Holmes[1,2,4]

[1] Centre for Antimicrobial Optimisation, Imperial College London
[2] Healthcare Protection Research Unit in Healthcare Associated Infections, Imperial College London
[3] Brighton and Sussex Medical School, University of Sussex, Brighton, UK
[4] Department of Global Health and Infectious Diseases, University of Liverpool

## Background

Effective management of bacterial bloodstream infection requires early, appropriate empirical antimicrobial therapy. Antimicrobial resistance is a major contributor to poor clinical response but can be challenging to ascertain because of limitations in turnaround time and sensitivity of culture-based diagnostics. We examined whether host response information during the early phase of treatment could predict antimicrobial susceptibility in Gram-negative bacteria bloodstream infections (GNBSI).

## Methods

We analysed data from 2,188 confirmed cases of GNBSI at Imperial College Healthcare NHS Trust in London, UK, between January 2021 and May 2023. We extracted blood biomarkers, demographics, and vital signs within a 60-hour window post-blood culture acquisition. Resistant was defined for aminoglycosides or carbapenems if prescribed empirically without concurrent susceptible antibiotics. Generalized Estimating Equation (GEE) methods were used to analyse the association between features and resistance. For prediction models, Time series deep learning using Long-Short Term Memory (LSTM) models were used. To mitigate selection bias, features were normalised relative to the time of blood culture acquisition, focusing only on relative changes in features. The dataset was split randomly, with 80%

(n=1,750) used for training and prospective evaluation against an independent holdout set (n=438). Five-fold cross-validation and post-hoc methods for interpretability were applied.

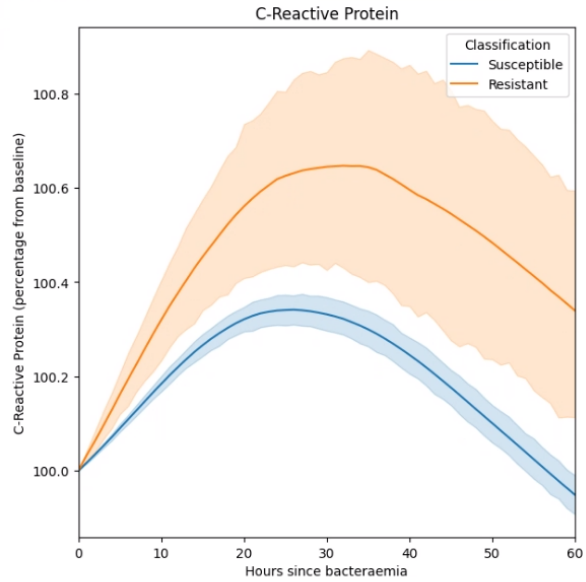
**Results**

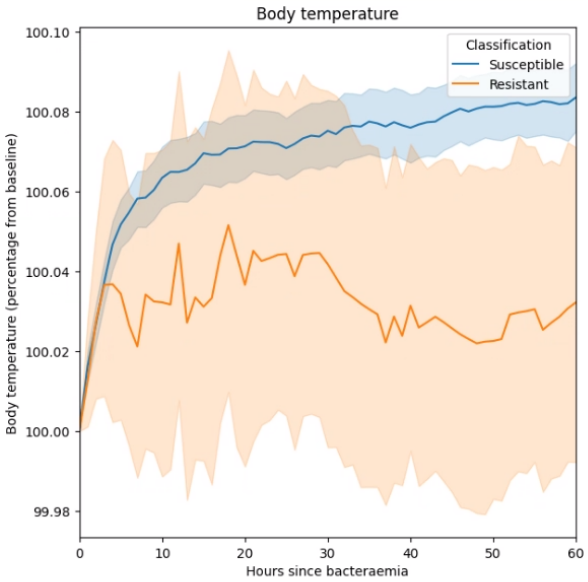
There were 7.9% (173/2,188) and 1.6% (36/2,188) GNBSI instances which were resistant to the aminoglycosides and carbapenems prescribed, respectively. Excluding instances with concurrent susceptible antibiotics, 65 cases were categorised as resistant. After the onset of GNBSI, patients with a resistant isolate had significantly higher C-reactive protein (CRP) (p=0.002), lower temperature (p=0.031), and lower blood pressure (p=0.041). The area under receiver operator curve (AUROC) for the validation and the holdout set through the LSTM model was 0.70 (IQR 0.59-0.75) and 0.69 (IQR 0.64-0.72), respectively. Dynamics of CRP, blood pressure, and temperature over the 60-hour period were the most important features for model prediction.

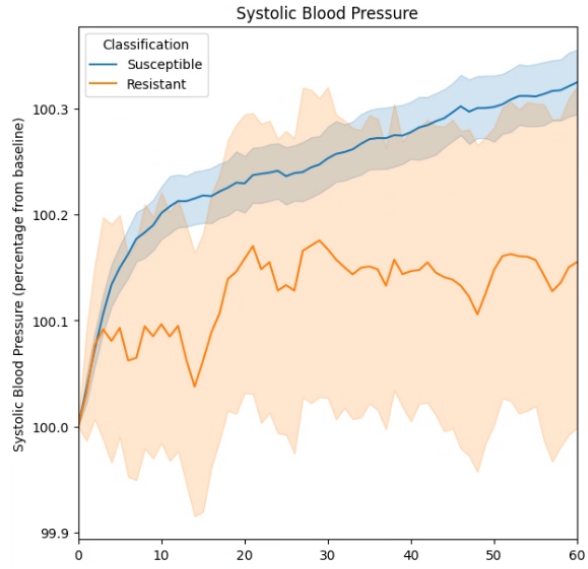
**Conclusion**

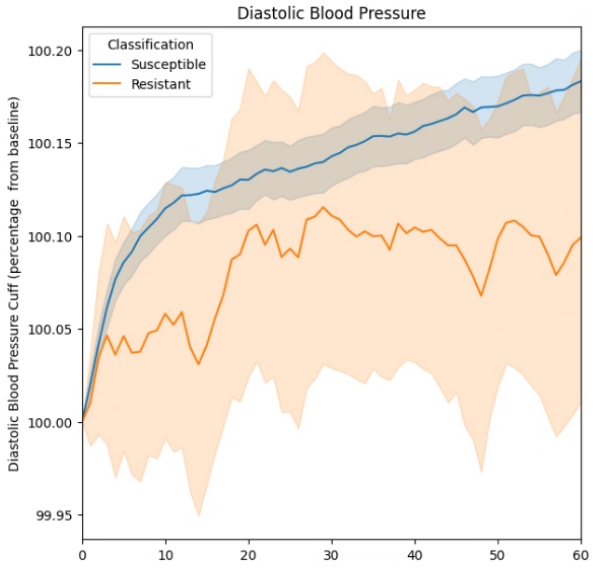
Use of dynamic host responses to antibiotics shows promise for improving antimicrobial prescribing. With a larger training set, this model has the potential to enhance antimicrobial optimisation in sepsis, particularly in cases of culture-negative infections or when susceptibility information is unavailable.

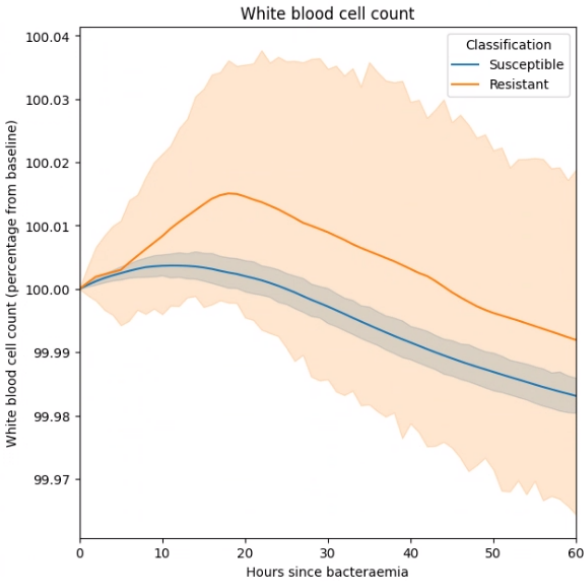
**Figure:** Dynamic changes of the selected features over 60-hour period between the two groups. Shaded areas represent 95% confidence interval.

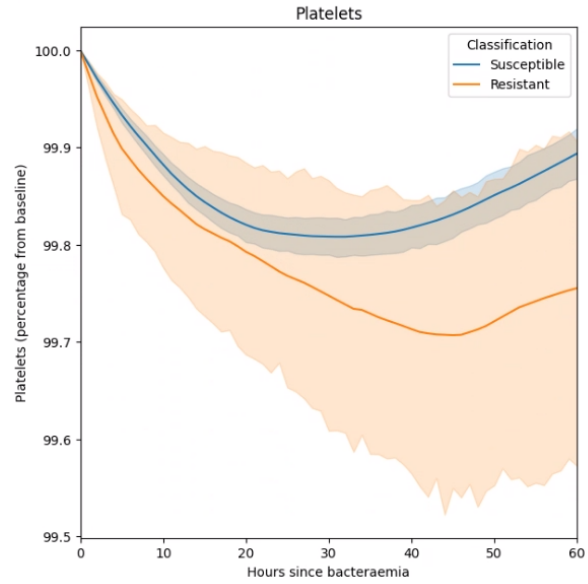

C-Reactive Protein
Classification
Susceptible
Resistant
C-Reactive Protein (percentage from baseline)
Hours since bacteraemia


Body temperature
Classification
Susceptible
Resistant
Body temperature (percentage from baseline)
Hours since bacteraemia


Systolic Blood Pressure
Classification
Susceptible
Resistant
Systolic Blood Pressure (percentage from baseline)


Diastolic Blood Pressure
Classification
Susceptible
Resistant
Diastolic Blood Pressure Cuff (percentage from baseline)


White blood cell count
Classification
Susceptible
Resistant
White blood cell count (percentage from baseline)
Hours since bacteraemia


Platelets
Classification
Susceptible
Resistant
Platelets (percentage from baseline)
Hours since bacteraemia