American Journal of Infection Control 42 (2014) 739-43

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

Are strict isolation policies based on susceptibility testing actually effective in the prevention of the nosocomial spread of multi–drug-resistant gram-negative rods?

Norio Ohmagari MD, MSc [a,c], Hanako Kurai MD [b], Yuka Yamagishi MD, PhD [c], Hiroshige Mikamo MD, PhD [c,*]

[a] Disease Control and Prevention Center, National Center for Global Health and Medicine, Aichi Medical University Graduate School of Medicine, Nagakute, Aichi, Japan
[b] Division of Infectious Diseases, Shizuoka Cancer Center, Aichi Medical University Graduate School of Medicine, Nagakute, Aichi, Japan
[c] Department of Clinical Infectious Diseases, Aichi Medical University Graduate School of Medicine, Nagakute, Aichi, Japan

Key Words:
Isolation
Precaution
Multi–drug-resistant gram negative bacilli

Background: The emergence of multi–drug-resistant gram-negative rods (MDR-GNRs) has become a worldwide problem. To limit the emergence of MDR-GNRs, a tertiary care cancer center in Japan implemented a policy that requires the pre-emptive isolation of patients with organisms that have the potential to be MDR-GNRs.

Methods: A retrospective analysis was performed. Any gram-negative bacillus isolates categorized as intermediate or resistant to at least 2 classes of antimicrobials were subjected to contact precautions. The incidence of patients with MDR-GNRs was analyzed.

Results: There was no difference between the preintervention and intervention time periods in the detection rate of nonfermenting MDR-GNR species (0.15 per 10,000 vs 0.35 per 10,000 patient-days, $P = .08$). There was an increase in the detection rate of multi–drug-resistant *Enterobacteriaceae* (0.19 per 10,000 vs 0.56 per 10,000 patient-days, $P = .007$), which was prominent for extended-spectrum β-lactamase (ESBL)-producing organisms (0.19 per 10,000 vs 0.50 per 10,000 patient-days, $P = .02$).

Conclusions: Our intervention kept the emergence of multi–drug-resistant non–glucose-fermenting gram-negative bacilli to a small number, but it failed to prevent an increase in ESBL producers. Policies, such as active detection and isolation, are warranted to decrease the incidence of these bacilli.

The increasing detection rate of multi–drug-resistant gram-negative rods (MDR-GNRs) is an emerging problem worldwide, including in Japan.[1] Controlling MDR-GNRs presents several challenges. First, rapid and sensitive detection of MDR-GNRs is difficult. Second, there is no consensus regarding the list of drug-resistant bacteria to target for infection control. Third, infection control policies for MDR-GNRs often lack strong evidence to identify the minimum interventions needed to reduce their transmission[2]; therefore, there is no consensus regarding which strategies to use.

Some drug-resistant bacilli sequentially acquire additional resistance mechanisms and become multi–drug-resistant strains.[3] *Pseudomonas aeruginosa* has inherent resistance to many drug classes and the ability to acquire resistance to antimicrobials via mutations.[1] The development of antimicrobial resistance is caused by the rapid evolution of the bacterial genome under the selective pressure of antimicrobials.[4,5] The transmission of antimicrobial-resistant organisms occurs when proper infection prevention and control methods are not applied.[6] It is difficult to manage multi–drug-resistant bacilli once they have spread. However, the spread of these bacilli can be stopped before multidrug resistance emerges, and appropriate infection control methods can prevent the acquisition or horizontal diffusion of multidrug resistance.

We hypothesized that we could prevent the horizontal transmission of targeted drug-resistant bacilli by detecting and appropriately controlling these species before they acquired multidrug resistance.[7] In January 2005, our hospital implemented a proactive strategy to prevent the spread of MDR-GNRs by establishing original criteria for drug-resistant bacilli based on antimicrobial susceptibility testing results. Assessing the results of this strategy

* Address correspondence to Hiroshige Mikamo, MD, PhD, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan.
E-mail address: mikamo@aichi-med-u.ac.jp (H. Mikamo).

Conflict of interest: None to report.

0196-6553/$36.00 - © 2014 Published by Elsevier Inc. on behalf of the Association for Professionals in Infection Control and Epidemiology, Inc.
http://dx.doi.org/10.1016/j.ajic.2014.04.003

would be valuable in the process of establishing future guidelines for MDR-GNR infection control. This study reviewed the effectiveness of this strategy.

METHODS

This was a retrospective study based on the examination of a bacterial testing database.

Setting

The Shizuoka Cancer Center was created in September 2002, and it is devoted to cancer patient care, research, education, and prevention. It includes a 615-bed hospital that provides tertiary medical and surgical services for cancer patients. Approximately 13,000 patients are admitted to the institution for cancer care each year.

Subjects

The study period was defined as January 1, 2003, to December 31, 2010, and the medical records database was examined throughout this period to identify patients for inclusion in this study. We did not include 2002 in the study period because the hospital was established in September 2002 and did not operate at full capacity that year. During the study period, all of the patients who were admitted to the hospital or who visited outpatient departments at Shizuoka Cancer Center were eligible for inclusion. There were no exclusion criteria. Clinical samples were collected as needed to diagnose infectious diseases. Active sampling from asymptomatic patients to find newly colonized patients was not conducted during the study period. Data from the bacterial testing results database of the in-house microbiology laboratory were used for this study. The data included dates of detection, types of culture samples, inpatient or outpatient status, names of the detected strains, and results of susceptibility testing. Inpatient days of care during the study period were defined as the sum of each daily inpatient census for the month.

Interventions

The Shizuoka Cancer Center did not have regulations in place for controlling hospital transmission of MDR-GNRs until December 2004, when we first identified patients with multi−drug-resistant *P aeruginosa*. In January 2005, a prevention policy against MDR-GNR infection was implemented. On the isolation of strains that satisfied the defined criteria for antimicrobial-resistant gram-negative bacilli (subsequently described), contact precautions were implemented by placing these patients in isolated rooms. Active interventions, such as requiring permission for specific antimicrobials prior to their use or regulating the prescription of certain antimicrobials, were not applied during the study period. In this study, we compared the preintervention period (January 1, 2003-December 31, 2004) with the intervention period (January 1, 2005-December 31, 2010).

Detection methods for bacterial strains

Clinical isolates were processed using the BacT/ALERT 3D Microbial Detection System (bioMérieux, Chemin de l'Orme, France). Identification and antimicrobial susceptibility tests were performed using the VITEK 2 system (BioMérieux, Marcy l'Étoile, France) (prior to March 31, 2008) or the WalkAway 40 plus System (Siemens, Erlangen, Germany) (beginning on April 1, 2008). Susceptibility was defined according to the interpretative breakpoints recommended by the Clinical and Laboratory Standards Institute (performance standards for antimicrobial susceptibility testing).[8]

Escherichia coli, *Klebsiella pneumonia*, *Klebsiella oxytoca*, *Proteus mirabilis*, and *Proteus vulgaris* strains that tested resistant to piperacillin were further subjected to a double-disk synergy test using clavulanic acid, cefotaxime, ceftriaxone, ceftazidime, and aztreonam disks (Kirby-Bauer disk; Eiken Chemical Co, Tokyo, Japan)[5] to isolate extended-spectrum β-lactamase (ESBL)-producing bacilli. Positive isolates were identified as ESBL-producing bacilli. For metallo-β-lactamase-producing bacilli, strains that tested as intermediate or resistant to meropenem or imipenem were subjected to additional testing. Mercaptoacetic acid was used as an inhibitor of metal β-lactamase (MBL) (sodium mercaptoacetic acid disk; Eiken Chemical Co, Tokyo, Japan), and the diameter of the inhibition zone on the imipenem and ceftazidime disks was measured.[6] The specimens were determined to be MBL-producing bacilli when a significantly larger zone was observed.

Criteria for isolation and precautions

The criteria for gram-negative bacilli that were subjected to contact precautions were defined as (1) gram-negative bacilli that were subjected to susceptibility testing and were insensitive (intermediate or resistant) to at least 2 of the following classes of antimicrobials: carbapenem (ie, imipenem/cilastatin), aminoglycoside (ie, amikacin), quinolones (eg, ciprofloxacin), and cephem (ie, ceftazidime); (2) metallo-β-lactamase-producing bacilli; or (3) ESBL-producing bacilli. *Stenotrophomonas maltophilia* and *Burkholderia cepacia* were not subjected to contact precautions because their antimicrobial resistance is generally intrinsic, and their multidrug resistance is less likely to be horizontally transferred to other bacteria via plasmids.

Definition of MDR-GNRs

Gram-negative bacilli that were (1) insensitive to at least 3 of the classes of antimicrobials mentioned in the Methods section, (2) metallo-β-lactamase-producing bacilli, or (3) ESBL-producing bacilli were defined as multi−drug-resistant ram-negative bacilli (MDR-GNRs). *S maltophilia* and *B cepacia* were not classified as MDR-GNRs in this study.

Metrics used

The criteria for calculating the incidence rates of targeted strains in inpatients were as follows: (1) we included strains detected at least 48 hours after hospital admission; (2) we included only newly detected strains and excluded cases in which the same strain was later detected in the same patient; and (3) we included each species when multiple species were isolated from the same patient. The incidence density of each detected strain was calculated by dividing the number of bacilli detected over a specific period of time by the total inpatient days at our hospital (calculated as previously described). The incidence density rate of MDR-GNRs and *S maltophilia* and *B cepacia* were calculated to determine the trends of organisms that were not targets of the intervention. The incidence density is reported per 10,000 patient-days. To assess the detection rate of ESBL-producing bacilli among outpatients, the incidence of ESBL-producing bacilli in the outpatient department was also calculated, and it is reported per 1,000 newly admitted patients.

Statistical analysis methods

Statistical analyses were performed to compare the preintervention period (September 2003-December 2004) with the