Development of a Machine-learning Model to Predict Resistance of Empiric Antibiotics using Urine Culture and Antibiotics Susceptibility Data

Chungsoo Kim[1], Rae Woong Park[1, 2, *], Sandy Jeong Rhie[3, *]

[1]Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, Republic of Korea; [2]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Republic of Korea;
[3]College of Pharmacy, Ewha Womans University, Seoul, Republic of Korea;
[*]Co-corresponding authors

Introduction

Background

- Challenges for an empiric antibiotic therapy
  → It is difficult to prescribe appropriate antibiotics before culture and antibiotic susceptibility test
- Previous studies
  → Models showed low discrimination (AUROC 0.60-0.70) and lack of calibration.
- Local antibiograms
  → Useful tools for selection of appropriate empiric antibiotics, however, they are not well adapted.

Objectives

- To develop models for predicting antibiotic resistances using patients' medical history, culture results, antibiotics susceptibility test results, and local antibiogram.

Methods

Study Population

- By AUSOM database (2.7M, 1998-2020)
- Suspicious urinary tract infection
  ≥ 18 years old
  Hospitalization (min 3 days)
  Having a urine culture result
  Having antibiotic susceptibility test results (13 types)

Outcome

- Resistant (Unsusceptible*) isolates events

$$^{*}\,Unsusceptibility\ rate = \frac{Resistant\ (R) + Intermediate(I)}{Total\ isolates\ (R+I+S)}$$

Model Settings

- Lasso Logistic regression
- Splitting: 75 (train) : 25 (test)
- 3-fold cross validation
- Evaluation metrics: AUROC, AUPRC, Calibration

Predictors

- Candidate predictors
  Demographics, condition, drug, measurement, procedure, visit and local antibiogram data
- Variable selection
  1. Lasso shirinkage
  2. Manual selection based on clinical guidelines

Table 1. Final covariates for the development of prediction model

Domain	Contents	Time period
Demographics	Age group by 5 years Sex	At index date
Conditions	Hypertension Type 2 diabetes mellitus Hyperlipidemia Cancer Dementia Osteoporosis Bleeding events Chronic kidney disease End stage renal disease Depressive disorder Pregnancy Benign prostate hyperplasia Prostatitis	-365 d ~ 0 d
	Pneumonia Sepsis Urinary tract infection Cystitis Nephritis	-365 d ~ -1 d / 0 d – 0 d
Antibiogram - Gram negative	Escherichia coli Klebsiella pneumonia Enterobacter aerogenes Enterobacter cloaceae Serratia marcescens	At index date

Domain	Contents	Time period
Drugs	Aminoglycoside (IV) Antipseudomonal penicillin and cephalosporin (IV) 3rd cephalosporin (IV) Cotrimoxazole (IV) Cephalosporine (PO) Fosfomycin (PO) Macrolide (IV, PO) Fluoroquinolone (IV, PO) Others (IV, PO)	-90d ~ -31d / -30 d ~ -1d
Measurement	Carbapenem resistant enterobacteriaceae Extended spectrum beta-lactamase producing spp. Methicillin resistant staphylococcus aureus Vancomycin resistant enterococcus	-90d ~ -1d
Procedures	Urinary catether / urine bag Continuous IV injection Tracheostomy	0 d ~ 0 d
Visits	Inpatient visit Intensive care unit visit	-90d ~ -1d
Antibiogram - Glucose-nonferment bacillin & Gram positive	Acinetobacter baumanni Pseudomonas aeruginosa Enterococcus faecalis Enteroccus faecium Stapylococcus aureus Coagulase negative staphylococcus	At index date

Clinical unmet needs and model-based approach

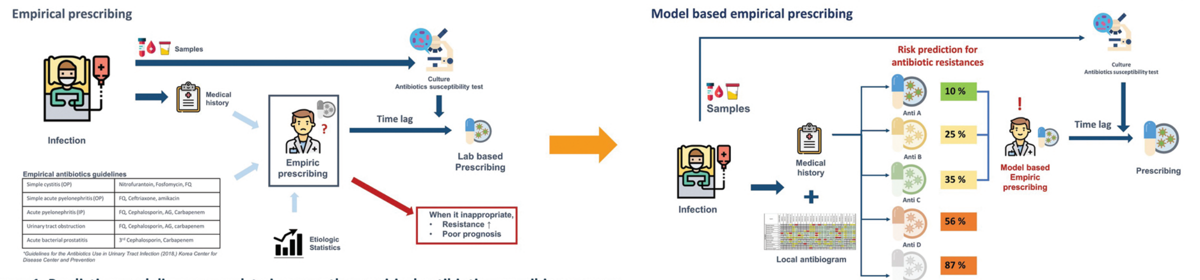

Figure 1. Predictive modeling approach to improve the empirical antibiotic prescribing process

Physicians decide on empiric antibiotics through limited factors (e.g. the patients' history, pathogens, guidelines, and consults) until lab test results are available. Therefore, a simple decision supporting through a predictive model could be considered and it would help prescribers to evaluate the resistance rate of each antibiotic numerically and select drugs more appropriate.

Results & conclusion

Table 2. Performance of antibiotic resistance prediction models

Performances	Antibiotics resistance prediction models												
	AMC	AMP	AMS	CAZ	CFP	CIP	CRO	FOF	FUR	GEN	PPT	SXT	TET
Total (n)	3,526	8,603	6,471	6,275	6,789	12,407	5,874	3,047	5,814	11,040	5,983	10,060	10,970
Outcome rates (%)	37.7	53.7	22.0	26.6	24.1	40.4	9.9	2.7	16.0	22.0	14.7	27.2	30.9
AUROC	0.62	0.70	0.78	0.67	0.69	0.70	0.87	0.94	0.73	0.68	0.67	0.69	0.68
AUPRC	0.50	0.71	0.53	0.41	0.43	0.59	0.55	0.17	0.34	0.42	0.29	0.43	0.47
Calibration slope	1.00	1.02	0.99	0.96	0.99	0.94	0.94	0.94	0.98	0.96	0.96	0.95	0.91

Key performances

- Mean calibration slope = 0.96
- Mean AUROC = 0.72
- Mean AUPRC = 0.45

Limitations

- Transfer status (e.g. from nursing home), which is an important covariate for antibiotic selection, could not be included.
- Further researches on the development of a more delicate prediction model considering the antibiogram data are needed.

Conclusion

- We developed machine-learning models for predicting antibiotic resistance having promising discriminations and excellent calibration performances. It would contribute to the proper selection of empiric antibiotics susceptible.

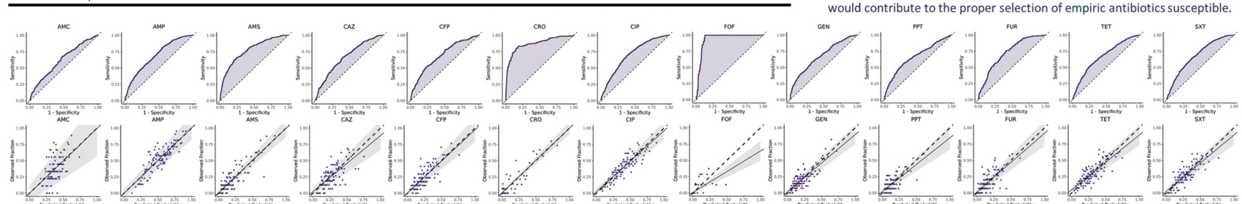

Figure 2. Discrimination and calibration curves of antibiotic resistance prediction models

Abbreviations

AMC: amoxicillin-clavulanate; AMP: ampicillin; AMS: ampicillin-sulbactam; CAZ : cefazolin; CFP: cefepime; CIP: ciprofloxacin; CRO: ceftriaxone; FOF: fosfomycin; GEN: gentamicin; PPT: piperacillin-tazobactam; SXT: trimethoprim-sulfamethoxazole; TET: tetracycline; AUROC: area under the receiver operating characteristic curve; AUPRC: area under the precision-recall curve

Acknowledgment : This work was supported by the Bio Industrial Strategic Technology Development Program (20003883, 20005021) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea) and a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea [grant number: HR16C0001]. This work was supported by the Ministry of Science and ICT (MIST) (2020R1A2C1009224) and by Basic Science Research Program funded by the Ministry of Education (NRF-2020R1A6A1A03043528) through the National Research Foundation of Korea (NRF).
Conflict of interest : We have no conflict of interest. / **Contact** : sandy.rhie@ewha.ac.kr(SJR); veritas@ajou.ac.kr(RWP)