

State of the Globe: The Rippling Effect of Multidrug-Resistant Gram-negative Infections

The continued emergence of multidrug-resistant (MDR) organisms in our hospital systems such as the Neonatal Intensive Care Unit as mentioned by Ramakrishnan *et al.* represents the need for continued vigilance and proactive plans to prevent the spread of these organisms. These multifaceted plans directed by infectious diseases teams have procedures in place via infection control, with subsequent components done in concert with microbiology labs and antimicrobial stewardship programs. If any of these moving parts are not appropriately coordinated then are lapses and patients pay for the consequences. Ramakrishnan's case series describes a 50% mortality rate to the youngest of possible age groups when an MDR strain of *Klebsiella pneumoniae* entered the microbiological flora of a single center.

Infection control interventions form the cornerstone to prevent the spread of MDR infections in a single facility. Hand hygiene and appropriate environmental cleaning, though basic are still very important. Numerous papers have cited increased transmission of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and other organisms as the percent of those participating in good hand hygiene decreases.^[1] In Australia, the pooled acquisition odds ratio for Gram-negatives was found to be 2.65 (95% confidence interval: 2.02-3.47) reflecting the bacterial flora from the prior occupant of the same room.^[2]

Once a patient has a presentation consistent with sepsis, empiric antimicrobials are chosen after cultures are drawn. Astute knowledge of the common flora related to a country or facility is needed in order to choose the appropriate entry level of antimicrobials. Understanding a particular patient's personal risk factors for MDR colonization as related to significant recent hospitalizations and/or previous receipt of broad-spectrum antimicrobials such as cephalosporins.^[3] Bacteremia with MDR organisms can occur *de novo* as

well and would not be picked up until blood cultures are finalized. Monitoring critically ill patients and readdressing the level of antimicrobials after approximately 48 h is an appropriate plan of care for such a situation. With standard microbiologic workup, there is often a lag of up to 48 h from the positivity of a blood culture to identification and sensitivity analysis with automated systems such as VITEK 2. There are an increasing number of platforms that utilize polymerase chain reaction (PCR) technology allowing for blood culture identification in approximately 1 h after Gram-stain production such as with the FilmArray system of Biofire (Biofire PDF).^[4] Reproducible sensitivity and specificity are 95% and 96.7%, respectively, for different multiplex PCR kits but only for known targets of drug mechanisms.^[5] Multiplex PCRs will miss novel mutations of MDR organisms as plasmids are exchanged or new mutations occur that otherwise would have been assessed phenotypically on plate cultures. Once an MDR organism is correctly identified, appropriate and timely therapy escalation is implemented if it had not already been done empirically. The use of aminoglycosides and polymyxins as part of the concerted treatment for MDR organisms has increased the rates of acute kidney injury as well as other unmitigated side effects. In addition, there is added selective antimicrobial pressure from the ongoing use of carbapenems leading to further issues with potential infections with organisms such as *Stenotrophomonas* sp.

Despite interventions with aggressive hand hygiene and appropriately placed critical care bundles, bacteremias with MDR organisms continue to occur. Root cause analyses are important as well as looking to the future for further improvements. Having teams and protocols in place when a single aberration occurs compared to the norm of a

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hospital helps get in front of a potential catastrophe that includes loss of life. Considering the concentration of patients with MDR organisms in a hospital, appropriate disposal of patient bodily fluids becomes an added issue. Hospital effluent has been assessed and been found to be contaminated with high level of MDR Gram-negative organisms that a standard sewage plant would be unable to create protocols to neutralize thus allowing it to mix with other environmental substances.^[6] The question of adequate assessing for and then treating MDR infections is an issue here to stay. Large steps have been made in diagnosing them faster, but further therapies are needed for treatment and minimizing spread within a hospital as well as the environment as a whole.

Aliyah Baluch

*Division of Infectious Diseases, Moffitt Cancer Center,
Tampa, FL, USA*

Address for correspondence:

Dr. Aliyah Baluch, E-mail: aliyah.baluch@gmail.com

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