ORIGINAL ARTICLE

New Antibiotic Prescription Pattern in Critically Ill Patients ("Ant-critic"): Prospective Observational Study from an Indian Intensive Care Unit

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Abstract

Introduction: This study aimed to address the issue of antibiotic prescription processes in an Indian Intensive care unit (ICUs).

Materials and methods:: In a prospective longitudinal study, all adult patients admitted in the ICU for 24 hours or above between 01 June 2020 and 31 July 2021 were screened for any new antibiotic prescription throughout their ICU stay. All new antibiotic prescriptions were assessed for baseline variables at prescription, any modifications during the course, and the outcome of antibiotic prescription.

Results: A total of 1014 patients fulfilled entry criteria; 59.2 and 7.2% of days they were on a therapeutic or prophylactic antibiotic(s). Patients, who were prescribed therapeutic antibiotic(s), had worse ICU outcomes. A total of 49.5% of patients (502 of 1,014) received a total of 552 new antibiotic prescriptions during their ICU stay. About 92.13% of these prescriptions were empirical and blood or other specimens were sent for culture in 78.81 and 60.04% of instances. A total of 31.7% of episodes were microbiologically proven and were more likely to be prescribed by an ICU consultant. A total of 169 modifications were done in 142 prescription episodes; 73 of them after sensitivity results. Thus, the overall rate of de-escalation was 13.95%. Apart from the negative culture result (36.05%), an important reason for a relatively low rate of de-escalation was the absence of sampling (12.32%). Longer ICU stay before antibiotic prescription, underlying chronic liver disease (CLD), worse organ dysfunction, and septic shock were independently associated with unfavorable treatment outcomes. No such independent association was observed between antibiotic appropriateness and patient outcome.

Conclusion: Future antibiotic stewardship strategies should address issues of high empirical prescription and poor microbiological sampling hindering the de-escalation process.

Keywords: Antibiotic(s), Intensive care unit, Patient outcome, Prescription process.

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Highlights

- This study addressed the hitherto unfulfilled need for a study of antibiotic prescription processes in an Indian ICU.
- This study addresses issues of timing and reasons behind new antibiotic prescription, any cultures sent, any change in antibiotic regimen throughout the prescription course with or without the culture results, outcome of antibiotic prescription, and independent factors associated with poorer outcome.

Introduction

The decision to initiate antibiotic(s) is one of the most critical issues in ICU.[1] In ICUs, the index of suspicion for invasive infection remains high because of obvious reasons, complicated further by poor accuracy and often delayed results of laboratory tests to diagnose infections.[2] As expected, antibiotic prescriptions are almost 10 times more common in ICUs compared to wards.[3] Need for initiating early empiric antibiotic prescription is emphasized in several studies and endorsed by guidelines.[4–7] Indeed it has now been recommended as a quality-of-care matrix in some healthcare systems.[8] However, the benefit of the early empirical antibiotic prescription must be balanced carefully with the potential for unnecessary prescription, promotion of antibiotic resistance, adverse drug reactions, superinfection, and additional cost.[1]

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Antibiotic stewardship program balances the benefits and risks of empiric antibiotic prescription, with an aim of curtailing the emergence of antibiotic resistance and reducing overall healthcare cost.[9] The first important step in this direction is perhaps to collect data on "motives for antibiotic use."[10] Only a

handful of studies have actually focused on this crucial aspect of antibiotic prescription in ICU settings.[10–14] Looking into the Indian context, with suboptimal public health infrastructure, inadequate insurance cover, unregulated prescription of antibiotics, and high burden of antibiotic resistance, this issue becomes particularly relevant.[15,16]

With this background and in the absence of quality Indian data, we felt it pertinent to conduct a longitudinal study to understand the process of antibiotic initiation, a pattern of changing prescription including de-escalation strategies, and outcome of antibiotic prescription in an Indian ICU. This study aimed to look for epidemiological differences between patients receiving new antibiotic(s) in ICU from remaining patient cohorts and factors leading to the favorable outcome of antibiotic prescription.

Materials and Methods

Setting

This prospective longitudinal study was conducted in the 18-bedded mixed ICU of Fortis-Escorts Hospital, Faridabad, Haryana. Patients with active coronavirus disease-2019 (COVID-19) infection were mostly treated in another ICU during the pandemic. The ICU is a semi-closed unit with a critical care team participating in every decision-making process, including the prescription of antibiotics. This study was approved by the institutional ethics committee (EC/2020/27, 17/06/2020) and was registered with the Clinical Trial Registry of India (CTRI/2020/06/026257). Because of the observational nature of the study, the need for informed consent was waived off.

Inclusion Criteria

All patients anticipated to remain in the ICU for 24 hours or more were prospectively evaluated. Patients receiving new antibiotic(s) for confirmed or presumed infection during ICU stay were included for further analysis. An "antibiotic prescription" was classified as "new," if it fulfilled any one of the following criteria:

- Antibiotic prescribed to a patient, who was not on any at ICU admission.
- Patient who was already on antibiotics but was changed within 24 hours of ICU admission.
- Antibiotics started for suspicion of a new site of infection, while the patient was already on antibiotics for some other confirmed or suspected source.
- New antibiotic for the same suspected or confirmed source of infection provided the patient was free from antibiotic(s) for at least 48 hours before the new prescription.

Exclusion Criteria

Antibiotics started for prophylaxis or started before ICU admission (and continued during ICU stay) were excluded from further analysis but their data were analyzed for calculation of antibiotic days.

Screening

Every patient admitted to the study ICU, between 01 June 2020 and 31 July 2021 and who remained in the ICU for at least 24 hours were followed up during their ICU stay for any new antibiotic prescription. Patients getting re-admitted to ICU, after 24 hours or more stay in the ward or following any duration of stay at home or other facilities, were considered as new admission and a new case report form was filled for the same. In cases of re-admission within 24 hours of discharge to the ward, ICU stay was shown as a continuation of the earlier admission, and the data were recorded as such.

Antibiotic Prescription

Written antibiotic policy is not strictly followed in the unit. Both the critical care team and other consultants are allowed to prescribe any antibiotic. The antibiotic prescription policy of the critical care team is guided broadly by the principles of antimicrobial therapy and local antibiogram.[1] On clinical suspicion of infection, relevant samples are sent for culture. As a routine practice, only aerobic cultures are sent including 10 mL of blood each in two BACTEC culture bottles (Becton, Dickinson and Company, NJ 07417-1815, USA) and samples from the suspected site of infection. A fully functioning microbiology facility is available around the clock and the critical care team maintains a close liaison with the microbiology department. All samples sent for culture are processed in a VITEK2 machine and antibiotic sensitivity cut-off follows guidelines provided by the clinical and laboratory standards institute (CLSI), USA. Certain antibiotic sensitivity pattern not provided by the VITEK2 machine is performed either by using E-strip or manually using the disc diffusion method.

Data Collection

At ICU admission, the data were collected for age, gender, source of admission (floor, emergency department, operation theatre/recovery room, and other hospitals), type of admission (medical, emergency surgery, elective surgery, and trauma), Acute Physiology and Chronic Health Evaluation (APACHE) II score for overall severity of illness, Charlson's comorbidity index to measure the burden of comorbidities, Sequential Organ Failure Assessment (SOFA) score for defining organ dysfunction (if any) and serum lactate. The need for respiratory or vasopressor support or urgent requirement for renal replacement therapy (RRT) on admission to ICU were also recorded. Antibiotic prescription before ICU admission was recorded as none, prophylactic, empirical, or definitive.

On new antibiotic prescription, the following parameters were recorded: The number of ICU-days before prescription of antibiotic, type of prescriber (non-ICU consultant, experienced ICU consultants or ICU fellows/junior consultants), time of the day prescribed (day shift or out of hour), patient's temperature, heart rate, respiratory rate, noradrenaline infusion if any, total leukocyte count, procalcitonin values (if measured), SOFA score and lactate value recorded before antibiotic prescription, presence of any therapeutic emergency, suspected or confirmed source of infection, type of antibiotic prescription (empirical, pre-emptive, or definitive), any relevant sample sent for culture and number of antibiotic(s) prescribed.

For patients started on a new antibiotic, the following parameters were recorded during the treatment course: Any change in antibiotic prescription since "new antibiotic" initiation, the reason for the change, number of times changes were made, and SOFA score on day 3 of antibiotic prescription. Relevant culture report (if available), appropriateness of antibiotic prescribed, type of organism grown along with selected resistance pattern [extended spectrum beta lactamase (ESBL), carbapenemase, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci or (VRE)] were recorded. The strategy for de-escalation[17] and the timing of de-escalation were also recorded. Appropriate antibiotic is defined following standard guidelines, as at least one of the agents prescribed initially shows *in vitro* activity against the etiologic pathogen(s). At the end of follow-up for each episode of a new antibiotic prescription, suspected or confirmed infections were classified by investigators based on clinical, laboratory,

radiological, and microbiological findings into one of four groups by a consensus – microbiologically documented infection, clinically documented infection, possible bacterial infection or no bacterial infection.[18] The outcomes of new antibiotic therapy were recorded as the clinical cure, clinical improvement at ICU discharge, and no improvement or death during ongoing antibiotics.

At discharge from ICU, all patients admitted during the study period were classified into one of the four classes on the basis of the antibiotic prescribed: No antibiotic used during ICU stay, only prophylactic antibiotic, a therapeutic antibiotic prescribed before ICU admission and continued during ICU stay or new antibiotic prescribed in the ICU. The following parameters were also recorded at discharge: Number of antibiotic episodes, number of prophylactic antibiotic days or therapeutic antibiotic days (as calendar days), number of days on ventilator or vasopressors (each 6-hours period taken as 0.25 day), any need for RRT and ICU days (calendar days). Patient outcome at discharge was recorded as one of the following: Discharged to floor or wards, death, transferred to another ICU, transferred to other hospital, and patient/family wishes to discontinue further treatment. Definitions used for the purpose of this study are provided in Table 1.

Statistical Analysis

Categorical data were summarized as numbers and frequencies. Continuous variables were presented as mean (±) standard deviation (SD) or median [interquartile range, IQR (Q1, Q3)], based on normality of data. Appropriate statistical tests were applied to

Table 1: Definitions of terms used in the study

- **Elective surgery:** Any surgical procedure, planned above 24 hours prior to ICU admission.
- **Emergency surgery:** Surgical procedures planned or performed within 24 hours of ICU admission.
- **Day shift:** Between 09.00 and 17.00 hours on all working days.
- **Out of hours:** Between 17.00 and 09.00 hours next day for working days and between 09.00 hours and 09.00 hours next day for Sundays/holidays.
- **Experienced ICU consultant:** Consultant intensivists with more than 10-years' experience in managing acutely ill patients.
- **Therapeutic urgency:** Presence of a condition requiring urgent prescription of antibiotic(s) – septic shock, hypoxemic respiratory failure requiring emergent intubation, febrile neutropenia, and suspicion of acute pyogenic meningitis.
- **Community acquired:** If the patient presents with symptoms or develops symptoms of possible infection within 48 hours of presenting to a healthcare facility.
- **Hospital acquired:** Patients who develops clinical suspicion of infection above 48 hours after presenting to a healthcare facility.
- **Empirical antibiotic:** Initiation of antibiotic based on clinical suspicion, routine laboratory findings, procalcitonin value, targeted radiological investigations for specific organ involvement or biochemical/cytological examination of body fluid without any culture and sensitivity report.
- **Pre-emptive antibiotic:** Starting antibiotic based on toxin assay or polymerase chain reaction (PCR)-based technology or isolation of pathogen in culture before the availability of sensitivity report, in addition to clinical suspicion and routine laboratory investigations and/or procalcitonin value.
- **Definitive antibiotic:** Antibiotic prescription based on culture and sensitivity report from suspected source of infection or from normally sterile body fluid or blood.
- **De-escalation:** Either replacement of broad-spectrum antibiotic with agent(s) of a narrower spectrum or a lower ecological impact or stopping non-pivotal antibiotic either by stopping accompanying agents initially prescribed with an intent of double cover for certain pathogen or stopping agents initially prescribed to cover additional pathogens, once culture and sensitivity report is available and patient is clinically stable.
- **Escalation:** Any change in antibiotic prescription or course with patient remaining unstable and pathogen isolated in culture showing resistance to currently ongoing antibiotic(s).
- **Microbiologically documented infection:** Presence of a clinical or radiological infectious focus, or both and isolation of pathogen from the appropriate culture sent.
- **Clinically documented infection:** Presence of a clinical or radiological infectious focus, or both, without any isolation of pathogen from appropriate sample or identification of only potential colonizer.
- **No bacterial infection:** Presence of all following criteria – the absence of clinical or radiological evidence of infectious focus, non-isolation of a bacterial pathogen from relevant culture, and patient's condition explained fully by non-infectious cause.
- **Possible infection:** Classified as all other situations other than microbiologically or clinically documented infection or no bacterial infection where antibiotics were prescribed.
- **Clinical cure:** Normalization of body temperature for consecutive 48 hours with a favorable and sustained change in inflammatory markers (leukocyte count, C-reactive protein, and procalcitonin), normalization of perfusion markers (capillary refill time, lactate, and central venous oxygen saturation), absence of vasopressor requirement and sustained improvement in the organ function with or without documented microbiological clearance.
- **Clinical improvement at ICU discharge:** Significant improvement in patient's clinical status but short of fulfilling criteria for clinical cure.
- **No improvement:** No improvement in patient's clinical status or on repeat microbiological sampling despite all possible changes in antibiotic regimen and source control when feasible.

test the level of significance. A two-tailed $p < 0.05$ was taken as the level of statistical significance. Baseline characteristics of patients were analyzed according to their final classification based on the use of antibiotics during ICU stay. All new antibiotic prescriptions were further analyzed for microbiologically documented infection, clinically documented infection, no infection, or possible infection. To identify factors associated with the outcome of new antibiotic prescription, all parameters at antibiotic prescription were compared between patients who had a favorable outcome (clinical cure or clinical improvement at ICU discharge) and patients who did not have one (no improvement or death during antibiotic prescription) and a multivariate backward regression analysis was performed to adjust for effects of simultaneous variables. The data analysis was done with the use of a statistical package for social sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 21.0.

Results

Baseline Characteristics

A total of 1,014 patients fulfilled the entry criteria. On 59.2% of days (2,977 of 5,027 patient-days), they were on therapeutic antibiotics and on another 7.2% of days (363 of 5,027 patient-days) on prophylactic antibiotics. New antibiotic(s) was prescribed in 49.5% of patients. In 9.66% patients, therapeutic antibiotics were prescribed before ICU admission and were continued during ICU stay. 30.67% did not receive any antibiotics throughout their ICU stay. Table 2 shows the baseline characteristics of the overall

Table 2: Overall cohort according to antibiotic prescription

Parameters	*None (N = 311)*	*New antibiotic prescription (N = 502)*	*Antibiotic prescribed before ICU admission (N = 98)*	*Only prophylactic (N = 103)*	*Total (N = 1014)*	*p-value*
Age (mean, SD)	59.94 ± 17.15	61.26 ± 15.79	60.69 ± 16.8	50.52 ± 18.4	59.71 ± 16.86	<0.0001‡
Female gender (%)	35.05	32.6	38.9	33.98	34.19	0.565
Type of admission (%)						
Medical	296 (95.18%)	443 (88.25%)	90 (91.84%)	26 (25.24%)	855 (84.32%)	<0.0001*
Elective surgery	1 (0.32%)	8 (1.59%)	5 (5.10%)	25 (24.27%)	39 (3.85%)	
Emergency surgery	3 (0.96%)	38 (7.57%)	3 (3.06%)	32 (31.07%)	76 (7.50%)	
Trauma	11 (3.54%)	13 (2.59%)	0 (0%)	20 (19.42%)	44 (4.34%)	
APACHE II score on admission (median, IQR)	9 (6–14)	15 (11–21)	14 (11–21)	10 (7–15)	13 (8–19)	<0.0001§
SOFA score on admission (median, IQR)	2 (1–4)	5 (3–7)	5 (3–7)	3 (1–6)	4 (2–6)	<0.0001§
Lactate on admission (mean, SD)	1.49 ± 1.46	2.14 ± 2.28	1.83 ± 1.85	1.81 ± 2.18	1.88 ± 2.03	0.0002‡
Charlson's comorbidity index (median, IQR)	3 (1–5)	4 (2–6)	4 (2–6)	2 (0–3)	3 (2–5)	<0.0001§
Comorbidities (%)						
Diabetes mellitus	100 (32.15%)	204 (40.56%)	36 (36.73%)	16 (15.53%)	356 (35.07%)	<0.0001†
CLD	8 (2.57%)	52 (10.34%)	14 (14.29%)	16 (15.53%)	90 (8.87%)	<0.0001†
Chronic kidney disease	30 (9.65%)	54 (10.74%)	13 (13.27%)	4 (3.88%)	101 (9.95%)	0.121†
Chronic lung disease	26 (8.36%)	37 (7.36%)	16 (16.33%)	4 (3.88%)	83 (8.18%)	0.009†
Heart failure	23 (7.40%)	39 (7.75%)	6 (6.12%)	4 (3.88%)	72 (7.09%)	0.547†
Immunocompromised	3 (0.96%)	16 (3.18%)	0 (0%)	1 (0.97%)	20 (1.97%)	0.059*
Respiratory support on admission (%)						
None	210 (67.74%)	170 (33.86%)	21 (21.43%)	51 (49.51%)	452 (44.62%)	1*
Low flow oxygen	43 (13.87%)	120 (23.90%)	43 (43.88%)	17 (16.50%)	222 (21.92%)	
High flow nasal cannula	1 (0.32%)	10 (1.99%)	0 (0%)	0 (0%)	11 (1.09%)	
Non-invasive ventilation	21 (6.77%)	36 (7.17%)	7 (7.14%)	1 (0.97%)	65 (6.42%)	
Invasive mechanical ventilation	35 (11.29%)	166 (33.07%)	27 (27.55%)	34 (33.01%)	262 (25.86%)	
Vasopressor support on admission (%)	11 (3.54%)	105 (20.87%)	16 (16.33%)	11 (10.68%)	143 (14.09%)	<0.0001†
Urgent RRT on admission (%)	23 (7.40%)	55 (10.93%)	11 (11.22%)	2 (1.94%)	91 (8.97%)	0.017†
Final outcome (%)						
Death	11 (3.54%)	99 (19.68%)	16 (16.33%)	3 (2.91%)	129 (12.71%)	<0.0001*
Discharged to floor/wards	278 (89.39%)	292 (58.05%)	67 (68.37%)	99 (96.12%)	736 (72.51%)	
Transferred to another ICU	0 (0%)	16 (3.18%)	1 (1.02%)	0 (0%)	17 (1.67%)	
Transferred to other Hospital	9 (2.89%)	21 (4.17%)	4 (4.08%)	1 (0.97%)	35 (3.45%)	
Family wishes to discontinue treatment	13 (4.18%)	75 (14.91%)	10 (10.20%)	0 (0%)	98 (9.66%)	
Days on invasive ventilation (mean, SD)	0.24 ± 0.68	2.43 ± 4.65	1.2 ± 2.71	0.58 ± 0.92	1.45 ± 3.56	<0.0001‡
Days on vasopressors (mean, SD)	0.08 ± 0.38	1.49 ± 2.88	0.88 ± 2.3	0.16 ± 0.57	0.86 ± 2.26	<0.0001‡
Need for RRT during ICU stay (%)	27 (8.68%)	102 (20.28%)	19 (19.39%)	2 (1.94%)	150 (14.78%)	<0.0001†
ICU days (median, IQR)	3 (3–4)	4 (3–7)	3 (3–5)	3 (3–4)	3 (3–5)	<0.0001§

*Fisher's exact test; †Chi-squared test; ‡Analysis of variance

cohort according to the antibiotic prescription status and their ICU outcome. Patients, who received therapeutic antibiotics (prescribed in the ICU or before ICU admission), were older with higher severity of illness on ICU admission, more comorbidities, higher need for vasopressor support and RRT at ICU admission. They had higher mortality, longer stay in ICU, longer time on mechanical ventilation or vasopressors or RRT.

New Antibiotic Prescription

A total of 552 new antibiotic(s) prescriptions were initiated in 502 patients (median prescription episode-1; range 1–6). Majority of these prescriptions were empirical (93.12%) and lung was the most common (46.92%) suspected or confirmed source of infection. A total of 32.6% of patients were in septic shock at the time of antibiotic prescription. Blood and other relevant specimens were sent for cultures in 78.81 and 60.04% of episodes, respectively. Overall, in 129 of 514 (25.09%) empirical prescriptions no culture was sent before antibiotic administration – 28/299 (9.36%) by ICU Consultants, 13/110 (11.81%) by fellows, and 88/105 (83.80%) by non-ICU Consultants.

In 31.7% of prescription episodes, a bacterial infection could be proved microbiologically. On retrospective review, 35.3% of prescription episodes could be classified as clinical infection without microbiological confirmation, 18.3% as possible bacterial infection and 14.7% as no bacterial infection. In 75% (61/81) of episodes where antibiotic(s) were prescribed for no bacterial infection, prescriptions were by either an ICU fellow or by a non-ICU Consultant. Baseline characteristics and outcomes of patients receiving new antibiotics are shown in Table 3 according to their bacterial infection status. Patients in the microbiologically proven infection group were more likely to have a hospital-acquired infection and were more likely to be prescribed by ICU consultants.

Change in Initial Prescription

In 25.73% prescription episodes some modification(s) was(were) done during the initial prescription: (1) Change in 124 episodes, (2) changes in 18 episodes, and (3) changes in 3 episodes. Figure 1 shows reasons for change in antibiotic prescriptions. Overall, in 13.32% episodes ($N = 73$) antibiotic regimen was modified after culture results (de-escalation or escalation). Figure 2 reveals de-escalation pattern in all prescription episodes. In 12.32% of episodes de-escalation could not be considered as appropriate cultures were not sent and in another 8.15% there was no scope for de-escalation as only one antibiotic was prescribed in them without any possibility of limiting spectrum.

Bacteriology

Rate of positivity for blood and other body fluid cultures sent before antibiotic(s) administration were 13.52% (56/414) and 42.41% (137 of 323), respectively. About 87.56% (169/193) organisms isolated were Gram-negative bacilli. Bacterial isolates and selected resistance patterns are shown in Table 4. In 31.7% of prescription episodes (175/552), appropriateness of initial antibiotic prescription could be ascertained and 73.71% (46/175) of them were judged to be appropriate.

Outcome

Favorable clinical outcomes were observed in 345 prescription episodes (clinical cure in 93 and significant clinical improvement in 252). In the remaining 207 episodes, the outcome was classified as unfavorable (death in 107 and no improvement at ICU discharge in 100). Table 5 compares the baseline characteristics of prescription episodes who had favorable or unfavorable outcome. In univariate analysis, unfavorable outcomes were associated with higher on admission APACHE II score, presence of CLD, hospital acquired infections, presence of therapeutic urgencies, longer ICU-days before prescription, higher SOFA score, higher lactate and higher procalcitonin at prescription. Whereas underlying chronic obstructive airway disease (COAD) and appropriateness of antibiotic prescription were associated with favorable outcome. However, after multivariate analysis, four variables remained independently associated with unfavorable outcome – longer ICU-days before antibiotic prescription, underlying CLD, higher SOFA score at prescription, and septic shock. Underlying COAD was independently associated with a favorable outcome. Sequential Organ Failure Assessment score was higher in the unfavorable outcome group both at baseline and at 72 hours (Fig. 3). Change in SOFA score at 72 hours (ΔSOFA) was also significantly different in two groups – median ΔSOFA of 1 (IQR 0 to 3) in favorable group vs 1 (IQR–1 to –3) in unfavorable group; $p < 0.0001$.

Discussion

Aiming to look for a comprehensive mapping of antibiotic prescription process in an Indian ICU, our study could make several important observations. First, in as high as 60% of days ICU patients were on some therapeutic antibiotics and half the patients received at least one new antibiotic(s) prescription during their ICU stay. Over 90% of new antibiotic prescriptions were empirical and ICU outcomes were worse in patients who received new antibiotic prescription. Second, patients receiving new antibiotic prescription had higher severity of illness scores, lactate level and more comorbidities. Third, even in a tertiary care setting, blood culture could not be sent before a fifth of antibiotic prescription and in about two-fifth of prescription no other relevant cultures were sent. Fourth, in one third of antibiotic prescription, bacterial infection was microbiologically documented and in three fourth of microbiologically proven episodes, the antibiotic prescription was deemed to be appropriate. Fifth, the overall rate of antibiotic de-escalation was found to be low primarily because of negative culture or because samples were not sent for culture. Interestingly, in 8% of the patients, there was no scope for de-escalation. Finally, four baseline variables were associated with unfavorable response to antibiotic prescription – longer ICU-days before prescription, underlying CLD, septic shock, and higher SOFA score on prescription day.

Comparison of Earlier Studies

The rate of new antibiotic prescription observed in this study (49.5%) is comparable with other contemporary international publications which in turn shows a wide variation from 30% to 77%.[10–14] In only other published study that looked into antibiotic prescription pattern in an Indian ICU, 70.85% of patients were reported to receive antibiotics during ICU stay.[19] However, the rate of empirical prescription (93.12%) in this study is substantially higher compared to 45–71% reported in earlier studies.[12–14] This high rate of empirical prescription could possibly reflect high burden of infections (both perceived and real), widely prevailed culture of fear-based prescription of antibiotic and lack of regulation on antibiotic prescription.[20] Predominance of Gram-negative pathogens and

Table 3: Patients prescribed new antibiotics according to their bacterial infection status

Parameters	*Microbiologically proven (N = 175)*	*Clinical infection (N = 195)*	*Possible infection (N = 101)*	*No bacterial infection (N = 81)*	*Total (N = 552)*	*p-value*
Age (mean, SD)	63.39 ± 14.35	59.78 ± 16.88	62.75 ± 14.96	60.83 ± 16.41	61.62 ± 15.73	0.131‡
Female gender (%)	57 (32.57%)	64 (32.82%)	36 (35.64%)	28 (34.57%)	185 (33.51%)	0.949†
APACHE II on admission (median, IQR)	16 (11–23)	16 (12–22)	16 (12–22)	15 (10–19)	16 (11–21.5)	0.043§
Charlson's comorbidity index (median, IQR)	4 (3–6)	3 (1–5)	4 (3–6)	4 (2–6)	4 (2–6)	0.003§
Comorbidities (%)						
Diabetes mellitus	86 (49.14%)	65 (33.33%)	41 (40.59%)	31 (38.27%)	223 (40.40%)	0.021†
CLD	17 (9.71%)	12 (6.15%)	18 (17.82%)	5 (6.17%)	52 (9.42%)	0.008†
Chronic kidney disease	13 (7.43%)	16 (8.21%)	15 (14.85%)	14 (17.28%)	58 (10.51%)	0.031†
Chronic lung disease	10 (5.71%)	9 (4.62%)	6 (5.94%)	18 (22.22%)	43 (7.79%)	<0.0001†
Heart failure	5 (2.86%)	15 (7.69%)	7 (6.93%)	10 (12.35%)	37 (6.70%)	0.035†
Immunocompromised	5 (2.86%)	7 (3.59%)	1 (0.99%)	1 (1.23%)	14 (2.54%)	0.569*
ICU days before prescription (median, IQR)	1 (0–6)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–2)	<0.0001§
Hospital acquired (%)	108 (61.71%)	72 (36.92%)	31 (30.69%)	11 (13.58%)	222 (40.22%)	<0.0001†
Prescribed by (%)						
Fellow	31 (17.71%)	41 (21.03%)	25 (24.75%)	21 (25.93%)	118 (21.38%)	
ICU consultant	130 (74.29%)	130 (66.67%)	46 (45.54%)	23 (28.40%)	329 (59.60%)	<0.0001†
Non-ICU consultant	14 (8%)	24 (12.31%)	30 (29.70%)	37 (45.68%)	105 (19.02%)	
Timing of prescription (%)						
Day shift	123 (70.29%)	117 (60%)	49 (48.51%)	46 (56.79%)	335 (60.69%)	0.004†
Out of hour	52 (29.71%)	78 (40%)	52 (51.49%)	35 (43.21%)	217 (39.31%)	
Temperature (mean, SD)	99.7 ± 1.63	99.24 ± 1.76	98.91 ± 1.62	98.7 ± 0.94	99.24 ± 1.63	<0.0001‡
Heart rate (mean, SD)	106.21 ± 20.98	106.67 ± 22.96	102.9 ± 22.6	99.3 ± 21.36	104.75 ± 22.15	0.049‡
Respiratory rate (mean, SD)	26.09 ± 6.75	25.38 ± 7.12	24.11 ± 6.81	23.59 ± 6.57	25.11 ± 6.91	0.019‡
Vasopressor support (%)						
None	106 (60.57%)	114 (58.46%)	73 (72.28%)	74 (91.36%)	367 (66.49%)	
Norepinephrine ≥ 0.1 µg/kg/min	32 (18.29%)	38 (19.49%)	16 (15.84%)	3 (3.70%)	89 (16.12%)	<0.0001†
Norepinephrine < 0.1 µg/kg/min	37 (21.14%)	43 (22.05%)	12 (11.88%)	4 (4.94%)	96 (17.39%)	
Total leukocyte count (mean, SD)	16729.4 ± 8754.1	18043 ± 11620	15686.7 ± 10430.2	11530.6 ± 6340.1	16238 ± 10097.3	<0.0001‡
Procalcitonin (in µg/L, mean, SD)	1.63 (0.491–7.085)	1.63 (0.5–7.18)	0.96 (0.376–2.745)	0.12 (0.079–0.183)	0.96 (0.234–4.81)	<0.0001§
Lactate (in mmol/L, mean, SD)	1.71 ± 1.33	2.36 ± 2.65	2.25 ± 2.92	1.69 ± 1.91	2.04 ± 2.28	0.017‡
SOFA at prescription (median, IQR)	6 (4–10)	7 (4–9.5)	6 (3.75–8)	4 (2–6)	6 (4–9)	<0.0001§
Type of prescription (%)						
Pre-emptive	14 (8%)	4 (2.05%)	1 (0.99%)	0 (0%)	19 (3.44%)	
Empirical	142 (81.14%)	191 (97.95%)	100 (99.01%)	81 (100%)	514 (93.12%)	<0.0001*
Definitive	19 (10.85%)	0 (0%)	0 (0%)	0 (0%)	19 (3.44%)	
Confirmed or suspected source of infection						
Lung	76 (43.43%)	93 (47.69%)	47 (46.53%)	43 (53.09%)	259 (46.92%)	
Urinary tract	62 (35.43%)	21 (10.77%)	16 (15.84%)	2 (2.47%)	101 (18.30%)	
Intra-abdominal	6 (3.43%)	38 (19.49%)	12 (11.88%)	2 (2.47%)	58 (10.51%)	
Skin and soft tissue	6 (3.43%)	17 (8.72%)	2 (1.98%)	1 (1.23%)	26 (4.71%)	<0.0001*
Blood stream	19 (10.86%)	5 (2.56%)	0 (0%)	0 (0%)	24 (4.35%)	
Central nervous system	3 (1.71%)	8 (4.10%)	0 (0%)	10 (12.35%)	21 (3.80%)	
Unknown	3 (1.71%)	13 (6.67%)	24 (23.76%)	23 (28.40%)	63 (11.41%)	

Therapeutic urgency (%)						
None	96 (54.86%)	81 (41.53%)	66 (65.35%)	60 (74.07%)	303 (54.89%)	
Septic shock	65 (37.14%)	82 (42.05%)	26 (25.74%)	7 (8.64%)	180 (32.61%)	
Hypoxemia requiring urgent invasive ventilation	10 (5.71%)	20 (10.25%)	8 (7.92%)	4 (4.94%)	42 (7.61%)	<0.0001*
Meningitis	2 (1.14%)	8 (4.10%)	0 (0%)	9 (11.11%)	19 (3.44%)	
Immunocompromised	2 (1.14%)	4 (2.05%)	1 (0.99%)	1 (1.23%)	8 (1.45%)	
Blood culture before antibiotic administration (%)	142 (87.65%)	156 (80%)	75 (74.26%)	41 (50.62%)	414 (76.81%)	<0.0001†
Other relevant culture before antibiotic administration (%)	146 (89.02%)	100 (51.28%)	46 (46.94%)	31 (38.27%)	323 (60.04%)	<0.0001†
Number of antibiotics (median, IQR)	1 (1–2)	2 (1–2)	2 (1–2)	1 (1–2)	1 (1–2)	<0.0001§
Antibiotic appropriateness (%)						
Not ascertained	2 (1.14%)	193 (98.97%)	101 (100%)	81 (100%)	377 (68.30%)	
No	44 (25.14%)	2 (1.03%)	0 (0%)	0 (0%)	46 (8.33%)	<0.0001†
Yes	129 (73.71%)	0 (0%)	0 (0%)	0 (0%)	129 (23.37%)	
Outcome of treatment						
Clinically improving at discharge from ICU	61 (34.86%)	84 (43.08%)	50 (49.50%)	57 (70.37%)	252 (45.65%)	
Clinical cure	40 (22.86%)	32 (16.41%)	9 (8.91%)	12 (14.81%)	93 (16.85%)	
No improvement at discharge from ICU	36 (20.57%)	34 (17.44%)	24 (23.76%)	6 (7.41%)	100 (18.12%)	<0.0001†
Death during ongoing treatment	38 (21.71%)	45 (23.08%)	18 (17.82%)	6 (7.41%)	107 (19.38%)	

*Fisher's exact test; †Chi-squared test; ‡Analysis of variance (ANOVA); §Kruskal–Wallis test, APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SD, standard deviation, IQR, interquartile range; ICU, intensive care unit

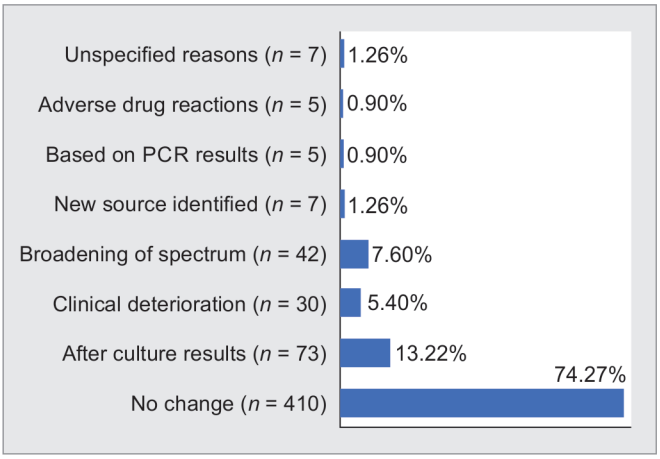

Fig. 1: Pattern of modification after initial antibiotic prescription

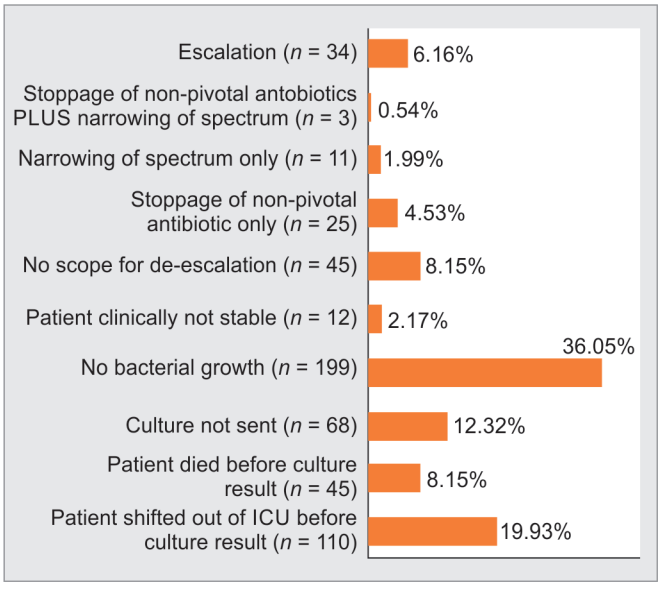

Fig. 2: De-escalation process post sensitivity result

the high rate of antibiotic resistance even in community-acquired pathogens, correlates with published national data.[21,22]

De-escalation

In published literature, rate of de-escalation varies widely, related mostly to methodological differences, definition of de-escalation used, severity of illness, isolation of multidrug resistant pathogens, broad spectrum of antibiotics used, and appropriateness of initial antibiotic regimen.[23] Using most recent consensus definition by international task force, we observed de-escalation rate of 13.95% in this study, which is closer to 16% rate observed in recently published multicenter DIANA study.[24] More aggressive microbiological sampling may improve this rate further. Interestingly in 8% of prescription episodes there was no scope for de-escalation that may be reflective of high rate of Gram-negative resistance, often susceptible to only Polypeptides and the unit practice of not adding aminoglycosides empirically for dual coverage.

Antibiotic Prescription and Outcome

Unlike earlier studies, we could not observe any independent association between the appropriateness of empirical antibiotics and the outcome of the antibiotic prescription.[25,26] However, this

Table 4: Organisms isolated during study period and their resistance pattern

Gram-negative organisms											
		Specimen type		*ESBL*		*Carbapenemase*		*Colistin resistance*		*Pan-drug resistance*	
Organism	*Number*	*Blood*	*Other fluid*	*CA*	*HA*	*CA*	*HA*	*CA*	*HA*	*CA*	*HA*
Escherichia coli	60	12	48	37	10	4	4	0			
Klebsiella pneumoniae	47	9	38	4	3	7	33	0	1		
Acinetobacter baumanii	28	13	15	0	1	2	10	0			2
Pseudomonas aeruginosa	11	2	9	1	4	1	2	0			
Enterobacter cloacae	8	5	3	0	5	0	2	0			
Serratia marcescens	7	2	5	1	5	0	0	NA	NA		
Proteus vulgaris	4	0	4	1	0	0	3	NA	NA		
Proteus mirabilis	4	0	4	0	0	2	1	NA	NA		1
Gram-positive organisms											
		Specimen type		*Penicillin resistance*		*Methicillin resistance*		*Vancomycin resistance*		*Linezolid resistance*	
Organism	*Number*	*Blood*	*Other fluid*	*CA*	*HA*	*CA*	*HA*	*CA*	*HA*	*CA*	*HA*
Staphylococcus aureus	9	3	6	2	4	1	3	0	0	0	0
Enterococcus faecium	10	4	4	0	8	NA	NA	0	3	0	2
Enterococcus faecalis	4	6	0	0	3	NA	NA	0	0	0	0
Streptococcus pneumoniae	1	0	1	0	0	NA	NA	0	0	0	0

CA, community acquired; HA, hospital acquired; NA, not applicable

Table 5: Patient characteristics and outcome antibiotic prescription

Parameters	*Favorable outcome (N = 345)*	*Unfavorable outcome (N = 207)*	*Total (N = 552)*	*p-value*
Age in years (mean, SD)	61.72 ± 16.34	61.45 ± 14.69	61.62 ± 15.73	0.845
Female gender (%)	134 (38.84%)	51 (24.64%)	185 (33.51%)	0.0006[†]
APACHE II on admission (median, IQR)	15 (10–20)	18 (14–24)	16 (11–21.5)	<0.0001[**]
Charlson's comorbidity index (median, IQR)	4 (2–6)	4 (2–5)	4 (2–6)	0.994[**]
Diabetes mellitus (%)	142 (41.16%)	81 (39.13%)	223 (40.40%)	0.638[†]
CLD (%)	22 (6.38%)	30 (14.49%)	52 (9.42%)	0.002[†]
Chronic kidney disease (%)	40 (11.59%)	18 (8.70%)	58 (10.51%)	0.282[†]
Chronic obstructive airway disease (%)	38 (11.01%)	5 (2.42%)	43 (7.79%)	0.0003[†]
Heart Failure (%)	25 (7.25%)	12 (5.80%)	37 (6.70%)	0.51[†]
Immunocompromised (%)	6 (1.74%)	8 (3.86%)	14 (2.54%)	0.124[†]
Type of prescriber (%)				
Fellow	81 (23.48%)	37 (17.87%)	118 (21.38%)	0.032[†]
ICU consultant	191 (55.36%)	138 (66.67%)	329 (59.60%)	
Non-ICU consultant	73 (21.16%)	32 (15.46%)	105 (19.02%)	
Time of the day (%)				
Day shift	203 (58.84%)	132 (63.77%)	335 (60.69%)	0.251[†]
Out of hour	142 (41.16%)	75 (36.23%)	217 (39.31%)	
Hospital acquired infection (%)	118 (34.20%)	104 (50.24%)	222 (40.22%)	0.0002[†]
Therapeutic urgency (%)				
None	228 (66.09%)	75 (36.23%)	303 (54.89%)	<0.0001[*]
Septic shock	74 (21.45%)	106 (51.21%)	180 (32.61%)	

Hypoxemia requiring urgent invasive ventilation	21 (6.09%)	21 (10.14%)	42 (7.61%)	
Meningitis	17 (4.93%)	2 (0.97%)	19 (3.44%)	
Immunocompromised	5 (1.45%)	3 (1.45%)	8 (1.45%)	
Source of infection (%)				
Lung	153 (44.35%)	106 (51.21%)	259 (46.92%)	0.011†
Urinary tract	69 (20%)	32 (15.46%)	101 (18.30%)	
Intraabdominal	33 (9.57%)	25 (12.08%)	58 (10.51%)	
Skin and soft tissue	22 (6.38%)	4 (1.93%)	26 (4.71%)	
Blood stream	11 (3.19%)	13 (6.28%)	24 (4.35%)	
Central nervous system	18 (5.22%)	3 (1.45%)	21 (3.80%)	
Unknown	39 (11.30%)	24 (11.59%)	63 (11.41%)	
Antibiotic appropriateness (%)				
Not ascertained	245 (71.01%)	132 (63.77%)	377 (68.30%)	0.017†
No	20 (5.80%)	26 (12.56%)	46 (8.33%)	
Yes	80 (23.19%)	49 (23.67%)	129 (23.37%)	
De-escalation strategy (%)				
No de-escalation	297 (86.09%)	182 (87.92%)	479 (86.78%)	0.089†
Some de-escalation	30 (8.70%)	9 (4.35%)	39 (7.07%)	
Some escalation	18 (5.22%)	16 (7.73%)	34 (6.16%)	
ICU days before prescription (median, IQR)	0 (0–1)	1 (0–4)	0 (0–2)	<0.0001**
Lactate at prescription (mmol/L) (mean, SD)	1.72 ± 1.9	2.56 ± 2.73	2.04 ± 2.28	0.0001
Procalcitonin at prescription (µg/L) (mean, SD)	0.61 (0.171–3.84)	1.69 (0.653–6.605)	0.96 (0.234–4.81)	0.0001**
SOFA score at prescription (median, IQR)	5 (3–7)	8 (5–11)	6 (4–9)	<0.0001**

Independent *t*-test; **Mann–Whitney test; *Fisher's exact test; †Chi-squared test; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; SOFA, Sequential Organ Failure Assessment

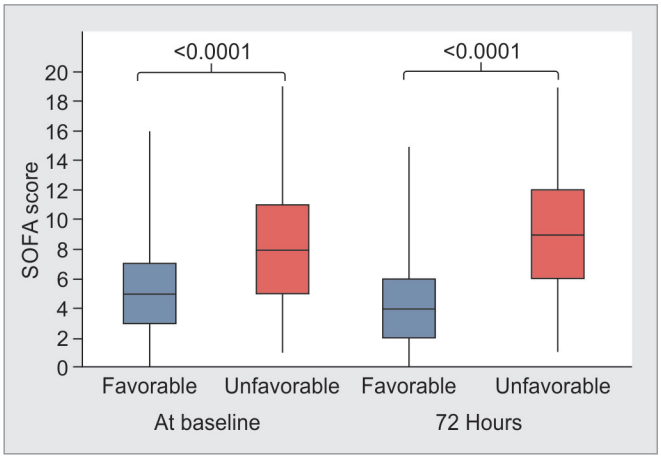

Fig. 3: Changes in SOFA score at 72 hours compared to baseline in patients with favorable and unfavorable outcome

could be related to the low rate of positive culture results. Similarly, no independent association could be established between the outcome of antibiotic therapy and out-of-hour prescription or type of prescriber. Not surprisingly, septic shock and worse organ function reflected by higher SOFA score at the time of antibiotic prescription were independently associated with unfavorable outcome.[4–6] Interestingly, underlying COAD was independently associated with favorable outcome, which may possibly be explained by less sick patients with acute exacerbation included in the subgroup.

Strength and Limitations

This study has several strengths. We included a large number of patients with data collected over 13 months, taking care of seasonal variations in an antibiotic prescription. Unlike most earlier studies, we reported data for all antibiotic prescriptions throughout the ICU stay. We provided a detailed account of the antibiotic prescription including circumstances in which antibiotics were prescribed, changes made in antibiotic prescription with or without the availability of a sensitivity report, reasons for such changes, the pattern of de-escalation, and the outcome of antibiotic prescription. We used uniform definitions for measuring all parameters, using international guidelines wherever available. To our knowledge, this is the first Indian study, that classified antibiotic prescription based on microbiological data and clinical findings as no bacterial infection, possible infection, only clinical infection, or microbiologically proven infection.

This study is limited by being a single-center study. However, many of our findings correlate well with multicenter data. Because of inadequate resources, we could not collect data for prescription pattern once the patient was shifted out of ICU. Because of the limitation of the design, we failed to collect data on reasons for not sending cultures before the antibiotic prescription. We also failed to record data for the quality of antibiotic prescription like the timing of administration, types of antibiotics prescribed, the dose used, bolus or infusion, and renal or hepatic modification pattern. However, with the availability of at least first dose of all routinely used antibiotics in our ICU inventory, it is expected that antibiotics are administered within 15–30 minutes of prescription following surviving sepsis campaign (SSC) guideline.[7]

Conclusion

To conclude, we believe that this study should be of interest to clinicians practicing in this field especially those from resource limited settings. The high rate of empirical precipitation and less than the desired rate of microbiological sampling as a hindrance to de-escalation, should encourage clinicians and healthcare administrators to develop a system to improve the rate of microbiological sampling. One possible way may be to involve bedside nurses in the decision-making process, apart from organizing antibiotic stewardship training for clinicians.

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