Accepted Manuscript

Title: Forecasting models of infections due to carbapenem-resistant Gram-negative bacteria in an intensive care unit in an endemic area

Authors: Theodoros Karampatakis, Katerina Tsergouli, Elias Iosifidis, Charalampos Antachopoulos, Eleni Mouloudi, Aggeliki Karyoti, Athanassios Tsakris, Emmanuel Roilides

PII: S2213-7165(19)30163-8
DOI: https://doi.org/10.1016/j.jgar.2019.06.019
Reference: JGAR 975

To appear in:

Received date: 20 October 2018
Revised date: 15 June 2019
Accepted date: 24 June 2019

Please cite this article as: Karampatakis T, Tsergouli K, Iosifidis E, Antachopoulos C, Mouloudi E, Karyoti A, Tsakris A, Roilides E, Forecasting models of infections due to carbapenem-resistant Gram-negative bacteria in an intensive care unit in an endemic area, Journal of Global Antimicrobial Resistance (2019), https://doi.org/10.1016/j.jgar.2019.06.019

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Forecasting models of infections due to carbapenem-resistant Gram-negative bacteria in an intensive care unit in an endemic area

Theodoros Karampatakis, MD, PhD, Katerina Tsergouli, MD, PhD, Elias Iosifidis, MD, MSc, PhD, Charalampos Antachopoulos, MD, PhD, Eleni Mouloudi, MD, PhD, Aggeliki Karyoti, MD, MSc, Athanassios Tsakris, MD, PhD, Emmanuel Roilides, MD, PhD, FIDSA, FAAM, FESCMID

1Infectious Disease Unit, 3rd Department of Pediatrics, Medical Faculty, Aristotle University School of Health Sciences, Hippokration General Hospital, Thessaloniki Greece, 2Microbiology Department, Hippokration General Hospital, Thessaloniki Greece, 3Infection Control Committee, Hippokration General Hospital, Thessaloniki Greece, 4Intensive Care Unit, Hippokration General Hospital, Thessaloniki Greece, 5Microbiology Department, National and Kapodistrian University School of Medicine, Athens Greece

*Corresponding author: Emmanuel Roilides, MD, PhD, FIDSA, FAAM, FESCMID, 3rd Department of Pediatrics, Hippokration General Hospital, Konstantinoupoleos 49, GR-546 42 Thessaloniki, Greece, Tel: +30-2310-8924, FAX: +30-2310-992981, E-mail: roilides@med.auth.gr
Highlights

- Time series was used to forecast the incidence of CRKP, CRPA and CRAB ICU infections
- The highest incidences for CRKP and CRAB infections were expected in Jan and Sept
- The highest rates of CRPA infections were expected in Feb and Mar
- Time series models with coordinated actions are essential in high-risk health care units

Abstract

**Objectives:** To forecast the monthly incidence rates of infections (infections/1000 bed-days, IBD) due to carbapenem-resistant Klebsiella pneumoniae (CRKP), Pseudomonas aeruginosa (CRPA), Acinetobacter baumannii (CRAB) and total Gram-negative bacteria (CRGNB) in an endemic intensive care unit (ICU) during the subsequent year (December 2016-December 2017).

**Methods:** An observational 52-month period (August 2012-November 2016) was used. Two forecasting models, simple seasonal model for
CRGNB, CRKP and CRPA, and Winters' additive model for CRAB infections, were applied.

**Results:** They predicted highest infection rates for CRKP, CRAB and CRGNB in January and September 2017 (23.8/23.4, 24.6/28.5 and 46.8/46.7 IBD, respectively) and for CRPA in February (8.3) and March 2017 (7.9). The highest observed rates for CRKP, CRAB, and CRGNB were indeed in January and September 2017 (25.6/19.04, 34.2/23.8 and 59.8/42.8 IBD, respectively); and for CRPA in February (15.2) and March of the same year (12.7). The increased rates may be associated with personnel's annual work program and behavioral factors.

**Conclusions:** Forecasting models in endemic ICU's may assist in the implementation strategies of infection control measures.

**Keywords:** forecasting model; carbapenem-resistant Gram-negative bacteria; Klebsiella pneumoniae; Pseudomonas aeruginosa; Acinetobacter baumannii; Intensive care unit

**Introduction**

Infections caused by carbapenem-resistant Gram-negative bacteria (CRGNB) have a negative impact on the outcome of patients’ hospitalization, especially in regions with high CRGNB prevalence.[1] The implementation of infection control measures (ICM) significantly
reduces their spread among critically ill patients in endemic health care areas.[2] Prediction of the incidence of CRGNB infections could potentially provide physicians with an additional tool to organize their infection control strategies more successfully. Previous studies have highlighted models for predicting CRGNB infections or predictive models for identifying patients harbouring CRGNB.[3, 4] On the other hand, other studies have attempted to produce forecasting models for predicting carbapenem-resistance rates from antimicrobial consumption surveillance, using time series analysis.[5]

The aim of this study was to use time series for forecasting the incidence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP), *Pseudomonas aeruginosa* (CRPA) and *Acinetobacter baumannii* (CRAB) infections in an intensive care unit (ICU) located in an endemic area and validate the results.

Methods

Setting

The study was performed in a 9-bed adult multivalent ICU from August 2012- November 2016 (Phase 1, 52 months) and from December 2016-December 2017 (Phase 2, 13 months).

The two phases were as follows:
Phase 1: Use of observed data of infections (see below) from a period of 52 months and forecast

Data collection was performed from August 2012 until November 2016 to obtain the appropriate number of observed monthly time points (incidence rates of infections expressed as infections/1000 bed-days, IBD). During August 2012 until January 2013 and December 2014 until November 2016 standard infection control measures were implemented. During the period from February 2013 until November 2014 active surveillance cultures (weekly, rectal swabs) was performed, as well as enhanced infection control measures (standard infection control measures followed by audits and feedback).[6]

Phase 2: Collection of observed data from forecasted period and validation of forecast period from December 2016 until December 2017. During this period, patients were screened for CRGNB carriage with rectal swabs upon admission (active surveillance cultures) and standard infection control measures were implemented.

Analysis of data and forecasting based on observations for Phase 2 was performed.

Patients

Out of 1226 patients, aged 15-95 years (median 60), hospitalised in the ICU during the study period, 804 (65.6%) were male. Days of
hospitalization were 19.6 ± 15.2 and number of admissions per patient was 1.2 ± 0.3, respectively.

**Microbiologic methods**

Clinical samples from various biological fluids (blood, urine, trauma, bronchial fluid), were processed in the clinical laboratory using standard microbiological techniques and procedures, as previously described.[2] Minimum inhibitory concentration determination to carbapenems and interpretation of results were determined according to the Clinical and Laboratory Standards Institute. Isolates with intermediate susceptibility to carbapenems were confirmed with E-testing (BioMerieux, Marcy l’Etoile, France).[7]

**Infection definition and recording**

CRGNB infection was defined according to standard proposed criteria.[8] CRKP, CRPA and CRAB infections were enlisted as bacteremias, urine tract infections, trauma infections and pneumonias, as proposed by the action plan Procrustes of the Hellenic Center for Disease Control and Prevention for the management of MDR Gram-negative bacterial infections.[9] Distinction between CRGNB colonization and infection was performed using previously defined criteria.[9, 10] The incidences of CRKP, CRPA, CRAB and CRGNB infections were
calculated monthly and expressed as numbers of infections/1000 bed-days (IBD), based on ICU occupancy.

**Forecasting model-Statistical analysis**

The ‘Expert Modeler’ method, an IBM proprietary software tool was used to forecast infection rates. It automatically identifies and estimates the best fitting autoregressive Integrated Moving Average (ARIMA) or exponential smoothing models for one or more dependent variable time series. Observation period was defined from August 2012 until November 2016 to obtain the appropriate number of monthly time points needed and forecast period from December 2016 until December 2017. Stationary R-squared was used to assess model’s goodness-of-fit. Ljung-Box statistic was used to estimate if the model was correctly specified. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, 22nd version, IBM).

**Ethics**

This retrospective study was part of the PhD thesis of TK and was reviewed and approved by the Aristotle University Medical Faculty Ethics Committee (ref. no. 106/15-10-2014).

**Results**
Phase 1: Forecasting

The ‘Expert Modeler’ method produced a simple seasonal model for future CRGNB, CRKP and CRPA infections and a Winters’ additive model for CRAB infections. Forecasting revealed that the highest incidences for CRKP, CRAB and total CRGNB infections were expected in January (23.8, 24.6 and 46.8 IBD, respectively) and September 2017 (23.4, 28.5 and 46.7 IBD, respectively) (Fig. 1A, 1B, 1C). The highest rates of CRPA infections were expected in February and March 2017 (8.3 and 7.9 IBD, respectively) (Fig. 1D).

Phase 2: Validation process

During 2017, the highest observed incidences for CRKP, CRAB and total CRGNB infections were indeed in January 2017, with rates of 25.6, 34.2 and 59.8 IBD respectively, and in September 2017, with rates of 19.04, 23.81 and 42.85 IBD, respectively (Fig. 2A, 2B, 2C). The highest incidence for CRPA infections was observed in February and March 2017 with 15.2 and 12.7 IBD, respectively (Fig. 2D).

Discussion

The forecasting model predicted successfully the following year’s CRKP, CRPA, CRAB and CRGNB peak infection rates. It depicted January and September as the months with the possible highest incidence
of CRKP, CRAB and total CRGNB infections, and this was indeed validated in our case. The same happened for CRPA infections, presenting the highest incidence in February and March, as proposed by the model. These findings could be explained because of several relevant behavioral parameters in the individual context.[11]

A plausible explanation of the seasonality of highest incidence could be lack of staff during winter holidays (end of December until beginning of January) and summer vacations (August) followed by a possible adjustment period for health care workers to revert to usual task activities. This may be associated with inaccurate ICM implementation, leading to increase of CRKP, CRPA, CRAB and total CRGNB infection rates during the upcoming months (January until February and September).

Several studies have created forecasting models for CRKP infections based only on the risk factors for their emergence without implementing time series analysis.[3, 4] Gharbi et al. have revealed the impact of meropenem consumption on OXA-48 producing CRKP incidence through time series analysis with yearly taken time points using aggregate data.[5]

One limitation of our study was that other factors affecting CRGNB emergence, such as monthly antimicrobial consumption rates were not co-estimated in our model as performed in previous studies.[5,
However, the vast majority of CRKP, CRPA and CRAB strains isolated in ICU displayed clonal dispersion [13], highlighting the significant role of ICM apart from antimicrobial prescription policies in their emergence. Another limitation was that the validation process was performed only for the year 2017.

Our study underlines the use of forecasting as a tool for Infection Control committees in order identify specific time points (i.e. December-February and August-September for our ICU) and intensify as well as strictly monitor the implementation of enhanced ICM during these periods. Moreover, it highlights the need to extend such models and implement them in departments with high incidence of infections, such as pediatric and neonatal ICUs, neurosurgery and solid organ transplantation departments. During the greatest part of phase 1, but not in phase 2 in this study, an intervention including an active surveillance for colonization by CRGNB was being performed. The forecasted IBD rates were generally lower compared to the observed ones. The latter highlights the success and usefulness of our intervention but also the lack of sustainability. The creation of relevant time series models combined with coordinated actions at ICU level using multidisciplinary approaches, are essential to have at least long-term decrease of CRGNB infection rates in endemic high-risk health care units.
Declarations

**Funding:** No funding

**Ethical Approval:** Aristotle University

**Competing Interests:** None

**Acknowledgements**

The authors would like to thank Vassiliki Pentsioglou for epidemiological data handling and her valuable collaboration during the study.
References


**Figure Legends**

**Fig. 1:** Forecasting of (A) total carbapenem-resistant Gram-negative bacteria (CRGNB) infections, (B) carbapenem-resistant *Klebsiella pneumoniae* (CRKP), (C) carbapenem-resistant *Acinetobacter baumannii* (CRAB) and (D) carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) infections, expressed as infections/1000 bed days (IBD). Observed period was defined from August 2012 until November 2016 and forecast period from December 2016 until December 2017.
**Fig. 2:** Modeled and observed infections of (A) total carbapenem-resistant Gram-negative bacteria (CRGNB) infections, (B) carbapenem-resistant *Klebsiella pneumoniae* (CRKP), (C) carbapenem-resistant *Acinetobacter baumannii* (CRAB) and (D) carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) infections, expressed as infections/1000 bed days (IBD) during the forecast period from December 2016 until December 2017.