Infectious Diseases in Critical Care
Case Based Approach

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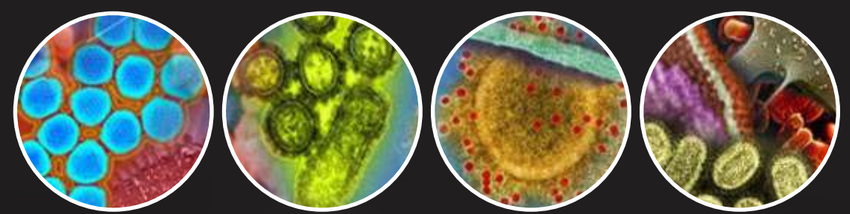

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Contents

Section 4: Infections in Special Populations in ICU

Section 5: Antibiotic Stewardship

Section 1

Introduction to Infectious Diseases in Critically Ill Patients

1. Epidemiology of infections
   Mechanism of Resistance in Micro-organism
2. Gram Negative
3. Gram Positive
4. Pharmacodynamics and Pharmacokinetics of Antimicrobial Therapy
5. Conventional Laboratory Approach for Diagnosis of ICU Infection
6. Molecular and Newer Diagnostic Modalities to Diagnose ICU Infections
7. Infection Control Practices in ICU

CHAPTER 1

Epidemiology of Infections

JV Divatia

Introduction

Sepsis is defined as the dysregulated host response to infection.[1] The global burden of sepsis continues to increase.[2] In the last decade, data from high-income countries suggested that the incidence rate was 437 (95% CI, 334–571) for sepsis and 270 (95% CI, 176–412) for severe sepsis cases per 100,000 person-years. Hospital mortality was 17% for sepsis and 26% for severe sepsis. However, population-level epidemiologic data for sepsis were non-existent for low- and middle-income countries.[3] The Intensive Care over Nations (ICON) audit of over 10,000 patients found that 29.5% had sepsis on admission or during the intensive care unit (ICU) stay. ICU mortality rates were 16.2% overall and 25.8% in patients with sepsis. Hospital mortality rates were 35.3% in patients with sepsis.[4] An analysis of the Global Burden of Disease study estimated that in 2017, there were 48·9 million cases of sepsis worldwide with 11·0 million sepsis-related deaths, representing 19.7% (18.2–21.4) of all global deaths. Age-standardised sepsis incidence fell by 37.0% and mortality decreased by 52.8% from 1990 to 2017. Sepsis incidence and mortality varied substantially across regions, with the highest burden in sub-Saharan Africa, Oceania, south Asia, east Asia, and southeast Asia.[5]

There is little information on the epidemiology and outcomes of sepsis in Indian ICUs. This article attempts to determine the prevalence of sepsis, its mortality, and the common micro-organisms involved and their resistance patterns. While there are several single-centre studies dealing with such data, this article only includes data from multicentre studies. Further, the article has largely focussed on adult patients and ICUs.

Prevalence and Mortality of Sepsis In India

In one of the first multicentre, prospective, observational studies, the prevalence of sepsis was 16.5% out of 5478 admissions in 4 ICUs in Eastern India, between June 2006 to June 2009.[6]

The median APACHE II score was 13 (IQR 13 to 14), but the ICU, in-hospital and 28-day mortality rates were high, being 59.3%, 65.2% and 64.6%, respectively. Gram-negative infections were present in 72.5% patients, and Gram-positive infections in 13.1%. Data for sepsis prevalence and mortality from other studies including the ICON audit,[4] The Indian Intensive Care Case Mix and Practice Patterns Study (INDICAPS Study),[7] Management of sepsis in Asian ICUs (MOSAICS)[8] and the randomized controlled trial of ulinastatin in sepsis[9] vary considerably, and are summarized in Table 1.1.

In the ICON audit, there were 982 patients from 36 ICUs in South Asia, most of them from India.[4] The MOSAICS study was a prospective, observational non-interventional study to assess the compliance of Asia's ICUs

TABLE 1.1: Severity of illness, sepsis prevalence and mortality in multicentre studies in Indian ICUs

	Sepsis in Eastern India[6]	*ICON audit*[4]	*MOSAICS*[8]	*INDICAPS study*[7]	*Ulinastatin in sepsis*[9]
Number of patients with sepsis	904	982	1144	162	114
Prevalence of sepsis	16.5%	13.6%	28.3%	5.5%	
APACHE II score	Median 13 (IQR 13 to 14	Mean 13.2 ± 8.2	Mean 21.7 ± 9.8	Mean 21.9 ± 8.4	Mean 13.4 ± 4.4
ICU mortality	59.3%,	10.9%	34%		
Hospital mortality	65.2%	14.4%	38.3%	38.3%	28-day mortality 20.3% in control group

ICON:Intensive care over nations; INDICAPS (Indian Intensive Care Case Mix and Practice Patterns); MOSAICS:Management of sepsis in Asian ICUs; APACHE: Acute physiology and chronic health evaluation; ICU:intensive care unit

and hospitals to the surviving sepsis campaign (SSC) recommendations and bundles at that time, to determine the outcomes of severe sepsis in Asia's ICUs and to assess the effect of compliance to the Sepsis bundles on mortality. It recruited 1285 consecutive patients with severe sepsis in July 2009, from 148 ICUs in 16 Asian countries.[8]

The INDICAPS study was a multicenter, all-India observational, point-prevalence study, performed on July 14, 2010, October 13, 2010, January 12, 2011 and April 13, 2011.[7] A total of 4038 adult patients from 120 ICUs present in the ICU on were included in the study. Overall ICU mortality (upto 30 days from each study day) was 18.1%. Severe sepsis or septic shock were present in 1144 patients (28.3%), with infection having developed in the ICU in 235 patients (20.5%). ICU mortality was 34% and hospital mortality, 38.3% (Table 1.2). In patients with septic shock, defined as patients with sepsis who required vasopressors, the mortality was 45.2%. The median ICU Stay was 10 days [IQR 5–20]. Table 1.3 details the characteristics of patients with severe sepsis/septic shock in the INDICAPS study. Sources of infection included: Respiratory system in 235 patients; urinary tract, 94 patients; gastrointestinal, 100 patients; central nervous system, 33 patients; skin and soft tissue infections, 46 patients; suspected or confirmed tropical infections (malaria, dengue, leptospirosis, scrub typhus), 231 patients and unknown source, 485 patients. Cultures were in 40.5% of 909 patients. 576 microorganisms were isolated, of which 69.4% were Gram negative organisms and 16% were Gram-positive. Fungi were cultured in 44 patients (7.6%) patients; 42 of these were candida species—candida albicans, 27 and non-albicans, 15. Details of major micro-organisms isolated are presented in Table 1.4.

TABLE 1.2: Characteristics of patients with sepsis and those without sepsis in the INDICAPS study[7]

Characteristic	*Patients*	*Age*	*APACHE II score*	*SOFA score*	*ICU mortality*
Severe sepsis/ septic shock	1144 (28.3%)	53.8 ± 17.7	21.7 ± 9.8*	5.9 ± 4.3*	34.0%*
No severe sepsis	2894 (71.7%)	54.2 ± 17.7	15.7 ± 8.4	2.9 ± 2.9	11.7%

APACHE: Acute physiology and chronic health evaluation; SOFA:sequential organ failure assessment; ICU:intensive care unit

TABLE 1.3: Characteristics of patients with severe sepsis / septic shock in the INDICAPS study

	Overall N = 1144	*ICU survivors N = 755 (66.0%)*	*ICU deaths N = 389 (34.0%)*
Age	53.8 ±17.7	53.2 ± 17.9	54.9 ± 17.5
Medical/surgical admissions	1031/113 (90.1%/9.9%)	669/86 (88.6%/11.4%)	362/27# (93.1%/9.8%)
APACHE II score	21.7 ± 9.8	19.7 ± 9.4	25.6 ± 9.4**
SOFA score	5.9 ± 4.3	5.2 ± 4.0	7.5 ± 4.5**
Mechanical ventilation	663 (58%)	308 (46.5%)	355 (77.1%) **
Vasopressors/inotropes	513 (44.8%)	281 (48.1%)	232 (59.6%) **
Renal replacement therapy	262 (22.9%)	116 (19.9%)	146 (28.8%) *

ICU: intensive care unit; APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment

TABLE 1.4: Major organisms cultured in patients with severe sepsis/septic shock in the INDICAPS study

Gram negatives	*N = 400 (69.4%)*	*Gram positives*	*N = 98 (17%)*
Pseudomonas aeruginosa	92 (23%)	MRSA	22 (22.4%)
Pseudomonas spp	13 (3.2%)	MSSA	17 (17.3%)
Acinetobacter spp	89 (22.3%)	Enterococcus (vancomycin sensitive)	14 (14.3%)
Klebsiella spp	84 (21%)	MR-CNS	13 (13.3%)
Escherichia Coli	76 (19%)	MS-CNS	9 (9.2%)
		Streptococcus pneumoniae	7 (7.1%)

Spp: species; MR: Methicillin resistant; MS: methicillin sensitive; SA: staphylococcus aureus; CNS: coagulase negative staphylococci

Patients received a median of 2.0 (IQR 1,3) or mean of 1.9 ± 1.1 antibiotics. The carbapenems, third generation cephalosporins and piperacillin-tazobactam were the commonest antibiotics used (Table 1.5 and Fig. 1.1).

TABLE 1.5: Major antibiotics used in patients with severe sepsis/septic shock in the INDICAPS study

- Carbapenems (346)
  - Meropenem 66%, Imipenem 25%
- Cephalosporins (309)
  - Ceftriaxone 34%, Cefoperazone-sulbactam 28%
- Penicillins (272)
  - Piperacillin-tazobactam 72%
- Glycopeptides (177)
  - Teicoplanin 70%, Vancomycin 30%
- Antifungals (154)
  - Fluconazole 56%, Caspofungin13%, Amphotericin B 10%
- Levofloxacin 111

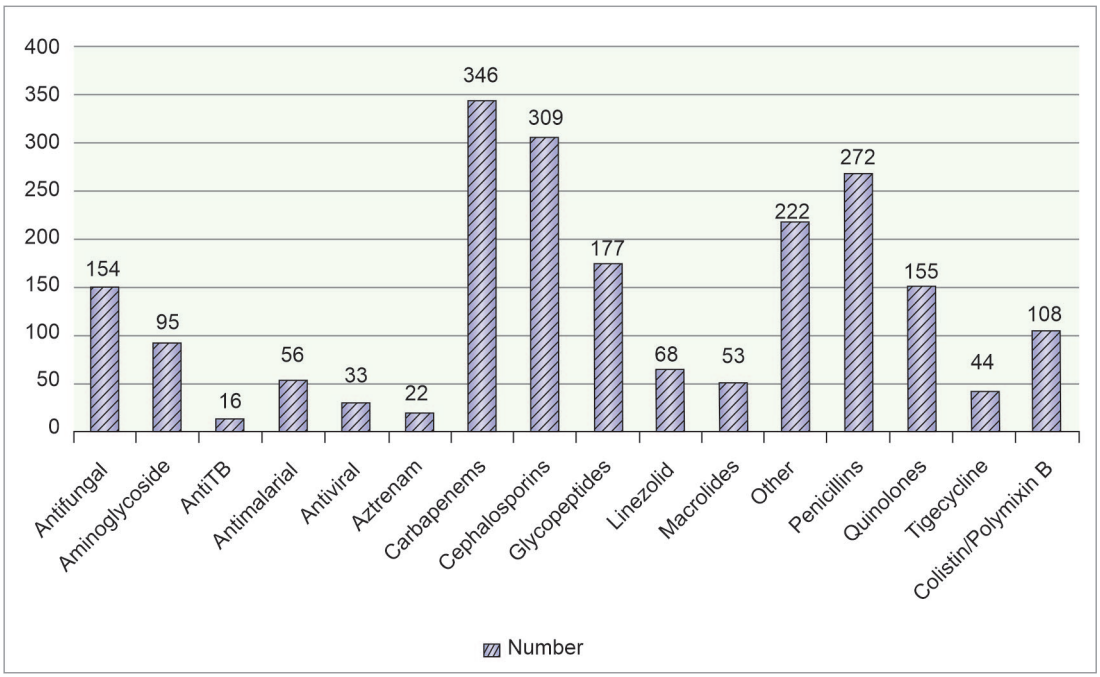

Fig. 1.1: Major antibiotics used in patients with severe sepsis/septic shock in the INDICAPS study

TROPICAL INFECTIONS IN THE ICU

Tropical infections (malaria, leptospirosis, dengue, scrub typhus) often present as undifferentiated fevers with organ failures and are a common source of hospitalisation in India. The Indian Society of Critical Care Medicine has advocated a syndromic approach to the diagnosis and treatment of tropical infections.[10] In the INDICAPS study, there were 289 patients with sepsis due to suspected or confirmed tropical infections (malaria, 148; dengue 88; leptospirosis, 42; scrub typhus,11) accounting for 7% of ICU admissions, and 25% of patients with severe sepsis or septic shock.[7] Patients with tropical infections had higher coagulation and hepatic sub-scores of the sequential organ failure assessment (SOFA) score compared to other patients with sepsis. Compared to other patients with sepsis, patients with tropical infections were younger (mean age 46.2+ 17.9 vs. 55.7 + 17.2, p <0.001), and had a lower ICU mortality (21.6% vs. 37.1%, p <0.001).

The ISCCM Research Group on tropical fevers in Indian ICUs performed a multicenter prospective observational study in 34 ICUs across India (July 2013-September 2014 to identify the prevalence, profile, resource utilization, and outcome of tropical fevers in Indian ICUs.[11] Critically ill adults and children with non-localizing fever >48 h and onset <14 days with any of the following: thrombocytopenia/rash, respiratory distress, renal failure, encephalopathy, jaundice, or multiorgan failure were included. Of the 456 cases enrolled, 173 were children <12 years. Thrombocytopenia/rash was the most common presentation (60%), followed by respiratory distress (46%), encephalopathy (28.5%), renal failure (23.5%), jaundice (20%), and multiorgan failure (19%). Dengue (n = 105, 23%) was the most common followed by scrub typhus (n = 83, 18%), encephalitis/meningitis (n = 44, 9.6%), malaria (n = 37, 0.8%), and bacterial sepsis (n = 32.7%). Mortality at 28 days was 18.4%. Mortality was higher (27% vs. 15%) in

patients with undiagnosed etiology. On multivariate analysis, multiorgan dysfunction syndrome at admission day 1 Sequential Organ Failure Assessment score and the need for invasive ventilation were independent predictors of unfavorable outcome.

FUNGAL INFECTIONS

There are limited multicentric data on the prevalence of fungal infections in Indian ICUs. The best data on candidemia in Indian ICUs are from a prospective, nationwide, multicentric, observational study conducted at 27 Indian ICUs between April 2011 through September 2012.[12] There were 1,400 ICU-acquired candidemia cases, with an incidence of 6.51 cases/1,000 ICU admissions. A notable feature was that candidemia occurred relatively early after admission to ICU (median 8 days; interquartile range 4-15 days), even infecting patients with lower APACHE II score at admission (mean 17.2 ± 5.9). There were 31 Candida species causing candidemia, and the most common was Candida tropicalis (41.6 %). The drug resistant C. auris was seen in 74 (5.3%) isolates. Azole and multidrug resistance were seen in 11.8 and 1.9% of isolates. The 30-day crude and attributable mortality rates of candidemia patients were 44.7 and 19.6 %, respectively. Independent predictors of mortality including admission to public sector hospital, APACHE II score at admission, underlying renal failure, central venous catheterization and steroid therapy.

A subgroup analysis of this data was performed to determine significant risk factors associated with C. auris infection.[13] The duration of ICU stay prior to candidaemia diagnosis was significantly longer in patients with C. auris candidaemia (median 25, IQR 12–45 days) compared with the non-auris group (median 15, IQR 9–28, P <0.001). Admission to north Indian ICUs, public-sector hospital, underlying respiratory illness vascular, prior antifungal exposure and low APACHE II score were significantly associated with C. auris candidaemia. A considerable number of isolates were resistant to fluconazole (n = 43, 58.1%), amphotericin B (n = 10, 13.5%) and caspofungin (n = 7, 9.5%).

HEALTH CARE ASSOCIATED INFECTIONS

The best multicentre data on healthcare-associated infection (HCAI) in Indian ICUs comes from the International Nosocomial Infection Control Consortium (INICC). Several Indian ICUs contribute data of HCAI infections surveillance, which are analysed using US National Healthcare Safety Network's criteria and definitions, and INICC methodology.

The initial report was from 12 ICUs of the seven hospitals of seven Indian cities, published in 2007.[14] It included the incidence of ventilator-associated pneumonia (VAP), central-line related blood-stream infection (CLBSI) and catheter-associated urinary tract infection (CAUTI).

A recent report covered data from 40 hospitals (20 cities) in India 2004-2013.[15] The data are summarized in Table 1.6. In the 2016 report, pooled device use ratios were 0.21 for mechanical ventilator, 0.39 for central line, and 0.53 for urinary catheter. These data suggest that despite a lower device use ratio in our ICUs, our device-associated healthcare-associated infection rates are higher than United States National Healthcare Safety Network, but lower than the overall INICC benchmark.

The INICC advocates a multidimensional intervention for the reduction of HCAIs. This includes a bundle of HCAI specific interventions, education, outcome and process surveillance, and feedback of HCAI rates and performance. This was applied in two studies, one concerning VAP in 21 ICUs, from 14 hospitals in 10 Indian cities,[16] and the other CLABSI, in in 16 adult intensive care units of 11 hospitals in eight cities of India.[17]

In both studies, there was baseline and intervention periods. During baseline, prospective surveillance of VAP/CLABSI rates

was performed applying standard definitions. The multidimensional intervention was then applied, and the HCAI rates were remeasured. The VAP rate reduced from 17.43/1000 ventilator days during baseline to 10.81/1000 ventilator days for intervention, showing a 38% VAP rate reduction.[16] Similarly, the CLABSI rate was reduced from 6.4 CLABSIs per 1000 CL-days at baseline to 3.9 CLABSIs per 1000 CL-days in the second year and maintained for 36 months of follow-up, accounting for a 53% CLABSI rate reduction.[17] Thus implementing the INICC approach was associated with a significant reduction in the VAP and HCAI rates in Indian ICUs.

Antimicrobial Resistance in HCAIs

Antibiotic resistance is a serious problem. Hospital acquired infections are often caused by resistant micro-orgasms. It is essential for each ICU to be familiar with the antimicrobial sensitivity ad resistance patterns in their hospitals, in order to prescribe effective antibiotics. Further, antibiotic resistance is increasing n community-acquired infections. Surveillance for antimicrobial resistance in the community is essential to prescribe appropriate empiric antibiotics in patients presenting with sepsis and septic shock due to community-acquired infections.

Data from the INICC on HCAIs in Indian ICUs published in 2007 showed an alarming incidence of antibiotic resistance.[14] Overall 87.5% of all staphylococcus aureus HCAIs were caused by methicillin-resistant strains, 71.4% of Enterobacteriaceae were resistant to ceftriaxone and 26.1% to piperacillin-tazobactam; 28.6% of the pseudomonas aeruginosa strains were resistant to ciprofloxacin, 64.9% to ceftazidime and 42.0% to imipenem. These data suggested that given the HCAI rates, mortality and bacterial resistance, infection control programmes including surveillance and antibiotic policies should be accorded high priority in India.

The ISCCM Multicenter Observational Study (MOSER Study) was performed in 15 ICUs between August 2011 to October 2012, to explore the microbiology and resistance patterns of ICU-acquired infections and evaluate their outcomes.[18] Patients in the ICU ≥48 h with any ICU-acquired infection within 14 days of index ICU stay were included. Of the 381 patients included in the study, 346 patients had one ICU infection and 35 had more than one ICU infection. Among patients with single infections, 223 had VAP with Acinetobacter being the most common isolate. Figures 1.2 and 1.3 detail the number of major organisms isolated and their resistance

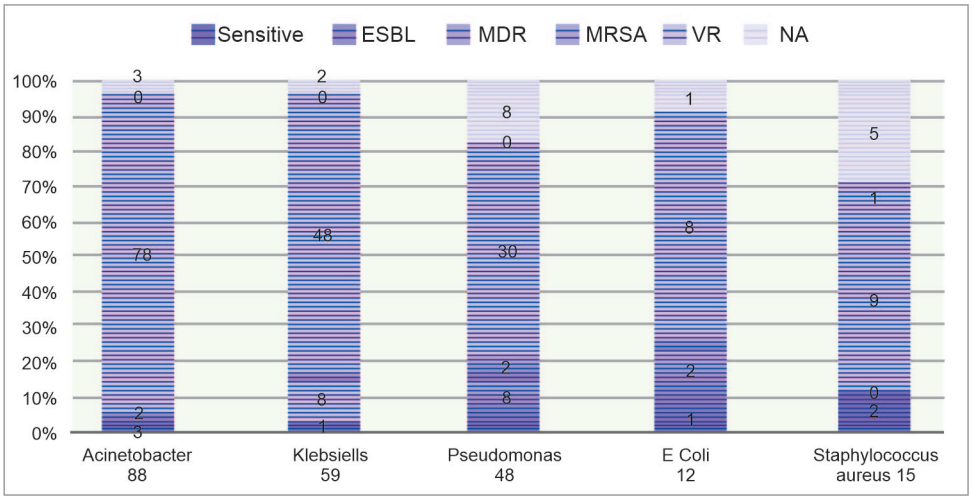

Fig. 1.2: MOSER study. Ventilator-associated pneumonia organisms–resistance pattern[18]

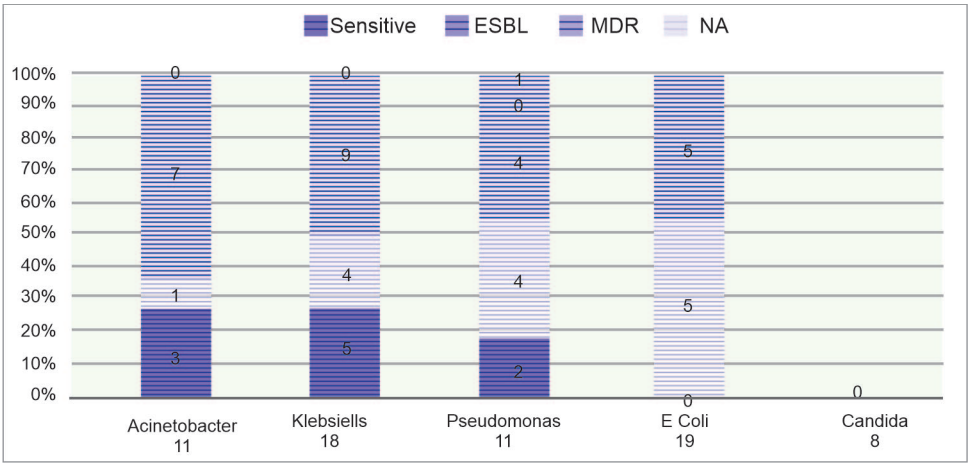

Fig. 1.3: MOSER study. Catheter related blood stream infections–resistance patterns[18]

patterns in patients with VAP and central-line related blood-stream infection (CRBSI), respectively. CAUTI was seen in 42 patients with *Klebsiella* as the most common organism. CRBSI was seen in 81 patients and *Klebsiella* was the most common causative organism. Multidrug resistance was noted in 87.5% of Acinetobacter, 75.5% of *Klebsiella*, 61.9% of *Escherichia coli*, and 58.9% of *Pseudomonas* isolates, July 14, 2010, October 13, 2010, January 12, 2011 and April 13, 2011 respectively. *Staphylococcus* constituted only 2.4% of isolates. While isolates in VAP were highly multidrug resistant, comparatively, they were less multidrug resistant in CAUTI and CRBSI. Of the Gram-negative isolates, 34% were ESBL producers. The major ESBL producer was *Klebsiella* (41.1%), followed by *Escherichia coli* (26.4%) and *Pseudomonas* (23.5%). Mortality rates were 26%, 11.9%, and 34.6% in VAP, CAUTI, and CRBSI, respectively.

The Indian Council of Medical Research published the report of its Antimicrobial Resistance Surveillance and Research Network for the period January 2019 to December 2019.[19] This includes data from ICUs as well as from the out-patient departments and hospital wards. Details of antimicrobial resistance have been documented in this report.

Enterobacteriaceae (isolated from of all specimens except urine and faeces).

Out of the carbapenems, overall, susceptibility to imipenem and meropenem was 55% and 65% with 60% to ertapenem. Piperacillin-tazobactam susceptibility was overall 51%. Only one third (32–33%) of isolates showed fluoroquinolone susceptibility. Susceptibility to third generation cephalosporins, cefotaxime and ceftazidime was seen in only in 22% and 26% of isolates overall. Over the period of study, imipenem susceptibility of *E. coli* dropped steadily from 86% in 2016 to 63% in 2019 and that of *Klebsiella pneumoniae* fell from 65% in 2016 to 46% in 2019. Colistin was the most effective antibiotic with an overall susceptibility of 96%, with *E. coli* showing complete susceptibility and *Klebsiella* and *Enterobacter* species showing more than 90% susceptibility. With increasing use over the last five years, colistin resistance is emerging. In E. Coli, resistance due to the NDM gene was seen in upto 42% isolates. In Klebsiella, NDM was seen in upto 51% isolates, and KPC in 29.6% isolates overall.

Non-lactose Fermenting Gram Negative Bacilli

A. baumannii isolates collected from ICU showed reduced susceptibility rates (<12%) to all the tested antibiotics compared to isolates from ward and OPD, except for minocycline which showed susceptible rate of 50%. Only

colistin showed>90% susceptibility. Molecular characterization of 429 isolates from various regional centers showed the co-occurrence of resistance genes. All the isolates harbored the *bla*OXA-51 like gene, which is intrinsic to *Acinetobacter baumannii*. Among ESBLs, *bla*PERand *bla*TEM were the predominant genes observed, and *bla*OXA-23and *bla*NDM were the predominant Metallo beta-lactamases found across all centers. Co-producers of various AMR genes like ESBLs with carbapenemases and combination of carbapenemases were observed across all the centers

Pseudomonas aeruginosa. Antimicrobial susceptibility testing revealed lower susceptibility rates in isolates from ICU settings (45–55%). More than 90% susceptibility was observed for colistin. Notably, carbapenem susceptibility was seen only in 50% of the isolates from ICU. Among the lower respiratory tract isolates, highest susceptibility was seen for colistin (96%), followed by piperacillin/tazobactam (75.4%), cephalosporins (71%), meropenem (73%), amikacin (78%) and tobramycin (80%). Non-susceptibility to imipenem has increased from 2016 to 2019 with no changes in the meropenem susceptibility. No significant changes were observed for fluoroquinolones and aminoglycosides. Notably, decreasing susceptibility to colistin increased from 2% in 2016 to 7% in 2019, respectively.

SUMMARY

The mortality from sepsis in Indian ICUs is high, with the ICU mortality ranging from 20%–59%. Most of the infections are caused by Gram-negative organisms. Tropical infections are not very frequent causes of sepsis in the ICU and are associated with a favourable outcome. Candida infections are increasing and constitute about 7–8% of infections in patients with sepsis. Resistance to third-generation cephalosporins and carbapenems is present in more than 50–80% of bacterial isolates, and colistin resistance has emerged, as have resistant candida species. It has been possible to reduce the incidence of device-related infections with meticulous attention to infection control bundles, education, feedback and communication. Antibiotic stewardship is the need of the hour, to optimize antibiotic therapy and to reduce further increase in antibiotic resistance. Nationwide surveillance of antimicrobial resistance is essential, and molecular mechanisms determining antibiotic resistance may help devise better strategies to mitigate the problem. More information on various aspects of sepsis in India will soon be available from at least three completed studies; these include the INDICAPS II study, the HERMES study and the MOSAICS II study.

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