EDITORIAL

Glimmer of Hope in the Trends of Antimicrobial Resistance

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In this issue of the Journal of Acute Care, Deshpande et al. have demonstrated that appropriate antibiotic therapy in patients with sepsis decreases intensive care unit (ICU) stay, thereby decreasing complications associated with prolonged stay, reduces the financial burden, and stress on patients.[1] Taking the aid of markers of sepsis and molecular diagnostics may help to ensure the appropriateness of empirical antibiotic therapy and timely administration.

Antibiotic and diagnostic stewardship interventions may reverse the tide despite widespread and ever-increasing resistance among common ICU bugs against presently available antimicrobials. There is a widespread and alarming rise in resistance of common ICU bugs against antimicrobials, including those reserved as a last resort drug. The resistance pattern among ICU microorganisms against antimicrobials is different in India compared to the Western world. This rampant resistance is responsible for the increased mortality among patients infected with multidrug and extended drug-resistant organisms. Further, this ever-increasing resistance of microorganisms to antimicrobials is associated with whopping costs, and India is the largest consumer of antimicrobials. Despite this alarming situation, antibiotic and diagnostic stewardship interventions together have the potential to reverse the tide. These interventions can improve the susceptibility pattern among the microorganisms and decrease the consumption of antimicrobials.

Chaudhry et al. pointed out that the epidemiology and resistance patterns of pathologic microorganisms in Indian ICUs differ from those in the Western world. While infections caused by gram-positive cocci (GPC) are dominant in critical care units of developed countries, Indian ICUs are frequently plagued by gram-negative bacteria (GNB). These GNBs recovered from our ICUs often exhibit high resistance to multiple antimicrobial agents.[2] A similar opinion was echoed by Mave et al. and Ghanshyam et al., in their findings from an Indian ICU of a tertiary care center, reported that the GNBs were the most commonly associated with infections and their prevalence in descending order were, *Acinetobacter baumannii (A. baumannii)* (20.9%), *Klebsiella pneumoniae* (*K. pneumoniae)* (19.7%), *Escherichia coli (E. coli)* (18.3%), and *Pseudomonas aeruginosa (P. aeruginosa)* (14.0%).[3,4] Only about 13% of infections were caused by GPCs, notably, *Staphylococcus aureus (S. aureus)* (8.2%) and *Enterococcus* species. Moreover, almost 7 years back, they cautioned about the widespread resistance to common antibiotics among common bugs detected in Indian ICUs. Moreover, the resistance of the microbes to carbapenems was detected in >50% and about 20% of *Klebsiella* and *E. coli* isolates, respectively.[4]

A similar trend was evident in the retrospective study by Singh et al. conducted in a center located in rural Northern India.[5] They reported that the GNBs were most preponderant among the isolates collected from critically ill patients. Among these GNBs, *P. aeruginosa* (38.17%) was most commonly detected, followed by *K. pneumoniae* (23.76%), *Acinetobacter spp* (14.96%), and *E. coli* (6%). GPCs contributed to a minuscule of all positive isolates with *S. aureus*, 2%; coagulase-negative *Staphylococcus* (CoNS), 2%; and *Enterococcus*, 0.6%.[5]

The INDICAPS study (2016) was a nationwide point prevalence study over four days involving several centers to examine the pattern of infections in ICUs. They identified a massive 68.9% GNBs from the isolates. About 15.9% were GPCs, and 7.5% were fungi.[6]

Mave et al. also reported that *E. coli* was the most common causative organism among GNBs. In contrast, *A. baumannii* accounted for the most common multidrug-resistant (MDR) infections, particularly carbapenem-resistant. As high as 52% of patients with acute febrile illness admitted to a tertiary care center in Western India had MDR organisms, most of which were GNBs.[3]

Mogasale et al. reported that extended-spectrum β-lactamase (ESBL) was responsible for multidrug resistance, including third-generation cephalosporins among a whopping 72% of *E. coli* and 63% of *Klebsiella* spp. A total of 53% of *S. aureus* were found to be methicillin-resistant *S. aureus* (MRSA). Only, 46% of the *Enterobacteriaceae* produced ESBL leading to resistance to carbapenems and third-generation cephalosporins.[7]

The World Health Organisation (WHO), in its antimicrobial resistance report of 2018, for the Indian sub-continent, showed that half of all isolates with the growth of *A. baumannii* and 31–50% of those exhibited growth of *P. aeruginosa* displayed resistance to carbapenems.[8] Walia et al. also reported that a massive 80% of isolates of *A. baumannii* and 30% of *P. aeruginosa* displayed resistance to carbapenems.[9]

The annual report of the Indian Council of Medical Research published in Sep 2021 reiterated the findings of the previous reports. It stated that the most frequently isolated bug was *E. coli*, trailed closely by *K. pneumoniae*, *P. aeruginosa*, *A. baumannii,* and *S. aureus,* in that order.[10]

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The identification of MDR *Enterobacteriaceae*, which produced the New Delhi metallo β-lactamase enzyme, created a hue and cry in 2010 but is now encountered frequently in our ICUs.[11] Thus, it was a no-brainer that the Indian Council of Medical Reseaech report (2021) highlighted the high incidence of carbapenem resistance among the isolates. While 86% of the *E. coli* were susceptible to imipenem in 2016, in <3 years, the number dropped precipitously to 63%, although it exhibited modest improvement to 72% in 2020. Similarly, while 65% of *K. pneumoniae* isolates were sensitive to imipenem in 2016, by 2020, not more than 45% remained so. The situation is grim with *A. baumannii*, where not >10–20% of isolates were found sensitive to several classes and combinations of antibiotics, for instance, β-lactams (cephalosporins, carbapenems, and monobactams) and β-lactam-β-lactamase inhibitors (BL-BLI). The only exception to this trend is minocycline, where a susceptibility of 54% was reported. Among isolates of *P. aeruginosa*, 60–70% displayed sensitivity to β-lactams and aminoglycosides, whereas only 40% were susceptible to fluoroquinolones.[10]

Staphylococcus aureus (S. aureus) has demonstrated a similar trend of rising resistance to several hitherto commonly used antibiotics. When compared, MRSA) had higher sensitivity rates to several antibiotics like erythromycin, clindamycin, ciprofloxacin, co-trimoxazole, and high-level mupirocin than MRSA. Vancomycin and tigecycline, common agents against MRSA, exhibited superb in vitro sensitivity (100% against MRSA isolates). Only 1 and 0.5% of MRSA showed resistance against linezolid and teicoplanin, respectively.[10]

As far as fungal infections are concerned, their incidence among hospitalized patients is significantly increasing. *Candida auris*, a yeast that had shown resistance against multiple antifungal agents, is increasingly reported across India. Most of the isolates of the *Candida auris* were resistant to fluconazole and, increasingly, even to echinocandins.[10]

The ever-growing resistance of the common ICU bugs to antimicrobials is associated with considerable mortality. Gandra et al. found a significant association between infections with MDR pathogens and mortality in a multicentric study. They reported two to three-fold higher mortality when the causative agents of the infection were multidrug or extensively drug-resistant GNBs like *E. coli*, *K. pneumoniae,* or *A. baumannii*. Similarly, mortality from infections with GPCs was higher when the culprit was MRSA than sensitive strains. Further, more patients died if they were afflicted with MRSA, which was also resistant to aminoglycosides.[12]

Among patients with MDR GNB infections. Mave et al. observed a five to six-fold increase in mortality.[2] The mounting resistance to antimicrobials entails enormous expenditure, and this is evident from the fact that the Indian population consumes the largest volume of antimicrobials globally.[7] To make matters worse, no promising antimicrobials in the pipeline can be expected to hit the markets soon.[13]

In such a grim situation, the questions beg for answers—have we lost the battle to the resistant bacteria? Have we reached the postantibiotic era, as warned by the WHO?[14] Chaudhry et al. suggested that Indian ICUs should expeditiously formulate and execute an antimicrobial stewardship (ASP) program considering the local epidemiological data and guidelines proffered by international societies to optimize the utilization of antimicrobials in hospitalized patients.[2] To give a further edge, ASP may be combined with a diagnostic stewardship program (DSP) to turn the tide against the ever-increasing resistance among the common ICU bugs.

The authors and his colleagues (2021) examined whether interventions related to ASP and DSP could reverse the increasing resistance patterns of the usual culprit bacteria that lead to bloodstream infections (BSI) in patients admitted to critical care units.[15] They reported that after the adoption of ASP and DSP interventions, there was reduced resistance of GNBs to aminoglycosides. Similarly, *E. coli* and *Klebsiella* spp showed enhanced susceptibility to BL-BLI combinations. Further, sensitivities of *Klebsiella* spp. and *Pseudomonas* spp. to carbapenems and doxycycline improved substantially. Even resistance of *E. coli* and *Klebsiella* spp to fluoroquinolones diminished to a large extent. Likewise, GPCs also demonstrated improved susceptibilities to various antibiotics. For instance, sensitivities of *S. aureus*, CoNS, and enterococci to aminoglycoside, levofloxacin, and clindamycin rose markedly. The corollary to the improved sensitivities was the remarkable drop in the consumption of antimicrobials in the ICU. This was true for drugs like levofloxacin, chloramphenicol, macrolide, doxycycline, linezolid, cephalosporin, and BL-BLI used to manage infection due to GPCs and also those like levofloxacin, cephalosporin, carbapenem, and colistin used to treat bloodstream infections caused by GNBs. Thus, they concluded that if ASP and DSP interventions are used together can effectively overturn the menace of ever-rising resistance among organisms that caused BSI and also reduce antibiotic utilization.[15]

The ASP interventions included establishing electronic medical records in the ICUs, periodic audits and feedback, evidence-based dosing, and limiting the course of each antibiotic. There were regular training sessions and reinforcement programs for clinicians to ensure the prudent use of antibiotics. Information from the institute's annual antibiogram was used to devise a protocol for initiating empirical therapy. Also, the microbiologists joined the critical care specialists during ICU rounds.

In addition, several infection prevention practices (IPP) had been duly incorporated, like the bundle approach to minimize central line-associated bloodstream infections and an emphasis on hand hygiene. Furthermore, the resident doctors and nurses were imparted practical training regarding proper sample collection methods and biomedical waste disposal. The importance of IPP cannot be over-emphasized because managing healthcare-associated infections (HAI) consumes a large chunk of antimicrobials, as most of these are caused by MDR organisms. ASP and IPP aim to prevent MDR-causing HAIs and *Clostridium difficile* infections.[16]

The DSP interventions comprised automated blood culture and sensitivity systems, which provided clinicians with earlier antibiotic sensitivity reports with minimum inhibitory concentration and breakpoints.

Thus, scrupulous adherence to combined ASP, good infection control practices, and DSP interventions provide hope to outsmart the bacteria and prevent the onset of the dreaded "postantibiotic era."

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