Clinical spectrum of severe community acquired infections in patients under General Medicine requiring admission to medical intensive care unit and medical high dependency unit in a tertiary care hospital in South India

A dissertation submitted in partial fulfilment of the rules and regulations for MD General Medicine examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai, to be held in October 2015

DECLARATION BY CANDIDIATE

This is to declare that this dissertation titled "Clinical spectrum of severe community acquired infections in patients under General Medicine requiring admission to medical intensive care unit and medical high dependency unit in a tertiary care hospital in South India"

is my original work done in partial fulfilment of rules and regulations for MD General Medicine examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai to be held in October 2015.

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CERTIFICATE

This is to certify that the dissertation entitled, "Clinical spectrum of severe community acquired infections in patients under General Medicine requiring admission to medical intensive care unit and medical high dependency unit in a tertiary care hospital in South India" is a bonafide work

Dr.Betsy Ann Joseph

towards the partial fulfilment of rules and regulations for MD General Medicine degree examination of the Tamil Nadu Dr.M.G.R Medical University, to be conducted in October 2015.

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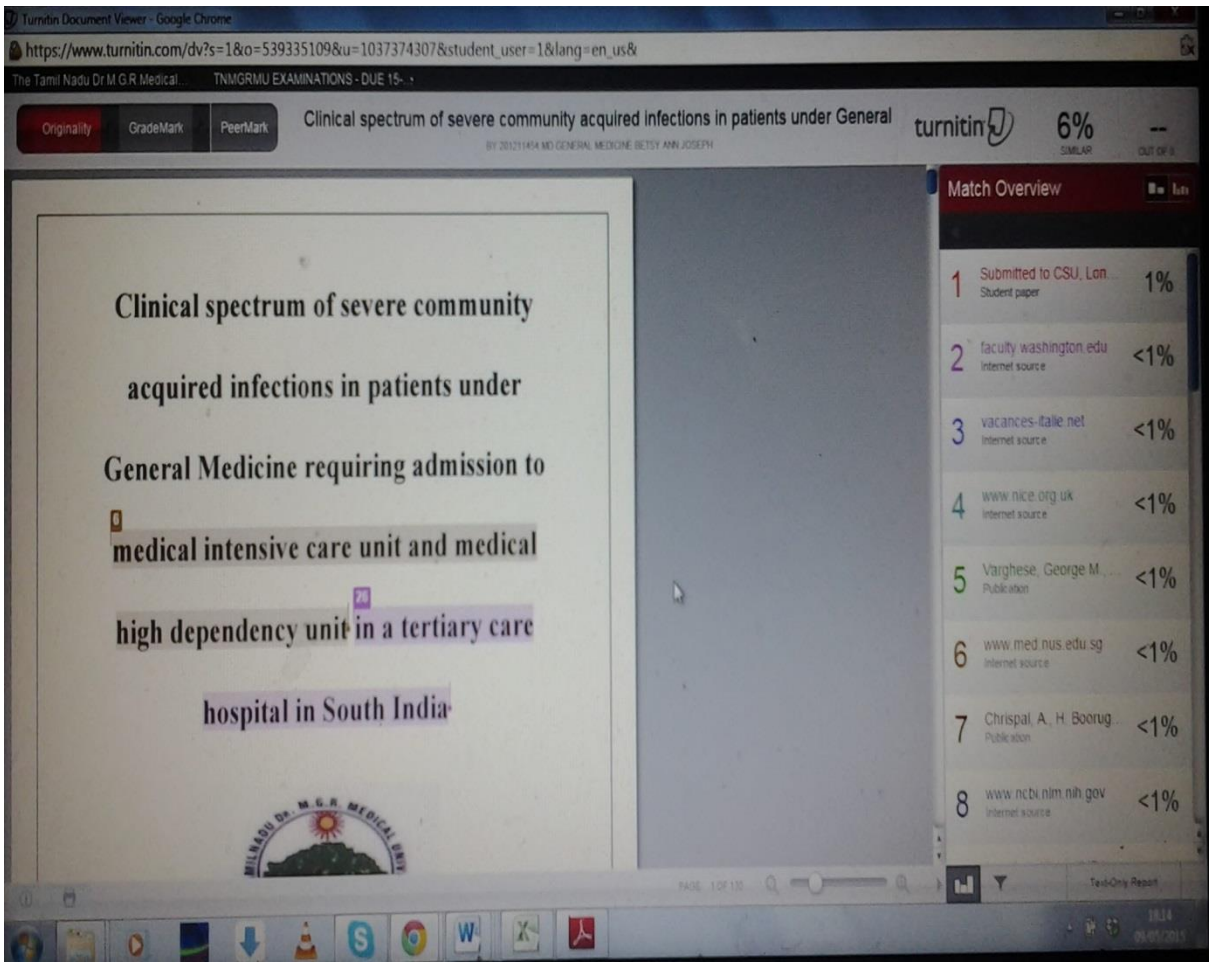

ACKNOWLEDGEMENT

This dissertation would be incomplete without expressing my gratitude to the people involved in its conceptualisation and completion.

My sincere gratitude to my guide, *Dr. Anand Zachariah,* Professor and Head of of Medicine, for the mentorship and guidance throughout this process, since its conception to completion.

I thank *Mrs.Reka K, Mrs.Gowri, Mr. Sudhir and Dr. Antonisamy,* Department of Biostatistics for their expertise in the statistical analysis.

I also express my sincere gratitude to my teachers particularly *Dr.Thambu David*, Professor of Medicine for effectively inculcating the principles and ethics of research into our curriculum, and my colleagues in the Department of Medicine who helped in patient recruitment.

I thank my spouse *Dr. Shalom Solomon Patole,* for his presence, constant support and words of encouragement.

I thank God for this opportunity and by whose grace this was possible.

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1. INTRODUCTION

Infectious diseases in South East Asia are associated with a high mortality and morbidity. The estimated deaths due to major preventable infections in children in South Asia were over two thirds of the total 3.7 million deaths. Despite advances in the field of medicine the inability in timely recognition of the various infectious syndromes, inappropriate use of antibiotics and the inappropriate interpretation of various serological tests are major players (1, 2). Lack of appropriate microbiological facilities and the high costs involved also play a major role in the rampant use of empirical antibiotics (3).

Severe community acquired infections that require admissions to intensive care unit (ICU) are associated with high morbidity and mortality. Prompt and accurate diagnosis of the infectious syndrome helps in initiating the appropriate therapy. The outcomes in these patients is determined by various factors, such as the disease itself, severity of the infection as evidenced by organ system dysfunction, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, initiation of appropriate antibiotics and co-morbidities. The data that we have on the clinical spectrum of the cohort of patients with severe community acquired infections in India is very sparse. Information regarding the clinical correlates and factors that contribute to the morbidity and mortality of this treatable disease is lacking. This study examines patients with severe acute community acquired infections warranting intensive or high dependency care with regard to the clinical spectrum of common infectious syndromes, the clinical outcome with reference to morbidity and mortality, implications of co-existing co morbidities on the outcome and to identify the risk factors associated with a poor outcome. It is also evident that in patients with severe infections, accurate diagnosis at admission and the initiation of appropriate specific therapy

and supportive therapy can alter the end result. We will therefore examine the admission diagnosis and treatment initiated and the impact it has on the outcome of patients with severe community acquired infections.

Thus we hope that we have a better clinical and evidence based understanding of severe community acquired infections in the Indian population, in order to aid in making accurate clinical diagnosis, initiate appropriate therapy and identify potential reversible risk factors.

2. AIM

To understand the clinical spectrum, etiology and outcome of community acquired infections requiring admission into Medical Intensive Care Unit and Medical High Dependency Unit presenting to the Department of General Medicine at Christian Medical College, a tertiary care hospital in South India.

3. OBJECTIVES

1. To determine the etiological and clinical spectrum of severe community acquired infections requiring ICU care.

2. To determine the admission correlates of etiological diagnosis.

3. To determine factors that determine clinical outcome including clinical severity score (APACHE), etiology, clinical co morbidities and choice of treatment,

4. REVIEW OF LITERATURE

4.1 INFECTION- EPIDEMIOLOGY

Infection is a microbial phenomenon which is characterized by an inflammatory response to the presence of micro-organisms or the invasion of normally sterile host tissue by those organisms (4).

The infection could either be a mild or a severe one. In order to help clinicians ascertain the severity of an infection various terms were introduced and defined by critical care specialists.

4.2 SEVERITY OF THE INFECTION

4.2.1 SYSTEMIC INFLAMMATORY RESPONSE

Systemic inflammatory response (SIRS) is a clinical syndrome that defined a state of dysregulated inflammation. This terminology was applicable to both infectious and non-infectious processes (5).

For simplicity SIRS is defined by four variables namely:

- Temperature: >38 deg C or < 36 deg C
- Heart rate : > 90 beats per minute
- Respiratory rate: >20 breaths per minute or PaCO2 < 32 mmHg
- White blood cell count: > 12,000/ cu mm or < 4,000/ cu mm, or > 10 % immature band forms

4.2.2 SEPSIS

Sepsis is a deleterious dysregulated inflammatory response of the body to an infection which results in severe sepsis, septic shock with or without multi organ dysfunction (6).

The definition of sepsis has been reconsidered since 1991, with the latest definition from the Society of Critical Care Medicine and European Society of Intensive Care Medicine in 2012 (6).

The diagnostic criteria for sepsis included:

Infection, documented or suspected, and some of the following:

General variables

1. Temperature; fever >38.3 ºC or hypothermia <36 ºC
2. Heart rate >90 beats/min or more than two standard deviations above the normal value for age
3. Tachypnea, respiratory rate >20 breaths/min
4. Altered mental status
5. Significant edema or positive fluid balance (>20 mL/kg over 24 hours)
6. Hyperglycaemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes

Inflammatory variables

1. Leucocytosis (WBC count >12,000 microL^{-1}) or leukopenia (WBC count <4000 microL^{-1})
2. Normal WBC count with greater than 10 percent immature forms
3. Plasma C-reactive protein more than two standard deviations above the normal value

4. Plasma procalcitonin more than two standard deviations above the normal value

Hemodynamic variables

Arterial hypotension (systolic blood pressure SBP <90 mmHg, MAP <70 mmHg, or an SBP decrease >40 mmHg in adults or less than two standard deviations below normal for age)

Organ dysfunction variables

1. Arterial hypoxemia (arterial oxygen tension [PaO_2]/fraction of inspired oxygen [FiO_2] <300)
2. Acute oliguria (urine output <0.5 mL/kg/hr for at least two hours despite adequate fluid resuscitation)
3. Creatinine increase >0.5 mg/dL or 44.2 micromol/L
4. Coagulation abnormalities (international normalized ratio [INR] >1.5 or activated partial thromboplastin time [aPTT] >60 seconds)
5. Ileus (absent bowel sounds)
6. Thrombocytopenia (platelet count <100,000 $microL^{-1}$)
7. Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 micromol/L)

Tissue perfusion variables

1. Hyperlactatemia (>1 mmol/L)
2. Decreased capillary refill or mottling (5, 6)

4.2.3 SEPTIC SHOCK

Septic shock is sepsis induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status (5, 6).

4.2.4 SEVERE SEPSIS

Sepsis associated with organ dysfunction, hypo perfusion or hypotension. Hypo perfusion and perfusion abnormalities may include lactic acidosis, oliguria, or an acute alteration in mental status (5, 6).

4.2.5 MULTI ORGAN DYSFUNCTION

Multi organ dysfunction (MODS): presence of altered organ functions in an acutely ill patient such that homeostasis cannot be maintained without intervention (5).

4.3 SEVERE COMMUNITY ACQUIRED INFECTIONS REQUIRING INTENSIVE CARE

Data on clinical outcomes of severe community acquired infections from a study done by Hounsom et al on 681 patients admitted to UK NHS international showed that the 7 and 30 day mortality rates were 18.2 % and 25 % respectively. This study however included all patients with community acquired bacteremia irrespective of the severity. The 30 day mortality in the critical care unit was 29.2%. The spectrum of infection in this cohort was bacteremic illnesses with the commonest site of infection being urinary tract infection followed by biliary tract infection. The most common organism that was isolated was *Escherichia coli* in 34.7% of the patients, followed by *Staphylococcus aureus* in 12.2% and Streptococcus pneumonia in 5.8 %. Among those with *E.coli* bacteremia, 8.8% was accounted for by extended spectrum beta lactamase producers (7).

The risk factors for mortality identified in this study and in another study by Ispahani et al included age, inadequate response to treatment, shock, leukopenia, polymicrobial bacteremia, pre-existing co morbidities and unidentified site infections (7, 8, 9).

Eykyn et al in another study in UK showed a similar microbiological spectrum in bacteremic illnesses. They also showed that *E.coli* bacteremia was common in those with diabetes, while *Streptococcus pneumoniae* was more common among alcoholics (10).

Even though the data is sparse, Reddy et al in the meta analysis on community acquired blood stream infections in Africa, looked at 22 studies on community acquired infections in both adults and children (11).

The prevalence of blood stream infections in the adult population was 13.5 % of which non-typhoidal *Salmonella* bacteremia was the prevalent isolate at 58.4 % followed by *S.pneumoniae* at 18.3%, *S. aureus* at 9.5 % and *E. coli* at 7.3%. The in- hospital case fatality rate was 18.1%. Through this meta analysis it is evident that though Africa is endemic for malaria, bacteremic febrile illnesses are common as well (11, 12). However none of these studies looked at the predictors of mortality.

Irrespective of the type of infection or the source of infection, the single most significant modifiable risk factor identified was early administration of appropriate antimicrobial agent (7, 8, 9).

In a prospective, multicentre, observational study, done by Valles et al in 30 ICUs in Spain, they showed that inappropriate and inadequate antimicrobial therapy was associated with poor prognosis and increase in mortality (13).

So in a patient with septic shock where the source of the infection or the infectious syndrome is not known, it is prudent to initiate on broad spectrum antibiotics. However one needs to be aware of the epidemiology of the infection in ones area to be able to decide on the most appropriate antibiotics therapy (13).

Also it is essential that clinicians are equipped to recognize the various infectious syndromes, are aware of the epidemiology and clinical spectrum of these infectious syndromes and initiate appropriate therapy in order to reduce the case fatality rate, more so in resource constrained settings such as in Africa and even in India.

It is also evident that there is lack of data from India and even from other developing nations such as Africa on clinical spectrum and outcomes of severe community acquired infections that require intensive care.

4.4 COMMUNITY ACQUIRED PNEUMONIA

According to the British Thoracic Society community acquired pneumonia (CAP) in a patient admitted to the hospital is defined as:

1. Symptoms of an acute lower respiratory tract illness (cough with purulent sputum production and at least one of the lower respiratory tract symptoms such as pleuritic chest pain, dyspnea and tachypnea)

2. New focal chest signs on examination

3. At least one systemic feature (either a symptom complex o sweating, shivers, aches and pains and/or temperature of 38°C or more)

4. No other explanation for the illness, which is treated as CAP with antibiotics.

5. New radiographic shadowing for which there is no other explanation (14).

CAP remains a common infection worldwide including India. The exact incidence of the disease in India is not known. Annually around 4 million cases of CAP occur with over 20 % of the patients require hospital admission (15, 16).

Mortality is higher in those with severe infection requiring ICU care.

The bacteriological profile varies in each country and in India there are few studies looking at the etiological agents implicated.

In a study in 2 tertiary hospitals in Delhi, the common organisms implicated as causative agents in CAP was *S. pneumoniae* (35.3%) *S.aureus* (23.5%), *Klebsiella pneumoniae* (20.5%) and *Haemophilus influenza* (8.8%) (17).

On the contrary in a study by Aroma et al from Christian Medical College Ludhiana, the most common organism isolated from the blood in patients with CAP was *Pseudomonas aeroginosa* (18).

But the most common organism implicated in CAP is *S. pneumoniae*, even in India (17, 19).

4.5 SCRUB TYPHUS

Scrub typhus is a rickettsial infection which is endemic to south and sout eastern Asia, Asian Pacific Rim and the northern Australia (20).

Scrub typhus is a mite-borne infection which is caused by an obligate intracellular gram negative coccobacillus *Orinetia tsutsugamushi* which is classifies in the Rickettsia genus. The disease is transmtted to man by the bite of the larval stage of trombiculid mite of *Leptotrombidium* genus (20, 21).

The true burden of the disease from Indian sub-continent is unavailable due to lack of community based data and often the disease is under diagnosed or mis diagnosed. However in the recent years there have been reports of the remergence of this infection from various states in India namely Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Rajasthan, Assam, West Bengal, Maharashtra, Tamil Nadu and Kerala (2, 21-25).

In a study conducted in Christian Medical College Vellore by Anugrah et al, the proportion of cases presenting with an acute febrile illness who had scrub typhus was 47.5 %.(2). In certain regions scrub typhus accounts for up to 50% of all cases of acute undifferentiated febrile illnesses (26, 27).

The commonest presenting symptom is short duration fever, and is often associated with dyspnea, cough, nausea, vomiting, myalgia and headache (2, 21, 28, 29). The most characteristic clinical finding seen in patients with scrub typhus is the presence of an eschar which is seen at the site of inoculation (2, 21).

The presence of an eschar is highly variable ranging between 10-92 %. In 2 studies from a tertiary hospital in South India the presence of eschar was seen in approximately 55% of patients (21, 30, 31).

The commonest site included chest and abdomen (42.3%) among females and the axilla, groin and genitalia (55.8%) in males (31).

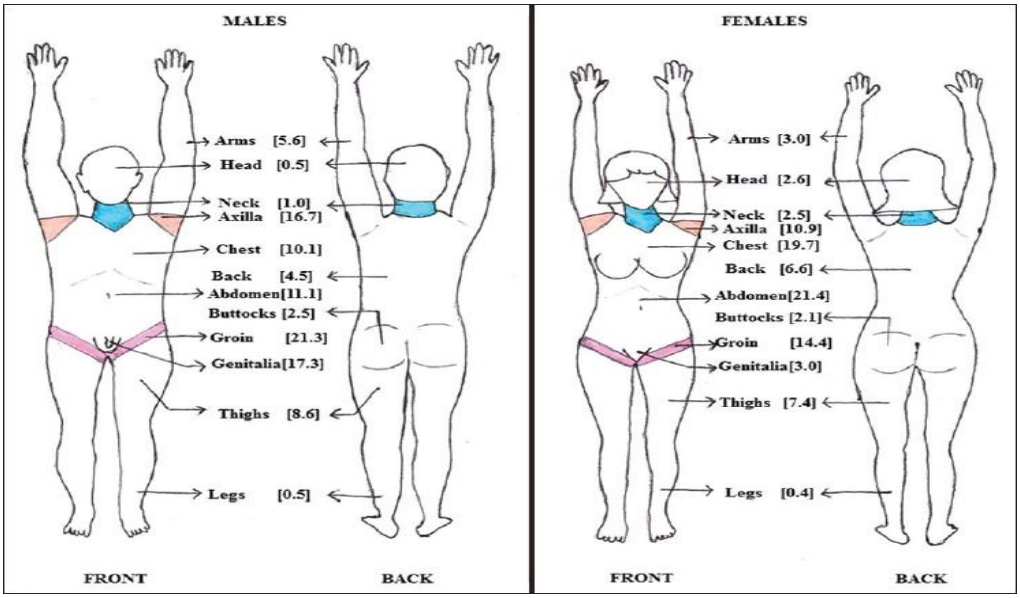


Fig 2.Sites of eschar (adapted from Ref 31)

The infection may be mild wherein the patients usually respond well to oral doxycycline.

However a small percentage of patient's may present with severe infection leading on to multi organ dysfunction and require intensive care. Patients with severe form of scrub typhus present with various organ dysfunctions namely acute kidney injury, meningo encephalitis, aseptic meningitis, myocarditis, septic shock, transaminitis, and acute respiratory distress syndrome (2, 21).

Mortality due to scrub typhus has been on down ward trend despite the varying mortality rates between various studies. The average case fatality rate reported by Varghese et al from a tertiary hospital in South India in 2014 was approximately 9% which was much lower than the 14% case fatality rate reported from the same institution in 2006 (21,32).

Even across India, there has been a declining trend in mortality from 14.6% in 2007 to 7.6% in 2010. (21).

This probably is a reflection of awareness among medical practitioners, early diagnosis and initiation of therapy.

The predictors of mortality included shock necessitating use of inotropic agents, renal dysfunction and CNS dysfunction. The commonest multi organ dysfunction seen was acute respiratory distress syndrome, as shown by Varghese et al, with an incidence of 34 % and more than half these patients required ventilatory support (21).

However the incidence of renal dysfunction varied across studies with an incidence of 18% as reported by Varghese et al to 23.2 % as reported by Attur et al. Nevertheless acute renal failure was one among the independent predictors of mortality (21, 33).

Patients with scrub typhus may have thrombocytopenia, transaminitis, leukopenia or leucocytosis and deranged renal functions. The severity of the laboratory abnormalities differ and tend to be more severe in those with multi organ dysfunction (2, 21, 32, 33).

The diagnosis of scrub typhus may be easier in the right clinical setting. Serologic test of choice available is IgM ELISA or immunofluorescence assay which is the gold standard (34, 35). So the diagnosis of scrub typhus can be made when either one of the following are present

- Eschar with Scrub IgM ELISA positive
- OR Scrub IgM ELISA positive WITH defervesence within 4 hours of initiation of doxycycline OR
- Scrub IgM ELISA seroconversion on convalescent sera
- OR Scrub IgM ELISA with other serologies negative (2, 34, 35).

The varying clinical presentations, and similarities with other undifferentiated illnesses such as malaria, dengue fever, severe gram negative bacterial infections, CNS infections, sometimes can make the diagnosis difficult.

4.6 MALARIA

Malaria is a parasitic infection which is caused by Plasmodium species, which is transmitted via the bites of infected mosquitoes namely. The Plasmodium species implicated are *Plasmodium vivax, Plasmodium falciparum, Plasmodium ovale, and.* Among these the species that are known to cause severe infections is the *Plasmodium falciparum* (36, 37).

Infections caused by *P.falciparum* and *P.vivax* are of great public health concern in the tropical countries. Malaria is transmitted by female Anopheles mosquito. Of the 400 species identified, 30 are vectors of significance in transmission. Two of the widely used antimalarials are derived from plant sources – artemisinin derivative (*Artemisia annua*), Quinine (*Cinchona*) are currently in use in areas endemic for malaria transmission (38).

Active transmission is documented in 104 countries and are presently endemic for malaria as of WHO global malaria report 2013 (39).

In a the acute febrile illness study conducted by Anugrah et in Christian Medical College Vellore, malaria accounted for 17.1 % (68 cases) of all cases of acute febrile illness. Of these *P.falciparum infection* was seen in 39 cases, *P.vivax* in 6 cases and mixed infection was accounted for by 6 cases and death occurred in 7.4 5 % of all cases (2).

95% population in India live in malaria endemic areas and 80% of malaria reported in the country is confined to areas which are hilly terrains, inaccessible to medical care (40).

50 % of reported cases are caused by *P.falciparum* species and 50% by *P.vivax* species. North and north eastern India are endemic for *P.falciparum* infection. The common anopheles species found include *An. fluviatilis, stephensi, dirus, minimus, annularis and culicifacies.*

Public sector based interventions by the NMEP have contributed significantly to the decline in incidence of malaria cases. Presently malaria diagnostic tests as well as ACT has been administered free of cost in the public sector. Extensive preventive measures are in place which includes larval control as well as the larval control measures (40).

Contrary to the national and WHO data of decline in the number of cases has been on a decline from the year 2002, a study published in The Lancet in 2010 by Dhingra et al showed that the malarial deaths are grossly underestimated and they had reported 1, 20,000 deaths/year in India, as compared to national statistics which reported the number to be 1230 deaths. The mortality occurred in geographical areas which are highly endemic for *P.falciparum* infections (41, 42).

Malaria is diagnosed in a patient with patient who presents with acute febrile illness with identification of the parasite (*Plasmodium vivax, Plasmodium falciparum* or mixed infection) on blood smears (2).

Artesunate and sulphadoxine- pyrimethamine combination is currently recommended first line treatment. Most patients with uncomplicated malaria respond to anti-malarial therapy and do not require intensive care (43)

However those with complicated malaria usually caused by *P. falciparum* tend to have multi organ dysfunction. The organ involvement can be metabolic acidosis, circulatory collapse/shock, acute respiratory distress syndrome/pulmonary edema, hemoglobinuria, anaemia, thrombocytopenia, acute kidney injury, acute liver failure/hepatic encephalopathy, hypoglycaemia, and altered sensorium/seizures/cerebral malaria. Severe malaria is managed by parenteral anti-malarial mainly quinine or artemisinin based combination therapy (36, 37).

Most cases of *P.vivax* malaria cause benign infections. However in a recent retrospective analysis in a tertiary care centre in Uttar Pradesh India, 62 patients with *P.vivax* infections were identified to cause severe malaria. In this study mixed infections and falciparum malaria was excluded. The reported complications included renal dysfunction (21 %), cerebral malaria (10%), hepatic dysfunction (29%), severe anemia (25.8 %), thrombocytopenia (56.5%), acute respiratory distress syndrome (9.7%), hypoglycaemia (4.8 %) and shock (16.1%) (44).

4.7 URINARY TRACT INFECTION/PYELONEPHRITIS

Urinary tract infections are common infection in India. However there are no large studies which have looked at the overall prevalence and epidemiology of the organisms in the country. In two clinico-microbiological profile studies on urinary tract infection done in India by Akram et al in Aligarh in 2007 and Eshwarappa et al in 2008, *E.coli* was the commonest organism with 61% and 66.9% respectively with ESBL rates of 42.2% and 42% respectively across all organisms (45,46).

In the study by Akram et al the other organisms found to cause UTI were *Klebsiella spp* - 22% and *Pseudomonas*. spp 34.4 % of ESBL producing organisms were *E.coli* and 27.3% in *Klebsiella spp* (46). A similar clinical microbiological profile was found in various studies conducted all across India (47-50).

Females are most commonly affected, with elderly age groups and diabetes mellitus being the two most common risk factors. (51,52).

Patients with diabetes also tend to have a complicated clinical course wherein they develop complications such as emphysematous pyelonephritis, papillary necrosis and worsening of renal failure with residual damage in some patients (51).

Even in the elderly the clinical presentation is complicated by the masking of the typical symptoms. Often they present with just an acute confusional state, thus the clinician ought to be astute to make the correct diagnosis (53).

4.8 ACUTE CENTRAL NERVOUS SYSTEM INFECTION

Acute central nervous system (CNS) infections form a spectrum of illnesses which include meningitis, encephalitis or meningoencephalitis. Meningitis is defined by presence of fever, headache, and meningeal irritation. Encephalitis is defined by the presence of inflammatory

process of the brain in association with clinical evidence of neurological dysfunction. In other words a patient with fever, headache, altered mental status, focal neurological signs

Meningoencephalitis is defined as a condition when the patient has features of meningismus and features of encephalitis. The diagnosis of acute CNS infection is based on the clinical features mentioned above and positive cerebrospinal fluid analysis.

Acute bacterial meningitis is a major cause of morbidity and mortality if untreated. The mortality in India and other developing countries due to acute bacterial meningitis ranges from 16-32 % (54).

In a 10 year retrospective study of all cases of community acquired bacterial meningitis at NIMHANS, Bangalore (January 1996 to December 2005), the etiological agent was identified in 284 (73.8%) of the total of 385 cases. The commonest organism implicated was *S. pneumoniae* which accounted for 61.8% of all the 385 cases. The other pathogens included *H.influenza* (1.8%) and *Neisseria meningitidis* (1%), gram negative bacilli (4.9%), *Streptococcus* spp. (2.3%) and *S. aureus* (1.8%). These organisms were identified using culture or gram stain or latex agglutination method (LAT) (55).

Contrary to the data of *S.pneumoniae* as the commonest agent implicated in acute bacterial meningitis, as obtained in most studies in India (54 - 57), Sonavane et al in a retrospective analysis of 7759 clinically suspected cases of meningitis, admitted in a tertiary Hospital in Bombay, from February 2005-February 2008, isolated *P. aeruginosa* (23.25%) as the most common pathogen. The other organisms included *Klebsiella pneumoniae* (20.93%), *Acinetobacter spp* (20.93%), *S.pneumoniae* (18.60%), *N.meningitidis* (4.65%), *Streptococcus pyogenes* (4.65%), *Enterococcus spp*. (2.23%) and other *Streptococcus spp*. (2.23 %.) (58).

Vibha et al analysed both retrospectively and prospectively all cases of clinically suspected community acquired bacterial meningitis admitted at AIIMS, Delhi, and found that the following factors namely patients from rural area, presentation after 24 hours of onset of illness, peripheral total leucocyte count of < 15000, CSF neutrophils of < 75%, low Glasgow coma scale at admission, and high creatinine levels were independent factors of mortality (59).

According to studies from international literature, acute bacterial meningitis is associated with acute systemic and neurological complications. In a prospective clinical study in a Germany, done by Pfister et al on 86 adult patients with acute bacterial meningitis, the major neurological complications included brain swelling in 14%, hydrocephalus in 11.6% and intracerebral haemorrhage in 2.3 % of cases. Seven patients had cerebral herniation. The major systemic complications seen included septic shock (11.6%), acute respiratory distress syndrome (3.5%) and disseminated intravascular coagulation (8.1%) (60).

There is however no Indian studies which have looked at the spectrum of acute neurological and systemic complications in acute bacterial meningitis in adult population.

Acute encephalitis syndrome constitutes a large proportion of cases with acute CNS infection. In India seasonal outbreaks of acute encephalitis have been reported since 1973. The common agents implicated in acute encephalitis include Herpes simplex virus type 1, West Nile virus, Chandipura virus, Japanese encephalitis B virus, enteroviruses (61).

In a record-based study which looked at cases of acute encephalitis syndrome in India and Nepal between 1978 and 2011, 125,030 cases were identified from India with mean Incidence rate of 0.42 for India (62).

Joshi et al looked at the clinical spectrum of acute encephalitis syndrome in rural central India, where 183 cases were identified between January 2007 and October 2007. Amongst these 152 cases were identified as possible viral encephalitis, however the etiology of the same was confirmed in only 31 cases. The etiological organisms identified using PCR analysis on the CSF were enterovirus (11.2%), flavivirus (5.2%), Varicella zoster (1.9%), herpes virus (0.6 %)%). The mortality rate was about 36 %. (63).

In a review article written by Rajinish et al published in 2012 looked at various studies done in India on acute viral encephalitis. In the article most of the studies identified Japanese encephalitis virus as the etiological agent in the years between 1975 and 1999. On the other hand newer viruses such as Chandipura virus and enetroviruses were identified as causative agents after 2000 (64).

In eastern India, Rathore et al through a hospital-based case enrolment study between April 2011 and July 2012 identified 91 cases of serology proven viral encephalitis from among 526 cases of acute encephalitis syndrome. The most common agent identified was Herpes simplex virus (16.1%). The other agents included measles virus (2.6%), Japanese encephalitis virus (1·5%), dengue virus (0·57%), varicella zoster virus (0·38%) and enteroviruses (0·19%) (65).

4.9 ENTERIC FEVER

Enteric fever is a systemic febrile illness caused gram negative bacteria namely *Salmonella enterica serotype Typhi*, and *Salmonella enterica serotype paratyphi A, B or C.* Enteric fever comprises both typhi and paratyphoid illnesses (66).

Crump et al looked at 22 population-based studies to estimate the global burden of the typhoid fever and as per data obtained the highest burden was seen in South central Asia and

South east Asia as evidenced by high incidence of > 100/100,000 cases/year. The estimated number of deaths globally due to typhoid disease was 216.510 and deaths due to paratyphoid caused 5,412,744 illnesses. This data high lights the burden of the disease globally (67).

Epidemiological data has shown that this is a disease of the developing countries (67, 68).

Looking at the burden of the disease in India, there have been 6 landmark population based studies which has reported varying incidence rates (69-74).

Of these 3 studies were vaccine trials done by Chuttani et al between 198- 1978, in the Delhi urban slums. The studies predominantly looked at paediatric population and adolescent age groups. The incidence reported were 9.6/1000 person years in 1971, 7.6/1000 person years in 1973 and 7.4/1000 person years in 1977 (69-71).

On the other hand similar study conducted in the urban slums of Kolkata by Ochelai et showed a much lower incidence (72, 73).

From these data it is evident that enteric fever is the most common bacetremic illness in south Asia, with special reference to the Indian sub-continent. Enteric fever accounted for 8% of all the cases of acute febrile illness studied by Anugrah et al at Christian Medical College Vellore (2).

The burden of this disease is enormous and to complicate matters, various studies from the Indian sub-continent have documented emerging resistance to antibiotics. (68)

Nagishetty et al analysed isolates from 1250 samples which included 1200 blood culture samples and 50 environmental samples for resistance pattern and showed an alarming pattern of resistance as evidenced by 31.57% of resistance against Nalidixic acid and 29.47% of resistance to ampicillin. *S. typhi* was isolated from 11 environmental samples and

84 blood samples (75). A similar pattern of resistance has been seen in various studies done at various centres in the country. In a 3 year study done in a tertiary hospital in Chandigarh in North India by Gupta et al 302 cases of *Salmonella spp* was isolated from 24390 blood culture samples over a 3 year period, and of these 257 cases were caused by *S. typhi* and the remaining 45 were caused by *S. paratyphi*. There was 100 % resistance recorded against Nalidixic acid (76).

Rupali et al in 2004, from Christian Medical College, Vellore in Tamil Nadu analysed for treatment failure in 109 hospitalized patients with blood culture proven *Sallmonella typhi* infection. All these patients were treated with ciprofloxacin. Clinical failure as defined by fever persisting for more than 6 days was documented in 25 of 46 cases who were evaluated, while microbiological failure positive blood culture even after 6 days of therapy with ciprofloxacin was seen in 8 (17.4 %). All the 8 strains of *S.typhi* was susceptible to ciprofloxacin with minimum inhibitory concentration <1 microgram/ml. However when compared to the pattern of MIC seen in the *S. typhi* strains isolated in 1995 there was 15 fold rise in minimum inhibitory concentration (77).

However the major limitation in most of the studies was that the clinical spectrum of involvement, outcome or the implications on mortality in relation to the alarming pattern of resistance of resistance documented was not analysed (78).

One landmark study done in a tertiary care center in New Delhi, north India by Kadhivaran et al over a period of 2 years, looked at the clinical outcomes in patients with Nalidixic acid resistant strains. In this study 60 cases of culture proven *S.typhi* was analysed. All the 60 isolates were susceptible to ciprofloxacin as per the MIC break points. However clinical failure was documented in 11 patients who were treated with fluoroquinolones and all these were NARST isolates. On the other hand 47 of the 60 cases that is 785 of the isolates

showed resistant pattern against Nalidixic acid. Though not statistically significant, the duration of fever at presentation and the total duration of illness were longer in those with NARST isolates. However other major complications due to the illness was not analysed in this study (79).

Considering the enormous burden of the disease in India, a deeper and evidence based understanding of whether the alarming pattern of resistance has any implications on the clinical outcomes and mortality is the need of the hour.

4.10 DENGUE FEVER

Dengue infection is a mosquito borne viral disease, caused by 4 closely related but serologically different dengue viruses. These viruses are called DENV-1, DENV-2, DENV-3 and DENV- 4 and belong to the genus *Flaviviridae*. As mentioned it is an arboviral disease transmitted mainly by the bite of *Aedes* mosquito (80, 81).

Over 2.5 billion of the world's population live in areas at risk for dengue fever. It is estimated that approximately 390 million dengue infections occur every year (81-83).

Moreover in the recent few decades the incidence of this infection has increased tremendously making dengue infection a serious public health disease, more so in the tropical countries (84-86).

In India the first epidemic of Dengue was recorded in Chennai in 1780. However the first virologically proven epidemic was in 1963-64 in Calcutta and the Eastern Coast of India (87-89).

This epidemic in 1963-64 spread gradually to involve the whole country. Initially it was confined to the northern parts of the country affecting people in Deli in 1967 (90), followed by Kanpur in 1968 (91, 92). Subsequently the southern part of the country was also affected

(93, 94). The virus spread in an endemic/ hyper endemic fashion and all 4 serotypes were implicated.

In 2010 there was an epidemic in India with nearly 28,066 serologically confirmed cases. In all the outbreaks various serotypes were implicated. Though infection with one serotype offers lifelong immunity, protection against other serotypes is transient. This change in the serotype with each outbreak and the transient cross protection between serotypes are major factors responsible for the large number of cases every year. (87, 95-97).

In human beings dengue virus can cause a spectrum of illness ranging from a self-limiting mild febrile illness to severe haemorrhagic illness. (102,103)

Dengue is classically characterized by short duration febrile illness, with non-specific signs and symptoms such as headache, retro-orbital pain, conjunctival congestion nausea, vomiting, joint pains, myalgia, and rash. The rash in dengue is variable ranging from facial flushing to scarlatiniform to Maculopapular eruptions typically involving the trunk initially followed by the face and extremities (102).

The term “break-bone” fever has been used in dengue as these patients have severe joint pains and myalgia (104).

On the contrary dengue haemorrhagic fever and dengue shock syndrome is more fatal. Patients can present with haemorrhagic manifestations of varying severity. They may have gum bleeding, epistaxis, GI bleeding hematuria or major intra-abdominal bleeding. Some may exhibit signs of circulatory failure as well. With supportive therapy, and fluid resuscitation with or without the support of blood products, these patients usually recover (103).

The common laboratory abnormalities seen are leukopenia, thrombocytopenia, hemoconcentration, elevated transaminases (102).

Considering the non-specific clinical presentation and lab abnormalities confirmation of dengue infection is accomplished using serology. There are 5 basic serologic tests available, namely hemagglutination-inhibition, complement fixation, immunoglobulin M capture enzyme-linked immunosorbent assay, neutralization test and indirect immunoglobulin G ELISA (105,106).

Hemagglutination-inhibition is one of most commonly used tests. It is a sensitive test that is easy to perform. The antibody begins to appear by day 5 of the illness. Though not a specific test, it is useful for seroepidemiologic studies as the antibodies persist for longer duration.

On the other hand neutralization test is both a sensitive and specific test (106).

4.11 RATIONALE AND JUSTIFICATION OF THIS STUDY

Normally infections are categorised on their anatomical site of involvement, the clinical syndrome and their etiology. With development of ICU care, there has been the physical segregation and specific protocols of management in patients with serious infections requiring high dependency and critical care. This is reflected in management trends such as surviving sepsis campaign bundle. In this group of patients with community acquired infections requiring ICU and HDU care, the clinical syndromes may not be differentiated and diagnosis may not be certain at admission. This is also the group of infections associated with highest mortality. Clinical decision making in relation to establishing diagnosis, early initiation of specific antimicrobial therapy and organ system support is of vital importance in determining outcome. The goal of this study is describe the clinical profile and outcomes of these seriously sick community acquired infections requiring ICU

and HDU care. This understanding may contribute to better clinical management of this group of patients.

5. METHODS

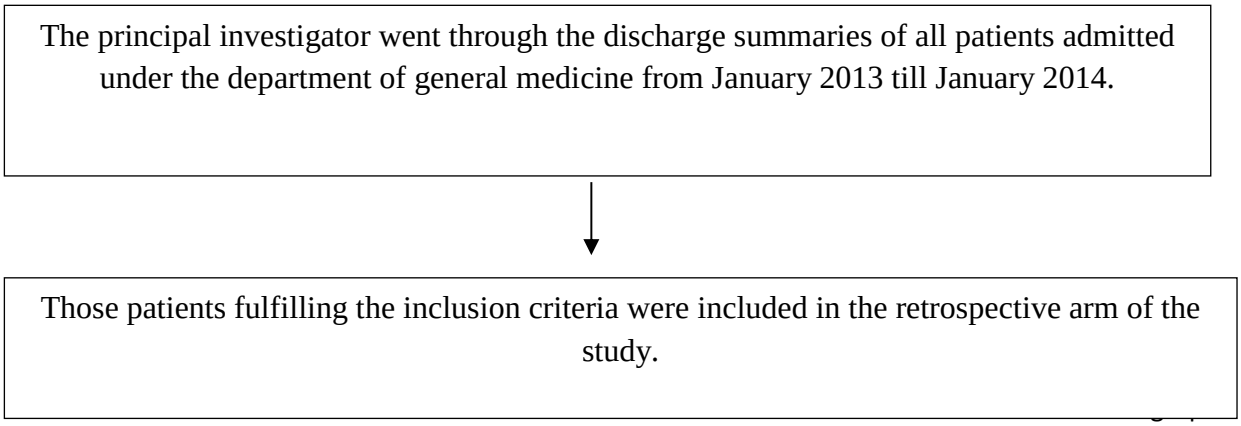
5.1 SAMPLE AND SETTING

The study was conducted between January 2013 and October 2014 at CMC, Vellore. Patients presenting with acute febrile illness, requiring admission into medical intensive care units and medical high dependency unit, fulfilling the inclusion criteria and willing to participate in the study were included into the study. There were two arms to the study- retrospective and prospective arms. The study and the research procedures were fully explained to the participants, participating in the prospective arm and those who gave written consent were allowed to participate in the study. The consent was obtained in the regional language that the patient/relative was conversant (Annexure 1)

RETROSPECTIVE ARM OF THE STUDY

All patients under the department of General Medicine who were admitted in Medical ICU/HDU after January 2013 who fulfilled the inclusion criteria were included in the study. As this is a retrospective arm of the study, patient information sheet and informed consent were not obtained. The primary investigator collected the hospital numbers of these patients after going through the discharge summaries.

The required details were entered in the data extraction form after going through the discharge summaries and IP records.



Details were entered in the data extraction form after going through the discharge summaries and, OPD charts and the IP records.

PROSPECTIVE ARM OF THE STUDY

All patients admitted in ICU/HDU who fulfilled the inclusion criteria were enrolled in the study after obtaining an informed written consent. The primary investigator visited the ICU/HDU on a daily basis to identify the cases. After the informed consent is obtained the data was filled using a primary admission sheet. The investigator followed up the patient on a daily basis till discharge.

The patient was assessed on a daily basis for development of any new onset organ dysfunction or any ensuing complications unrelated to the disease.

The in patient records were reviewed at discharge for completion of the data. Cost of care with reference to antibiotics and total cost of ICU/HDU care and hospital stay was entered after discharge or death.

After obtaining informed consent, patients fulfilling the inclusion criteria were recruited after they are admitted into MICU/MHDU

The patients were recruited by the primary investigator.

Data was entered in the data sheet or data extraction form.

Patients were followed up on a daily basis while in MICU/MHDU, and till discharge or death.

↓

Details of existing multi organ dysfunction, new onset organ dysfunction and complications unrelated to the primary illness were entered

↓

OPD chart, emergency room notes, in patient records, clinical work station were used for completion of records

5.2 STUDY DESIGN

The study design is a retrospective and prospective observational study of patients with community acquired infections admitted by the Department of General Medicine into Medical Intensive Care Unit and Medical Hugh Dependancy Unit in Christian Medical College Vellore, Tamil Nadu, India.

5.3 SAMPLE SIZE

We went through the records of all patients admitted into medical intensive care unit/medical high dependency unit between January 2013 and August 20013. There 589 admissions in MHDU/MICU. Of the 589, 87 patients had severe community acquired infections. Therefore the prevalence of severe community acquired infection was around 14.77%.

The prevalence of severe community acquired infection was around 14.77 %,

The primary objective is to look at the spectrum of severe community acquired infections and the outcome of this group of patients.

Assuming the expected prevalence of severe community acquired infections in medical intensive care unit/ medical high dependency unit to be 15 % with 95% confidence interval and precision of 3%, the sample size required is 566.

5.4 PARTICIPANTS

The participants in this study fulfilled the following inclusion criteria:

Inclusion criteria

I. Age more than 16 years

II. Patients with SIRS and with features of community acquired infection (<3 weeks duration at presentation). These include the diagnoses such as community acquired pneumonia. Urinary tract infections, skin and soft tissue infections, meningitis /acute CNS infections, undifferentiated febrile illnesses, rickettsial infections, malaria, viral fever, enteric fever and unidentified source.

Exclusion criteria

I. Admitted to another hospital for more than 1 week

II. Suspected nosocomial infection at admission

5.5 MEASUREMENTS – DATA COLLECTION

The data collection was done in data abstraction forms (Annexure 2) by the principal investigator of the study once the patients are admitted into medical intensive care unit or medical high dependency unit and they were followed up until discharge. The following details were recorded specifically:

1) Demographics – Age, sex, occupation.

2) Symptoms and duration of symptoms

3) Clinical assessment details – vital signs, systemic examination

4) Presence and duration of complications

5) Laboratory parameters including haematological, biochemical tests, serology and microbiological tests.

5.5.1 SVERITY OF INFECTION

INFECTION: A microbial phenomenon characterized by an inflammatory response to the presence of micro-organisms or the invasion of normally sterile host tissue by those organisms.

BACTEREMIA: presence of viable bacteria in the blood in the absence of contamination.

SEVERITY OF THE INFECTION

a) **SIRS**-

- Temperature: >38 deg C or < 36 deg C
- Heart rate : > 90 beats per minute
- Respiratory rate: >20 breaths per minute or PaCO2 < 32 mmHg
- White blood cell count: > 12,000/ cu mm or < 4,000/ cu mm, or > 10 % immature band forms

b) **SEPSIS**: systemic response to infection manifested by two or more of the following conditions as a result of infection:

- Temperature: >38 deg C or < 36 deg C.
- Heart rate : > 90 beats per minute
- Respiratory rate: >20 breaths per minute or PaCO2 < 32 mmHg
- White blood cell count: > 12,000/ cu mm or < 4,000/ cu mm, or > 10 % immature band forms (elaborated in the literature review text).

c) **SEPTIC SHOCK**: septic shock is sepsis induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.

d) **SEVERE SEPSIS**: Sepsis associated with organ dysfunction, hypo perfusion or hypotension. Hypo perfusion and perfusion abnormalities may include, lactic acidosis, oliguria, or an acute alteration in mental status

e) **MODS (multi organ dysfunction**): presence of altered organ functions in an acutely ill patient such that homeostasis cannot be maintained without intervention.

5.5.2 DEFINITION OF INDVIDUAL INFECTIONS/ SYNDROMES

Pneumonia:

Pneumonia is defined as inflammation and consolidation of the lung tissue.

Acute undifferentiated febrile illness

SCRUB TYPHUS- either one of the following

- Eschar with Scrub IgM ELISA positive
- OR Scrub IgM ELISA positive WITH defervesence within 4 hours of initiation of doxycycline OR
- Scrub IgM ELISA seroconversion on convalescent sera
- OR Scrub IgM ELISA with other serologies negative

Malaria:

Positive malaria pararsite- (trophozoites – Falciparum, Vivax or mixed) visualized on thin blood

smears.

Enteric fever

Enteric fever – Blood culture positive for Salmonella typhi or S. paratyphi OR Typhidot (IgM) positive plus other serologies negative OR fourfold rise in titre on the WIDAL

Dengue fever

High fever with any tow of the following symptoms- severe headache, pain behind the eyes, muscle and joints, nausea, vomiting swollen glands or rash

Warning signs- with a decrease in temperature (below 38°C/ 100°F) and include: severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, fatigue, restlessness, blood in vomit.

Dengue fever – Dengue IgM positive or other serologies negative OR seroconversion on convalescent sera.

Dengue haemorrhagic fever (DHF) – Above criteria along with thrombocytopenia with haemorrhage.

Dengue shock syndrome (DSS) – Shock (BP, 90mmHg) and other features of DHF.

Urinary tract infections:

Patients who present with fever with chills and lower urinary tract symptoms such as dysuria, frequency, urgency, supra pubic pain/ tenderness associated with any of the following systemic symptoms, such as nausea, vomiting, flank pain, delirium.

Presence of haematuria or cloudy urine.

Presence of pyuria and isolation of a typical organism in the urine and/or blood, that causes urinary tract infection.

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Acute CNS infection:

Meningitis: Fever with headache, meningismus and altered mental status

Encephalitis: Fever with headache, altered mental status, focal neurological signs.

Table 1. CSF analysis in acute CNS infections

CAUSE	WBC	PRIMARY CELL TYPE	GLUCOSE	PROTEIN
Bacterial	>500 (usually > 1000). Early: May be < 100.	POLYMORPH	<45 mg/dL	> 250 mg/dL
Viral	< 100 cells/µL.	Early: neutrophils. Late: lymphocytes	Normal (> 45 mg/Dl).	<100 mg/dL

5.5.3 DISEASE SEVERITY SCALE

APACHE II SCORE

Total Acute Physiology Score (APS) Sum of the individual 12 points = A

Total APACHE 2 score = Sum of A (APS) +B (age) + C (chronic health points)

C= Chronic health points

- Elective post op +2 pts
- Non operative or emergency post op +5 pts
- If any of the below is yes give +5 pts:

1) Cirrhosis with portal hypertension or hepatic encephalopathy

2) Class IV angina at rest

3) Chronic hypoxemia, hypercapnia or polycythaemia

4) Chronic peritoneal or haemodialysis

5) Immunocompromised host

Table 2. APACHE II SCORE

	HIGH ABNORMAL					LOW ABNORMAL			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (rectal)	>41	30-40.9		38.5	36-38.4	34-35.9	32-33.9	30-31.9	<29.9
MAP= (2xdaistolic+ systolic)/3	>160	130-159	110-129		70-109		50-69	40-54	<49
Heart rate	>180	140-179	110-139		70-109		55-69	40-54	<39
Respiratory rate	>50	35-49		25-34	12-24	10-11	6-9		<5
Oxygenation FiO2>0.5 then A-aDO2 FiO2<0.5 then PaO2	>500	350-499	200-349		<200 PO2 >70	PO2 61-70		pO2 55-60	pO2 <55
Arterial pH/serum Bicarb if no ABG avail.	>7.7/>52	7.6-7.69/ 41-51.9		7.5-7.59/ 32-40.9	7.33-7.49 / 22.31.9		7.25-7.32 / 18-21.9	7.15-7.24 / 15-17.9	<7.15/ <15
Na	>180	160-179	155-159	150-	130-149		120-129	111-119	<110
K	>7	6-6.9		5.5-5.	3.5-5.4	3-3.4	2.5-2.9		<2.5
Creat	>3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Haematocrit	>60		50-59.9	46-49.9	30-45.9		20-29.9		<20
WBC count	>40		20-	15-	3-		1-2.9		<1

			39.9	19.9	14.9				
GCS (15-actual GCS)= The Score									

Age points (years): <44=0, 45-54= 2, 55-64= 3, 65 to 74= 4, > 75 = 5.

6. OUTCOMES

The following parameters were specifically assessed in this study.

6.1 PRIMARY OUTCOMES

PRIMARY OUTCOME

1. Death
2. Duration of stay in ICU/HDU and duration of hospitalization

6.2 SECONDARY OUTCOMES

1. Supervening complications un related to the underlying medical condition

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7. DATA ANALYSIS AND STATISTICAL METHODS

Data entry was done by the principal investigator in Microsoft Excel Spreadsheet (Annexure 4). The quantitative variables will be assessed using mean or standard deviation, and median with inter quartile ranges. The variables at admission will be correlated with the outcome variables using Chi square test.

The clinical severity score, APACHE score will be analysed in relation to the outcome using logistic regression analysis.

All analysis was performed using SAS version 9.4.

8. FUNDING AND APPROVAL

8.1 Funding Source

No funding was required for this study as all the investigations and treatment regimens were decided by the treating physician.

8.2 Institutional Research Board approval and ethical considerations

The research proposal was discussed by the Institutional Review Board in April 2014, and approval was obtained [IRB Min No: 8838 dated 07.04.2014]

There were no ethical issues related to this study.

9. RESULTS

9.1 OVERALL CHARECTERISTICS OF THE STUDY POPULATION

9.1.1 DEMOGRAPHIC CHARACTERISTICS

A total of 135 adult patients more than 16 years of age, with community acquired infections admitted into medical intensive care unit and medical high dependency unit were evaluated. There were 107 patients in the retrospective study and 28 patients in the prospective study. The mean age (+_SD) was 52.85 (16.81) with a range of 16 - 87 years. There was male preponderance (Figure 3). The mean duration of stay in the hospital (+_SD) was 11.21 days (8.07) with a range of 1-58 days. The mean duration of stay in the medical intensive care unit/medical high dependency unit (+_ SD) was 6.07 days (4.16) with a range of 1-28 days.

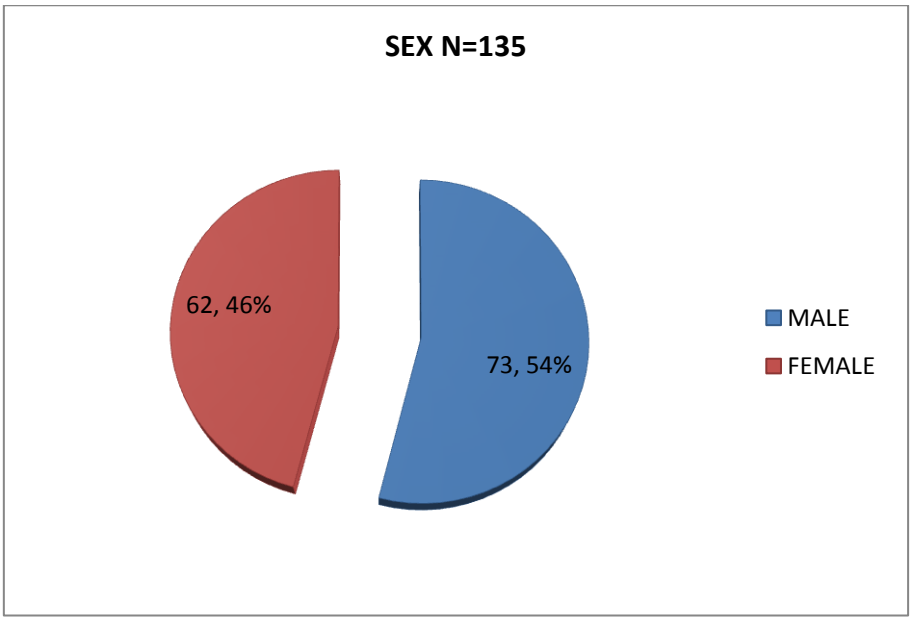

Fig 2.Sex distribution in the study population

9.1.2 PROFILE OF COMORBID ILLNESS

The most common co-morbid illness seen was diabetes in 63 patients (46.67%). Other common comorbid conditions included hypertension, IHD and chronic obstructive airway

disease. 2 out of the 135 subjects were pregnant. The profile of comorbid illness is summarised below in table 3.

Table 3. Profile of co morbid illnesses in the study population

Variable	Number	%
Diabetes Mellitus	63	**46.7**
Hypertension	44	**32.6**
Ischemic Heart Disease	9	**6.7**
Chronic obstructive airway disease	8	**5.9**
Chronic Liver Disease	3	**2.2**
Chronic Kidney Disease	3	**2.2**
Asthma	**2**	**1.5**

9.1.3 SUMMARY OF CLINICAL SYMPTOMS

The most common presenting symptom was fever which was present in all the patients. The median duration of fever prior to presentation was 7 days with minimum of 2 days to maximum of 12 days. 91.1 % reported breathing difficulty at presentation and 59.3 % reported cough at presentation .Altered sensorium was present in 28.2% which included drowsiness, decreased verbalisation or irrelevant speech, inadequate response to call or commands. Ten patients had seizures at presentation, which was of generalised tonic clonic

convulsions semiology requiring anti-epileptic therapy. Neither of these patients had focal neurological deficits.

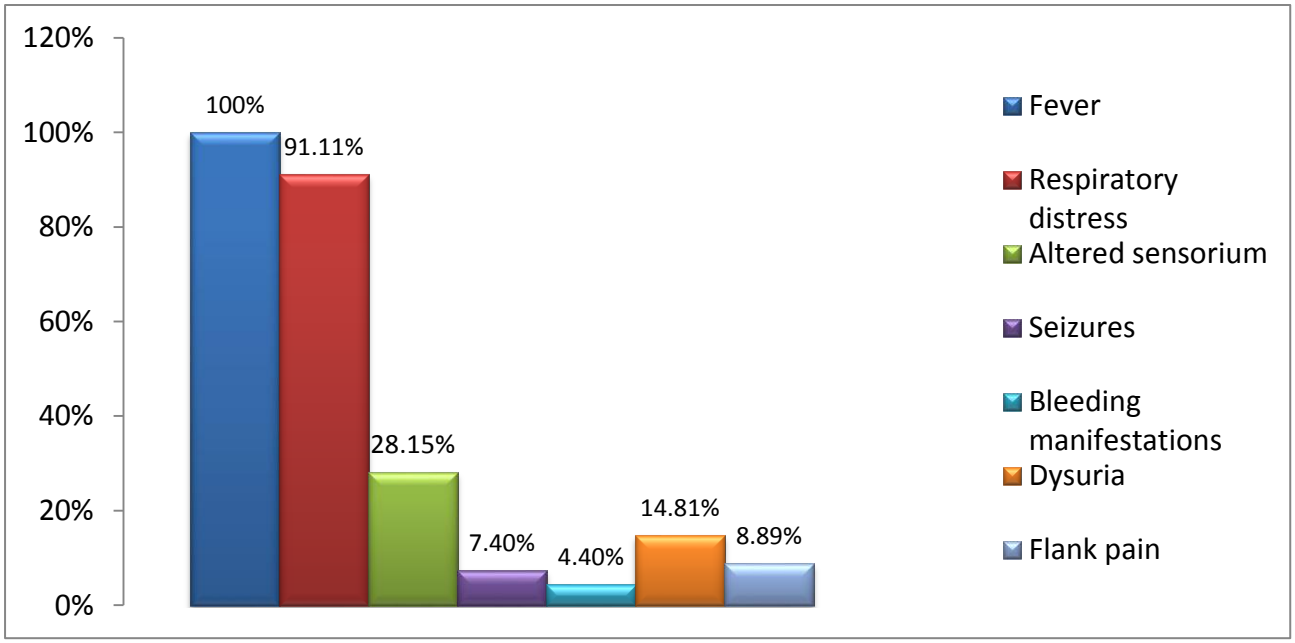

Fig. 3 - Summary of clinical symptoms in the study population at admission

9.1.4 SUMMARY OF CLINICAL SIGNS

Fever was present in all patients (n = 135). 9 patients had features of systemic inflammatory response (6.7%), 15 presented with features of sepsis (11.1%), 93 had septic shock (68.9%), and 18 presented with severe sepsis (13.3%).

Table 4. Summary of clinical signs in the study population at admission

Variable	Mean	SD	Minimum	Maximum
Pulse Rate(/min)	112.6	11.9	82	144
Respiratory rate(/min)	31.41	7.2	20	62
Temperature (deg.F.)	101.460	1.9635	95.7	105
Systolic blood pressure(mm Hg)	92.24	12.43	40	120
Diastolic blood pressure(mm Hg)	58.41	13.53	10	82
Pulse oximeter (%)	91.21	6.4	60	100

9.1.5 SUMMARY OF LABORATORY INVESTIGATIONS IN THE STUDY POPULATION

9.1.5.1 SUMMARY OF HAEMATOLOGICAL PARAMETERS

Severe anaemia (<7g/dl) was noted in 3.7% of the patients, while mild to moderate anemia (7-10g/dl) was seen in 62.9 %, with mean haemoglobin of 11.42 gm/dl. 62.9 % of the patients had thrombocytopenia, which was found to be the most common haematological abnormality. Leucopoenia was seen in 1.5%, while leucocytosis was seen in 54%. 20.8% (n=28) required transfusion of blood products most commonly packed cells. 5 patients required multiple units of fresh frozen plasma and 4 received cryoprecipitate.

Table 5 Summary of haematological parameters in the study population

Variable	Mean	SD	Minimum	Maximum
Haemoglobin(gm/dl	11.42	2.24	6	19
Total leucocyte counts(cu mm)	16490.96	23497.94	900	215000
Platelets(/cu mm)	106007.4	120588.14	3000	795000

9.1.5.2 SUMMARY OF BIOCHEMICAL PARAMETERS

Among the metabolic derangements, liver injury was the most common biochemical abnormality with predominantly transaminitis in SGOT being elevated in 110 patients and SGPT in 72 patients. Acute kidney injury was seen in 66.67% (n = 90), with maximum value noted to 9.4 gm/dl. Hypoalbuminemia was seen in 91.9 % (n=124), a mean of 2.63 g/dl.

The summary of the biochemical parameters is in table..

Table 6. Summary of biochemical parameters in the study population

Variable	Mean	SD	Minimum	Maximum
Creatinine(mg/dl)	2.5	1.77	0.57	9.44
Total Bilirubin(mg/dl)	2.15	1.92	0.2	13
Direct Bilirubin (mg %)	1.52	1.63	0.1	11
Total protein(gm/dl)	6.06	1	1.7	8.2
Albumin(gm/dl)	2.63	0.66	0.5	4.4
SGOT(U/l)	148.44	180.78	11	1416
SGPT(U/l)	63.36	68.35	1	521
Alkaline phosphatase(U/l)	174.69	105.81	33	517

9.1.5.3 SUMMARY OF MICROBIOLOGICAL PARAMETERS

75.6% of the blood culture was sterile and growth was noted in 24.4% of the patients. The most common organism isolated was extended spectrum beta lactamase producing *Escherichia coli (54.5%),* followed by non ESBL *E.coli* (12.1%), *S. Pneumonia (12.1%), and Klebsiella sp* (9.1%).

Urine culture grew organisms in 14.81 % of the patients with the most common organism being extended spectrum beta lactamase producing *Escherichia coli* (11.9%).

Sputum gram stain in 3 patients with community acquired pneumonia grew organisms, which was subsequently isolated in the cultures. The organisms isolated were *Streptococcus pneumonia, methicillin resistant Staphylococcus aureus* and *Pseudomonas aeruginosa*.

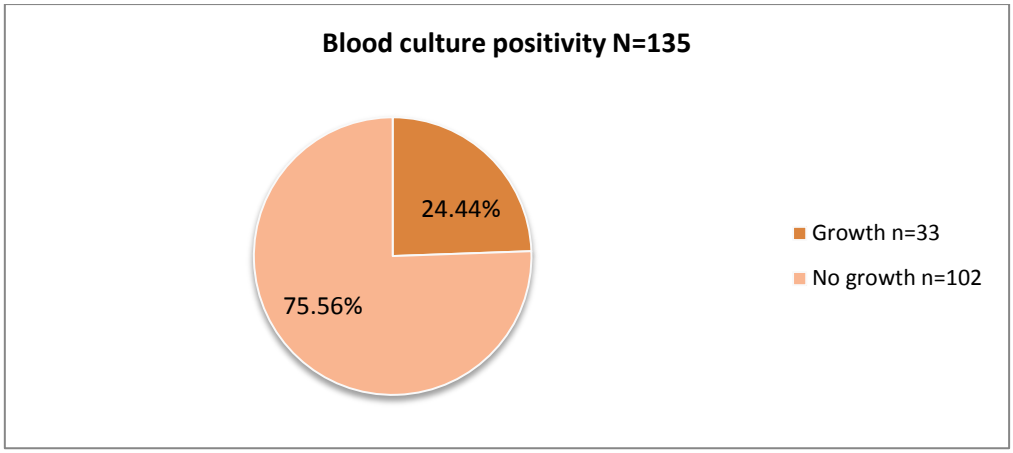

Fig 4.Growth on blood culture in the study population

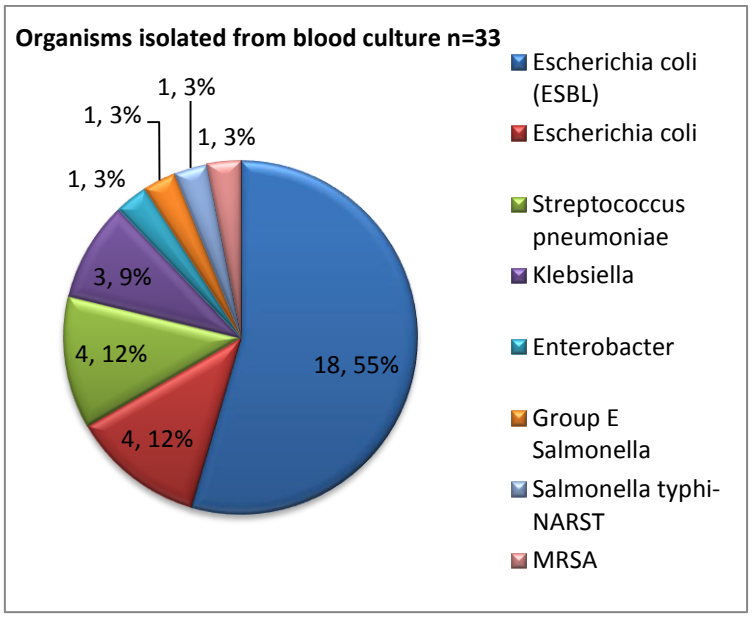

Fig 5.Distribution of organisms isolated in blood culture

9.2 SPECTRUM OF COMMUNITY ACQUIRED INFECTIONS

The most common infection was scrub typhus, and it was seen in 75 out of 135 of the patients. Followed by pyelonephritis which was reported in 20 patients and community acquired pneumonia in 12 patients. 4 out of the 135 had bacteremia where the source of the bacteremia could not be identified and 8 had undifferentiated febrile illness where the

diagnosis could not be ascertained. Other infections included soft tissue infection, Dengue, Viral encephalitis, Malaria, Typhoid, pyogenic meningitis and acute gastroenteritis.

Table 7 Clinical spectrum of community acquired infections

FINAL DIAGNOSIS	RETROSPECTIVE (n=107)	PROSPECTIVE (n=28)	TOTAL N=135	Percent (%)
Scrub typhus	62	13	75	55.6
Pyelonephritis	13	7	20	14.9
Community acquired pneumonia	10	2	12	8.9
Acute febrile illness without cause (AFI)	7	1	8	5.9
Bacteremia without source	4	0	4	2.9
Soft tissue infections	4	0	4	2.9
Dengue	2	1	3	2.2
Viral encephalitis	2	1	3	2.2
Pyogenic meningitis	2	0	2	1.5
Enteric fever	0	2	2	1.5
Malaria	0	1	1	0.7
Acute gastroenteritis	1	0	1	0.7

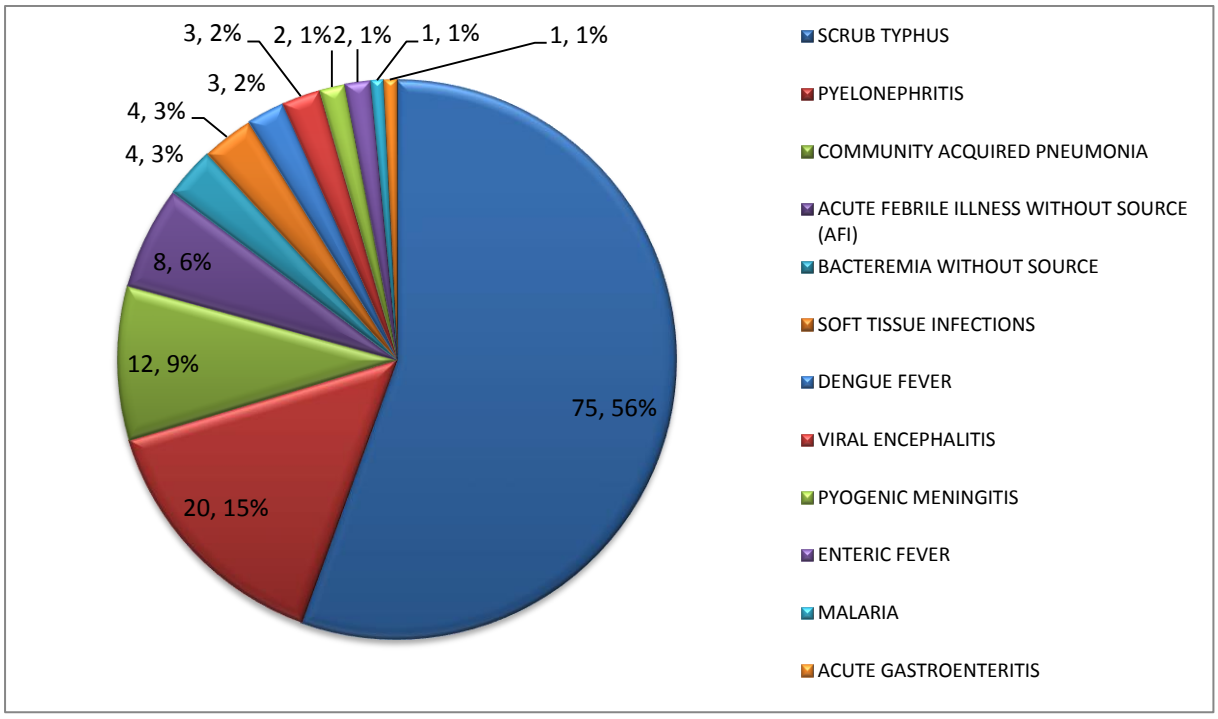

Fig 6. Distribution of clinical spectrum of community acquired infections N=135

9.3 ETIOLOGY/MICROBIOLOGY OF INDIVIDUAL INFECTIONS

9.3.1 PYELONPHRITIS

Out of 20 patients with pyelonephritis, 18 were found to have bacteremia. The most common organism isolated was extended spectrum beta lactamase producing Escherichia coli (83.3%). The others included non ESBL E.coli (11.1%) and Klebsiella (5.5%). In 14 (77.8%) patients extended spectrum beta lactamase producing Escherichia coli was isolated from urine culture.

Table 8 Etiology of pyelonephritis (isolate from blood culture) (n=20)

VARIABLE	BLOOD CULTURE ISOLATE	
Growth on blood culture n=20	18	90%
Escherichia coli (ESBL) n=18	15	83.3%
Escherichia coli n=18	2	11.1%
Klebsiella n=18	1	5.5%
No growth n=20	2	**10%**

Table 9. Etiology of pyelonephritis (isolate from urine culture) (n=20)

VARIABLE	URINE CULTURE ISOLATE	
Growth on urine culture n=20	18	**90%**
Escherichia coli (ESBL) n=18	14	77.8%
Escherichia coli n=18	2	11.1%
Klebsiella n=18	2	11.1%
No growth n=20	2	**10%**

9.3.2 COMMUNITY ACQUIRED PNEUMONIA

4 patients with community acquired pneumonia had bacteremia, with Streptococcus pneumoniae being isolated in 25% of cases. Methicillin resistant staphylococcus aureus was isolated from the blood and sputum in 1 patient.

Table 10. Etiology of community acquired pneumonia (isolates from blood culture) (n=12)

VARIABLE	BLOOD CULTURE ISOLATE	
BLOOD CULTURE POSITIVE	**4**	**33.3%**
Streptococcus pneumoniae	3	75%
Pseudomonas	0	
Methicillin resistant Staphylococcus aureus	1	25%
NO GROWTH	**8**	**66.7%**

Table 11.Etiology of community acquired pneumonia (isolates from sputum culture) (n=12)

VARIABLE	SPUTUM GRAM STAIN AND CULTURE	
SPUTUM CULTURE POSITIVE	**3**	**25%**
Streptococcus pneumoniae	1	8.3%
Pseudomonas	1	8.3%
Methicillin resistant Staphylococcus aureus	1	8.3%
NO GROWTH	**9**	**75%**

9.3.3 BACTEREMIA OF UNKNOWN SOURCE

4 patients had bacteremia with no source of infection identified. Of the 4 patients, 2 had E.coli bacteremia. The other 2 organisms isolated included Klebsiella and Enterobacter.

Table 12. Etiology of bacteremia with unknown source (n=4)

Variable	BLODD CULTURE ISOLATE	
Escherichia coli	2	**50%**
Klebsiella	1	**25%**
Enterobacter	1	**25%**

9.3.4 SKIN AND SOFT TISSUE INFECTION

4 patients had skin and soft tissue infection, and 3 of them had bacteremia.

The organisms isolated included E.coli, Klebsiella and Streptococcus pneumoniae

Table 13. Etiology of skin and soft tissue infections (n=4)

VARIABLE	BLOOD CULTURE ISOLATES n=4	
Escherichia. Coli	1	**25%**
Klebsiella	1	**25%**
streptococcus pneumoniae	1	**25%**
No growth	1	**25%**

9.3.5 ENTERIC FEVER

2 patients were diagnosed to have enteric fever, and the organisms isolated was group E Salmonella in 1 and Nalidixic acid resistant Salmonella typhi in the other

9.3.6 SEROLOGICAL PARAMETERS

Scrub IgM ELISA was sent for 68 patients out of 75 and was positive in all 68 (90.7%).

Dengue infection was identified in 3 patients, and Dengue IgM was positive in 2 patients.

One patient was identified to have malaria and the smear was positive for Plasmodium falciparum.

9.3.7 ACUTE CENTRAL NERVOUS SYSTEM INFECTIONS

5 patients were noted to have acute CNS infection. Of these 3 were diagnosed to have viral encephalitis. CSF multiplex PCR was negative in 2 patients, but they had radiological features consistent with temporal lobe involvement.

2 patients were identified to have pyogenic meningitis. Of which one was diagnosed to have meningococcal meningitis as Latex agglutination of the CSF tested positive for Neisseria meningitidis. In the other patient, no organism was isolated from CSF.

9.4. ADMISSION CORRELATES OF SPECIFIC CLINICAL SYNDROMES

Among the 12 infections identified the 3 most common infections were scrub typhus, pyelonephritis and community acquired pneumonia. Hence the admission correlates of these diagnoses will be presented.

9.4.1 CORRELATION OF SEX WITH SCRUB TYPHUS, PYELONEPHRITIS, AND COMMUNITY ACQUIRED PNEUMONIA

Of the 75 cases of scrub typhus, 56 % were females. 55% of the patients with pyelonephritis were males and 67% of the cases with community acquired pneumonia were males.

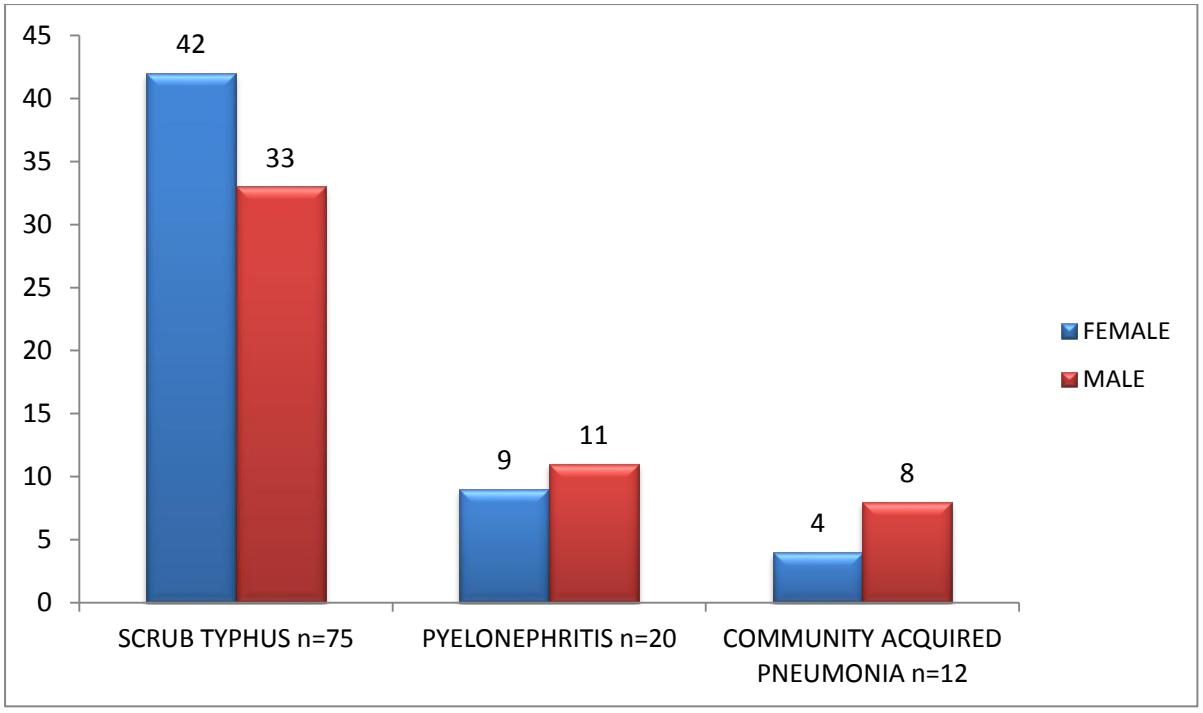

Fig 7. Sex distribution among the patients with scrub typhus, pyelonephritis, and community acquired pneumonia.

9.4.2 CORRELATION OF AGE WITH SCRUB TYPHUS, PYELONEPHRITIS, AND COMMUNITY ACQUIRED PNEUMONIA

Scrub typhus was seen in 52% of patients above the age of 51 years, while 48 % as less than 50 years. Only one patient (5%) with pyelonephritis was less than 50 years. Of the 12 patients with community acquired pneumonia, 9 were more than 51 years of age (75%).

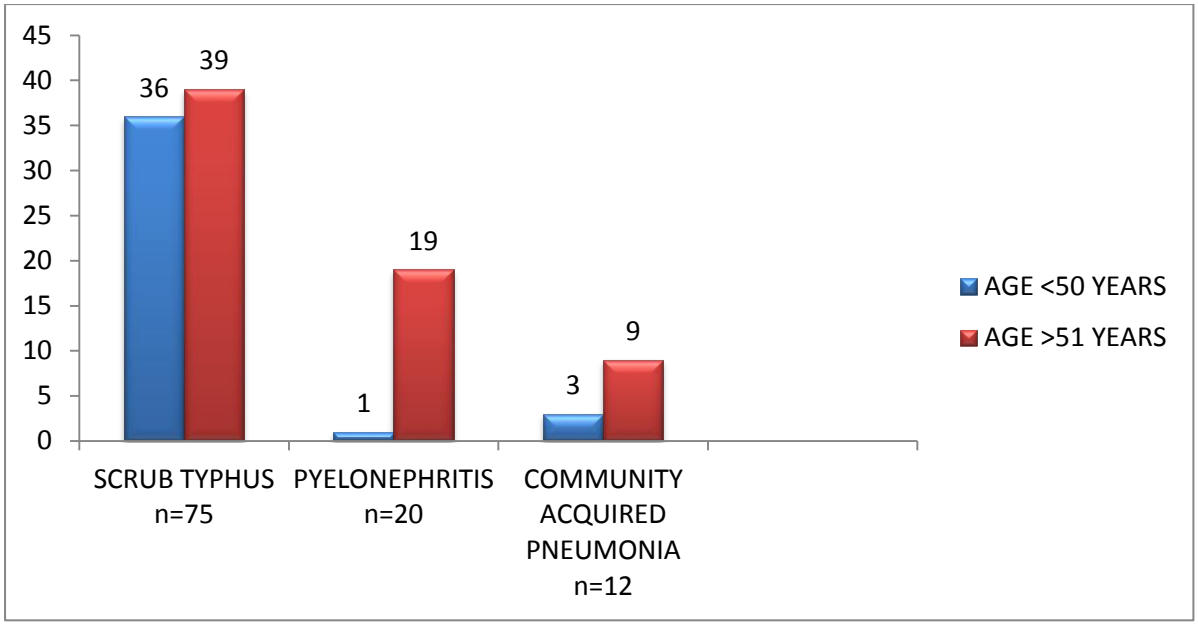

Fig . Distribution of age among the patients with scrub typhus, pyelonephritis, and community acquired pneumonia

9.4.3 CORRELATION OF CO-MORBIDITIES WITH SCRUB TYPHUS, PYELONEPHRITIS, AND COMMUNITY ACQUIRED PNEUMONIA

9.4.3.1 SCRUB TYPHUS

The most common co-morbidity seen was diabetes mellitus (32%), while hypertension was reported in 14.7% of the 75 cases of scrub typhus.

Table 14. Profile of co-morbid conditions in patients with scrub typhus

VARIABLE, n=75	FREQUENCY	PERCENTAGE (%)
Diabetes mellitus	24	32
Hypertension	11	14.7
Chronic obstructive pulmonary disease	1	1.3
Asthma	1	1.3
Ischemic heart disease	2	2.7

9.4.3.2 PYELONEPHRITIS

17 patients diagnosed with pyelonephritis had diabetes mellitus (85%), while only 2 patients (10%) were known to have underlying chronic kidney disease.

Table 15. Profile of co-morbid conditions in patients with pyelonephritis

VARIABLE, n=20	FREQUENCY	PERCENTAGE (%)
Diabetes mellitus	17	85
Hypertension	14	70
Ischemic heart disease	3	15
Chronic liver disease	2	10
chronic kidney disease	2	10
Chronic obstructive pulmonary disease	1	5
HIV	1	5

9.4.3.3 COMMUNITY ACQUIRED PNEUMONIA

Of the 12 patients, 9 patients had Diabetes Mellitus, 4 patients had underlying chronic pulmonary disease, while 1 patient had bronchial asthma.

Table 16. Profile of co-morbid conditions in patients with community acquired pneumonia

VARIABLE	FREQUENCY, n=12	PERCENTAGE (%)
Diabetes mellitus	9	75
Hypertension	7	58.3
Chronic obstructive pulmonary disease	4	33.3
Ischemic heart disease	3	25
Asthma	1	8.3
Smoking	6	50
Alcohol	2	16.7

9.4.4 CORRELATION OF CLINICAL SYMPTOMS WITH SCRUB TYPHUS, PYELONEPHRITIS, AND COMMUNITY ACQUIRED PNEUMONIA

9.4.4.1 SUMMARY OF THE CLINICAL SYMPTOMS IN SCRUB TYPHUS

The commonest symptom was fever which was present in all 75 patients. Of the 75, 96% patients presented with breathlessness requiring respiratory support. 22.7% of the patients presented with altered sensorium and 3 had seizures as well.

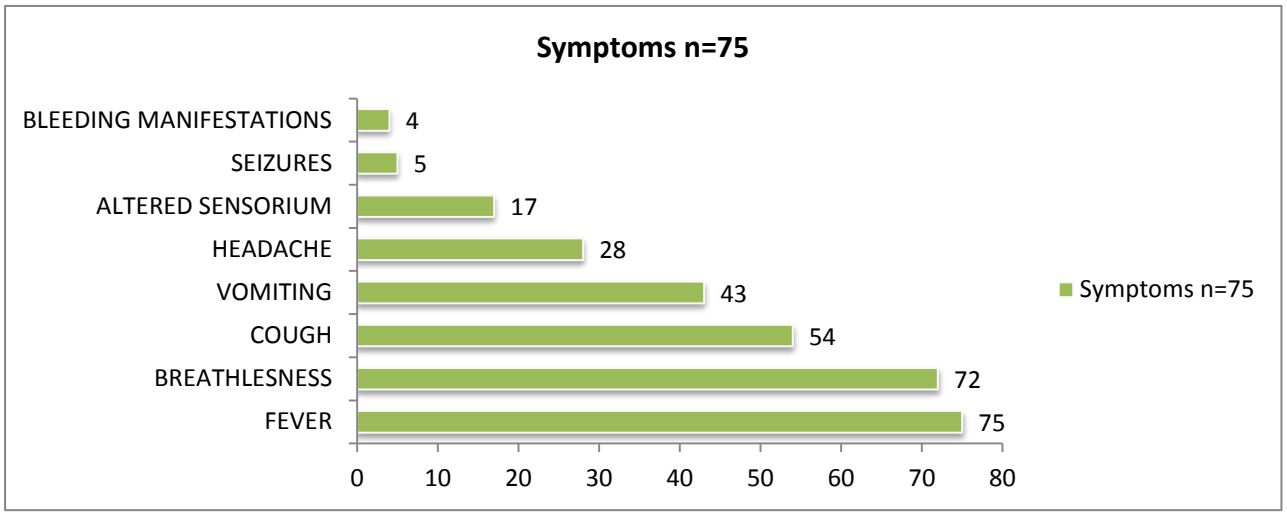

Fig 9 Distribution of clinical symptoms in patients with scrub typhus

9.4.4.2 SUMMARY OF CLINICAL SYMPTOMS IN PATIENTS WITH PYELONEPHRITIS

The most common symptom was fever, which was seen in all 20 patients and dysuria was seen in all 20 cases, but flank pain was reported only in 60%. Additionally 30% of the patients had altered sensorium

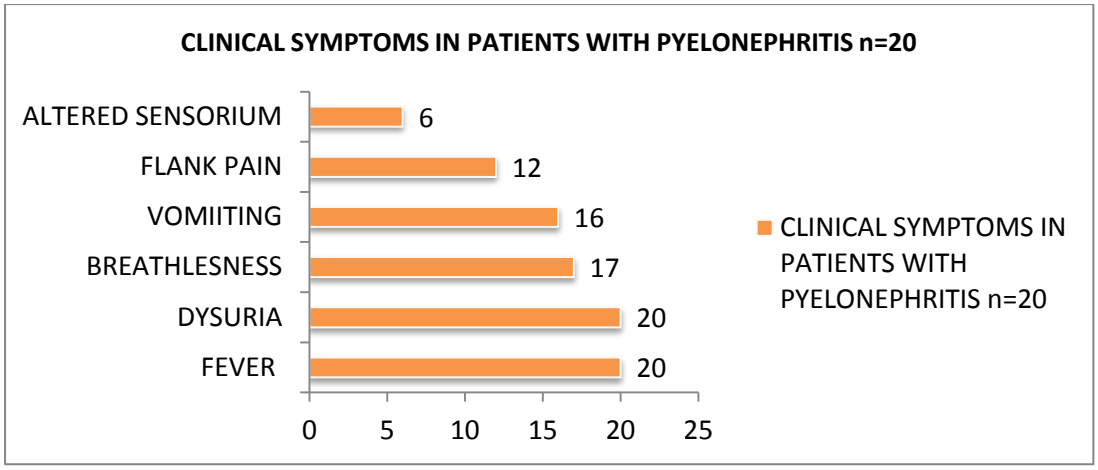

Fig 10. Distribution of clinical symptoms in patients with pyelonephritis

9.4.4.3 SUMMARY OF CLINICAL SYMPTOMS IN PATIENTS WITH COMMUNITY ACQUIRED PNEUMONIA

All 12 patients with community acquired pneumonia had fever with cough and productive cough. All 12 presented with breathing difficulty as well.

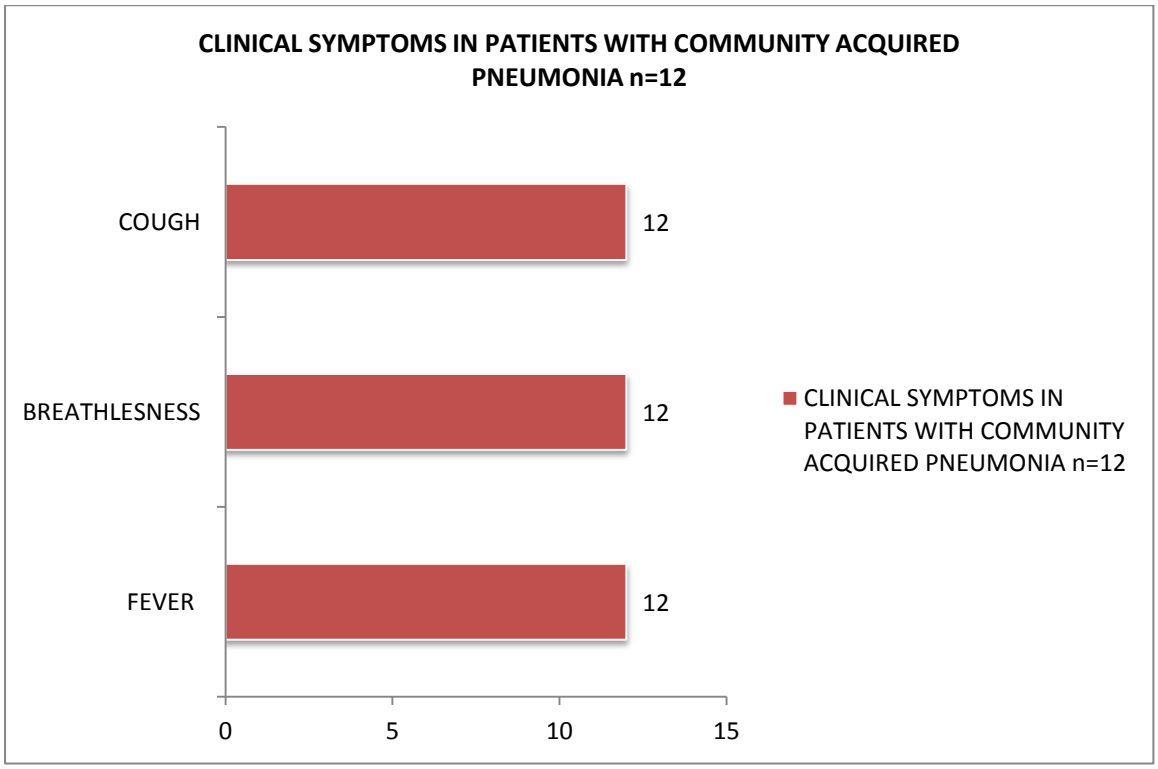

Fig 11. Distribution of clinical symptoms in patients with community acquired pneumonia

9.4.5 CORRELATION OF CLINICAL SIGNS WITH SCRUB TYPHUS, PYELONEPHRITIS, AND COMMUNITY ACQUIRED PNEUMONIA

9.4.5.1 SUMMARY OF THE CLINICAL SIGNS IN SCRUB TYPHUS

62 patients (83%) with scrub typhus had heart rate more than 101 beats per minute, ranging between 102 to 144 beats per minute.39 patients had systolic blood pressure more than 90 mmHg, ranging between 92 mmHg and 110 mmHg. 36 patients had systolic blood pressure less than 90 mmHg, with the lowest recorded systolic blood pressure of 60 mmHg. 31 patients had diastolic blood pressure less than 40 mmHg.

68 patients had tachypnea with maximum respiratory rate of 62 beats per minute. 26 patients had saturation less than 90 %. 62 out of 75 patients were noted to have eschar.

Table 17. Summary of clinical signs in patients with scrub typhus

VARIABLE	FREQUENCY	PERCENTAGE
Heart rate <100 bpm	36	48
Heart rate >101 bpm	39	52
Respiratory rate <24 bpm	31	41
Respiratory rate >25 bpm	44	59%
SBP < 90 mmHg	36	48%
SBP > 91 mmHg	39	52%
DBP < 60 mmHg	31	41%
DBP > 61 mmHg	44	59%
SaO2 < 90 mmHg	26	35%
SaO2 > 91 mmHg	49	65%

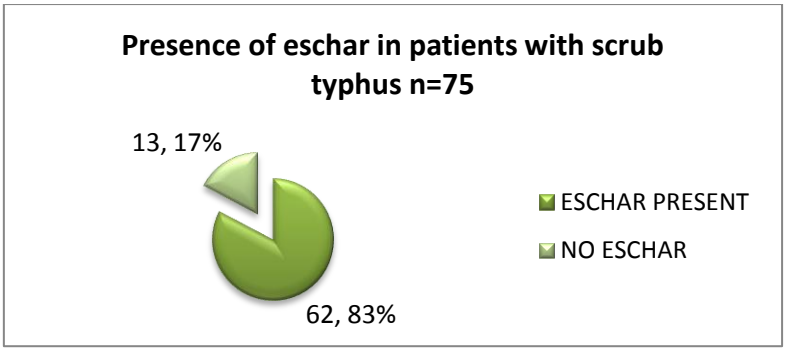

Fig 12 Distribution of eschar in patients with scrub typhus

9.4.5.2 SUMMARY OF THE CLINICAL SIGNS IN PYELONEPHRITIS

15 patients with pyelonephritis had heart rate more than 101 beats per minute, with maximum heart rate of 128 beats per minute. 10 patients had systolic blood pressure less than 90 mmHg and 15 patients had diastolic blood pressure less than 40 mmHg.

Table 18.Summary of clinical signs in patients with pyelonephritis

VARIABLE	FREQUENCY	PERCENTAGE
Heart rate <100 bpm	10	50%
Heart rate >101 bpm	10	50%
Respiratory rate <24 bpm	5	25%
Respiratory rate >25 bpm	15	75%
SBP < 90 mmHg	10	50%
SBP > 91 mmHg	10	50%
DBP < 60 mmHg	5	25%
DBP > 61 mmHg	15	75%
SaO2 < 90 mmHg	26	35%
SaO2 > 91 mmHg	49	65%

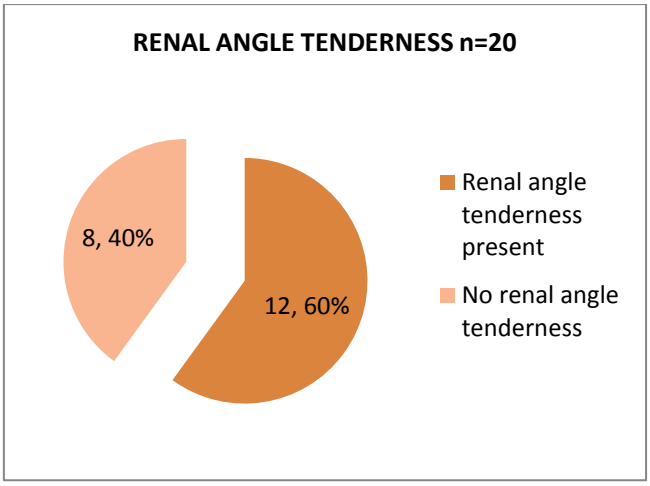

Fig 13 Distribution of presence of renal angle tenderness in patients with pyelonephritis

9.4.5.3 SUMMARY OF THE CLINICAL SIGNS IN COMMUNITY ACQUIRED PNEUMONIA

11 patients with CAP had heart rate more than 101 beats per minute, with maximum heart rate of 124 beats per minute. 10 patients had systolic blood pressure less than 90 mmHg and 25 patients had diastolic blood pressure less than 40 mmHg. All 12 had tachypnea with respiratory rate of more than 24 beats per minute.8 patients had saturation less than 90 %.

Table 19. Summary of clinical signs in patients with community acquired pneumonia

VARIABLE	FREQUENCY	PERCENTAGE
Heart rate <100 bpm	8	67%
Heart rate >101 bpm	4	33%
Respiratory rate <24 bpm	2	17%
Respiratory rate >25 bpm	10	83%
SBP < 90 mmHg	8	67%
SBP > 91 mmHg	4	33%

DBP < 60 mmHg	2	17%
DBP > 61 mmHg	10	83%
SaO2 < 90 mmHg	8	67%
SaO2 > 91 mmHg	4	33%

9.4.6 CORRELATION OF LABORATORY ABNORMALITIES WITH SCRUB TYPHUS, PYELONEPHRITIS, AND COMMUNITY ACQUIRED PNEUMONIA

9.4.6. 1 HEMATOLOGICAL ABNORMALITIES IN SCRUB TYPHUS

Leucocytosis was seen in 44 % of the patients with scrub typhus. 64 patients had thrombocytopenia, of these 17 patients had severe thrombocytopenia with platelet counts less than 20,000 cells/mm3.

Table 20.Summary of hematological abnormalities in patients with scrub typhus,

VARIABLE	FREQUENCY	PERCENTAGE
< 4000 cell/mm3	1	**1.3%**
4001- 11,000 cells/mm3	41	**54.7%**
>11,001 cells/mm3	33	**44%**
< 7g/dl		**2.7%**
7.1-12g/dl	47	**62.7%**
>12.1 g/dl	26	**34.7%**
<50,000 MM3	43	**57.3%**
50,001-100,000 MM3	21	**28%**
>100,001 MM3	11	**14.7%**

9.4.6.2 HEMATOLOGICAL ABNORMALITIES IN PYELONEPHRITIS

85% of patients with pyelonephritis had WBC counts more than 11,000 cells/mm3, and thrombocytopenia was seen in 45 % of the patients.

Table 21.Summary of hematological abnormalities in patients with pyelonephritis

VARIABLE	FREQUENCY	PERCENTAGE
< 4000 cell/mm3	0	
4001- 11,000 cells/mm3	3	**15%**
>11,001 cells/mm3	17	**85%**
< 7g/dl	1	**5%**
7.1-12g/dl	16	**80%**
>12.1 g/dl	3	**15**
<50,000 MM3	2	**10%**
50,001-100,000 MM3	7	**35%**
>100,001 MM3	11	**55%**

9.4.6.3 HEMATOLOGICAL ABNORMALITIES IN COMMUNITY ACQUIRED PNEUMONIA

9 patients with community acquired pneumonia had WBC count more than 11,001 cells/mm3. The platelet counts were more than 100,000 cells/mm3 in all patients.

Table 22.Summary of hematological abnormalities in patients with community acquired pneumonia

VARIABLE	FREQUENCY	PERCENTAGE
< 4000 cell/mm3	0	
4001- 11,000 cells/mm3	3	**25%**
>11,001 cells/mm3	9	**75%**
< 7g/dl	0	
7.1-12g/dl	7	**58.3%**
>12.1 g/dl	5	**41.7%**
<50,000 MM3	1	8.3%
50,001-100,000 MM3	0	
>100,001 MM3	11	**91.7%**

9.4.6.4 BIOCHEMICAL ABNORMALITIES IN SCRUB TYPHUS

44 patients had acute kidney injury with maximum creatinine value of 9.44 mg/dl. Liver enzymes were deranged, with 73 patients had elevated SGOT, ranging between 41 IU to 512 IU and 53 patients had elevated SGPT, with the maximum value of 200 IU.

Table 23. Summary of biochemical abnormalities in patients with scrub typhus

VARIABLE	FREQUENCY	PERCENTAGE
<1.4 g/dl	31	**41.3%**
>1.5 g/dl	44	**58.7%**
SGOT <40 IU	2	**2.7%**
SGOT >41IU	73	**97.3%**
SGPT <40 IU	22	**29.3%**
SGPT >40 IU	53	**70.7%**

9.4.6.5 BIOCHEMICAL ABNORMALITIES IN PYELONEPHRITIS

All patients with pyelonephritis had acute kidney injury with 80 % had creatinine more than 2.1 g/dl.

Table 24 summary of biochemical abnormalities in patients with community acquired pneumonia

VARIABLE	FREQUENCY	PERCENTAGE
<1.4 g/dl	0	
>1.5 g/dl	20	**100%**
SGOT <40 IU	10	**50%**
SGOT >41IU	10	**50%**
SGPT <40 IU	15	**75%**
SGPT >40 IU	5	**25%**

9.4.6.6 BIOCHEMICAL ABNORMALITIES IN COMMUNITY ACQUIRED PNEUMONIA

Serum creatinine was elevated in 8 patients. The liver enzymes, SGOT and SGPT were elevated in 5 and 2 patients respectively.

Table 25. Summary of biochemical abnormalities in patients with community acquired pneumonia

VARIABLE	FREQUENCY	PERCENTAGE
<1.4 g/dl	4	33.3%
>1.5 g/dl	8	**66.7%**
SGOT <40 IU	7	**58.3%**
SGOT >41IU	5	**41.7%**
SGPT <40 IU	10	**83.3%**
SGPT >40 IU	2	**16.7%**

9.4.7 APACHE II SCORE IN PATIENTS WITH COMMUNITY ACQUIRED INFECTIONS

16 patients with scrub typhus had APACHE II score more than 11, of which 5 patients had score more than 26 and the maximum score was 35.

1 patient with pyelonephritis had APACHE II score more than 35, while 7 had scores between 26- 34. The maximum noted score was 41.

7 patients with community acquired pneumonia had score between 11- 25, while 1 had score of 27 which was the maximum noted APACHE II score in this study population.

Table 26. Summary of APCHE II SCORE in patients with scrub typhus, pyelonephritis and community acquired pneumonia

VARIABLE	APACHE II SCORE < 10		APACHE II SCORE 11-25		APACHE II SCORE 26- 34		APACHE II SCORE > 35		MISSING DATA	
	FREQUENCY	PERCENT	FREQUENCY	PERCENT	FREQUENCY	PERCENT	FREQUENCY	PERCENT	FREQUENCY	PERCENT
SCRUB TYPHUS n=75	8	**11%**	55	**73%**	5	**7%**	0		7	**9%**
PYELONEPHRITIS n=20	1	**5%**	10	**53%**	7	**37%**	1	**5%**	1	**5%**
COMMUNITY ACQUIRED PNEUMONIA n=12	0		7	**59**	1	**8%**			4	**33%**

9.4.8 ORGAN SYSTEM FAILURE IN SCRUB TYPHUS, PYELONEPHRITIS, COMMUNITY ACQUIRED PNEUMONIA

9.4.8.1 SUMMARY OF ORGAN SYSTEM FAILURE IN SCRUB TYPHUS

Acute respiratory distress syndrome was seen in 70 patients, while renal failure was seen in 64 patients. Shock requiring inotropes was seen in 64 patients.

Table 27. Summary of organ system failure in patients with scrub typhus

VARIABLE	FREQUENCY n=75	PERCENTAGE
ACUTE RESPIRATORY DISTRESS SYNDROME	70	93.3
SEPTIC SHOCK	64	85.3
ACUTE KIDNEY INJURY	45	60

9.4.8.2. SUMMARY OF ORGAN SYSTEM FAILURE IN PYELONEPHRITIS

All 20 patients had acute kidney injury and septic shock, while 18 patients had acute respiratory distress syndrome

Table 28. Summary of organ system failure in patients with Pyelonephritis

VARIABLE	FREQUENCY n=20	PERCENTAGE %
ACUTE RESPIRATORY DISTRESS SYNDROME	18	90
SEPTIC SHOCK	20	100
ACUTE KIDNEY INJURY	20	100

9.4.8.3 SUMMARY OF ORGAN SYSTEM FAILURE IN COMMUNITY ACQUIRED PNEUMONIA

All 12 patients had acute respiratory distress syndrome and septic shock. 8 patients out of 12 had acute kidney injury.

Table 29. Summary of organ system failure in patients with Community acquired pneumonia

VARIABLE	FREQUENCY n=12	PERCENTAGE
ACUTE RESPIRATORY DISTRESS SYNDROME	12	100
SEPTIC SHOCK	12	100
ACUTE KIDNEY INJURY	8	66.7

9.5 CHOICE OF ANTIBIOTICS FOR INDIVIDUAL COMMUNITY ACQUIRED INFECTIONS

Doxycyline was the antibiotic of choice in 72 patients with scrub typhus, and 63 patients received azithromycin in addition. Azithromycin alone was given in 3 patients, of which one patient was a pregnant lady.

In patients with pyelonephritis, meropenem was used in 16 patients, while ertapenem was administered to 1 patient. 2 patients received Pipericillin- tazobactum, in addition to meropenem and in one patient Pipericillin tazobactum alone was used.

The choice of antibiotics varied in patients with community acquired pneumonia. 3 patients received combination of azithromycin and Pipericillin tazobactum, 2 received Pipericillin tazobactum and meropenem, 1 patient received Pipericillin-tazobactum and 2 patients were treated with meropenem alone. One patient who had MRSA was given Vancomycin, however the first choice of antibiotic prior to availability of the culture reports was Pipericillin-tazobactum and azithromycin.

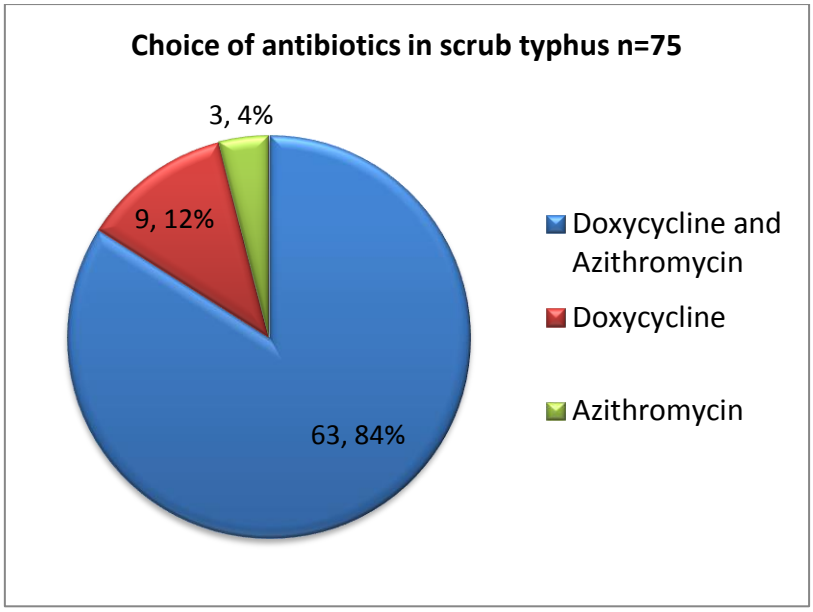

Fig 14. Distribution of choice of antibiotics in patients with scrub typhus

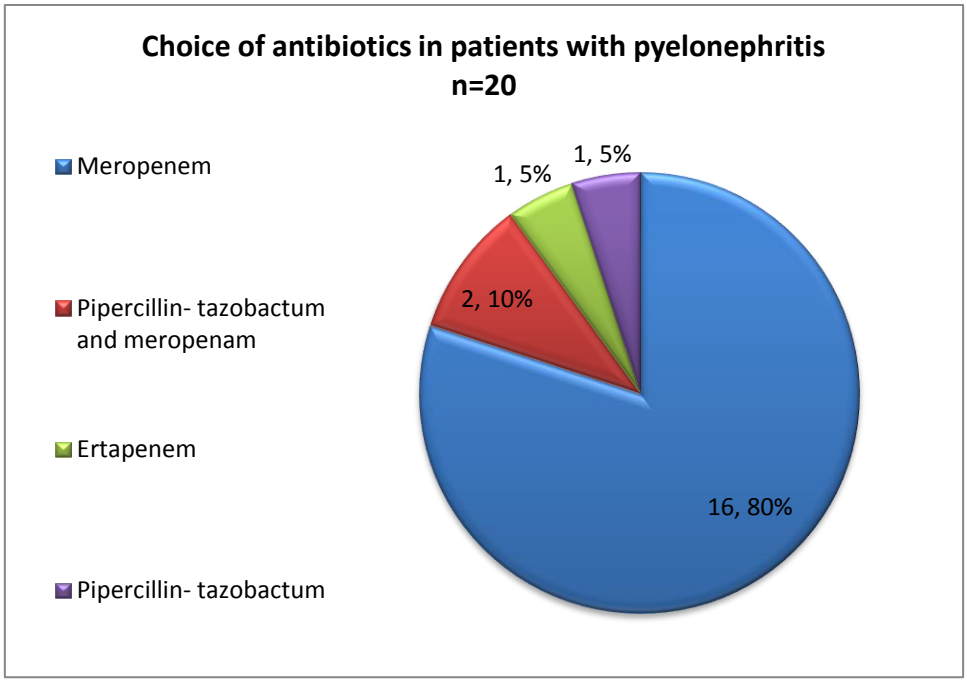

Fig 15. Distribution of choice of antibiotics in patients with pyelonephritis

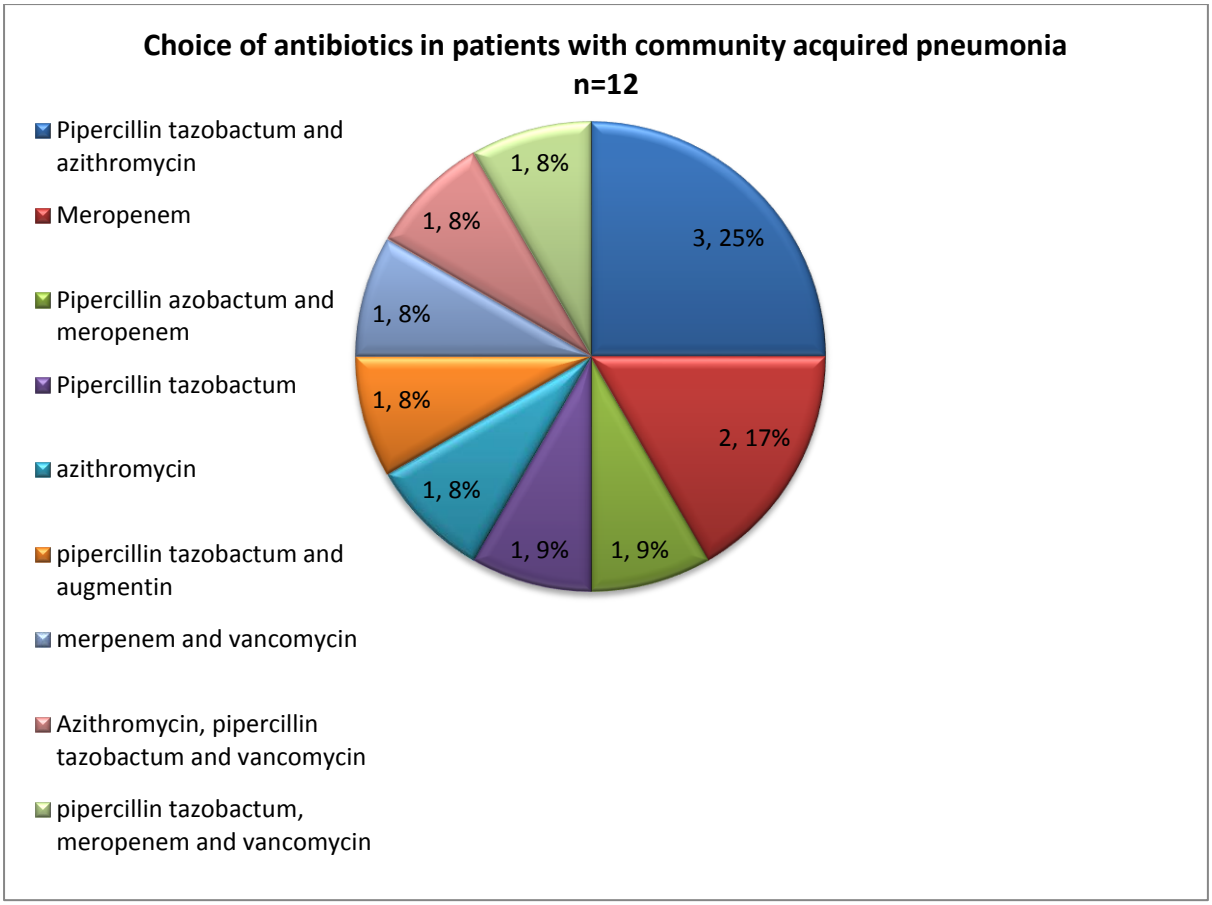

Fig 16. Distribution of choice of antibiotics in patients with community acquired pneumonia

9.6 ORGAN SYSTEM SUPPORT REQUIRED FOR PATIENTS WITH SCRUB TYPHUS, PYELONEPHRITIS, COMMUNITY ACQUIRED PNEUMONIA

9.6.1 REQUIREMENT OF VENTILATORY SUPPORTS IN PATIENTS WITH SCRUB TYPHUS, PYELONEPHRITIS, COMMUNITY ACQUIRED PNEUMONIA

94.7% of patients with scrub typhus required ventilatory support with 55 patients requiring invasive ventilation. The duration of ventilatory support requirement ranged from 1 day to 23 days.

All 20 patients with pyelonephritis had respiratory distress syndrome and 80% of them required invasive ventilation. The duration of ventilatory support requirement ranged from 1 day to 21 days.

83.3 % of the patients with community acquired pneumonia required invasive ventilation, while 16.7% was managed with non-invasive ventilation. The maximum duration was 14 days.

9.6.2 REQUIREMENT OF DIALYSIS IN PATIENTS WITH SCRUB TYPHUS, PYELONEPHRITIS, COMMUNITY ACQUIRED PNEUMONIA

6 patients with scrub typhus required renal replacement therapy with haemodialysis.

50% of patients with acute pyelonephritis required haemodialysis.

In the cohort with the diagnosis of community acquired pneumonia, only 2 out 8 with acute kidney injury required haemodialysis.

9.6.3 REQUIREMENT OF INOTROPES IN PATIENTS WITH SCRUB TYPHUS, PYELONEPHRITIS, COMMUNITY ACQUIRED PNEUMONIA

88.9 % of patients in the study required use of inotropes or vasoactive agents due to septic shock. The most common inotrope used was dopamine, noradrenaline and adrenaline. In patients with scrub typhus, 85.3% of them required inotropes, while all patients among those with pyelonephritis and community acquired pneumonia required inotropic support.

9.7 NOSOCOMIAL COMPLICATIONS IN COMMUNITY ACQUIRED INFECTIONS

Of the 135 patients, 40 patients developed nosocomial complications, of which 23 patients had ventilator associated pneumonia (VAP), 6 had line related catheter associated blood stream infection (CRBSI-L) and 6 had urinary catheter associated catheter related blood stream infection (CRBSI-U).

21 patients with scrub typhus developed nosocomial complications of which 12 had VAP, 4 had CRBSI-U, 2 had CRBSI-L and 1 patient had both VAP and CRBSI-L.

Among those with community acquired pneumonia, 5 developed nosocomial complications, of which 3 had VAP, and 1 had CRBSI-U.

6 out of 20 patients with pyelonephritis developed nosocomial complications.

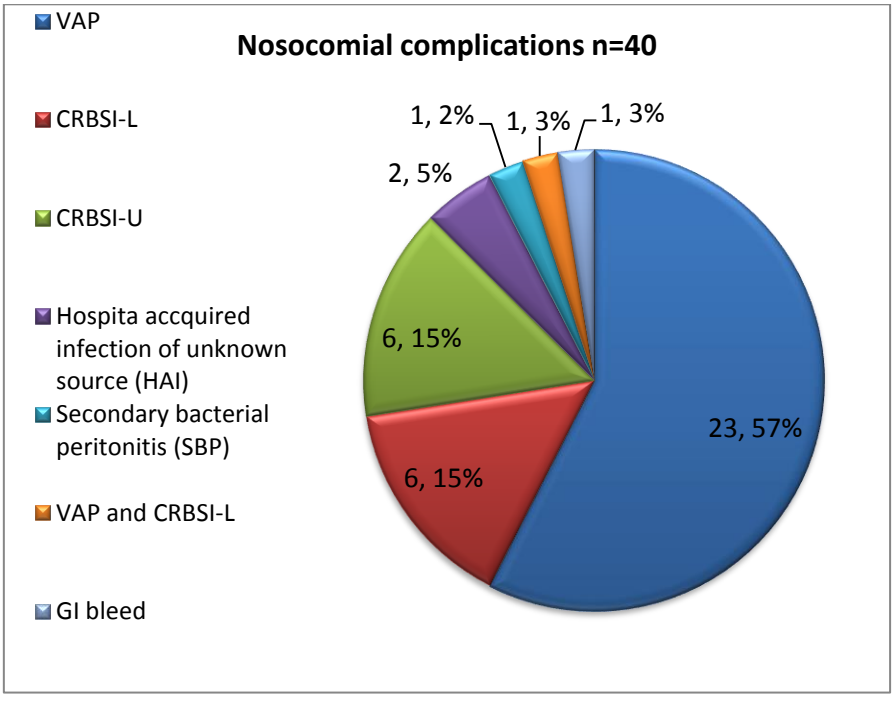

Fig17.Distribution of nosocomial complications in the study population

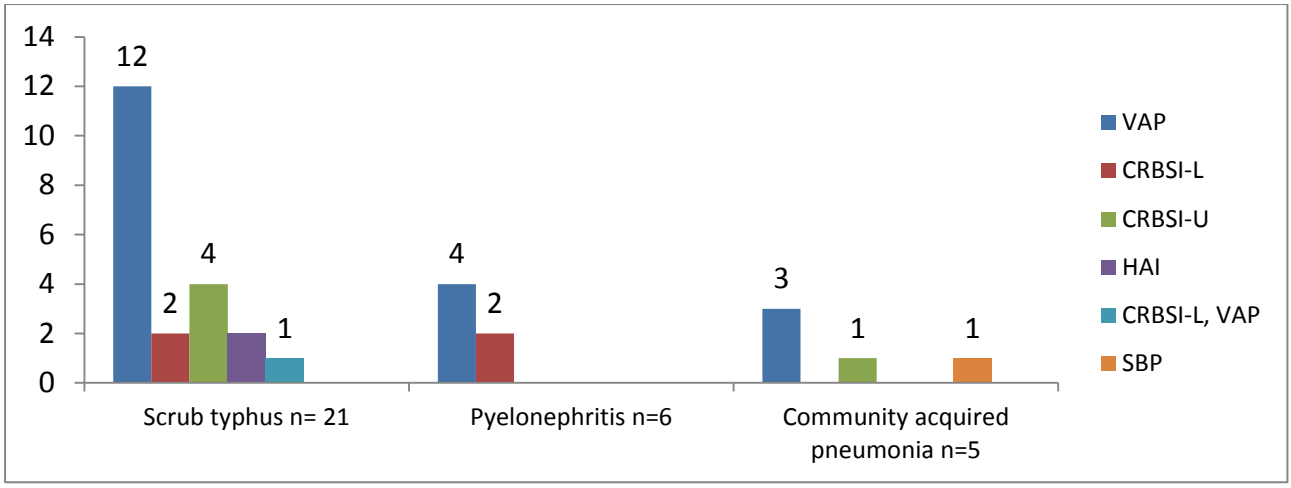

Fig 18 Distribution of nosocomial infections in patients with scrub typhus, pyelonephritis, and community acquired pneumonia, n= 32

9.8 MORTALITY RATES IN COMMUNITY ACQUIRED INFECTIONS

Of the 135 subjects in the study, 35 patients expired. The overall mortality rate was 25.9%. The infection specific mortality rates were 13.3% in scrub typhus, followed by pyelonephritis (40%) and CAP (41.7%). Early death (within 7 days of hospital admission) occurred in 6 patients with scrub typhus, 1 patient with pyelonephritis and 3 patients with community acquired pneumonia. In scrub typhus, 7 out of the 10 who died were over the age of 50 years.

Table 30 Infection specific mortality rates of scrub typhus, pyelonephritis, community acquired pneumonia

VARIABLE	FREQUENCY	INFECTION SPECIFIC MORTALITY RATE
Scru typhus, n=75	**10**	**13.3%**
Pyelonephritis, n=20	**8**	**40%**
Community acquired pneumonia, n=12	**5**	**41.7%**

9.9 DURATION OF HOSPITALISATION

The median duration of stay in the hospital for patients with scrub typhus was 9 days with a range of 1 to 31 days, for patients with pyelonephritis was 10 days with a range of 3 to 58 days, and for patients with community acquired pneumonia was 10.5 days with a range of 2 to 40 days. The median duration of stay in the MICU/MHDU was, 5 days for scrub typhus, 7 days for pyelonephritis and 5.5 days for community acquired pneumonia.

9.10 CORRELATION OF CLINICAL AND LABORATORY PARAMETERS IN PREDICTING THE DIAGNOSIS

The three most common infections identified in the study population were scrub typhus, pyelonephritis and community acquired pneumonia.

9.10.1 SCRUB TYPHUS

Presence of fever and eschar was seen in 83%. These parameters predicted the diagnosis of scrub typhus. The sensitivity of eschar for diagnosis of Scrub typhus in the ICU setting was 0.84 and specificity was 1.

Table 31. Eschar in scrub typhus

	Eschar present	Eschar absent	
Scrub typhus	63	12	75
No scrub typhus	0	60	60
TOTAL	63	72	135

44% of patients with Scrub typhus had leucocytosis (WBC count>11,000 cell/mm3). The sensitivity and specificity of leucocytosis for diagnosis of scrub typhus were 0.44 and 0.317 respectively.

Table 32.Leucocytosis in scrub typhus

	Leucocytosis	**No leucocytosis**	
Scrub typhus	33	42	75
No scrub typhus	41	19	60
	74	61	135

Thrombocytopenia (platelet count <100,000 cells/mm3) was present in 85.3% of patients with Scrub typhus. The sensitivity and specificity of thrombocytopenia for diagnosis of scrub typhus were 0.85 and 0.65 respectively.

Table 33. Thrombocytopenia in scrub typhus

	Thrombocytopenia	**Normal platelets**	
Scrub typhus	64	11	75
No scrub typhus	21	39	60
	85	50	135

Liver enzyme, SGOT was elevated in 97.3% of patients with scrub typhus. The sensitivity and specificity of thrombocytopenia for diagnosis of scrub typhus were 0.97 and 0.38 respectively.

Table 34. Elevated liver enzyme (SGOT) in scrub typhus

	Elevated SGOT >41IU	Normal SGOT <40IU	
Scrub typhus	73	2	75
No scrub typhus	37	23	60
	110	25	135

Liver enzyme, SGPT was elevated in 70.6% of scrub typhus. The sensitivity and specificity of thrombocytopenia for diagnosis of scrub typhus were 0.7 and 0.68 respectively.

Table 35. Elevated liver enzyme (SGPT) in scrub typhus

	Elevated SGPT >41IU	Normal SGPT <40IU	
Scrub typhus	53	22	75
No scrub typhus	19	41	60
	72	63	135

The clinical signs and laboratory tests with the highest sensitivity for diagnosis of scrub typhus were Eschar (0.84), thrombocytopenia (0.85) and elevated SGOT (0.97). The clinical signs with highest specificity for diagnosis of scrub typhus were Eschar (1), thrombocytopenia (0.65) and elevated SGOT (0.68).

9.10.2 PYELONEPHRITIS

The sensitivity and specificity of dysuria for diagnosis of pyelonephritis in ICU was 1 and 1.

Table 36. Dysuria in pyelonephritis

	Dysuria	**No dysuria**	
Pyelonephritis	20	0	20
No pyelonephritis	0	115	115
	20	115	135

The sensitivity and specificity of renal angle tenderness for diagnosis of pyelonephritis in ICU was 0.6 and 1.

Table 37. Renal angle tenderness in pyelonephritis

	Renal angle tenderness +	**No renal angle tenderness**	
Pyelonephritis	12	8	20
No pyelonephritis	0	115	115
	12	123	135

Dysuria had a sensitivity for 1 for diagnosis of pyelonephritis and dysuria and renal angle tenderness had specificity of 1 for diagnosis of pyelonephritis.

9.10.3 COMMUNITY ACQUIRED PNEUMONIA

The sensitivity and specificity of cough for diagnosis of community acquired pneumonia in ICU was 1 and 0.45.

Table 38. Cough in Community acquired pneumonia

	COUGH +	NO COUGH	
CAP	12	0	12
No CAP	68	55	123
	80	55	135

The sensitivity and specificity of breathlessness for diagnosis of community acquired pneumonia in ICU were 1 and 0.09 respectively.

Table 39. Breathlessness in community acquired pneumonia

	breathlessness +	No breathlessness	
CAP	12	0	12
No CAP	111	12	123
	123	12	135

The sensitivity and specificity of chest x-ray findings for diagnosis of community acquired pneumonia in ICU were 0.67 and 1 respectively.

Table 40. Patch on Chest X ray in community acquired pneumonia

	Patch on chest xray +	No patch on chest xray	
CAP	8	4	12
No CAP	0	123	123
	8	127	135

The sensitivity of cough and chest x-ray findings for diagnosis of community acquired pneumonia in the ICU was 1 and 0.67 and specificity of chest x-ray for diagnosis of community acquired pneumonia was 1.

9.11 PREDICTORS OF MORTALITY

The age of diagnosis was not statistically significant in neither of the 3 infections.

Table 41 Age and scrub typhus

	ALIVE	DEATH	
AGE ≤50 YEARS	33	3	36
AGE >50 YEARS	32	7	39
	65	10	75

Table 42. age and pyelonephritis

	ALIVE	DEATH	
AGE ≤50 YEARS	1	0	1
AGE >50 YEARS	11	8	19
	12	8	20

Table 43 Age and Community acquired pneumonia

	ALIVE	DEATH	
AGE ≤50 YEARS	3	1	4
AGE >50 YEARS	4	4	8
	7	5	12

In patients with pyelonephritis, 17 patients had diabetes mellitus. The presence of diabetes mellitus as a co-morbidity was compared with the outcome of death in this sub group and this was found to be statistically significant. But presence of underlying chronic kidney disease (CKD) was not found to be significant.

Table 44. Diabetes and pyelonephritis

	DIABETES +	NO DIABETES	
PYELONEPHRITIS	17	3	20
NO PYELONEPHRTIS	46	69	115
	63	72	135

Table 45. Chronic kidney disease and pyelonephritis

	CKD +	NO CKD	
PYELONEPHRITIS	2	18	20
NO PYELONEPHRTIS	1	114	115
	3	132	135

In those with community acquired pneumonia, presence of underlying respiratory illness such as chronic obstructive pulmonary disease (COPD) and asthma was not found to be statistically significant with the outcome of death.

In patients with scrub typhus, 29% of patients with shock requiring inotropes died compared to 2.3% of patients who did not have shock and this difference was statistically significant (p-value 0.001) with mortality. The difference in mortality rate between patients with acute

kidney injury (AKI), and acute respiratory distress syndrome (ARDS) and those without were not significantly different.

Table 46. Shock and scrub typhus

	ALIVE	DEATH	
NO SHOCK	43	1	44
SHOCK REQURING INOTROPES	22	9	31
	65	10	75

There was no statistically significant correlation found with organ dysfunction and mortality in those with pyelonephritis

Table 47 Shock and pyelonephritis

	ALIVE	DEATH	
NO SHOCK	0	0	0
SHOCK REQURING INOTROPES	12	8	20
	12	8	20

Table 48 Acute kidney injury and pyelonephritis

	ALIVE	DEATH	
AKI present	0		0
AKI absent	12	8	20
	12	8	20

Table 49 Shock and community acquired pneumonia

	ALIVE	DEATH	
NO SHOCK	0	0	44
SHOCK REQURING INOTROPES	7	5	12
	7	5	12

Table 50. Acute respiratory distress syndrome and community acquired pneumonia

	ALIVE	DEATH	
ARDS present	7	5	12
ARDS absent	0	0	0
	7	5	12

APACHE II score of > 26 was associated with mortality of 60% in scrub typhus compared to 10.9% with APACHE II score of 11-25 and 12.5% with APACHE II score of <10 and this difference was statistically different (0.05). Table APACHE II score and scrub typhus

Table 51 APACHE II score and scrub typhus

	ALIVE	**DEATH**	
APACHE II SCORE <10	7	1	8
APACHE II SCORE 11 – 25	49	6	55
APACHE II SCORE >26	2	3	5
	58	10	68

APACHE II score of > 26 was associated with mortality of 62.5 % in pyelonephritis compared to 20 % with APACHE II score of 11-25 and this difference was statistically different (p=0.04)

Table 52 APACHE II score and pyelonephritis

	ALIVE	**DEATH**	
APACHE II SCORE <10	0	1	1
APACHE II SCORE 11 – 25	8	2	10

APACHE II SCORE >26	3	5	8
	11	8	19

There was no relationship between APACHE II score and mortality associated with community acquired pneumonia probably due to the small number of cases.

10. DISCUSSION

In this prospective and retrospective study of severe community acquired infections requiring ICU care we studied 135 patients with almost equal sex distribution and mean age of 53 years. Diabetes was the most common co-morbid condition in 47% of patients followed by hypertension, Ischaemic heart disease and COPD. 20 patients with diabetes died, with a mortality rate of 31.7% indicating the severity of the morbidity profile in this patient group.

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10.1 SPECTRUM AND ETIOLOGY -OF SEVERE COMMUNITY ACQUIRED INFECTION

Our study showed that the three most important community acquired infections requiring admission in the medical intensive care unit (MICU) and medical high dependency unit (MHDU) were scrub typhus (55.6%), pyelonephritis (14.8%) and community acquired pneumonia (8.9%) together occupying 79.3% of the community acquired infections. A wide spectrum of infections caused the remaining 20.7% of infections ranging from skin and soft tissue infection, meningitis, encephalitis, malaria, enteric fever, bacteremia with unknown source, Dengue and undifferentiated febrile illness without identified cause.

This was consistent with the study on acute febrile illness by Anugrah et al in2007 (2). The reasons for such high proportion may be due to the ongoing epidemic, lack of disease awareness and high referral rates due to morbidity of the illness and inability of local practitioners to diagnose this early. Despite numerous case reports from across the country, medical practitioners are still unaware of this disease. Consequently majority of the cases presenting with varying degrees of severity are undiagnosed or misdiagnosed.

According to Foxman, urinary tract infection accounts for the second most common bacterial infection in the United States (52). Though the accurate incidence is not available from India, it still accounts for one of the commonest bacterial infections (45, 46, 50). In none of these studies, the proportion of cases with severe illness was addressed. In our study population, 14.8% of the cases were due to pyelonephritis or complicated urinary tract infection.

From the clinico-epidemiological and bacteriological studies conducted in India, *Escherichia coli* appears to the most common organism isolated from blood and urine culture (45,46). Eswarappa et al and Akram et al, in two independent studies reported an incidence of ESBL *E.coli* in 42% of the isolates (45, 46). In our study the most common organism isolated from blood culture was *E. coli* (85%), of which 83.3% was ESBL *E. coli*. The proportion of urine culture isolates of *E.coli* was 88.9% and 77.8% of these were ESBL *E.coli*. The proportion of extended spectrum beta lactamase (ESBL) producing *Escherichia coli* as the causative agent is showing an increasing trend which is alarming. The resistant strains among gram negative bacteria are higher in India as opposed to western countries (107).

Among the 135 cases, 8.9% was due to severe community acquired pneumonia (CAP). In this case as well, there is a paucity of data pertaining to the exact proportion of

cases from India. A study by Garibaldi in United States, pneumonia was ranked as the sixth commonest cause of death (16).

In 33.3% of the cases with CAP, a causative organism was isolated from blood culture. The rate of isolation of organisms from blood culture in this study was higher than that seen in a study by Shah et al (15). However the observed rates in the isolation of causative agents from Western literatures varied from 10-33% (110,111). This was consistent with the finding in this study, suggesting that one-fourth to one-third of cases are not bacteremic (15).

Isolation of organisms from sputum culture in this study was 25% and was similar to the other Indian studies (15).

Overall the isolation of a causative agent was obtained in 50% of the study population which was higher than that reported by Shah et al. Proper collection of the sputum sample, from endo tracheal aspirate may have probably contributed to this high rate of isolation. However prior use of antibiotics still accounts for the low rates of isolation from blood culture (15).

The most common agent isolated from blood culture in this study was Streptococcus pneumoniae, which was similar to the findings in other studies from India (17, 18). The isolation of gram negative bacteria in this study was lower compared to other Indian studies. The reason for the same is not clear.

There were 4 cases of bacteremia with unidentified source due to E.coli, Klebsiella and Enterobacter.

In patients with Scrub typhus the Scrub ELISA test was positive in 90.7 % of cases.

10.2 ADMISSION CORRELATES AND MORTALITY

Severe scrub typhus was found to be higher in the elderly age group (>50 years) which was consistent with the study by Varghese et al. However neither of the studies showed a significant relation between age and mortality (30). This may be because both the study population were from the same catchment area, and the index of suspicion in patients presenting with acute febrile illness with MODS is high, thus leading to early initiation of appropriate antibiotics.

Among those with pyelonephritis, the proportion of males was higher in males this study contrary to that reported from other Indian studies (45, 46). The reason for this could be referral bias, as all female patients with non-severe urinary tract infection would have been treated with antibiotics elsewhere. The proportion of males with severe pyelonephritis could imply those with benign prostatic hypertrophy, considering that all of them were above 50 years.

The proportion of cases with pyelonephritis presenting in patients of age group > 50 years is consistent with other Indian studies (45). The risk of presenting with severe form of the illness was also higher in the elderly. Though a statistical significance was not found, it is important to note this finding.

Diabetes mellitus was seen in 85% of the cases with pyelonephritis and the risk of mortality was statistically significant in this group. Long duration of diabetes, poor glycaemic control and pre-existing renal dysfunction in older age group are likely to be pre disposing factors to develop severe urinary tract infection (51). Considering these factors, prompt diagnosis and early initiation of therapy is warranted to reduce the risk of complications and mortality. Diabetes was not just a risk factor for pyelonephritis but also for severe scrub typhus (32% were diabetic) and community acquired pneumonia (75% were diabetic)

75 % of cases with CAP was higher in the elderly age group (>50 years) in this study. Contrary to what was seen in the study by Shah et al, elderly age group did not predict mortality in this study. In this study population, the presence of underlying lung diseases were seen only in 5 cases, but no relation to mortality was found. The smaller sample size may be the reason for this.

Among the cases with scrub typhus, the most common clinical presentation was fever which was seen in all cases. The clinical signs and laboratory tests with the highest sensitivity for diagnosis of scrub typhus were Eschar (0.84), thrombocytopenia (0.85) and elevated SGOT (0.97). The clinical signs with highest specificity for diagnosis of scrub typhus were Eschar (1), thrombocytopenia (0.65) and elevated SGOT (0.68).

These findings are consistent with the studies of Chrispal et al, which showed that fever, leucocytosis, thrombocytopenia and elevated liver enzymes correlated with the diagnosis of scrub typhus. In this study eschar was noted in 83% of the cases. Though the reported incidence of eschar has been variable across studies, this finding is characteristic of scrub typhus. So even in the absence of availability of serological studies, diagnosis of scrub typhus can be made and treatment may be initiated, and this is likely to reduce the severity of the illness (2, 21, 30, 31).

In patients with pyelonephritis, 12 patients presented with typical features of fever, dysuria and renal angle tenderness. In 30% of the cases, altered sensorium was reported in addition to the above symptoms. Dysuria had a sensitivity of 1 for diagnosis of pyelonephritis and dysuria and renal angle tenderness had specificity of 1 for diagnosis of pyelonephritis.

This was similar to that reported by Mahesh et al (53%). In this study population all 20 patients had fever as the presenting illness, while Meyers et al in their study on bacteremia

in the elderly reported occurrence of fever in 90% of the cases (112). So presence of febrile illness with dysuria, and renal angle tenderness is characteristic of pyelonephritis.

All patients with CAP in this study, had fever and respiratory symptoms of productive cough and dyspnea, which was similar to that reported in other Indian studies (15). Though a significant correlation was not observed, presence of these clinical symptoms and radiological findings of patch characterised community acquired pneumonia in this study population. The sensitivity of cough and chest x-ray findings for diagnosis of community acquired pneumonia in the ICU was 1 and 0.67 and specificity of chest x-ray for diagnosis of community acquired pneumonia was 1.

Among the organ system failure in scrub typhus, shock requiring vasoactive agents significantly correlated with death and this was consistent with the finding reported by Varghese et al (30).

All patients with pyelonephritis and underlying diabetes mellitus had serum creatinine values more than 1.5 g/dl, suggesting the possibility of a pre-existing renal dysfunction. However baseline serum creatinine value was not available in these patients.

10.3 LABORATORY PARAMETERS AND CORRELATION WITH PREDICTING DIAGNOSIS

Presence of fever with eschar helped in making the diagnosis of scrub typhus. This was consistent with other studies as well (2, 30). In the absence of eschar, laboratory parameters such as leucocytosis and elevated liver enzymes along with fever characterised the diagnosis of scrub typhus as reported by Anugrah et al (2).

Presence fever with dysuria was not specific for the diagnosis of pyelonephritis. However with added clinical symptom of flank pain and isolation of typical organism from either blood

or urine culture was characteristic of pyelonephritis. This was consistent with other Indian studies (45).

For the diagnosis of CAP, symptoms of fever with respiratory symptoms alone was not specific, especially in the setting of severe illnesses, as dyspnea and cough was seen in other infections also, suggesting presence of acute respiratory distress syndrome. However radiological features of consolidation or interstitial infiltrates and isolation of typical organism either from the blood or sputum help in the diagnosis of CAP (15,16) .

Acute Physiology and Chronic Health Evaluation II (APACHE II) score is a validated clinical severity index used to assess severity of a disease in intensive care unit (109). In this study, higher APACHE II score correlated with mortality in patients with scrub typhus and pyelonephritis.

10.4 CHOICE OF ANTIBIOTIC AND APPROPRIATE USE OF ANTI MICROBIAL AGENTS IN SCRUB TYPHUS, PYELONEPHRITIS AND CAP

In all cases of scrub typhus appropriate antibiotic was used, where 72 patients received doxycycline. In addition to doxycyline, azithromycin was administered to 63 patients, with the hypothesis that oral absorption of doxycycline is lower in severe forms of scrub typhus. However there are no studies which has looked into the difference in efficacy and drug of choice in severe forms of the disease. Except in special situations such as in children <8 years, pregnant women, and documented resistance to doxycyline, the drug of choice for scrub typhus remains is doxycycline (108).

95 % of the patients with pyelonephritis received carbapenems (meropenem or ertapenem). The appropriate antibiotic of choice in severely ill patients suspected to have

pyelonephritis should be carbapenems considering the alarming increase in the rates of isolation ESBL E.coli noted in our study as compared to other Indian studies (45).

In patients with CAP, the choice of antibiotics was varying. In our study population the most common micro organism isolated was *Streptococcus pneumoniae*, which was similar to that reported by Bansal et al (19). The appropriate antibiotic of choice should be based on the local epidemiology and the susceptibility. In our study, all the strains of S.pneumoniae was susceptible to penicillin.

10.5 MORTALITY RATES AND PREDICTORS OF OUTCOME

The overall mortality rate in our study was 25.9%. The infection specific mortality rates of the three infections were scrub typhus (13.3%), pyelonephritis (40%) and community acquired pneumonia (41.7%). However due to the larger number of patients with Scrub typhus was the chief cause of death.

In our study the infection specific mortality rate due to with scrub typhus was 13.3%, but this was higher than that reported by Varghese et al in 2010 (30). The reason for the high rates of mortality in our study population may be due to selection as our study focussed on patients with severe scrub typhus requiring ICU care.

In our study we were able to show that shock requiring inotropes was found to be a predictor of mortality which was similar to that reported by Varghese et al (30). On bivariate analysis presence of eschar, pre-existing medical co- morbidities, acute respiratory distress syndrome, and acute kidney injury with serum creatinine > 1.5 g/dl, need for mechanical ventilation did not have any statistically significant impact on mortality. In Varghese et al's study in addition to shock, found significant correlation with mortality in patients with acute kidney injury, and

acute respiratory distress syndrome. The reason that we were unable to show the same in our study may be because of the small sample size.

In our study all patients with pyelonephritis presented with shock and the mortality rate was 22.9 %. In a retrospective study, Efthasthiou et al showed that presence of shock was an independent predictor of mortality. This is consistent with the finding in our study, however since all our patients had shock we were unable to analyse the parameter for the statistical significance(112).

11. CONCLUSIONS

In our study three community acquired infections presenting with severe illness identified were scrub typhus (55.6%), pyelonephritis (14%) and community acquired pneumonia (8.9%). Together these infections contributed to 79% of all the community acquired infections requiring admission to MICU/MHDU.

Escherichia coli contributed to 66.7% of all the etiological micro-organisms isolated from blood culture and the rate of ESBL E.coli was 55%. Streptococcus pneumoniae (12%) was second most commonly isolated organism.

Presence of fever and eschar characterized the clinical diagnosis of scrub typhus. Febrile illness, with leucocytosis, deranged liver enzymes and leucocytosis can help make the diagnosis in addition.

Fever, upper urinary tract symptoms such as dysuria, and renal angle tenderness, and isolation of typical organism either from blood or urine culture, characterise the diagnosis of pyelonephritis.

Fever with cough and breathlessness, with radiological finding of consolidation characterize community acquired pneumonia.

The overall mortality rate was 25.9%. Mortality due to scrub typhus was 13.3%, pyelonephritis (40%) and that due to CAP was 41.7%

The choice of antibiotic for scrub typhus, was doxycycline.

Additionally azithromycin was also administered in severely ill patients with scrub typhus

Considering the alarming rates of ESBL E.coli, empirical therapy for pyelonephritis and unidentified source of sepsis with carbapenems is advised.

Penicillin and penicillin group of drugs are still the drug of choice in CAP.

Shock requiring vasoactive agents was an independent predictor of mortality in patients with scrub typhus.

All patients with pyelonephritis presented with shock and was significant for mortality.

Diabetes mellitus was a significant risk factor to develop pyelonephritis.

As the APACHE II score increased, there was increased risk of poor outcome, as seen in patients with scrub typhus and pyelonephritis.

Based on the clinical profile and microbiology of community acquired infections requiring ICU care in this study we suggest the following algorithm for diagnosis and management of acute febrile illness admitted to ICU at Christian Medical College, Vellore.

This algorithm may be beneficial in improving the management of seriously ill community acquired infections.

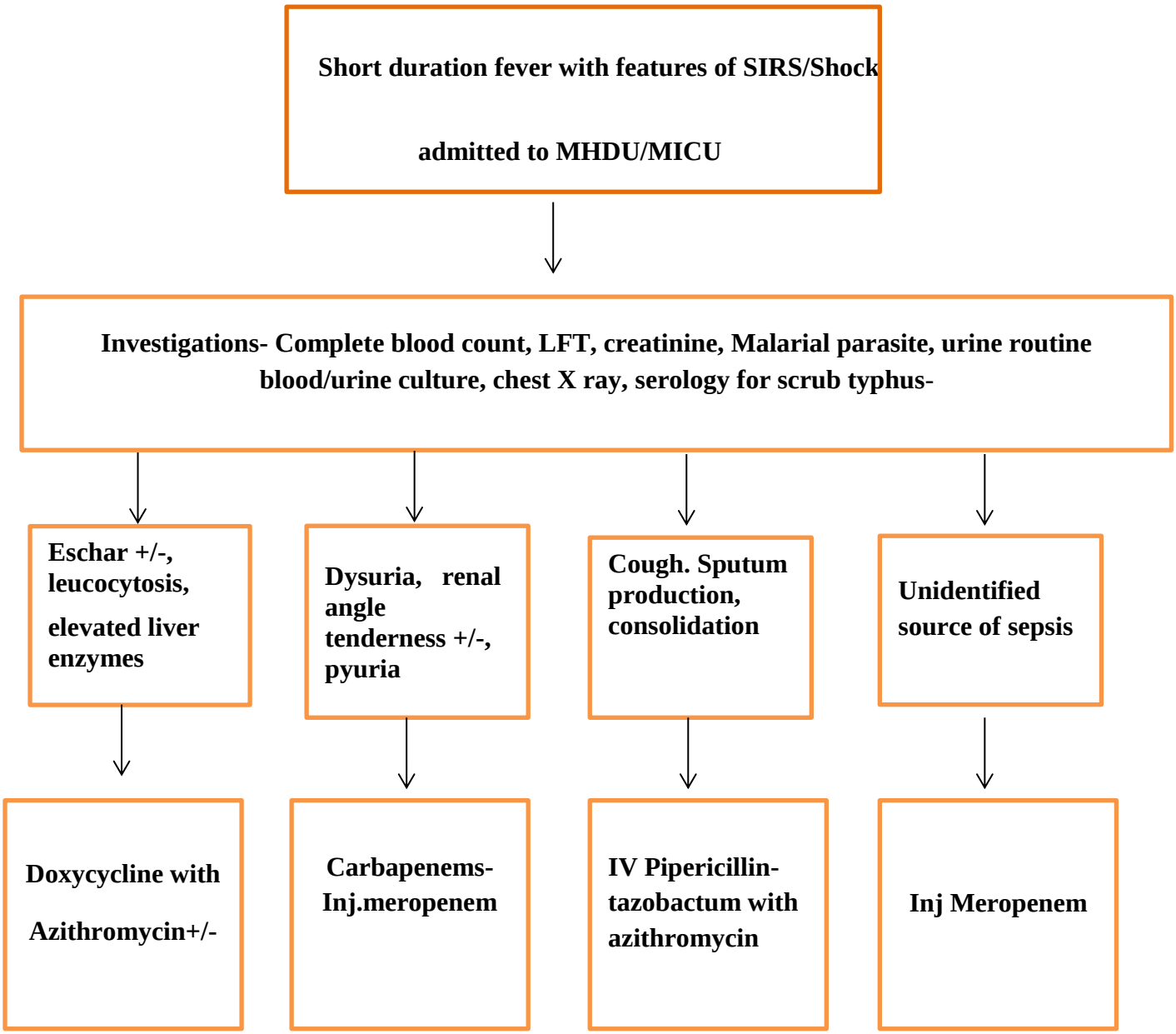

Figure 19.Approach to diagnosis and management of acute febrile illness admitted to ICU at Christian Medical College, Vellore

12. LIMITATIONS

1) The sample size was small, in view of the patient recruitment in the tertiary care referral centre.

2) Assessment of severity of infection with analysis of blood gases

3) Study of the economic impact of these infections.

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ANNEXURES

1) PATIENT INFORMATION SHEET

2) PATIENT CONSENT FORMS

3) DATA ABSTRACTION SHEET

4) DATA WORKSHEET

5) FLUID RESEARCH GRANT APPROVAL AND CONSENT OF THE INSTITUTIONAL REVEIW BOARD (IRB)

ANNEXURE 1

PATIENT INFORMATION SHEET

TITLE: Clinical spectrum of severe community acquired infections in patients under General Medicine requiring admission to medical intensive care unit and medical high dependency unit in a tertiary care hospital in South India.

1) ABOUT THE STUDY:

You/ your patient are being requested to participate in a study to look at the different kinds of infections that are seen in the community. This study looks at the different types of severe infections with which people come to hospital.

We hope to include all the people who come with severe infections to the department of General Medicine and then get admitted in medical intensive care unit or medical high dependency unit at Christian Medical College in this study.

2) WHAT ARE THE INFECTIONS WE ARE LOOKING AT?

We have observed that the common infections with which people come to hospital with include pneumonia, urinary tract infection, typhoid, malaria, scrub typhus, dengue fever, and other common viral infections. Some of these patients can have severe infections and hence come to the hospital in a serious condition. These patients require care in ICU or HDU.

We hope to study in detail about these infections. In this study we will be studying in detail about the signs and symptoms of the infection, the treatment and the outcome of the disease.

3) IF YOU TAKE PART WHAT WILL YOU HAVE TO DO?

If you /your patient agree to participate in this study, you/ your patient will have to consent for the same. All the information relevant to the you/ your patient's condition will be obtained from the Outpatient chart, In patient charts and clinical work station.

This study will not affect your treatment. All the treatments that you are already on will be continued and your regular treatment will not be changed during this study.

We will not perform extra or un necessary tests or investigations if it is not required for your treatment.

4) CAN YOU WITHDRAW FROM THIS STUDY AFTER IT STARTS?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

We do not expect any injury to happen to you.

Will you have to pay for the study?

You do not have to pay any money for the study. The treatment that you/ your patient will receive during the hospital stay will continue and the expenses involved in the treatment will be decided by the hospital.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr.Betsy Ann Joseph

Contact details:

Dr.Betsy Ann Joseph

New PG Quarters # 2/7

Christian Medical College

Vellore

Tamil Nadu- 632004

Mob no: 9500528304

Email: betsyshalom2010@gmailcom

ANNEXURE 2

Study Title: *Clinical spectrum of severe community acquired infections in patients under General Medicine requiring admission to medical intensive care unit and medical high dependency unit in a tertiary care hospital in South India*.

Study Number: _____

Subject's Initials: _____ Subject's Name:
_____

Date of Birth / Age: _____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the investigator of this study and, others working on the investigator's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

(v) I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

ASSENT FORM

Christian Medical College, Vellore

Department of General Medicine

Clinical spectrum of severe community acquired infections in patients under General Medicine requiring admission to medical intensive care unit and medical high dependency unit in a tertiary care hospital in South India.

We are doing a research study on people with severe infections that get admitted in the intensive care unit in our hospital. Research is a way to learn more about various things for example in this case we are studying about infections.

Infections are diseases that are caused by microorganisms. We have observed that some people who have severe infections require special care and they require to be in intensive care units. Intensive care unit is that part of the hospital where very sick patients are kept.

We will be studying in detail about these infections. The problems that these infections cause to people, the treatment and the end result of the same.

If you decide that you want to be part of this study, you will be asked to give details about your problems. The good thing is that we will not be doing any un necessary tests or additional tests. Our study will not affect your treatment.

If you do not want to be in this research study, you are free to do so.

When we are finished with this study we will write a report about what was learned. This report will not include your name or that you were in the study.

You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that's okay too. Your parents know about the study too.

If you decide you want to be in this study, please sign your name.

I, _____, want to be in this research study.

(Sign your name here) (Date)

If you have any further questions, please ask Dr.Betsy Ann Joseph

Contact details:

Dr.Betsy Ann Joseph

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Tamil Nadu- 632004

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ANNEXURE 3

Serial No:	**Hosp. No:**

SEVERE COMMUNITY ACQUIRED INFECTIONS NEEDING ICU/HDU CARE
DATA ABSTRACTION FORM

Name: **Age:** **Sex: Male / Female**
Address:

Contact number:

PRIMARY ADMISSION / RE-ADMISSION

Date of hospital admission:

Date of ICU admission: **Discharge date:**

Day of illness:

Admission diagnosis:

Final diagnosis:

Risk factors/Co-morbidities: (Circle features present at admission)

Asthma	COPD	Other chronic lung disease
Diabetes	Ischaemic heart disease	Chronic heart failure
Rheumatic heart disease	Chronic renal failure	Chronic liver disease
Steroid use >3 months	Immunosuppressive therapy	HIV infection
Pregnancy	Seizure disorder	Smoking
Morbid obesity	Auto immune diseases	

Symptomatology at presentation: (Circle features present at admission and list duration)

Symptomatology	**Duration of symptom**	**Symptomatology**	**Duration of symptom**

Fever		Breathlessness	
Running nose/blocked		Sore throat	
Headache		Myalgia/body pain	
Wheezing		Loose stools	
Focal neurological deficits		Vomiting	
Seizures		Bleeding manifestations	
Cough		Altered sensorium	
Dysuria		Flank pain	

CLINICAL EXAMINATION

BP: HEART RATE

TEMPERATURE: RESPIRATRY RATE:

SATURATION SENSORIUM (GCS): E.. V.. M..

LOCALISING SIGNS

Respiratory system:

Cardiovascular system

Abdomen

CNS:

Skin and miscellaneous

INVESTGATIONS

Date		Date		
	WBC COUNTS		Urine culture	
	DIFFERENTIAL COUNTS		serology	
	Platelets		Scrub typhus	
	haemoglobin		dengue	
	Creatinine		H1N1	
	LFT		Leptospirosis	
	Urine analysis		MP/MF	
	Blood culture		CHEST X RAY	
	FUID ANALYSIS (ASCITIC/ PLEURAL/ CSF)			
	TC			
	DC			
	GLUCOSE		SERUM GLUCOSE	
	PROTEIN		SERUM PROTEIN	
	ALBUMIN		SERUM ALBUMIN	
	LDH		SERUM LDH	
	CULTURE			

BLOOD GAS ANALYSIS

pH		
Pco2		
Po2		
BE		
Bicarb		
lactate		
Fi O2		
PF ratio		

Treatment details: (antibiotics)

Drug	Dose	Date started	Date stopped	Duration

ADMISSION SCORE- APACHE III

Ventilation and renal replacement therapy data:

Ventilated: Yes / No Non-invasive ventilation: Yes / No Invasive: Yes / No

Duration of ventilation (invasive) days:

Need for muscle relaxants: Yes / No Duration of relaxants:

Tracheostomy: Yes / No

Time from intubation to tracheostomy (days):

Dialysis done: Yes / No Day of initiation: Type:

Duration of dialysis:

Inotropes: yes/no

Choice of inotropes: dopamine/noradrenaline/adrenaline/vasopressin/others (specify)

Number of days:

Nosocomial infections:

Type	Yes / No	If yes, day	Organism (s)	Treatment
VAP	Yes / No			
CRBSI	Yes / No			
Uro-sepsis	Yes / No			
Other infections	Yes / No			

Other complications:

Seizures	Myocarditis	Pulmonary embolism	
Decubitus ulcers	GI bleed		

Duration of ICU stay (days): Duration of hospital stay (days):

ICU outcome: Dead / Alive / Discharged at request/ PVS

Hospital outcome: Dead / Alive / Discharged at request / PVS

Probable cause (s) of death:

ANNEXURE 4

DATA WORK SHEET

retrospective/p	*Hosp.No.*	*Age*	*Sex*	*days- total hospital stay*	*Days-ICU*
R	657997F	32	1	7	4
R	664673F	73	1	6	6
R	630936F	65	0	6	5
R	534247D	53	0	8	4
R	657019F	25	0	5	2
R	713176F	47	0	7	5
R	585364C	30	0	42	15
P	912219F	75	1	11	10
R	696024F	50	0	10	7
P	922578F	47	1	13	3
R	441600F	52	1	2	2
R	389037F	64	1	12	7
R	401660F	30	1	12	7
P	917471F	75	0	58	7
P	922084F	87	1	21	21
R	740773F	40	1	20	10
R	726303F	24	0	10	7
R	611403F	35	0	20	4
R	618582F	57	1	13	7
R	623512F	65	1	26	8
R	688915F	56	0	11	6
P	917357F	65	1	2	2
P	922562F	68	0	11	9
P	926835F	62	0	17	3
P	923778F	45	1	14	7
R	604763F	50	1	15	9
R	696497F	22	0	7	5
R	750101F	60	0	19	10
R	657814F	31	1	11	2
P	159506f	52	0	12	5
P	054566F	74	1	9	5
P	063519G	45	0	11	7
R	675012F	60	1	5	5
R	562477B	71	0	4	3
R	688462F	77	1	2	2
R	675288F	28	1	21	8
R	750340F	48	0	25	15
P	750778F	28	0	22	2
R	740678F	55	0	11	8
P	751783F	45	1	8	4
R	720214F	55	1	30	28
R	445501C	67	1	10	9
R	598904	68	1	16	9
P	751571F	74	1	11	11
P	308044C	74	1	40	5
R	190391C	64	1	7	3
R	675091F	50	0	2	2
R	865765D	86	1	2	2
R	696282F	41	0	10	3

R	379593F	65	1	17	16
R	384175F	85	1	2	2
R	696092F	25	1	10	5
R	384030F	40	1	10	5
R	384358F	19	1	2	2
R	611505F	65	1	7	6
R	740299F	65	0	12	7
R	820816D	57	1	3	3
R	713506F	18	1	10	8
R	623586F	17	1	3	3
R	282088B	58	1	9	2
P	917382F	23	1	1	1
R	448439F	16	0	7	2
R	849453C	55	1	17	2
P	630509D	62	0	10	7
P	914041F	64	1	10	3
P	914812F	19	1	11	6
R	389565F	49	0	10	5
R	691285F	55	1	11	7
R	713689F	62	0	7	3
P	917379F	48	0	12	7
R	441367F	43	0	13	9
R	384603F	78	0	8	6

R	384659F	34	1	12	8
R	361235F	35	1	6	2
R	379930F	37	1	5	1
R	379063F	42	0	12	6
R	394265F	54	0	8	5
R	415118F	60	0	22	15
R	406100F	63	1	10	5
R	491258C	57	0	8	4
R	639809F	78	1	7	3
R	426570A	70	0	17	14
R	671589F	32	1	12	9
R	688880F	60	1	2	2
R	696423F	63	1	8	5
R	704375F	60	1	11	8
R	329399D	50	0	31	19
R	696813F	32	1	31	21
R	509060F	40	1	14	4
R	740541F	19	0	13	8
R	657912F	45	0	11	7
R	675877F	55	0	7	3
P	751582F	69	0	12	5
P	751493F	59	1	9	5
P	753826F	63	1	9	3

R	389619F	52	0	6	3
R	664501F	72	1	10	3
R	726988F	40	1	7	4
R	713324F	48	1	5	5
R	361362F	48	0	8	5
R	639822F	82	0	9	5
R	720149F	72	1	9	7
R	361362F	48	0	8	5
R	639822F	82	0	9	5
R	720149F	72	1	9	7
R	720153F	42	1	8	5
R	750308F	40	1	8	6
R	675222F	69	0	9	9
R	508484F	30	0	3	3
R	675057F	68	1	5	5
R	379510F	64	1	8	4
R	999978D	53	0	10	7
P	933061D	44	0	8	6
R	750078F	65	0	4	4
R	379729F	43	0	15	12
R	688956F	70	0	6	4
R	688844F	68	1	10	2
R	726836F	38	1	7	2
R	696067F	41	0	8	5
R	713226F	51	1	8	4
R	657690F	24	0	16	6
P	799060F	37	0	8	3
R	696571F	58	1	9	6
R	675855F	65	1	1	1
P	922815F	40	0	7	5
R	485648F	47	0	15	4
R	651965F	67	1	8	7
R	704229F	65	0	8	7
R	704766F	72	1	10	9
R	743979D	59	0	3	3
R	350929F	54	0	12	6
P	366124F	68	1	15	7
P	750738F	55	0	24	4
R	977663D	55	0	7	7
R	415467F	55	1	20	8

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2	999	13
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2	20	1
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1	13	6
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1	999	6
2	20	6

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2	13	10
1	999	9
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2	19	6
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2	11	1
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2	10	7
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2	13	3
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2	32	3
2	19	3

Organ system failure- respiratory system

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organ system failure- cardiovascular

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Organ system failure-renal	*treatment- ventilation*
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number of days- ventilation	*treatment-.INOTROPE*	*treatment-dialysis*
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3	2	2
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8	1	2

COMPLICATIONS	*FEVER*	*BREATHLESNESS*	*COUGH*
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DYSURIA	*FLANKPAIN*	*ESCHAR*	*DIABETES MELLITUS*	*HYPERTENSION*	*CHRONIC OBST*
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2	2	no	100	60	120	44	88
2	2	no	80	30	132	32	90
2	2	no	110	82	102	32	93
2	2	no	100	68	102	28	90
2	2	no	90	60	120	29	96
2	2	no	100	60	120	32	92
2	2	no	90	70	122	32	90
2	2	no	92	50	120	28	91
2	2	no	70	20	123	40	89
2	2	no	90	60	108	38	88
2	2	no	80	40	132	34	91
2	2	no	60	20	120	44	81
2	2	no	104	70	120	34	91

2	2 no	90	60	118	44	80
1	2 no	90	40	110	42	88
2	2 no	102	60	110	24	99
2	2 no	92	44	112	34	88
2	2 no	90	62	110	28	94
2	2 no	100	60	119	27	92
2	2 no	90	70	100	28	94
2	2 no	90	70	102	32	99
2	2 no	90	60	120	32	92
2	2 no	100	60	110	22	96
2	2 no	90	40	110	28	94
2	2 no	90	60	110	29	90
2	2 no	92	60	109	32	92
2	2 no	100	70	116	32	99
2	2 no	90	60	118	21	91
2	2 no	98	58	88	25	88
2	2 no	90	60	99	30	79
2	2 no	100	60	109	38	88
2	2 no	80	60	112	29	100
2	2 no	90	60	113	30	90
2	2 no	90	60	120	27	90
2	2 no	90	60	113	28	90
2	2 no	80	60	110	44	94

2	2 no	102	60	90	32	96
2	2 no	90	72	108	32	93
2	2 no	94	62	100	28	98
2	2 no	90	60	130	29	95
2	2 no	90	60	112	32	94
2	2 no	100	70	110	32	94
2	2 no	100	70	110	28	88
2	2 no	80	40	124	40	90
2	2 no	94	48	88	38	95
2	2 no	100	64	132	28	94
2	2 no	90	50	112	26	90
2	2 no	90	58	100	27	94
2	2 no	100	70	122	22	96
2	2 no	100	80	100	26	93
2	2 no	90	60	112	22	90
2	2 no	100	70	110	30	94
2	2 no	100	70	110	34	96
2	2 no	90	60	88	28	93
2	2 no	100	70	118	29	98
2	2 no	104	60	88	32	95
2	2 no	108	70	99	32	94
2	2 no	90	60	109	21	90
2	2 no	90	50	112	25	94

2	2	no	90	40	113	30	96
2	2	no	106	60	120	38	93
2	2	no	80	60	132	29	90
2	2	no	110	68	102	30	94
2	2	no	90	70	102	27	96
2	2	no	90	60	120	32	93
2	2	no	100	70	120	32	98
2	2	no	90	70	102	27	96
2	2	no	90	60	120	32	93
2	2	no	100	70	120	32	98
2	2	no	104	60	122	21	95
2	2	no	100	70	120	25	94
2	2	no	90	60	123	29	94
2	2	no	90	50	108	32	88
2	2	no	90	40	132	32	90
2	2	no	90	60	120	21	96
2	2	no	100	70	113	25	93
2	2	no	104	60	110	30	98
2	2	no	100	70	90	38	95
2	2	no	90	60	108	29	88
2	2	no	104	60	100	30	90
2	2	no	80	68	130	25	96
2	2	no	110	58	90	27	96
2	2	no	90	70	122	32	98
2	2	no	104	60	90	32	94
2	2	no	100	70	112	21	93
2	2	no	92	60	113	25	94
2	2	no	104	60	110	22	94
2	2	no	80	60	113	39	88
2	2	no	110	70	110	35	90
2	1	yes	90	70	90	27	96
2	1	yes	90	40	100	33	87
2	2	no	92	60	113	26	93
2	2	no	100	70	110	27	98
2	2	no	104	60	90	22	95
2	2	no	100	70	108	26	94
2	2	no	90	60	100	22	95
2	2	no	90	50	130	30	92
2	2	no	90	40	123	34	99
2	2	no	90	50	108	32	96

antibiotics	*WBC*	*HB*	*PLATELET*	*CREATINII*	*SGOT*	*SGPT*	*BLOOD CULTU*
1,5,8	11300	12.4	116000	0.66	161	128	0
2,3	12300	11.9	125000	1.07	27	21	0
3,4,7	28400	12	76000	4.05	125	74	1
1,2,3	6700	9.8	20000	1.09	165	49	0
2	11100	9.6	118000	1	47	10	0
1,2	15800	10.5	17000	3.47	253	55	0
1,5.6	7800	13.2	163000	0.63	50	42	0
1,2	8400	8	20000	4.52	109	27	0
1,2	9300	13.4	86000	2	194	97	0
1,2,5,6	11300	11.8	275000	1.01	48	18	0
1,2,4	15700	9	10000	5.16	124	24	0
1	20300	15.2	177000	2.62	52	27	0
5,6	36500	13.4	209000	2.69	48	27	0
4,9,10	28700	10	9000	6.83	141	49	1
4,11,12	23400	10.4	352000	6.84	24	34	0
4,11,13	10100	10	346000	0.66	17	14	0
2,3,4,11	2400	9	5000	0.55	228	41	0
1,2,11,13	5900	9.9	38000	1.04	133	67	0
4,14	15500	11.2	110000	2.22	57	13	1
4,14,15	24300	10.8	409000	1.32	139	66	1
1,2,4	13200	6.1	41000	1.35	39	14	0
4	18200	12	176000	2.3	30	12	0
1,2	13200	12	4000	0.53	138	63	0
1,2,4	14300	13.7	14000	4.38	221	81	0
1,2,4,11	17800	16	14000	1.89	134	88	0
4,14	900	13.7	109000	1.99	793	300	1
2	10500	10	5000	0.7	96	61	0
2,4	12700	8	132000	3.01	28	6	0
1,5	13500	12.1	251000	1.8	317	133	0
4	11400	11	117000	2	126	38	1
4	8200	10.5	137000	2.2	128	33	1
2	6200	10	71000	0.99	150	110	0
1,4	11400	14	22000	5.15	310	242	1
2,4	6000	12	53000	2.77	77	35	0
2,3	10900	7	86000	2.48	536	206	0
4	153000	9	161000	6.18	18	10	0
3,4	9800	11.5	18000	1.9	162	193	1
1,2,4	8000	9	30000	2.86	41	30	0
1,2,5	7600	13.4	15000	3	109	72	0
1,2	10300	13	57000	2.3	60	26	0
4	12100	13	169000	1.08	22	25	1
1,2,4	16800	8.6	76000	1.7	52	26	0
1,4	17000	7.7	90000	1.98	20	7	1
3,4,12	57200	11	500000	2.2	37	23	1
4,12	7700	12	208000	2.53	21	12	1
2,3	13500	11	213000	2.57	57	11	0
3	21500	13	154000	2.65	43	33	0
4	18100	13	313000	2.79	50	14	0
3,16	17300	14	109000	1.01	21	22	0

2,3,12		13700	14	236000	1.53	32	1	1
2,3		26000	13	267000	3.15	361	106	0
1,3		5000	6.8	7000	1.28	800	324	0
1,4,3		9300	15	47000	2	166	91	0
1,3		8900	15	11000	2	726	141	1
4,12,15		15300	12	178000	4.4	262	122	0
1,2		15600	9	272000	0.79	14	12	0
4,15		18800	9.7	48000	1.7	42	40	1
1,4		8400	14	38000	1.15	243	80	0
5,6		12000	14	162000	1.14	86	16	0
4,12		17800	12	226000	0.99	24	12	1
1,5,8		4050	7.7	9000	4	45	19	0
	3	10600	12	146000	0.93	40	12	0
	4	14200	13	78000	4.53	21	7	1
3,16		11200	12	300000	2.9	29	7	1
	4	15500	6	333000	4.87	57	22	1
	4	4600	12	85000	0.85	98	37	1
1,3		13400	7	29000	1	138	27	0
1,2		6400	12	82000	1.6	111	65	0
1,2		10800	8	65000	0.7	152	49	0
1,2		6650	10	33000	2.7	344	64	0
1,2,11,13		9500	9.2	16000	0.95	129	31	0
1,4		5700	9.7	53000	3.12	68	41	0

1,4,11

		10900	12	48000	6.44	335	88	0
1,2		9500	12	34000	1.3	81	60	0
1,2		9800	15	112000	2.9	132	80	0
1,2		12900	12	57000	2	114	99	0
1,2		21500	9.8	142000	2.53	108	27	0
1,2		16100	11	11000	1.5	292	188	0
1,2		11100	12	37000	2.4	117	54	0
1,2		10000	10	34000	1	158	79	0
1,2		12100	13	160000	3.15	77	89	0
1,2		16600	11	40000	2.16	77	89	0
1,2		22700	16	10000	1.2	505	200	0
1		27400	14	31000	1.9	512	176	0
1,2		7300	13	67000	1.3	102	76	0
1,2		6600	11	59000	1.06	69	29	0
1,2		11000	10	40000	2	89	49	0
1,2,12		102000	14	59000	3.2	163	75	0
1,2,4		4200	12	45000	8	298	80	0
1,2		6700	10	76000	2.45	98	51	0
1,2		12800	9	7000	1.3	104	66	0
1,2		7000	9	57000	1.97	35	20	0
1,2		19000	11	3000	9.44	182	62	0
1,2		8300	11	75000	2	55	33	0
1,2		10400	12	109000	1.18	95	54	0

1,2		5000	10	58000	0.7	174	38	0
1,2		9900	13	151000	4.5	65	51	0
1,2		9100	12	45000	0.52	74	99	0
1,2		15100	16	10000	4	292	71	0
1,2		9900	11	3000	1.05	77	45	0
1,2		19800	11.4	87000	1.05	91	35	0
1,2		15800	12.6	54000	1.7	55	12	1
1,2		9900	11	3000	1.05	77	45	0
1,2		19800	11.4	87000	1.4	91	35	0
1,2		15800	12.6	54000	1.7	55	12	1
1,2		8400	13	101000	3.22	77	39	0
1,2		11000	12	12000	2	225	98	0
1,2		7000	11	16000	1.19	291	60	0
1,2		13400	10	54000	0.85	80	77	0
1,2		23300	8.6	18000	4.28	107	22	0
1,2		8100	12.9	81000	3.16	88	77	0
1,2		7600	11	185000	1.24	77	29	0
1,2		14880	11	91000	2.52	115	46	0
1,2		5300	12,5	10000	2.14	140	25	0
1,2		16300	14	110000	2	96	104	0
1,2		13600	13.2	31000	2.72	64	6	0
1,2		11800	10	52000	1.59	271	86	0
1,2		14300	14	12000	1.04	93	105	0
1,2		8500	11.9	36000	1.96	201	124	0
1,2		10200	13	18000	2.22	109	39	0
1,2		8700	11	47000	2.72	180	142	0
	1	8300	13	137000	1.2	185	54	0
1,2,4		215000	19	41000	2.72	226	93	0
1,4		10100	12.6	39000	4	250	60	0
	1	14500	11	28000	2	155	61	0
4,11,13		11700	12.2	89000	5.33	18	11	1
	4	34800	11	129000	9	62	55	1
	4	9100	10	83000	4.98	20	11	1
7,9		13300	11	88000	3.99	18	7	1
	4	26100	9.6	164000	2.53	1416	521	1
	4	29700	8.1	795000	8.65	11	10	1
4,12		25400	7.3	657000	1.63	31	10	1
3,5		11000	17	194000	1.94	524	137	1
	4	14900	9	272000	5.01	40	19	1
3,4		7100	10	109000	3.16	55	23	1

BLOOD CL	chest X ra	SCRUB SEROLO	urine cultı	URINE CULTURE ORGANISM
9999	no patch	1	9999	9999
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2	no patch	9999	9999	9999
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9999	no patch	0	9999	9999
9999	no patch	1	9999	9999
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9999	no patch	9999	9999	9999
9999	no patch	9999	9999	9999
2	no patch	9999	1	2
9999	no patch	9999	1	3
9999	patch	9999	9999	9999
9999	no patch	1	9999	9999
9999	no patch	1	9999	9999
1	no patch	9999	9999	9999
3	no patch	9999	9999	9999
9999	no patch	1	9999	9999
9999	no patch	9999	9999	9999
9999	no patch	1	9999	9999
9999	no patch	1	9999	9999
9999	no patch	1	0	9999
3	no patch	0	9999	9999
9999	no patch	1	9999	9999
9999	no patch	0	9999	9999
9999	no patch	1	9999	9999
2	no patch	0	1	2
2	no patch	9999	9999	9999
9999	no patch	0	9999	9999
2	no patch	9999	1	2
9999	no patch	0	0	9999
9999	no patch	9999	9999	9999
9999	no patch	0	0	9999
5	patch	1	9999	9999
9999	no patch	1	9999	9999
9999	no patch	1	9999	9999
9999	no patch	1	9999	9999
1	no patch	9999	0	9999
9999	no patch	0	1	2
3	no patch	9999	1	3
5	patch	9999	9999	9999
5	patch	9999	9999	9999
9999	patch	9999	9999	9999
9999	patch	9999	9999	9999
9999	patch	9999	9999	9999
9999	no patch	9999	9999	9999

13	patch	9999	9999	9999
9999	no patch	9999	9999	9999
9999	no patch	9999	9999	9999
9999	no patch	0	9999	9999
6	no patch	0	0	9999
9999	no patch	9999	9999	9999
9999	no patch	9999	9999	9999
2	no patch	9999	0	9999
9999	no patch	1	9999	9999
9999	no patch	9999	9999	9999
5	no patch	9999	9999	9999
9999	no patch	9999	9999	9999
9999	no patch	0	9999	9999
2	no patch	9999	1	2
2	no patch	9999	1	2
2	no patch	9999	1	2
10	no patch	9999	9999	9999
9999	no patch	1	9999	9999
9999	no patch	1	9999	9999
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9999	no patch	1	9999	9999
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9999	no patch	1	9999	9999
9999	no patch	1	9999	9999
2	no patch	9999	1	2
9999	no patch	9999	9999	9999
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9999	no patch	1	9999	9999
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9999	no patch	1	9999	9999
9999	no patch	9999	9999	9999
9999	no patch	9999	9999	9999
2	no patch	9999	1	2
2	no patch	9999	1	2
2	no patch	9999	1	2
2	no patch	9999	1	2
1	no patch	9999	1	1
2	no patch	9999	1	2
2	no patch	9999	1	2
12	no patch	9999	9999	9999
2	no patch	9999	1	2
1	no patch	9999	1	1

ANEXURE 5

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glas
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

August 14, 2014

Dr. Betsy Ann Joseph
PG Registrar
Departmentof Medicine
Christian Medical College
Vellore 632 004

Sub: **Fluid Research grant project:**
Clinical spectrum of severe community acquired infections in patients under General Medicine requiring admission to medical intensive care unit and medical high dependency unit in a tertiary care hospital in South India.
Dr. Betsy Ann Joseph, Medicine, Dr. Anand Zachariah, Medicine, Dr. J. V. Peter, Medical Intensive Care Unit, Dr. Thambu David, Medicine 2, Dr. Sowmya Sathyendra, Medicine, Dr. Samuel George Hansdak, Medicine, Dr. B. Antonisamy, Biostatistics, CMC, Vellore.

Ref: IRB Min No: 8838 [OBSERVE] dated 07.04.2014

Dear Dr. Betsy Ann Joseph ,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Anand Zachariah, Medicine, CMC, Vellore.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
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Ref: IRB Min No: 8838 [OBSERVE] dated 07.04.2014

Dear Dr. Betsy Ann Joseph ,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Clinical spectrum of severe community acquired infections in patients under General Medicine requiring admission to medical intensive care unit and medical high dependency unit in a tertiary care hospital in South India." on April 7th 2014.

The Committees reviewed the following documents:

1. IRB Application format
2. Curriculum Vitae' of Drs. Betsy Ann Joseph, Anand Zachariah, J. V. Peter, Thambu David, Sowmya Sathyendra, Samuel George Hansdak, B. Antonisamy.
3. Proforma
4. Informed Consent form (English, Tamil & Telugu)
5. Consent form (English, Tamil & Telugu)
6. No of documents 1-5

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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Director, Christian Counseling Center,
Chairperson, Ethics Committee.

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Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on April 7th 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Paul Ravindran	PhD, Dip RP, FCCPM	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Dr. J. Visalakshi	MPH, PhD	Lecturer, Dept. of Biostatistics, CMC.	Internal, Statistician
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC	Internal, Clinician
Dr. Anup Ramachandran	Ph. D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Jacob John	MBBS, MD	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Vivek Mathew	MD (Gen. Med.) D.M (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Dr. Anand Zachariah	MBBS, PhD	Professor, Medicine, CMC, Vellore	Internal, Clinician
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMC, Vellore	Internal, Clinician
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Mr. C. Sampath	B. Sc, BL	Legal Expert, Vellore	External, Legal Expert
Dr. Denise H. Fleming	B. Sc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMC, Vellore	Internal, Scientist & Pharmacologist
Dr. Anuradha Rose	MBBS, MD	Assistant Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Jayaprakash Muliyil	B. Sc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist & Epidemiologist
Mrs. Sheela Durai	M Sc Nursing	Addl. Deputy Nursing Superintendent, Professor of Nursing in Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMC, Vellore	Internal, Legal Expert
Dr. Vathsala Sadan	M.Sc, PhD	Professor, Community Health Nursing, CMC, Vellore	Internal, Nurse
Dr. Nihal Thomas,	MD, MNAMS, DNB(Endo), FRACP(Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

IRB Min No: 8838 [OBSERVE] dated 07.04.2014

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Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 2,500/- INR (Rupees Two Thousand Five Hundred only) will be granted for 6 months.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

NOT TO BE MINISTERED UNTO BUT TO MINISTER
CHRISTIAN MEDICAL COLLEGE
VELLORE
INDIA

Cc: Dr. Anand Zachariah, Medicine,, CMC, Vellore.

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