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RESEARCH ARTICLE

Study on Initial Management of Sepsis in Tertiary Care Centre: A Prospective Study

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ABSTRACT

Background: Sepsis and septic shock are the major health problems affecting millions of people around the world each year and the incidence is as many as 1 in 4. According to Centers for Disease Control and Prevention the incidence of sepsis continues to increase and is now the 3rd leading cause of infectious death. In India, sepsis claims more than 90,000 lives every year and is one of the leading causes of death. Early effective management of sepsis as per Surviving sepsis Campaign guidelines can improve the patient outcomes, prevent further complications, and decrease the mortality. **Aim:** Our study aims to evaluate the Initial Management of Sepsis in an Institution and identify the areas of improvement. **Methods:** It is a prospective observational study conducted in a tertiary care center. A structured data collection form was designed to collect the information from medical records of the patients. Sepsis investigation details such as source of infection, blood, and urine cultures were collected. Additional information such as initial antibiotic started, door to first antibiotic, fluids used, and other supportive care (Deep vein thrombosis and Stress ulcer prophylaxis) was collected, assessed, and reviewed for the initial 2 days. **Results:** A total of 100 cases were collected. Number of patients diagnosed with sepsis and septic shock was found to be (78%) and (22%), respectively. Males (55%) were more affected compared to females (45%). Diabetes with hypertension and hypothyroidism (40%) was the common comorbid observed. Common source of infections were found to be lower respiratory tract infection (41%) followed by urinary tract infections (19%). Majority of the patients received appropriate Antibiotics within 1 h as per guidelines. A Sequential Organ Failure Assessment score of >3 was found in 26%. Fluid therapy was given to 78% of the patients. Vasoactive medications were given to all patients with septic shock (22%). **Conclusion**: In our hospital setting, the overall adherence to guidelines was found to be optimal and satisfactory. However, there is need for improvement in some areas.

Keywords: Sepsis, septic shock, surviving sepsis campaign guidelines, sequential organ failure assessment score

INTRODUCTION

Sepsis and Septic Shock

Sepsis and septic shock are the major health problems affecting millions of people around the world each year and the incidence is as many as 1 in 4 [Table 1].

According to center for disease control and prevention the incidence of sepsis continues to increase and is now the 3rd leading cause of infectious death.[1] Sepsis is a life threatening organ dysfunction caused by dysregulated host response to infection. It affects neonatal, pediatric, and adult patients worldwide.[2] Organ dysfunction can be represented by an increase in the Sequential Organ Failure Assessment score of two points or more, which is associated with an in-hospital mortality >10%.[3,4-6]

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Epidemiology

Sepsis, defined as the condition arising when the host response to infection causes organ dysfunction in the host, remains a major killer. Probably the most often quoted article on the epidemiology of sepsis is the 2001 publication by Angus *et al*., which used administrative data to estimate that there were 751,000 cases (3.0/1000 population) in the United States each year, resulting in more than 200,000 deaths.[4]

More recent research suggests that sepsis causes or contributes to between one-third and one-half of all deaths occurring in hospitals in the United States, with the majority of patients presenting to hospital with sepsis rather than acquiring sepsis in hospital.[7]

In the most recent report, published in 2015, sepsis is considered a pathway to death from an infection and is referred to as a "garbage code," with death being attributed to the infection that initiated sepsis.[8-11]

Pathophysiology

The pathophysiologic sequelae resulting from the interaction between the invading pathogen and the human host are diverse, complex, and incompletely understood. Definitive relationships between infection and progression to sepsis have been difficult to demonstrate.

CASCADE OF SEPSIS

Diagnosis

Evaluation of patient history

Evaluation of patient history, in this case, is done to get information on the following:

- Whether the infection that caused sepsis was community acquired.
- Whether it is nosocomially acquired.
- Whether the patient has an impaired immune system.

Details of situation that can expose the patient to specific infectious agents are collected [Figure 1].

Physical Examination

If the patient has neutropenic or other pelvic infections, physical examination that can reveal rectal, perirectal, or perineal abscesses, pelvic inflammatory disease or abscesses, or prostatitis should be done. It includes rectal, pelvic, and genital examinations.[12-14]

Laboratory tests

For patients suspected with sepsis, a large number of tests are ordered so that the doctor gets details on the potentiality and severity of the patient's condition. The different tests done include urine

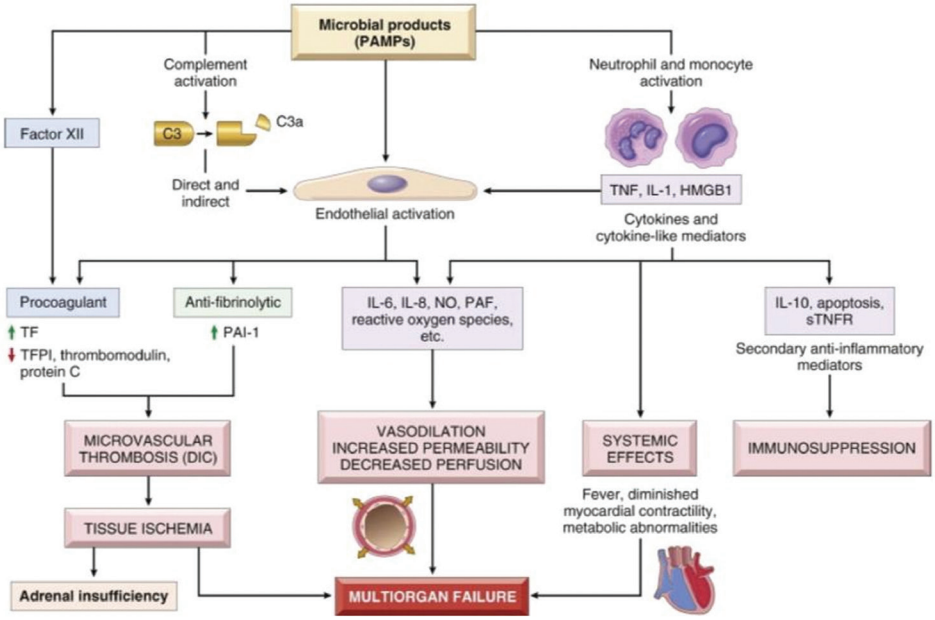


Figure 1: Sepsis cascade[16]

Table 1: Clinical conditions associated with sepsis

Associated with sepsis (Fever≥102°F)	Not associated with sepsis (Fever≤102°F)
GI tract source, Liver, Gallbladder, Colon, Abscess, Intestinal obstruction, Instrumentation	GI tract source, Esophagitis, Gastritis Pancreatitis, Small bowel disorders, GI bleeding
GU tract source, Pyelonephritis, Intra- or perinephric abscess, Renal calculi, Urinary tract obstruction, Acute prostatitis/abscess, Renal insufficiency Instrumentation in patients with bacteriuria	GU tract source, Urethritis, Cystitis, Cervicitis Vaginitis Catheter-associated bacteriuria (in otherwise healthy hosts without genitourinary tract disease)
Pelvic source Peritonitis	Upper respiratory tract source Pharyngitis
Abscess	Sinusitis, Bronchitis, Otitis
Lower respiratory tract source Community-acquired pneumonia (with asplenia), Empyema, Lung abscess	Lower respiratory tract source Community-acquired pneumonia (in otherwise healthy host)
Intravascular source IV line sepsis, Infected prosthetic device, Acute bacterial endocarditis	Skin/soft-tissue source Osteomyelitis, Uncomplicated wound infections
Cardiovascular source Acute bacterial endocarditis Myocardial/paravalvular ring abscess	Cardiovascular source Subacute bacterial endocarditis
	CNS source Bacterial meningitis

test, blood test, and tests related to other medical conditions.[15, 16]

Blood tests

For patients with possible signs of sepsis, there are various blood tests available are:

Complete blood count, lactate, C-Reactive Protein test, blood culture, prothrombin time (PT) and partial thromboplastin TIME, platelet count, and D-dimer test.

Confirmatory Tests

There are three types of blood tests that can confirm sepsis. They are:

Endotoxin test, Procalcitonin test, and Septicyte test.

Urine test

Two types of urine tests are ordered in cases of sepsis.

Urinalysis: This tests urinary tract infections (UTI) or problems with the kidneys.

Urine culture: Used to determine which bacteria or fungi caused UTI.

Tests for Related Medical Conditions

Apart from blood and urine tests, tests related to other diseases that can cause sepsis are also done. Few examples are:

- Chest X-ray, Pulse Oximetry and Sputum test for Pneumonia.

Lumbar puncture, magnetic resonance imaging, and computed tomography scan for Meningitis.

- The rapid antigen test and the throat culture for strep throat.
- Rapid influenza diagnostic tests and symptom analysis for influenza.
- Skin culturing for infections related to skin.

Pseudosepsis is a common cause of misdiagnosis in hospitalized patients, particularly in the emergency department and in medical and surgical intensive care unit (ICUs). The most common causes of pseudosepsis include gastrointestinal hemorrhage, pulmonary embolism, acute myocardial infarction, acute pancreatitis (edematous or hemorrhagic), diuretic-induced Hypovolemia, and relative adrenal insufficiency. Patients with pseudosepsis may have fever, chills, Leukocytosis, and a left shift, with or without Hypotension. All causes of pseudosepsis produce Swan-Ganz catheter readings that are compatible with sepsis (e.g., increased cardiac output and decreased peripheral resistance), which could misdirect the unwary clinician [Table 2].[17]

Treatment for Sepsis

- Surviving sepsis guidelines recommendations for initial management of Sepsis include, appropriate antibiotics within 1 h, removal of source of infection, rapid resuscitation, Hemodynamic stabilisation, administration of Vasoactive agents for cardiovascular support and Deep vein thrombosis (DVT), Stress ulcer prophylaxis.[18]
- Surviving Sepsis Campaign Guidelines are mentioned in Appendix.

Table 2: Characteristics of pseudosepsis and sepsis

Parameters	Pseudosepsis	Sepsis
Microbiologic	No definite source PLUS≥1 abnormalities Negative blood cultures excluding contaminants	Proper identification/process/source PLUS≥1 microbiologic abnormalities Positive buffy coat smear result OR 2/3 or 3/3 positive blood cultures
Hemodynamic	⇓ PVR ⇑ CO	⇓ PVR ⇑ CO Left ventricular dilatation
Laboratory	⇑ WBC count (with left shift) Normal platelet count ⇑ FSP ⇑ Lactate ⇑ D-dimers ⇑ PT/Partial Thromboplastin Time ⇓ Albumin ⇓ Fibrinogen ⇓ Globulins	⇑ WBC count (with left shift) ⇓ Platelets ⇑ FSP ⇑ Lactate ⇑ D-dimers ⇑ PT/Partial Thromboplastin Time ⇓ Albumin
Clinical	≤102°F±Tachycardia±Respiratory alkalosis±Hypotension	≥102°F OR Hypothermia±Mental status changes±Hypotension

⇑Increase, ⇓Decrease, ± Present/Absent

METHODOLOGY

Study Design

Design: Single-center, prospective, and observational study.
Duration: 8 months (January–June 2018).
Sample size: 200.

Selection of Subjects

Inclusion criteria

The following criteria were included in the study:

- Age ≥18 years
- Patients in ICUs
- Patients with suspected or proven infection (including hospital acquired infections)
- Patients for whom antibiotics are given for the 1st time for a specific infection.

Exclusion criteria

The following criteria were excluded from the study:

- Pediatric patients
- Pregnant women
- Cancer patients
- Outpatients.

Study Procedures

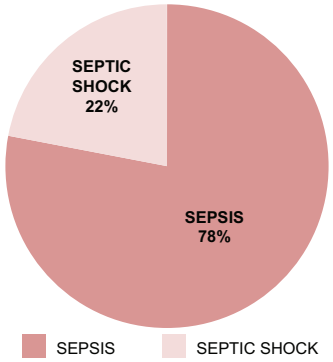
Data collection form was designed to collect the demographics of the patients being treated with antibiotics from patient charts who were admitted in the hospital. The data regarding risk factors, clinical presentation, suspected or confirmed infection, diagnostic tests performed, radiology and pathologic labs, culture and sensitivity tests, treatment regimen that is antibiotics prescribed were collected. The pattern of antibiotic use in each subject was studied and analysis was done [Tables 3-6].

RESULTS

Gender	No of patients (*n*=100)
Female	45%
Male	55%
Age group (in years)	
18–30	10%
31–50	15%
51-70	51%
>70	24%
History of present illness	
Fever with chills and nausea and vomiting	42%
Fever with reduced Urine output	15%
SOB, followed by cough and greenish expectoration, Bed ridden	23%

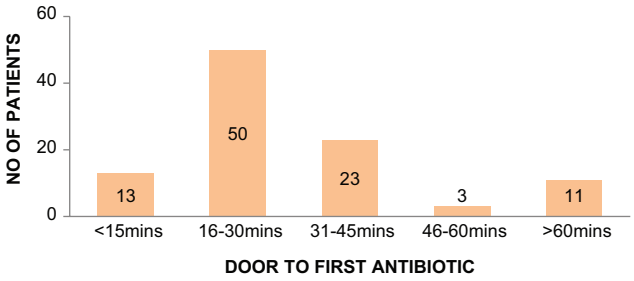
Generalized weakness, Headache, Fever with chills	12%
Abdominal pain, Fever and 2 episode vomiting and SOB	8%
Co-morbid conditions	
Diabetes Mellitus	3%
Hypertension	4%
Hypothyroidism, Parkinsonism	2%
Diabetes Mellitus with Hypertension and Hypothyroidism	40%
Chronic obstructive pulmonary disease	2%
Coronary artery disease	1%
Tuberculosis, AIDS	2%
None	14%
Hypertension and Diabetes Mellitus	13%
Hypertension, Diabetes Mellitus and Seizures	3%
Diabetes Mellitus and Cerebrovascular accident	1%
Diabetes Mellitus and Chronic kidney disease	4%
Diabetes Mellitus with Hypertension and Hyperthyroidism	2%
Diabetes Mellitus with Hypertension and Coronary artery disease	6%
Diabetes Mellitus with Hypertension and Chronic kidney disease	3%

Comorbidities in sepsis patients.



Number of patients diagnosed with sepsis and septic shock.

Other diseases include meningitis, peritonitis, intravenous (IV) catheter, and Foleys catheter related infections.



Antibiotic therapy in sepsis and septic shock patients.

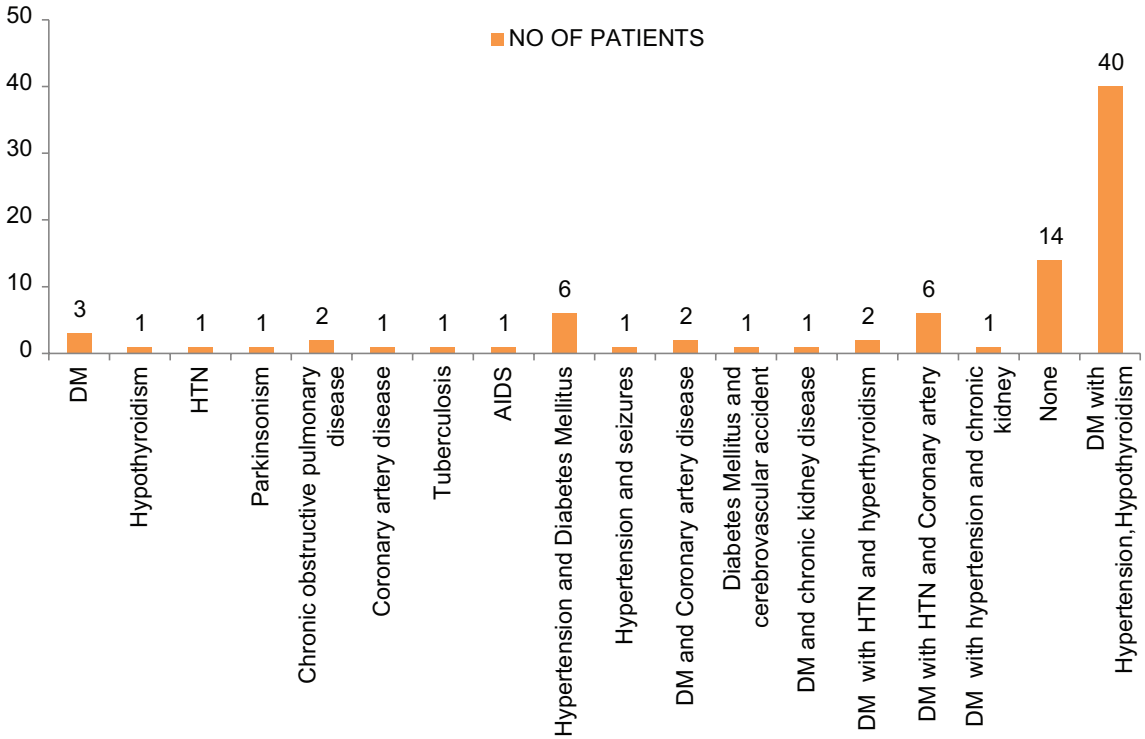
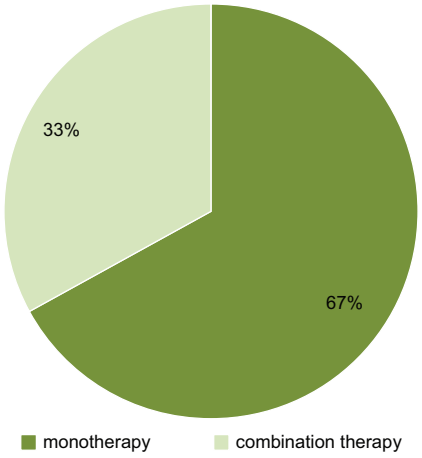


Table 3: Distribution based on source of infection

Source of infection	No of patients
Lower respiratory tract infection	41%
Urinary tract infections	19%
Urosepsis	6%
Cellulitis	5%
IV catheter	3%
Other diseases	18%
Unknown source	8%

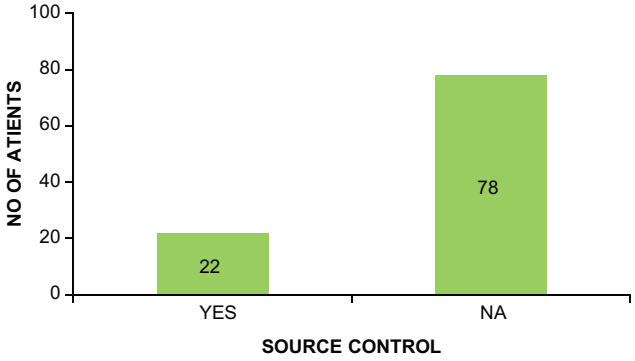
Table 4: Positive cultures in initial 2 days

Urine culture	No of patients with positive culture
Escherichia coli	3
Enterococcus	1
Klebsiella pneumonia	1



Source Control in Sepsis Patients

- **REMOVAL OFIV CATHETER**
- **SURGICAL PROPYLAXIS**

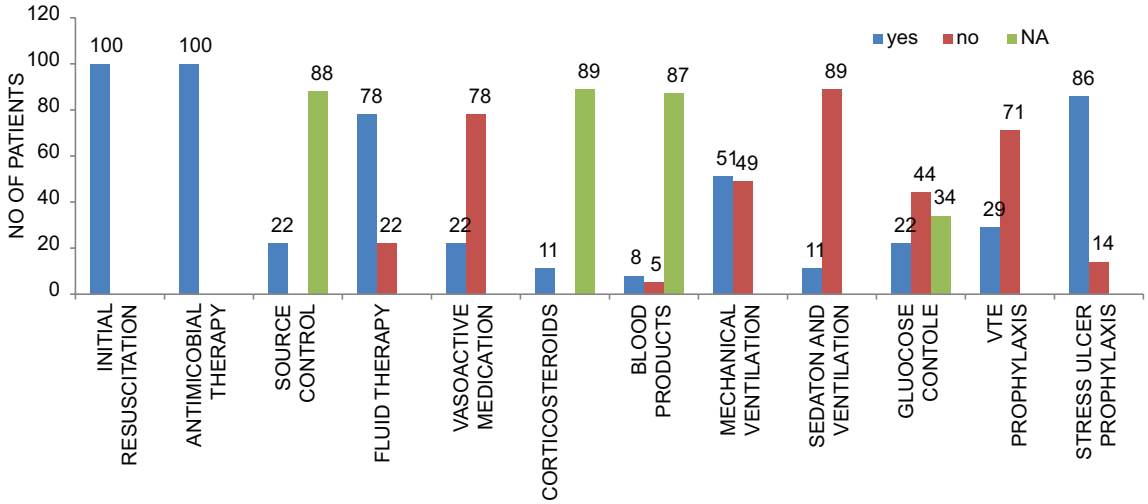


DISCUSSION

In our study, entitled "Initial Management of Sepsis in Tertiary Care Centre: A Prospective Study," we observed the initial treatment for 2 days given to about 100 subjects. The results are discussed below. Patients newly diagnosed with sepsis and who met the criteria of HR >90/min, RR >20/min, temperature≥38°C and Altered Mental Status (GCS <15) are included in our study.

During the course of our study period, data were collected from 100 patients, newly diagnosed with sepsis, among them 78 were diagnosed with sepsis and 22 were diagnosed with septic shock [Tables 7-10].

Looking into the demographics, Males (55%) were at higher risk for sepsis than women (45%). The



possible reason could be direct and indirect effects of sex steroids (DHT) in males synergistically modulate immune and cardiovascular response.[19] Comorbid plays a major role in the development of sepsis and organ dysfunction after an infection. In our study, diabetes with hypertension and hypothyroidism (40%) was the common comorbid observed. The possible reason might be defects in immune function. In our study the most common infections that led to sepsis were lower respiratory tract infection (pneumonia) (41%) and UTI (19%), followed by Meningitis, Peritonitis were most common.

Table 5: Door to first antibiotic

Time (min)	No of patients (*n*=100)
>60	11%
Within 1 h	**No of patients (*n*=89)**
46–60	3%
31–45	23%
16–30	50%
<15	13%

In our study, 95% of the urine culture reports were negative (no growth) and only 5% of cultures were positive in the initial 2 days. In our study, we concluded that outcomes of septic patients with culture negative reports are similar to those with culture-positive septic patients in nearly all cases. Early appropriate antimicrobial therapy, recognition and eradication of infection are the most obvious effective strategy in both types of patients to improve hospital survival.[20]

Surviving sepsis Campaign guidelines suggest early administration of antibiotic within 1 h, fluid resuscitation within 3 h, vasoactive medication for

Table 6: Spectrum activity of antibiotics prescribed for sepsis in hospital setting

Class	Spectrum activity	Spectrum
Carbapenem Meropenem	G+ve, G –ve, anerobicbacteria, against extended-spectrum β-lactamase	Broad spectrum
Imipenem	Aerobic and anaerobic and G+ve, G-ve, against *Pesudomonas aeruginosa* and *Enterococcus* species	Broad spectrum
Fluroquinolones Moxifloxacn	Both G+ve, G-ve bacteria.	Broad spectrum
Levofloxacin	G+ve, G-ve bacteria and atypical respiratory pathogens and against both penicillin susceptible and penicillin resistant *Strpotococcus pneumoniae*	Broad spectrum
Cephalosporines Cefoperazone	Enterobacteriaceae, *Pseudomonas aeruginosa*	Broad spectrum
Ceftazidime	*Pseudomonas* and G-ve infection in debilitated patients	Broad spectrum
Cefepime	G+ve, G –ve bacteria	Extended spectrum
Ceftriaxone	G-ve bacteria, but less than earlier generation of cephalosporins against many G+ve bacteria	Broad spectrum
Penicillins Piperacillin	G-ve bacilli, G+ve cocci. S anerobic pathogens such as clostridium difficile and bacteroides	Broad spectrum
Amoxicillin	Broad range of G+ve, limited range of G-ve organism.	Moderate spectrum
Macrolide Clarithromycin	G+ve, G-ve bacteria, mycoplasma, Chlamydia and mycobacteria	*In vitro* and *in vivo* activity, broad spectrum
Azithromycin	G+ve organism, G-ve bacilli, including *Haemophilus influenzae*	*In vitro* and Broad spectrum
Nitroimidazole Metronidazole	Various protozoans and most G-ve anerobic bacteria	Broad spectrum and fight broad range bacteria
Clindamicin	Staphylococci, streptococci and pneuococci	Broad spectrum
Tigecycline	G+ve, G-ve, anerobic organism, multi drug – resistant MRSA and MRSE, penicillin-resistant *Streptococcus pneumoniae*	Broad spectrum
Spemax	G-ve, G+ve	Broad spectrum
Vancomycin	Staphylococcal infection G+ve cocci bacteria and G-ve cocci	Narrow spectrum
Nitftron	Most strains of multidrug-resistant G-ve bacilli, including extended spectrum β-lactamase producing strains	Broad spectrum

Table 7: Change of antibiotic in sepsis patients

Day 1	Day 2	No of patients (*n*=8)
Cefperazone+ Salbactum (Magnexforte)	Meropenam	2
Cefperazone+Salbactum (Magnexforte)	Clarithromycin (Claribid)	2
Cefperazone+Salbactum (Magnexforte)	Ceftriaxone (Oframax)	1
Moxifloxacin (moxicip)	Piperacillin+ Tazobactum (zosyn)	1
Clarithromycin (Claribid)	Colistimethate Sodium (Xylistin)	1
Piperacillin+Tazobactum (Zosyn)	Clarithromycin (Claribid)	1

Table 8: Change of antibiotic in septic shock patients

Day 1	Day 2	No of patients (*n*=5)
Cefperazone+Salbactum (Magnexfortm)	Meropenam	3
Meropenam (Penmer)	Vancomycin (Vancomycin)	1
Doxycycline+ Cefperazone+Salbactum (Doxycycline)+ Magnexforte	Piperacillin+ Tazobactum (Piptaz)	1

MAP maintenance, source control, corticosteroid administration, blood transfusion, adequate nutrition if required and supportive care like DVT and Stress ulcer prophylaxis. Implementation of this guidelines for initial management improves patient outcomes, prevents complications and reduces the risk for mortality. It is always necessary to initiate any empiric antibiotic as early as possible in sepsis. In our study the door to first antibiotic was recorded and majority (89%) of the patients received antibiotic within the 1st h as per the guidelines.[21]

Antibiotics were initiated both as Monotherapy and combination therapy for sepsis (78). Out of 78 patients, 52 patients received monotherapy and 26 were on combination therapy, whereas out of 22 patients diagnosed with septic shock it was 15 and 7 patients, respectively. The most common class of antibiotics prescribed were Cephalosporins (71%) followed by carbapenams (32%), Penicillins (9%).

Change of antibiotics from day 1 to day 2 was recorded and observed in nearly 13% of the patients. The most common change was from cephalosporins to carbapenams followed by Cephalosporins to Macrolide. The possible reason might be no significant improvement in TLC count following cephalosporin administration. Optimization of antibiotic dosing was observed in very few patients. Addition of antibiotic was done in one patient. Tobramycin was added on day 2 along with cefperazone. In our study, source control was initiated in all the 22% patients who had previously undergone any surgery or were under catheterization.

In our study, 78% of the patients received fluid therapy. Crystalloids like Normal Saline, Ringer Lactate were given in fluid therapy. About 22% of the patients did not receive any fluids. This study concluded that Sepsis causes massive vasodilation and increases membrane permeability leading to an intravascular fluid deficit hence fluids need to be administered within 3 h immediately after administration. Among fluids, crystalloids should be preferred as they reduce the mortality improving lactate levels.[22]

Corticosteroids are given in septic shock patients who are on vasoactive medications. In our study Corticosteroid therapy was given to 11% of the patients. All of them received 200 mg Hydrocortisone. Remaining 11% of the patients did not receive any corticosteriods. The study concluded that treatment with low doses of hydrocortisone (200 mg) should be preferred as they reduce the risk of death in patients by reducing inflammation, relative adrenal insufficiency without increasing adverse events and by improving outcomes.[23]

Generally there will be changes in Hemoglobin in some of the sepsis patients during initial days after admission. Further hemodyanamic changes can lead to reduced tissue oxygenation. In our study, out of 100 patients, 13 patients had Hb <7 g/dl, out of 13, 8 patients were initiated on blood products like RBC transfusion, and 5 patients were not given any blood products.[24]

In our study, out of 100 cases, 66 patients had a glucose level of >180 mg/dL, Out of which of 22 patients were treated with insulin for glucose control and 44 patients were not treated for glucose control. The study stating that hyperglycemia

Table 9: Analysis of checklist

Initial Management of Sepsis in Tertiary Care Centre: A Prospective Study (SEPSIS CHECK LIST)						
1. Initial resuscitation ✓ At least 30 ml/kg of IV crystalloid fluid (within the first 3 h) ✓ Monitoring: (HR, BP, Arterial O2 sat, RR, Temp, Urine output, Lactate levels)	Day 1 Day 2 Y (100) Y (100) N N					
2. Diagnosis Routine microbiologic cultures	Blood culture: Urine culture: 5 Cultures					
3. Antimicrobial therapy ✓ IV antimicrobials (within 1 h) ✓ Empiric broad-spectrum therapy ✓ Narrow Empiric antimicrobial therapy ✓ Optimizing of doses Measurement of procalcitonin levels	Y (100)		N	Y (100)		N
4. Source control ✓ anatomic diagnosis of infection removal of intravascular access devices	Y (22)		NA (78)	Y (22)		NA (78)
5. Fluid therapy ✓ Fluid administration ✓ Crystalloids ✓ Albumin in addition to crystalloids	Y (78)		N (22)	Y (78)		N (22)
6. Vasoactive medications ✓ Norepinephrine as the first-choice ✓ Vasopressin (up to 0.03 U/min) or epinephrine to reach goal MAP ✓ Dopamine as an alternative vasopressor ✓ Dobutamine (if persistent hypo perfusion)	Y (22)		N (78)	Y (22)		N (78)
7. Corticosteroids ✓ IV hydrocortisone if fluid resuscitation and vasopressor therapy do not restore	Y (11)		N (89)	Y (11)		N (89)
8. Blood products ✓ RBC transfusion - only if the Hb<7 g/dl. Prophylactic platelet transfusion	Y (8)	N (5)	NA (87)	Y (8)	N (5)	NA (87)
9. Mechanical ventilation Neuromuscular blocking agents for≤48hrs in ARDS and PaO_2/FiO_2<150 mmHg	Y (51)		N (49)	Y (51)		N (49)
10. Sedation and analgesia Minimized in mechanically ventilated patients	Y (11)		N (89)	Y (11)		N (89)
11. Glucose control ✓ When 2 consecutive blood glucose levels are>180 mg/dl ✓ Monitoring of glucose q. 1–2 h	Y (22)	N (44)	NA (34)	Y (45)	N (55)	NA (34)
12. Renal replacement therapy (in AKI) CRRT/Intermittent RRT	Y (3)		N (97)	Y (3)		N (97)
13. VTE Prophylaxis LMWH	Y (29)		N (71)	Y (29)		N (71)
14. Stress ulcer prophylaxis PPIs/H2RAs	Y (86)		N (14)	Y (86)		N (14)
15. Nutrition Early hypocaloric feed, Prokinetic agent	Y (100)		N	Y (100)		N

Y: YES (Received), N: NO (Not received), NA: Not Applicable

is seen in sepsis condition due to uncontrolled inflammatory response. Hence, a strict glycemic control with Insulin is required.

In our study, VTE prophylaxis was given to 29% of the patients and the remaining 71% patients did not receive any VTE prophylaxis. Among 71% of patients, 61% patients had some contraindications like Increased PT, thrombocytopenia, this might be the reason for not receiving any prophylaxis. Remaining 10% of patients did not receive prophylaxis though they had normal values. Majority of the study population received Enoxaparin 40 mg[25] followed by Inj Fragmin.[3] The doses of Enoxaparin varied from 20 mg,[2] 40 mg,[26] and 60 mg.[1]

Stress Ulcer prophylaxis was given to 86% of the patients in our study group. All of them received IV pantoprazole 40 mg.

Table 10: Distribution based on vasoactive medication

Vasoactive medication given	**Yes**	**No**	
	22	78	MAP Goal>65 mmHg
Medication	**No of patients**		
Noradrenaline	21		Yes
Vasopressin	1		Yes

Adequate nutritional therapy optimizes the chance of survival in sepsis patients. In our study, all the patients received adequate nutritional therapy.

CONCLUSIONS

- The present study indicates the use of antibiotics in ICUs in a multispeciality hospital.
- Duration of antibiotics for prophylaxis is not as per the standard guidelines.
- Colistin is found to be resistant in MDR *Klebsiella pneumonia*.
- De-escalation of antibiotics is mostly preferred in MDR organisms.
- Proper laboratory tests such as culture and sensitivity patterns reports may aid in directing the specific antibiotic treatment which favours cost minimization during the course of treatment and decreases the spread of resistance patterns.
- The patient must expect to receive the right antibiotic, at the right time, with right dose and duration.

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