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Facing the rising tide of multidrug resistant Gram-negative pathogens

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There is a clear pattern of rapidly increasing prevalence and spectrum of multidrug-resistance (MDR) among Gram-negative bacilli (GNB).[1] Several newly-identified and rapidly spreading types of carbapenemase have been reported among MDR GNB recently. Additionally, community-onset infections with MDR GNB are now frequently seen in clinical practice. Moreover, infections caused by MDR GNB are associated with substantial mortality, prolonged hospital stay and high healthcare costs.[2] The emergence of MDR GNB is a critical threat to public health, which has prompted healthcare providers and researchers alike to assess the evolving epidemiology, perpetuating factors and intervention strategies for the current epidemic of MDR GNB.[3]

Changing epidemiology

Beta-lactam antibiotics have been the mainstay of therapy for GNB for decades. However, many β-lactam antibiotics are hydrolysed and rendered ineffective by Gram-negative organisms that produce extended-spectrum β-lactamases (ESBLs). Worse still, many ESBL-producing pathogens concurrently carry genetic elements that code for resistance against other classes of antibiotics, such as aminoglycosides and fluoroquinolones. Over the last 5 years, ESBL-producing GNB have become widely disseminated in the community setting in numerous countries, including Australia.[4] This trend has not been observed in the United States until recently. A retrospective study of 16 community hospitals in four states in south-eastern USA revealed substantial increase in the incidence of infections with ESBL-producing *E. coli* from 2005–2008, and 83% of such infections were categorised as community-onset.[5] A separate study examined the molecular basis for the increase in community-onset ESBL-producing GNB infections in the USA and it showed the rise was primarily due to emergence of ST131 *E. coli*, which is typically associated with CTX-M-15 ESBL genotype and frequently co-carries resistance to fluoroquinolones, aminoglycosides and co-trimoxazole.[6] The implications from these studies are far-reaching for the USA, Australia and other countries with similar patterns of ESBL-producing GNB; Gram-negative infections from the community are now frequently caused by ESBL-producers and may no longer respond to first-line β-lactams, quinolones or co-trimoxazole. Thus, more patients will require hospital admission for intravenous antibiotics and the challenge is for health systems to deal with an influx of community-acquired MDR GNB infections and colonisation.

For many years, carbapenems remained effective against infections caused by ESBL-producing GNB. However, many new carbapenemases have emerged and have limited the number of therapeutic options for MDR GNB. For instance, *Klebsiella pneumoniae* carbapenemase (KPC)-producing GNB are resistant to all β-lactam antibiotics. These KPC-producing GNB have spread across the USA and many regions around the globe in the last 5 years.[7] KPC has become the most common carbapenemase enzyme among GNB in the USA. However, the detection and control of KPC resistance remain a complex process for several reasons. First, automated susceptibility testing with meropenem or imipenem is not sensitive for detection of KPC activity; laboratories and machines need to upgrade to ertapenem to screen for KPC-producers and the Modified Hodge Test to confirm carbapenemase activity.[8] Second, KPC genes reside on mobile genetic elements that may be transferred between GNB.[9,10] Finally, KPC-producing organisms could perpetuate and establish low-level endemicity in hospitals and long-term care facilities.[11,12] The threat of KPC-producing organisms is real and the Centers for Disease

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Control and Prevention (CDC) certainly recognised that threat. Despite already having guidelines for management of multidrug-resistant organisms,[13] the CDC specifically published recommendations for the management and control of carbapenem-resistant *Enterobacteriaceae* (CRE) control of carbapenemease-resistant *Enterobacteriaceae* in 2009.[14]

In 2010, a new carbapenemase was described that belongs to the metallo-β-lactamase (MBL) family. This new carbapenemase, known as New Delhi metallo-β-lactamase (NDM-1), was reported in patients in the UK, USA, Canada, Belgium, Taiwan and Australia.[15–17] Although some patients infected with NDM-1-producing GNB had a travel history through the Indian subcontinent, the origin and the extent of NDM-1 remained uncertain. The fact that NDM-1 was detectable in patients who did not travel to the Indian subcontinent led many experts to believe that NDM-1 may already be widely disseminated globally and was posing a problem much bigger and wider than KPC resistance.

While KPC and NDM-1 producing organisms are new and becoming more common, they certainly do not represent the majority of MDR GNB in clinical practice. Instead, the real story of MDR GNB is better represented in a recent cross-sectional analysis showing increasing rates of multi-class antibiotic resistance among GNB in the USA. For instance, 10% of all *Pseudomonas aeruginosa*, 15% of *Klebsiella pneumoniae* and 60% of *Acinetobacter baumanii* isolates submitted to the National Healthcare Safety Network (NHSN) from 2006 to 2008 showed resistance to at least three classes of antibiotics.[1] MDR *Acinetobacter* is an important opportunistic pathogen that causes devastating bloodstream infections, ventilator-associated pneumonias, wound infections and meningitis among critically ill patients.[18] Due to many intrinsic and acquired mechanisms of antimicrobial resistance, infections with MDR *Acinetobacter* are often limited to few therapeutic options, such as polymyxins, aminoglycosides and tetracyclines/glycylcyclines.[19] In this issue of the journal, Buchan *et al.* writes a succinct and up-to-date review of the important *Acinetobacter* sp., covering clinical disease, changes in epidemiology and diagnostic and infection control considerations.

MDR *Acinetobacter*, along with KPC- and NDM-1-producing organisms described above, truly indicates that the era of MDR GNB is here. The challenge for infection control now is how we identify and interrupt the transmission of MDR pathogens from colonised patients and contaminated environments to other susceptible patients.

Identification and surveillance concerns

Infection control of aforementioned MDR GNB in healthcare setting is not straightforward. Active surveillance of MDR GNB is generally not performed outside of an outbreak or an endemic setting. Furthermore, there is debate over which body site is the most sensitive for detection of colonisation status and the answer varies by organism. For example, researchers in Israel have used rectal swabs to detect colonisation with KPC-producing organisms in their attempt to control extended outbreaks.[20] Another group in Melbourne, Australia identified that swabs of the groin had the highest sensitivity to detect *Acinetobacter* sp. colonisation among ICU patients.[21] The merit and practicality of asymptomatic surveillance for MDR GNB colonisation remain unresolved.

Another layer of complexity for infection control of MDR GNB lies in the definition and identification of MDR GNB that require isolation precautions. Many hospitals rely on identification or recognition of a known resistance mechanism, for example ESBL, as a trigger to initiate isolation precautions. This practice may no longer be adequate or reliable. In 2010, the Center for Laboratory Standards Institute (CLSI) lowered the antibiotic susceptibility breakpoints for almost all cephalosporins and no longer required clinical microbiology laboratories to perform confirmatory testing for ESBLs. These changes are likely to push infection control programs to implement contact precautions based on multi-class antibiotic resistance; rather than relying on testing for specific types of antibiotic phenotype such as ESBL.

Role of the environment and impact of cleaning

Like many nosocomial pathogens, MDR GNB can persist on surfaces for a prolonged period of time;[22] such contaminated surfaces could act as vectors for cross-transmission and subsequent infection. For example, MDR *A. baumannii* can persist on dry surfaces such as bed rails for up to a month and has been implicated in hospital outbreaks.[23,24] Thus, many researchers are now: (i) assessing the role of the hospital environment in healthcare-associated infections (HAIs); (ii) defining high-risk surfaces to focus decontamination efforts; and (iii) evaluating novel cleaning strategies to reduce problems with nosocomial MDR GNB infections.

Inanimate surfaces in hospitals are frequently colonised with nosocomial organisms. High-touch surfaces are probably more likely to harbour nosocomial pathogens than other surfaces in hospitals and there is immense interest to better define such high-touch and high-risk surfaces. Researchers from the University of North Carolina observed healthcare workers in standard patient rooms and quantitatively defined high-touch areas as bed rails, bed surfaces, supply carts, over-bed tables and intravenous pumps.[25] These high-risk surfaces should receive rigorous cleaning with hospital-grade disinfectants. Moreover, these high-risk areas could potentially receive regular tests for adequacy of cleaning.

There is also intense interest to find new and more effective technologies to reduce the burden of nosocomial organisms in hospitals. Several promising technologies have been evaluated formally with respect to decontamination of hospital rooms and healthcare equipment; promising technologies include ultraviolet-C (UVC) irradiation and hydrogen peroxide vaporisation.

UVC is invisible, is microbicidal and has been extensively used in the food industry to reduce microbial burden in raw and packaged foods and beverages. UVC has a major advantage of a short kill-time for common nosocomial pathogens (less than an hour) compared with hydrogen peroxide vaporisation. Adaptation of UVC technology for healthcare settings may ultimately allow safe and rapid decontamination of rooms and heat-, water- and electronic-sensitive surfaces, such as critical-care monitors, computer keyboards and ventilator equipment.[26] Researchers from the Cleveland Veterans Affairs Medical Center showed that a UVC device consistently reduced the burden of methicillin-resistant *S. aureus* and *C. difficile* spores by 2–3 $\log_{10}$ and vancomycin-resistant enterococci (VRE) by 3–4 $\log_{10}$ colony-forming units (CFUs)/cm^2 following 45 min of irradiation. A separate study showed that UVC is also effective for MDR *A. baumannii*, producing an average of 3–4 $\log_{10}$ CFU reduction following 15 min of irradiation.[27]

Hydrogen peroxide vapour (HPV) was effective for environmental decontamination in an outbreak of MDR GNB (*Serratia* and *Acinetobacter* sp).[28] However, the HPV technology required modifications/disabling of the heating, ventilation and air-conditioning system and sealing of all vents and doors of a room being processed to reduce inadvertent escape of HPV. Furthermore, a full HPV decontamination cycle in this study took ~12 h, although another feasibility study showed only 3–3.5 h were required for decontamination.[29]

In addition to the recent interest in novel cleaning technologies, there has been a parallel push to establish a standardised method to assess the quality of cleaning in hospitals. Many healthcare institutions rely on visual assessment of surfaces to assess cleaning, which is unreliable and highly subjective. Now, two approaches for monitoring effectiveness of hospital cleaning have been used over the last few years: use of bioluminescence assay with adenosine triphosphate (ATP) and testing for residual ultraviolet visible markers. Bioluminescence assay of ATP is a relatively easy method for assessing cleanliness and has been used in the food and beverage industry to detect contamination of surfaces or liquids. During the ATP bioluminescence assay, test surfaces are sampled using a specialised swab which is then analysed in a luminometer. Current generation of ATP bioluminescence assays are performed in one step following cleaning and can provide quantitative measurement of residual organic matter – the quantitative data may be collected and used to track trends in performance and to motivate improvements in cleaning.[30]

The ultraviolet (UV) visible marker test is an inexpensive two-step process to assess cleanliness of surfaces. First, UV marks are placed on surfaces of patient rooms before cleaning takes place. Following cleaning, residual and unerased UV markers can be detected using a UV light. Although the number of detectable residual UV marks provides semiquantitative data of cleanliness, this technology is more laborious and time-intensive because of the two-step process. However, one advantage of the UV visible marker technology is the ability to immediately show the number and location of residual UV markers which can provide a visual feedback for cleaning staff to improve their processes.[31]

No discussion of potential vectors for nosocomial pathogens is complete without mention of uniforms and white coats. Whether uniforms for physicians and nurses could act as vectors still remains a debate. White coats and non-essential clothing are frequently colonised with bacteria and were banned in the UK and other countries despite very little data to support a causal association between colonisation of uniforms and nosocomial infection in patients. Moreover, no study has determined whether banning white coats, ties and long-sleeved shirts had reduced bacterial colonisation of unprotected clothing of staff and reduced nosocomial infections. In this issue of *Healthcare Infection*, Halliwell *et al*. elegantly describes the history and the evolution of protective garments for nursing staff, and how uniforms may impart a perception of professionalism at a cost of harboring nosocomial pathogens.

The oft-cited disdain in the infection control field for uniforms and white coats may very well be misplaced. A recent randomised-controlled trial from Denver, Colorado, studied bacterial colonisation of staff wearing clean short-sleeved uniforms changed each day compared with continuing to wear the participant's own (and infrequently laundered) long-sleeve white coat. The study showed that freshly laundered uniforms were colonised with MRSA within 3 h of wear and that after 8 h of wear, there was no difference in the proportion or quantity of bacterial colonisation between the short-sleeved uniforms and the infrequently laundered long-sleeved white coats.[32] Will this study reverse the ban of uniforms and white coats? Perhaps not. However, this might just be that first piece of data showing short-sleeved uniforms are just as susceptible to bacterial colonisation as white coats.

Uniforms and white coats aside, most experts believe that hands of healthcare staff remain the most important vector for transmission of nosocomial and MDR pathogens. Alcohol-based hand gels or foams are the preferred hand hygiene products for healthcare settings due to their ease of use and convenience in product placement compared with soap and water. In this edition of the journal, Miller *et al*. examined whether applying firm friction during hand hygiene with soap and water provided any incremental benefits in decreasing bacterial colony counts compared with hand hygiene: (i) with just running water without soap or hand-hand friction; and (ii) with running water and hand-hand friction but no soap. Among three techniques of hand hygiene in the study, the investigators found 20 s of frictioned hand wash with soap and water was the most effective.

Performance of hand hygiene (HH) is the most important process to reduce transmission of nosocomial pathogens. Despite the availability of hand sanitizers, the compliance of hand hygiene among healthcare staff in hospitals in USA and other countries has historically averaged around 30–40%.

These data are not accurate since no standard methodologies exist for auditing compliance to hand hygiene. Furthermore, historic data were severely limited by observer and recall bias. At Duke University Medical Center, Durham, NC, USA, direct observation for hand hygiene compliance is performed by trained auditors who use wireless handheld devices to record data. These data are transmitted to a central server, which provides real-time feedback to managers of each service area of the hospital. Performance data are used by directors and managers to improve HH compliance. Since the adoption of this technology, we have seen a dramatic increase in the overall rate of HH compliance in our hospital (from ~40% to 85%). Many institutions are now using a similar in-house or commercial solution to assess HH compliance. Each institution should examine their needs and implement a reliable HH audit program and use the data to motivate healthcare staff to improve adherence to hand hygiene.

Conclusions

The era of MDR GNB is here. Hospitals and community settings face the same challenge of increasing prevalence and spectra of MDR GNB. Transmission of nosocomial MDR GNB pathogens between patients involves a complex interaction of contaminated surfaces, clothing and hands of healthcare workers. However, we are armed with the knowledge of epidemiology; we have new technologies for disinfection and to monitor cleaning; and we understand the importance of auditing and improving HH performance. There is hope – we can make a difference to interrupt the cycle of transmission of nosocomial and MDR pathogens in healthcare.

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