

Convergence of Minds: For Better Patient Outcome in Intensive Care Unit Infections

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Abstract

Background: There is emergence of resistance to the last-line antibiotics such as carbapenems in Intensive Care Units (ICUs), leaving little effective therapeutic options. Since there are no more newer antibiotics in the armamentarium in the near future, it has become imperative that we harness the interdisciplinary knowledge for the best clinical outcome of the patient. **Aims:** The aim of the conference was to utilize the synergies between the clinical microbiologists and critical care specialists for better patient care and clinical outcome. **Materials and Methods:** A combined continuing medical education program (CME) under the aegis of the Indian Association of Medical Microbiologists – Delhi Chapter and the Indian Society of Critical Care Medicine, Delhi and national capital region was organized to share their expertise on the various topics covering epidemiology, diagnosis, management, and prevention of hospital-acquired infections in ICUs. **Results:** It was agreed that synergy between the clinical microbiologists and critical care medicine is required in understanding the scope of laboratory tests, investigative pathway testing, hospital epidemiology, and optimum use of antibiotics. A consensus on the use of rapid diagnostics such as point-of-care tests, matrix-assisted laser desorption ionization-time of flight mass spectrometry, and molecular tests for the early diagnosis of infectious disease was made. It was agreed that stewardship activities along with hospital infection control practices should be further strengthened for better utilization of the antibiotics. Through this CME, we identified the barriers and actionables for appropriate antimicrobial usage in Indian ICUs. **Conclusions:** A close coordination between clinical microbiology and critical care medicine opens up avenues to improve antimicrobial prescription practices.

Keywords: Antimicrobial stewardship, clinical microbiologists, critical care, Intensive Care Unit, synergy

INTRODUCTION

In typical health-care settings, Intensive Care Units (ICUs) have 10%–15% of the total hospital beds, but the hospital-acquired infections (HAIs) in ICUs account for 20%–30% of all nosocomial infections.^[1] In addition, ICUs are the epicenters of multidrug-resistant organisms (MDROs) which may increase the chances of inadequate empirical antibiotic therapy resulting in excess mortality.^[1] With the emergence of carbapenem-resistant *Enterobacteriaceae* (CRE) along with the recent reports of colistin resistance,^[2] ICUs are facing the prospect of a “postantibiotic era.” This calls for the urgent and definitive measures to prevent the situation slipping into further abyss.

To address the above issues, for the first time in the country, a combined meeting of the Indian Association of Medical Microbiologists – Delhi Chapter and the Indian Society of

Critical Care Medicine Delhi and national capital region (NCR) was held on May 7, 2016, with an aim of developing common understanding in treating infections as seen in critical care medicine practice.

Need for synergy and convergence of minds

- There are increasing reports of difficult-to-treat infections by MDROs in hospital settings. Resistance to the last-line effective antibiotics, carbapenems, has reached alarming proportions (12%–83%) in Gram-negative bacteria (GNB) in Indian ICUs.^[3,4] Not only that, there is also an increasing prevalence of fungi in ICUs.^[3]

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The above factors make appropriate empirical therapy difficult, before the availability of culture and sensitivity report

- Early diagnosis is required for targeted therapy of the patients in ICUs, but there are delayed turnaround time and poor sensitivity of the conventional tests.^[1,5] Therefore, clinicians expect clinical microbiology laboratories to give them rapid and accurate results. At the same time, the treating unit can also be benefitted by having a better understanding of the sample collection practices, advantages and pitfalls of these assays.

As every discipline of medicine has become vast but focused on certain aspects of diseases, it is imperative to harness interdisciplinary knowledge of medicine for the optimum management of patients with whatever limited armamentarium we have at our disposal.

Objective of the synergy

The aim of the meeting was to utilize the synergies between the clinical microbiologists and critical care specialists for better patient care and clinical outcome.

MATERIALS AND METHODS

A continuing medical education program (CME) was organized titled, “Convergence of Minds-Bench to Bedside.” The activity was accredited with 4.5 h of credits by the Delhi Medical Council. Several experts from the field of clinical microbiology and critical care came together on a common platform to share their knowledge and experience on the various topics covering epidemiology, diagnosis, management, and prevention of HAIs in ICUs. This day-long event was attended by 33 clinical microbiologists and 37 intensivists from NCR. The agenda of the CME [Table 1] included various issues of concern such as the practice of performing adequate blood cultures, understanding of minimum inhibitory concentrations (MICs) of antibiotics in day-to-day practice, treatment of multidrug-resistant (MDR) infections, and a possible algorithm for rapid diagnosis of infections in Indian ICUs. A scope for syndromic approach of diagnosis was further explored.

Table 1: Agenda of the continuing medical education

Topic/session
Blood culture practice: Can we do better?
Demystifying MIC: Making MIC work for you
Case presentation: Novel therapies in MDR infection
MDR infections in ICUs: Need for rapid diagnosis
Respiratory viral infections: Challenges and solutions
Candiduria in ICU settings: When and how to treat?
Antibiotic stewardship in ICUs
Advances in molecular diagnosis: Syndromic approach
ICU: Intensive Care Unit; MIC: Minimum inhibitory concentration; MDR: Multidrug resistant

RESULTS AND DISCUSSION

Epidemiology of infections

The epidemiology of the prevalent infections in ICU settings was the point in focus and discussed in detail along with its outcome. It was discussed that there is emergence of infections by MDROs in Indian ICUs.^[3] As a result, there is a lack of effective antibiotics for the treatment of such infections. All participants expressed concern over the increasing emergence of fungal infections in ICUs, especially *Candida* spp.^[3,6,7] In a survey of Indian ICUs, *Candida* spp. was observed as the single most common pathogen (17.5%) in patients with sepsis.^[3,6] In another multicentric study from 27 Indian ICUs, a high incidence of candidemia (6.5/1000 ICU admissions) was seen.^[7] There was also a shift in the distribution to species other than *Candida albicans* along with emerging resistance to azole group of antifungals.^[3]

Appropriate treatment of bloodstream infections (BSIs) within the first hour has shown to result in a favorable outcome in upto 80% of cases, and increase in mortality with each passing hour has been documented in literature.^[8] Therefore, there was a consensus to give broad-spectrum antibiotics, after collecting samples for investigations, as early as possible to “Hit hard and hit early” MDROs causing the HAIs. However, these broad-spectrum antibiotics need to be de-escalated according to the culture and antibiotic susceptibility report.^[9] In a study by Gonzalez *et al.* in critical care, it was observed that de-escalation in most cases, including septic shock, reduced the antibiotic prescription without adversely altering the short- and long-term prognosis.^[9]

Optimum utilization of diagnostic tests

It was accepted by all that each investigation has certain limitations due to the type of technology used or the basic biology of the organisms causing the disease. Therefore, it can be best addressed when the diagnostic tests are chosen in consultation of clinicians and microbiologists to prevent a “garbage in and garbage out” scenario. The close communication is useful in understanding the laboratory’s test menu, specimen collection and transport guidelines, and testing policies. The participation of a clinical microbiologist in clinical rounds can help interpreting the microbiology reports and recommendations of additional tests and choice of antimicrobial therapy on appropriate samples at the patient’s bedside.^[10] In a survey of more than 500 infectious disease physicians in the USA, 78% of respondents reported that consultation services by a clinical microbiologist were extremely helpful in improving the quality of services.^[10]

Rapid diagnostic tests

Clinicians are also increasingly looking up to the microbiologists for rapid and accurate diagnosis of infections. Although cultures remain the gold standard for the diagnosis of the infectious etiology, it takes minimum 16–24 h for the growth to result positive from the specimen and another 8–12 h for phenotypic identification and antibiotic susceptibility results. Therefore,

the consensus recommendation was for the introduction of newer and rapid diagnostic algorithms for earlier diagnosis of infections as shown in Table 2.

Novel therapies for multidrug-resistant infections

In recent years, treating MDR pathogens in ICUs has become a challenging task. Infections primarily due to vancomycin-resistant enterococci (VRE) and carbapenem-resistant GNBs such as *Klebsiella* and *Acinetobacter* are the most common therapeutic conundrums faced by the critical care physicians.^[3]

Therapy for vancomycin-resistant enterococci infections

Actions based on risk factors (e.g., removal of lines and catheters) for such infection must be considered for first confirming the diagnosis and then initiating antimicrobial therapy. Uncomplicated urinary tract infections (UTIs) by VRE have been treated successfully with nitrofurantoin or doxycycline, if susceptible.^[11] For serious infections such as BSI due to VRE, linezolid can be an option.^[12,13] Linezolid may be particularly useful in patients due to glycopeptide-resistant enterococci (GRE) infections who require oral or outpatient therapy (when intravenous therapy is undesirable). Although linezolid is a reserved drug, due to its oral availability, it has a potential for its overuse, especially in outpatient situations. Moreover, linezolid-resistant VRE isolates are also being reported increasingly again due to their overuse.^[14] Daptomycin

is another new drug, which can be used to treat GRE infections. Recent data indicate that daptomycin is associated with better clinical outcomes in proven infections due to GRE, especially in bacteremia and tissue infections, compared to linezolid.^[12] This is due to the bacteriostatic activity of linezolid in comparison to the concentration-dependent bactericidal activity of daptomycin.^[12,13,15] There are some case report series where daptomycin has been observed to be useful in the treatment of GRE UTIs. Its urinary availability in native form has been reported to be as high as 50%–70% which is higher than linezolid whose availability in urine is reported to be 30%–40%.^[16] However, more clinical data are required before a firm opinion regarding its use in GRE UTIs can be recommended. Tigecycline, a glycylcycline antibiotic released in 2005, is more useful in treating VRE intra-abdominal and soft-tissue infections.^[11]

Therapy for carbapenemase-producing Gram-negative bacteria

Polymyxins have become the cornerstones of therapy for CRE, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. Treatment of carbapenem-resistant isolates is dependent on both the site of infection and the susceptibility testing. Uncomplicated infections can often be successfully treated with an aminoglycoside or fosfomycin (for *Enterobacteriaceae*) when sensitive.^[17] For serious infections due to carbapenem-resistant

Table 2: Rapid tests for diagnosis of infections^[32-35]

Infection	Methodology	Sensitivity (%)	Specificity (%)	Time to reporting of results
MRSA	CHROMagar	95-100	100	24 h
	Real-time PCR	100	92	Within hours
	MALDI-TOF	100	100	Minutes
VRE	CHROMagar	86-99	95-100	Within hours
	Multiplex PCR	98	>99	Within hours
	MALDI-TOF	100	100	3-4 days
<i>C. difficile</i>	Culture	93	97	
	EIA for antigen glutamate dehydrogenase	100	93	
	PCR: Detection of gene sequences associated with toxigenic <i>C. difficile</i>	74-100	97-100	<45 min
Pulmonary tuberculosis: smear positive; culture positive	PCR: Nucleic acid amplification and hybridization (respiratory specimens)	94-100	70-100	2-4 days
Pulmonary tuberculosis: smear negative; culture positive	PCR: DNA amplification and hybridization (respiratory specimens)	50-92	70-100	2-4 days
Sepsis	Automated culture	2 sets: >90		1-5 days
	PCR/microarray platform	95	99	1 day
Influenza A (H1N1)	Rapid antigen assays (respiratory specimens)	70	99	Minutes
	Real-time PCR	95-100	93-100	Within 2-3 h
Malaria	Blood film	75-85	100	Hours
	Molecular: PCR	97	99	Hours
Invasive aspergillosis	Galactomannan EIA	32	98	Hours
Respiratory infections	Multiplex PCR detecting up to 33 respiratory pathogens simultaneously	80.3-92.3	84.3-94.3	Hours
Ventilator-associated pneumonia	Gram staining	79	75	Minutes

EIA: Enzyme immunoassay; PCR: Polymerase chain reaction; *C. difficile*: *Clostridium difficile*; MALDI: Matrix-assisted laser desorption/ionization; TOF: Time-of-flight; VRE: Vancomycin-resistant enterococci

isolates, a colistin-based combination regimen can be used.^[17,18] The combination therapy for colistin depends on the susceptibility profile of the other antibiotics. Carbapenems (if the isolate has an MIC ≤ 8 mcg/mL), or amikacin or tigecycline/minocycline (for *Enterobacteriaceae* and *Acinetobacter* spp.), can be added to colistin as a combination regimen.^[17] High dose of tigecycline (200 mg twice daily) instead of standard dose (100 mg twice daily) in the treatment of infections with MDR organisms has shown better clinical outcomes.^[19] In only colistin-sensitive isolate, a combination of colistin and meropenem is regarded as the most preferred treatment option whereas monotherapy with colistin results in the selection of colistin-resistant strains.^[17,18] Emergence of colistin resistance is mainly due to previous exposure to colistin in a patient, especially as a monotherapy or suboptimal dosage. This results in the selection of subpopulation of resistant strains in a heterogeneous colistin-resistant population.^[18] Expert consensus opinion recommendation for the treatment of colistin-only-sensitive isolate was high dose and/or extended infusion of a carbapenem in combination with colistin although outcome studies on its efficacy from India are lacking.^[17] Extended infusion of β -lactam drugs is one of the methods for using the least amount of drug with minimum toxicity for optimizing the clinical outcomes.^[20] Newly introduced ceftazidime-avibactam is a promising agent for the treatment of *Klebsiella pneumoniae* carbapenemase-producing CRE.^[21] Avibactam has a broad activity against Ambler class A and C-lactamases and certain class D-lactamases by covalent acylation of the β -lactamase active site serine residue. It restores susceptibility to extended-spectrum β -lactamases, AmpC cephalosporinases, and class A carbapenemases to ceftazidime or ceftaroline in *Enterobacteriaceae*.^[21] However, this new drug is currently not available in India. The recent reports of emergence of colistin resistance were also discussed.^[18,22] The capability of transfer of colistin resistance to other bacteria, through a novel plasmid, *mcr-1*, in addition to chromosomal mutation is a cause of much concern as we may now see a sudden increase in its resistance.^[21] However, there is no plasmid-mediated colistin resistance reported from India as on today. As there is no definite approach to treat such infections, prevention of infections due to MDROs by rationale use of antibiotics and implementation of hospital infection control was agreed upon.

Hospital infection control

It was unanimously accepted by the members of both the societies that infection control practices could further be strengthened in the era of MDR and pandrug-resistant organisms. We all know treating such difficult patients may not be easy and more often than not it is difficult to salvage such patients in ICUs settings. Effective implementation and continuous surveillance of hospital infection control activities is the cornerstone for effectively minimizing emergence and spread of MDROs. It was appreciated by both the specialties that the guidelines for infection control practices in critical care areas should be framed with the help of a clinical

microbiologist, which can go a long way in preventing HAIs and mortality. The following measures were deemed necessary for hospital infection control practices:

- Constituting a hospital infection control committee
- Surveillance of health care-associated infections
- Institution of proper hand hygiene for the prevention of transmission of infections
- Prevention and control of health care-associated infections such as: Catheter-associated UTIs, surgical site infections, ventilator-associated pneumonia, and catheter-related BSIs
- Cleaning, disinfection, and sterilization
- Taking adequate isolation precautions for patients infected with MDROs
- Framing of antimicrobial policy and implementation of antimicrobial stewardship
- Strict implementation and monitoring of biomedical waste management.

Optimum utilization of antibiotics

As the patients admitted in ICUs have altered hemodynamics and fluid volumes, it is important to give the correct dosage and duration of drugs based on the principles of pharmaco-vigilance (pharmacodynamics and pharmacokinetics), keeping in view the following criteria:

- Therapy based on bacterial MIC of antibiotics is a necessity in critical care, and the clinical microbiology colleagues need to work in that direction. Using knowledge of MIC of antibiotics has shown to optimize antimicrobial choice and dose to ensure the best use of our dwindling anti-infective resources^[23]
- Understanding of time- and concentration-dependent antibiotic concepts needs to be inculcated in the practice of the treating physicians
- Continuous infusion of β -lactam antibiotics, rather than the bolus dose, should be practiced as it may improve outcomes because of its time-dependent antibacterial activity. It has been shown that continuous infusion of vancomycin was associated with less adverse effects and nephrotoxicity in children^[20,24]
- Adequate doses as per kilogram body weight need to be followed in patients admitted in ICUs and elsewhere^[20]
- Recommended route and adequate duration of therapy are issues that cannot be ignored to prevent recurrences and treatment failures. Various randomized control trials have demonstrated that a shorter course of antibiotic therapy is associated with similar outcomes as those with longer antibiotic course in both the adults and children for different varieties of infections^[24]
- It is essential to differentiate between colonizers and pathogens for initiating antibiotic treatment. This could be crucial for treatment outcomes, development of resistance, and cost of therapy. In an interventional study by Zabarsky *et al.*, the antibiotic treatment was discouraged in asymptomatic bacteriuria. After the intervention, the overall rate of treatment declined from 1.7 to 0.6 per

1000 patient-days ($P = 0.0017$), and the total days of antibiotic therapy were reduced from 167.7 to 117.4 per 1000 patient-days ($P < 0.001$), without any change in mortality and morbidity.^[25]

Evidence-based antifungal therapies

Antifungal therapies based on new evidence are gaining more and more significance to successfully treat fungal infections, particularly yeast infections. It is necessary to identify the type of yeast or filamentous fungi to achieve the desired results. This gains more significance when there is emergence of fluconazole- and amphotericin-resistant *Candida* spp., in Indian hospital settings.^[26] Newer species are evolving which if not identified can lead to inappropriate therapy and increased mortality.^[3,17,26,27] However, it was felt that automated systems may give higher resistance values in MIC testing. Consensus needs to be arrived over treatment and significance of candiduria in ICU settings. Candiduria in asymptomatic patients always represents colonization and elimination of source, such as indwelling catheters are often adequate to eradicate candiduria. Treatment of candiduria with antifungals is usually required in patients belonging to high-risk group such as neutropenia, very low birthweight infants (<1500 g), and patients who need to undergo urologic manipulation.^[28]

It was also desired that efforts should begin toward formulation of antifungal stewardship guidelines.^[29]

Identifying barriers

The faculty and the members present discussed the possibility of various barriers in achieving the desired synergy between the two specialties. The following came up for discussion and it was unanimously accepted that the following should be resolved amicably for desired results:

- Collaborative efforts between clinicians and microbiologists are crucial to achieve the best outcomes. Administrative synergy between the two specialties should be achieved
- It is important to encourage practice and evidence-based medicine in critical patients to achieve desired outcomes. To generate high-quality evidence, the laboratory needs to have robust quality control processes in place despite added costs
- The inertia on the part of both the specialties needs to be overcome and both the specialties need to be pro-active in the management of HAIs. The electronic reporting could help in this activity, but again the acquisition of software is costly and can be a barrier yet again
- At times, it is perceived by the primary treating unit that the junior infectious disease faculty attending to a referral does not have enough experience or knowledge to assist in patient diagnosis and therapy.^[30,31]

Panel discussion

At the end of the conference, a panel discussion was held on convergence of minds: “What to expect” as a theme of the discussion.

Table 3: Consensus on actionables

Microbiology laboratories should be open 24 h
Regular antibiograms must be made available by all clinical microbiology laboratories at least yearly, and if the number of isolates are enough, then 6 monthly
Bedside rounds in the ICUs should be held along with the clinical microbiologists and difficult-to-treat patients should be discussed in detail
The critical care specialty needs to work in close association with microbiology counterpart to achieve best benefit and this can result in representative sampling, minimum turnaround time for the results of some investigations for the benefit of patients
The diagnostic test should be discussed with clinical microbiologist for better understanding and interpretations. This will also help in identifying colonizers versus pathogens

ICU: Intensive Care Unit

Outcomes of panel discussion: Various thoughts of experts from both the specialties were discussed for possible synergy. Various questions raised were as follows:

- Do you think convergence of minds is important?
- How to implement better coordination between the specialties?
- What are the strengths of such participative activity?
- What algorithm one can work on?
- Can we better understand/identify the gaps in the current knowledge in understanding limitations?
- Way forward!

The outcome of discussion addressing the consensus actionables on the above questions was reviewed by the participants and faculty across the subspecialties [Table 3].

CONCLUSIONS

In the era of high antibiotic resistance and use in the ICUs, it is imperative that the synergies of diagnostic microbiology and critical care specialists should be fully harnessed by the way of close coordination among the two departments. The coordination is useful in understanding the scope of laboratory services, investigative pathways, hospital epidemiology, and optimum use of antibiotics. Through this CME, we could identify the actionables and barriers for better patient care and outcomes in the ICUs.

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Conflicts of interest

There are no conflicts of interest.

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