Journal of Global Antimicrobial Resistance 2 (2014) 11–16

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Action Plan to combat infections due to carbapenem-resistant, Gram-negative pathogens in acute-care hospitals in Greece

Helena C. Maltezou *, Flora Kontopidou, Xanthi Dedoukou, Panagiotis Katerelos, Georgios-Michael Gourgoulis, Paraskeui Tsonou, Antonis Maragos, Panagiotis Gargalianos, Achilleas Gikas, Charalambos Gogos, Ioannis Koumis, Moyssis Lelekis, Efstratios Maltezos, Georgia Margariti, Pavlos Nikolaidis, Angelos Pefanis, George Petrikkos, George Syrogiannopoulos, Athanassios Tsakris, Alkiviadis Vatopoulos, George Saroglou, Jenny Kremastinou, George L. Daikos; Working Group for the National Action Plan to Combat Infections due to Carbapenem-Resistant, Gram-Negative Pathogens in Acute-Care Hospitals in Greece

Hellenic Center for Disease Control and Prevention, 3–5 Agrafon Street, Athens 15123, Greece

ARTICLE INFO

Article history:
Received 9 January 2013
Received in revised form 24 May 2013
Accepted 13 June 2013

Keywords:
Infection
Nosocomial
Gram-negative
Carbapenem-resistant
Action Plan
Infection control
Hospital

ABSTRACT

The prevalence of carbapenem-resistant pathogens (CRPs) has increased worldwide. Given the importance of CRPs for public health and the high rates of carbapenem resistance observed in Greece, the Hellenic Center for Disease Control and Prevention (HCDCP) under the auspices of the Ministry of Health has undertaken initiatives to develop an Action Plan (i) to estimate the burden of CRP infections in acute-care hospitals in Greece and (ii) to implement infection control measures to limit the intrahospital transmission of these organisms. Starting in November 2010, specific infections caused by CRPs were reported to the HCDCP weekly. Results showed that CRP infections constitute a significant public health problem in acute-care hospitals in this country, with a mean incidence of 0.48 per 1000 patient-days and a crude 28-day mortality rate of 34.4%. The second phase of the Action Plan consists of systemic evaluation for adherence to an infection control bundle including enhanced standard infection control practices, separation of carriers and infected patients from non-carriers, and strict implementation of contact precautions. Communication between hospitals and public health authorities has been established to facilitate rapid notification and feedback.

1. Introduction

Carbapenems are among the last resorts for the management of infections caused by multidrug-resistant Gram-negative bacteria. Over the last decade, however, infections with carbapenem-resistant Gram-negative pathogens are emerging as a major public health threat worldwide [1,2]. This type of resistance is mediated by β-lactamases (carbapenemases) hydrolysing virtually all of the available β-lactams including carbapenems. The most predominant among these enzymes are the serine carbapenemase KPC (class A), the metallo-β-lactamases VIM, IMP and NDM (class B) and the OXA-type carbapenemases (class D), which are mainly found in *Acinetobacter* strains, although OXA-48 is also produced by Enterobacteriaceae [3]. These enzymes are encoded by *bla* genes harboured in transferable genetic elements with the potential for rapid horizontal spread.

The increased prevalence of carbapenem-resistant pathogens (CRPs) worldwide has important public health implications for several reasons. First, infections with CRPs are associated with poor patient outcomes, prolonged length of stay and increased costs [1,4,5]. Second, the therapeutic options against these pathogens are very limited [1,6–9]. Third, several clones of these organisms (e.g. *Klebsiella pneumoniae* ST258) have been shown to disseminate very efficiently from patient to patient in the acute-care setting and through patient transfer between healthcare facilities within the same country and/or across borders [8,9].

Whilst most European countries have a low prevalence of CRPs, Greece is among the European countries with highest rates of carbapenem resistance in Gram-negative bacteria [10,11]. The

* Corresponding author. Present address: Department for Interventions in Health-Care Facilities, Hellenic Center for Disease Control and Prevention, 3–5 Agrafon Street, Athens 15123, Greece. Tel.: +30 210 5212 175; fax: +30 210 5212 177.
E-mail address: helen-maltezou@ath.forthnet.gr (H.C. Maltezou).

2213-7165/$ – see front matter © 2013 International Society for Chemotherapy of Infection and Cancer. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jgar.2013.06.002

importation of carbapenemase-producing *K. pneumoniae* in Greece (VIM in 2003 and KPC in 2007), their rapid spread and their establishment in many acute-care hospitals across the country [8,12–16] was alarming for the medical community and the public health authorities. In response to that, in May 2010 the Hellenic Center for Disease Control and Prevention (HCDCP) under the auspices of the Ministry of Health established a working group of infectious diseases specialists, microbiologists, and experts on infection control and epidemiology of nosocomial infections to develop the 'Action Plan to Combat Infections due to Carbapenem-Resistant, Gram-Negative Pathogens in Acute-Care Hospitals' [17]. The Action Plan was implemented in November 2010, initially in hospitals in Athens metropolitan area and gradually expanded to all seven health districts of the country. Here we present the results of the first 18 months of operation.

2. Methods

2.1. Setting

Greece is a southeastern European country with a population of 10.9 million residents. There are 128 acute-care hospitals with 37,016 beds distributed in seven health districts. Starting on 1 November 2010, all newly detected cases of infections caused by carbapenem-resistant *Klebsiella* spp., *Pseudomonas* spp. and *Acinetobacter* spp. in hospitalised patients were notifiable to the HCDCP on a weekly basis. When no new case of infection caused by a CRP was detected within the past week, a zero-case report was sent to the HCDCP. All cases with an infection caused by carbapenem-resistant *Klebsiella* spp., *Pseudomonas* spp. or *Acinetobacter* spp. reported from 1 January 2011 to 30 June 2012 were included in this study. Carriage of the aforementioned organisms was not reported, thus CRP carriers were not included in the study. However, active surveillance was recommended to promptly identify undetected carriers and to trigger the implementation of infection control measures. In particular, active surveillance (pharyngeal and rectal swab testing) was recommended for high-risk patients, including patients admitted to intensive care units (ICUs), patients hospitalised in the same room with a CRP carrier, patients admitted in an ICU within the last 6 months, administration of carbapenems within the last 6 months, patients with a history of infection or colonisation due to CRPs, or patients admitted in a healthcare facility in India or Pakistan within the last 6 months (for NDM colonisation).

2.2. Definitions

A case of clinical infection caused by a CRP was defined by the presence of clinical signs and/or symptoms, laboratory and imaging findings compatible with a clinical infection, plus microbiological detection of carbapenem-resistant *Klebsiella* spp., *Pseudomonas* spp. or *Acinetobacter* spp. in a relevant clinical specimen. Clinical infections included bacteraemia (primary and intravascular catheter-associated), pneumonia (community-acquired, nosocomial, ventilator-associated and healthcare-associated), urinary tract infection (UTI) and surgical-site infection (SSI). Clinical infections were defined in accordance with the US Centers for Disease Control and Prevention (CDC) definitions [18]. Outcome was defined at 28 days after the first CRP-positive culture as 'discharged from hospital', 'still hospitalised' or 'died' (crude mortality) and was notified to the HCDCP accordingly.

2.3. Data collection

The following data were collected prospectively using one standardised form per case: age; sex; underlying disease(s); date and cause of hospital admission; hospitalisation and administration of broad-spectrum antibiotics including carbapenems within the last 6 months; department where the patient was admitted when the first CRP was isolated; invasive procedures before CRP isolation; site of CRP isolation; type of infection; resistance to colistin, gentamicin and/or tigecycline; mechanism of CRP resistance; and outcome.

2.4. Microbiological confirmation

Phenotypic resistance to at least one carbapenem was assessed in accordance with the current breakpoints of the Clinical and Laboratory Standards Institute (CLSI) [19] or through detection of carbapenemase production using boronic acid and ethylene diamine-tetra-acetic acid (EDTA) combined with a carbapenem in a combined disk test format, modified Hodge test methodology or molecular methods (PCR) for the detection of genes encoding the production of carbapenemases depending on the hospital [20]. Susceptibility testing was performed with the Vitek 2 automated system (bioMerieux, Marcy l' Etoile, France). In several instances tigecycline and colistin MICs were also verified by the Etest (bioMerieux).

2.5. Statistical analysis

The χ^2 test was used to investigate the association between the department of hospitalisation, the type of clinical infection and the outcome. The rate of change (trend) regarding the mean monthly incidence of infections caused by CRPs per 1000 patient-days was estimated using Linear Regression over time (totally and per pathogen). Multiple linear regression (stepwise selection) was then applied to investigate the independent association between the incidence of clinical infections caused by CRPs and specific hospital characteristics (health district, secondary-care vs. tertiary-care hospital, number of beds per hospital, number of Infection Control Nurses per hospital and the presence of an ICU in the hospital). The results of the regression were re-tested using univariate tests: One-way analysis of variance (ANOVA) was used to investigate the association between the number of beds per hospital ($<$200 beds, 201–500 beds and $>$500 beds), the health district and the incidence of infections caused by CRPs; T-test was used to investigate the association between the incidence of infections and the presence or absence of an ICU in the hospital, the number of Infection Control Nurses, and the type of hospital (secondary-care vs. tertiary-care hospital). *P*-Values of $\leq$0.05 were considered statistically significant.

3. Results

From 1 January 2011 to 30 June 2012, a total of 7477 cases of infections caused by CRPs were notified by 119 hospitals. The number of notified infections ranged from 308 to 489 cases per month (median number of monthly notified cases, 431). Table 1 shows the characteristics of the notified cases. Pneumonias and bacteraemias were the most frequent types of infection, accounting for 34.0% and 31.3% of cases, respectively. Ventilator-associated pneumonia was the prevalent type of pneumonia, followed by nosocomial pneumonia (74.7% and 18.2% of all pneumonia cases, respectively). Most infections (3865 cases; 51.7%) concerned patients admitted in ICUs. Pneumonias and bacteraemias more frequently concerned ICU patients (48.3% and 39.2% of ICU cases, respectively) compared with 23.4% and 24.1% of the cases notified in Internal Medicine Departments and 9.4% and 20.8% of those notified in Surgical Departments, respectively ($P < 0.001$ for all comparisons). In contrast, UTIs were more frequent among patients admitted to the Internal Medicine Departments compared