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Incidence of Septicemia among Infants at El-Nassr Hospital - Gaza Governorate - 2007

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Incidence of Septicemia among Infants at El-Nassr Hospital - Gaza Governorate - 2007

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Master of Public Health (Epidemiology and Biostatistics)

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Deanship of Graduate Studies

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Declaration

I certify that all this thesis submitted for the degree of Master is the result of my own research, except where otherwise acknowledged, and that this thesis (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Signed: ……..

Ameed Awny Fawzy Mushtaha

Date: March-2009

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Abstract

A descriptive and analytical cross sectional study was performed in Gaza Governorate from 1 October (2006) to 30 September (2007). The aim of this study was to identify the incidence, the distribution and the risk factors of septicemia disease among infants less than 1 year admitted to El-Nassr pediatric hospital, and to assess the association between certain laboratory results and the severity and prognosis of the disease. Data was collected through a structural questionnaire administered to 366 subjects' parents. Response rate was 100%. The incidence rate of septicemia disease in El-Nassr pediatric hospital was 58/1000 infant. Clear variations were found in the incidence according to sex, age groups, governorates, socio-demographic, economic status, microorganisms causing septicemia and antibiotic resistance. The disease was prominent among neonates with age less than 28 day with percentage 49.5%. The risk age group was children less than 8 days with fatality rate 20%. The total fatality rate was 10.1%, and it was higher among females. Low socio-economic status, families of high crowding index, parents of low educational level and with low income jobs were associated with the disease, and its severity. There was clear seasonal variation in incidence of disease with a peak in winter and summer.

Gram positive bacteria was more prominent in our study pateints with percent of 79%, while Gram-negative bacteria was less prominent in percent of 21%. However the fatality rate in Gram-negative bacteria was 23.4% compare with 6.6% in Gram-positive bacteria.

Results show that high percentage of bacteria was resistant to cloxacillin (77.8%) while it was lower with Meropenem (25%). On other hand the study demonstrates that bacteria were sensitive to Ciprofloxacin (100%), Penicilline (90%) and Amikacin (86.2%).

Our study contributes in highlighting the major risk factors for implementing strategies that could help in prevention of Septicemia disease. Therefore, we recommend the need for application of vaccination programs against some types of bacteria that cause Septicemia

as H. influenzae type b, S. pneumoniae and N. meningitides serogroup W135 especially for infants. Furthermore, high index of suspicion is needed among the medical staff for early diagnosis and treatment of septicemia.

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Operational definition of variables

Date

The date of admission of patient was taken from the patient chart. The data was collected in the first day of admission before starting treatment in the hospital. In addition the date was needed to determine the season of disease occurrence.

Father and child ID

To help the researcher to review the patient chart and preventive medicine records if there is any missing information.

Age

The age of children was determined by days. The age was classified into three groups (<8, 8-28, 29-366). This classification was depending on the classification of (WHO) as early neonates, late neonates, postneonate. In Palestine, according to cultural considerations, the pediatric hospitals receive the cases of children of age equal or less than 12 years. In this study the children were considered whose ages less than 1 year.

Weight

The weight in grams, was taken at delivery of children from patient chart to be used in classification of weight into three groups; underweight (below 2500 gm), normal weight (2500-4000 gm), and overweight (above 4000 gm).

Address

The address of children was classified according to the governorates of Gaza Strip, according to classification of PCBS. The address was determined from the parents of children by interview.

Parents' education

The educational level of children parents was determined by years of education. The educational level was classified into four groups according to PCBS 2006 report; illiteracy (not reading and writing), basic (1-10 years), secondary (11-12 years), and high (more than 12 years). The education of parents was known by asking the parents during the interview.

Parents' occupation

The occupation of parents of children was known from the parents of children during the interview. The occupation of fathers was classified into two categories; the first which is unemployed, the second category which is employed. The occupation of mothers was classified into house wives and employed.

Crowding index

The crowding index was determined by dividing number of persons in the house by number of rooms in the house. The crowding index was classified into three groups; less than 2, two or less than 3, and three and more.

Family income

The family income was determined by asking the parents of children. The income was classified into three groups; high (over 2300 new shekalim), moderate (1800- 2300 new shekalim) , and low (less than 1800 new shekalim)as the parents of children perceived according to PCBS 2006 report.

History of URTI

It was determined by asking the parents of children if the child was complaining upper respiratory tract infection, one week preceding the onset of septicemia disease.

Fever

Fever was determined by a mercury thermometer and was known from the chart of patient. The temperature degree more than 37.8º C was considered fever and less than 37.8º C was considered hypothermia (Kliegman, et al, 2007).

Skin lesions

The skin lesions were characterized by petechial rash or purpura which determined from the chart of patient.

Diagnosis

The diagnosis was taken from the patients' charts. The diagnosis was classified into two groups according to laboratory criteria for diagnosis and clinical manifestations. These groups are; septicemia, and combination of meningitides and septicemia.

Antimicrobial Resistance

Antimicrobial resistance is the ability of infectious organisms to adapt quickly to new environmental conditions. According to the culture and sensitivity test results, antimicrobial resistance was classified in to three categories: Sensitive, Intermediate and resistant. Antimicrobial resistant was taken from laboratories records.

Prognosis

The prognosis of case was known from the patient chart. The prognosis was classified into two groups; either recovery or death.

Anorexia, Tachycardia, Tachypnea, Vomiting, Convulsion, Coma and Shock

All these variables were determined from the chart of patient according to Kliegman, et al, 2007.

Sepsis

The presence of various pus-forming and other pathogenic organisms or their toxins in the blood or tissues. Septicemia is a common type of sepsis.

List of Abbreviations

ABE	Actual Base Excess
API	Analytical Profile Index
APTT	Active Partial Thromboplastin Time
AR	Attack Rate
BAP	Blood Agar Plate
BUN	Blood Urea Nitrogen
BW	Birth Weight
Cº	Degree Centigrade
Ca	Calcium
CAP	Chocolate Agar Plate
CBC	Complete Blood Count
CDC	Centers For Disease Control And Prevention
CI	Coefficient Interval
CNS	Central Nervous System
CO^2	Carbon Dioxide
CONS	Coagulase Negative Staphylococcus
CRP	C-Reactive Protein
CSF	Ceribrospinal fluid
C5a	Complement Factor
DIC	Disseminated Intravascular Coagulation
E.Coli	Escherichia Coli
EDTA	Ethylenediaminetetraacetate
EOS	Early Onset Septicemia
G	Gaza Governorates
GAS	Group A Streptococcus
GBS	Group B Streptococcus
GDP	Gross Demestic Product
GDS	Group D Streptococcus
GNI	Gross National Income
GNP	Gross National Product
GOD	Glucose Oxidase

Hb	Haemoglobin
HCO3	Bicarbonate
ICD	International Coding of Diseases
ICU	Intencive Care Unit
IgG	Immunoglobuline
INF	Interferon
INR	International Normalized Ratio
IL	Interleukin
IV	Intervenous Infusion
K	Potassium
LBW	Low Birth Weight
LOS	Late Onset Septicemia
LPS	Lipopolysaccharide
MCH	Maternal Childhood Health
MOH	Ministry Of Health
MODS	Multiple Organ Dysfunction Syndrome
MRSA	Methicillin-resistant Staphylococcus aureus
N.meningitids	Neisseria meningitidis
Na	Sodium
NGO	Non-Governmental Organization
NH	Neisseria Haemophilus
NICU	Neonatal Intencive Care Unit
PBPS	Penicillin Binding Proteins
PCBS	Palestinian Central Bureau of Statistic
PCR	Polymerase Chain Reaction
PH	Pro-hydrogenium
PHC	Primary Health Care
Plts	Platelets
P-V	P- Value
PROM	Premature Rubture of Membranes
RBC	Red Blood cells
SD	Standerd Diviation
SIRS	Systemic Inflammatory Response Syndrom

SPSS	Statistical Package For Social Sciences
TNF	Tumor Necrosis Factor
TSB	Trypticase Soy Agar
µl	Micro liter
UNRWA	United Nation Relief Work Agency
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
VLBW	Very Low Birth Weight
W.B	West Bank
WBC	White Blood Cell
WHO	World Health Organization

DEDICATION

I dedicate this study to

To

my father

my mother

my wife

my brothers

my sisters

& my sons;

Who gave me inspiration, motivation and continued sustain my commitment.

Al Quds University
Deanship of Graduate Studies
School of Public Health

Thesis Approval

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Chapter One

Introduction

Septicemia or sepsis, refers to generalized bacterial infection in the blood stream (Whaley and Wong, 1997), isolation of an organism from blood culture of an infant with clinical symptoms of infection constitutes the common definition of sepsis (Kaufman and Fairchild, 2004).

Worldwide, infection, as a disease category, is responsible for the majority of deaths and loss of good health in children (Forfar and Arneils, 2003).

According to the World Health Organization (WHO) at least 6 million children die each year of pneumococcal infection (e.g. pneumonia, meningitides, bacteremia), most of these fatalities occur in developing countries (Gielbink, 2001).

Internationally: sepsis is a common cause of mortality and morbidity worldwide (Cunha, 2003), neonatal septicemia is an important cause of mortality and morbidity among infants (Ako-Nai, Ajayi and Onipede, 1999).

Globally about 5 million neonatal deaths occur worldwide every year, 98% of which occur in developing countries particularly in Asia and Africa. Infections such as tetanus, pneumonia, septicemia, meningitis and diarrhea, account for 30 – 50% of neonatal deaths in developing countries (Darmstadt, 2001).

In Palestine, septicemia and other infectious diseases are considered the 4^{th} causes of death among infants in the past five years with a proportion of 7.3% of total infant death in 2005 (Palestine, MOH, October, 2006).

Neonates are susceptible to infection because they have diminished nonspecific and specific immunity (Whaley and Wong, 1997), and they have high mortality and morbidity rate (Misallati, El-Bargathy, and Shembesh, 2000), immunocompromised children (those

with neutropenia, malignancy and AIDS) are more susceptible to the development of septicemia (Behrman and Kliegman, 2002).

1.1 Problem statement

Infant septicemia is a common cause of mortality and morbidity in worldwide, and associated with other factors as, socioeconomic factor, health status and source of infection. The financial burden of septicemia have been well documented in literatures, Determining the incidence and case fatality rate, identifying the most common types of bacteria causing septicemia, and to examine the relationship between certain laboratory results and prognosis are important for the design of effective preventive public health strategies to combats the rise in communicable diseases including septicemia. No such information existed in the Palestinian infants in Gaza Strip population before this study.

1.2 Rationale of the study

In Gaza Strip infant septicemia is still considered one of main causes of morbidity and mortality in hospitalized newborns, and considered the 4^{th} causes of death among infant in Palestine in the past five years.

Septicemia increase the length of time spent in the hospital and incurs costs relating to the involvement of medical staff, antimicrobial drugs, laboratory tests and other factors depending on the treatment employed.

The geographical, social and economical conditions that are found in our region permit the spread of septicemia among infants.

Gaza Strip is considered one of the highest over crowded areas in the world with incomplete infrastructure and bad housing conditions.

In Gaza Governorates', Palestine, no previous studies have been carried out about risk factors of infant septicemia. So we need further study which is intended to discover more about incidence of septicemia among infants, and identify the risk factors.

1.3 General objectives

To estimate the incidence rate of septicemia among infants at El-Nassr pediatric Hospital and to identify the causative organisms.

1.4 Specific objectives

1- To determine the incidence and case fatality rate of septicemia among infants at El-Nassr Pediatric Hospital.

2- To identify the most common types of bacteria isolated from blood among infants.

3- To study demographic characteristics associated with septicemia among infants.

4- To investigate the relationship between septicemia and seasons among infants.

5- To determine antibiotics resistance for the isolated bacteria among infants.

6- To examine the relationship between certain laboratory results and prognosis and complications of septicemia.

1.5 Research questions

1- What is the incidence and case fatality rate of septicemia among infants at El-Nassr Pediatric Hospital?

2- What are the most common types of bacteria isolated from blood among infants?

3- What are the demographic characteristics associated with septicemia among infants?

4- Is there an association between septicemia and seasons among infants?

5- What is the antibiotic resistance for the isolated bacteria among infants?

6- Is there an association between certain laboratory results and prognosis and complication of septicemia?

1.6 Geographical and demographical background

This study aims to find out the incidence of septicemia among infants admitted to El-Nassr pediatric Hospital and to identify the causative organisms and risk factors in Gaza Strip. Because of the political situation, it is hard to apply the study in all the Palestinian territories, and for that the study took place in Gaza Strip at El-Nassr pediatric Hospital as the main pediatric hospital in the Gaza Strip. The researcher found that presenting general information about the geographical and demographical situation of Palestine would be an asset.

1.6.1Geographical background

Palestine constitutes the southwestern part of a huge geographical unity in the eastern part of the Arab world, which is Belad El-Sham. In addition to Palestine, Belad El-Sham consists of Lebanon, Syria and Jordan. It used to have common borders with these countries, in addition to Egypt. Palestinian region stretches from Ras Al-Nakoura in the north to rafah in the south. The entire area of Palestine is about 27,000 sq. Km, including Tabariya, El-Hoola lakes and half of the area of Dead Sea (Palestine, MOH, October, 2006).

Israel was established on 78% of Palestine in 1948, leaving 22% of its land (the West bank and the Gaza Strip) for Palestinian, was also occupied it in 1967. A peace accord was signed between PLO and Israel in 1993, leaving the control of the Palestinian people in the hands of the Palestinian National Authority, which lead the way into an independent Palestinian state (Palestine, MOH, 1999).

Now, Palestine comprises two areas separated geographically: the West Bank and the Gaza Governorates.

The Gaza Governorates is a narrow piece of land lying on the coast of Mediterranean sea. Its position on the crossroads from Africa to Asia made it a target for occupiers and

conquerors over the centuries. The Gaza Strip is a very crowded place with an area of 365 sq. Km, and constitute 6.1% of total area of Palestinian territory land. Gaza Governorates is administratively divided into five governorates: North, Gaza city, Mid-zone, Khan-younis, Rafah. It consists of four cities, fourteen villages and eight refugee camps (Palestine, MOH, 1999).

In August, 2005 the Israel evacuated the occupied Gaza Strip, including all existing Israeli settlements and all military installations which redeployed outside the Gaza Governorates.

The West Bank is located west the river Jordan with area of 5,655 sq. Km. It has been under Israel Military Occupation, together with East Jerusalem and Gaza Strip since June 1967. The West Bank is divided into four geographical regions. The North of West Bank includes the districts of Jenin. Tulkarem, Qalqylia, Salfit and Tubas districts. The Center includes the districts of Ramallah and albireh, and Jerusalen. The South includes the Bethlehem and Al-Khaliel districts, and the sparsely populated Jordan valley including Jericho.

The West Bank has main eleven Governorates: Al-Quds (Jerusalem), Al-Khaliel (Hebron), Bethlehem, Jericho and Al-Aghwar, Ramallah and Al-Bireh, Nablus, Qalqiliah, Salfit, Tulkarem, Jenine and Tubas. And in this region there are 10 cities, with 430 villages and 18 refugee camps (Palestine, MOH, October, 2006).

1.6.2 Demographical characteristics

1.6.2.1 Population size and structure

The mid year population size of Palestine in 2005 was estimated at 3,762,005, out of total number 2,372,216 in West Bank and 1,389,789 in Gaza Governorates with percent (63%) and (37%) respectively. Out of which 50.65% are males, and 49.35% are females. The population pyramid of Palestine shows that 46.3% of population under the age of 15 years, this pattern is more pronounced in Gaza Strip, where 49.1% of population is under 15

years old, while it is 44.2% in the West Bank. The age group 0-5 years old still constitutes the largest population (17.5%), (19.2% in Gaza Strip and 16.6% in West Bank), while it constitutes 2.8% for ages over 65 years. The median age was 16.7 years and the life expectancy at birth for males was 71.7 years and for females was 73 years. The dependency ratio was 96% for whole Palestine (107% for Gaza Governorates and 90% for West Bank).

Population density in the Gaza Strip is very high, compared with the density in West Bank, and it reaches 3,808 people per Km2 in Gaza Governorates, and around 420 people per Km2 in West Bank, taking into consideration that a considerable part of the land is still under Israeli occupation and occupied by Israeli settlements, which aggravated the problem of density. The annual growth rate of Palestinian population was dropped from 5.2% in 1995 to 3.1% in 1998, to 3% in 1999 and 2000 to 2.61 in 2001 to reach 2.6 in 2005 (Palestine, MOH, October, 2006). The population growth rate in Palestine is the same as that of Syria and Lebanon. In Egypt, it is 2.0%, Cyprus 1.5%, and in Jordan 3.8% (Palestine, MOH, 2000).

1.7 Economic situation

The World Bank stated that the Gross National Production (GNP in Palestine has been subjected to high fluctuations during the last five years. Gross National Production (GNP) was 5,454 million US$ in 1999 and decrease to 4,169 million US$ in 2005. Gross Domestic Production (GDP) was 4,517 million US$ in 1999 and decreased to 3,832 million US$ in 2005. Gross National Production per capita (GNP/capita) was 1,806 US$ in 1999 and decreased to 1,039 US$ in 2005. Gross Domestic Production per capita (GDP/capita) was 1,496 US$ in 1999 and decreased to 955 US$ in 2005.

The number of workers in Israel decreased from 135,000 in 1999 to 36,000 in 2005 . The World Bank reported that the unemployment rate was 32%, (30.3% in Gaza Governorates

and 20.3% in West Bank). This revealed sharply increasing of unemployment rate from 11.8% in 1999 to 32% and the poverty rate in Palestine was 44% in 2005. This situation is a result of Israeli enforced restriction on Palestinian movement, military operation, land confiscation and leaving and the construction of Barrier in addition to other escalating activities imposed on Palestinian people (Palestine, MOH, October, 2006).

According to WHO report, 2007, the poverty in Gaza Strip has deepened to an unprecedented level, affecting 80% of households compared with 63% in 2005, with about two thirds experiencing deep poverty. Poverty levels are about 30% lower in the West Bank. Unemployment in Gaza Strip rose from 30% in 2005, to almost 35% in 2006 and 38% in the third quarter of 2007 (WHO, 2008).

1.8 Health status

The crude birth rate was estimated as 27.5 /1000 by 2005 , in the Gaza Governorates 33.7/1000 and 23.9/1000 for West Bank (Palestine, MOH, October, 2006). According to PCBS (Palestinian Central Bureau of Statistics), in (2006) the reported that the total fertility rate in Palestine was estimated as 4.8, in the West Bank was 4.2, and 5.8 in the Gaza Governorates (PCBS, 2007). The crude death rate in 2005 was estimated as 2.5/1000 for the West Bank and 3.1/1000 for Gaza Strip. The infant mortality rate in Palestine was 20.8/1000 live birth in 2005 , and the neonatal mortality rate was 11.2/1000 live births (Palestine, MOH, October, 2006).

1.8.1 Communicable diseases in Palestine

The Palestinian health authorities have succeeded in the prevention and complete control of many infectious diseases. Where there are no cases of schistosomiasis, leprosy, diphtheria, plague, poliomyelitis, rabies, relapsing fever or malaria has been reported in the last years. Other infectious diseases, such as meningococcal meningitis, brucellosis, HIV,

hepatitis, tuberculosis, diarrhea, pneumonia and parasitic infestation remain challenges. Regular notification is needed for the success of their prevention and control programs. According to Palestine, MOH, October, 2006, 1,044 deaths were reported due to the infectious diseases in 2005 with a proportion of 10.3% of total deaths, with a rate of 27.8 per 100,000 populations. Among infants and children under five years, 179 and 233 deaths were reported with a rate of 1.7 and 0.3 per 1000 infant and children respectively. 44 deaths and 159 deaths were reported among ages 5-19 and 20-59 with a rate of 2.9 and 10.8 per 100,000 population respectively. The mortality rate due to the infectious diseases among adult aged 60 and above was 369.4 per 100,000 population. Distribution of mortality by sex due to the infectious diseases was 53.4% among males with a rate of 29.2 per 100,000 and 46.6% among females with a rate of 26.2 per 100,000. Mortality rate due to pneumonia and other respiratory infections still the highest incidence rate of infectious disease, per 100,000 population which constituted 17.8, septicemia 7.7, diarrhea and gastroenteritis 0.2 and meningococcal disease 0.4. Moreover 65 deaths (47 deaths in G and 18 deaths in WB) were reported due to other infectious diseases with mortality rate of 1.7 per 100,000 population, including hepatitis and pulmonary TB (Palestine, MOH, October, 2006).

1.8.2 Healthcare System

There are four groups of healthcare providers in Palestine. The Palestinian Ministry of Health (MOH), the United Nation Relief and Works Agency (UNRWA), the non-governmental sector non-profit agencies (NGO), and the private for profit providers (El-Telbani, 1999).

1.8.2.1 Healthcare facilities

1.8.2.1.1 Primary healthcare

Primary health care system (PHC) is a major component of Palestinian health care system, this system has provided health care to all Palestinian people especially for children and other vulnerable groups (Palestine, MOH, October, 2006). The (MOH), is working with other health sectors in providing the primary health services mainly with (UNRWA), and (NGOs) sector. At the end of 2005, there are 654 PHC centers in Palestine, these centers are cared for about 3.7 million people (129 centers in Gaza Strip and 525 centers in West Bank). The MOH is considered the main provider with 63.6% from the total PHC centers, followed by the (NGOs) with 28.3% then (UNRWA) with 8.1%.

The average ratio of persons per center was 5,752. The number of PHC centers per 10,000 persons was 1.7 in 2005 while it was 1.9 in 2000 (Palestine, MOH, October, 2006).

1.8.2.1.2 Secondary Healthcare

In Palestine the secondary health care is provided by the governmental, non-governmental, (UNRWA and private sectors). The MOH is responsible for a significant portion of the secondary healthcare delivery system (60-70% of general and specialized hospital beds) and more than this proportion in hospital services (about 70% of hospital services).

In Palestine in 2005, there are 76 hospitals, distributed to 43 general hospitals with 3,726 beds, 10 specialized hospitals with a total bed capacity of 812 beds, 19 maternity hospitals at a total bed capacity of 322 beds and four rehabilitation centers with a total bed capacity of 165 beds.

In Palestine, the comparison between hospital beds in 2001 and 2005 shows a little increase in the bed capacity from 4,522 in 2001 to 5,025 in 2005 with an increase percentage of 11.1% in comparison with 2001 with an annual increase of 2.2% although the population annual increase in the last five years was 2.8%.

The MOH owns and operates 24 hospitals (13 in Gaza Strip and 12 in the West Bank), furnished with 2,815 beds (1,499 in Gaza Strip and 1,316 in the West Bank) (Palestine, MOH, October, 2006).

The MOH hospitals in Gaza Governorates are distributed as the following: Al-Shifa hospital, El-Nassr pediatric hospital, Specialized pediatric hospital, Al-Dora pediatric hospital, Ophthalmic hospital and Psychiatric hospital are in Gaza governorate, Kamal Odwan hospital, Beit-hanoon hospital in the north Gaza governorate, Al-Aqsa hospital in middle zone governorate, Nasser hospital, European hospital in Khanyouns governorate, Al-Najar hospital and Tal elsoltan hospital in Rafah governorate (Palestine, MOH, 2004).

1.8.2.1.3 El -Nassr pediatric hospital

El–Nassr pediatric hospital deals only with children aged 12 years or less. It is located in Gaza and it had been constructed in 1962 for gynecological and obstetric cases but it was charged in 1972 to pediatric hospital.

The hospital developed very much especially after the arrival of Palestinian National Authority in 1994, so as to meet philosophy which is based on delivery of high standard health care to Palestinian children with in the available resources.

As we see, the number of beds has increased from 135 beds to 200 in addition to improvement of qualification and abilities of the staff in quality and quantity.

Also, subspecialty departments like hematology and oncology department were created to offer treatment for blood diseases and cancer which ultimately lead to substantial decrease in referrals of patients to abroad.

Intensive care unit and nephrology department deal with the peritoneal dialysis for patients with renal failure.

Great development in both quality and quantity was also observed in laboratory and X-ray departments. A big advance occurred in nursing power as the number of nurses was

doubled in addition to achievement in qualification and training and a significant number of nurses has got a master degree in nursing, administration and mental health.

Finally it was a big achievement when El–Nassr pediatric hospital has been recognized as teaching hospital by Egypt, faculty of medicine and paramedical colleges.

The fiscal consequences of political developments in the occupied Palestinian territory in 2006 have had an impact on the Ministry of Health's budget, and consequently on the delivery of health services and programmes. For instance, they affected its capacity to maintain a stock of pharmaceuticals and consumables and pay salaries to its staff, which has resulted in a prolonged health workers' strike across the West Bank.

1.8.2.1.4 The Laboratories

Laboratories and Blood Banks Directorate in MOH provides widespread and advanced services in all primary and secondary health care centers. These are advanced and distinguished around all Gaza governorates (Palestine, MOH, 2001).

The laboratory services in the MOH are offered to the Palestinian people at three levels: Central laboratory is referral one specialized for advanced analysis and receives samples from governorates. The intermediate laboratory is a hospital based serving in and out patients and collaborates with nearby hospitals. While, peripheral laboratory is located in the PHC centers.

MOH Hospitals Laboratories are considered the only diagnostic centers in Gaza Strip governorates which confirm the septicemia disease through the blood culture , skin lesion and cerebrospinal fluid examinations for admitted patients. In this study the confirmation of cases carried out in MOH El-Nassr Pediatric Hospital Laboratory , in Gaza Strip MOH Hospital Laboratories which counted 8 laboratories. In addition to this number , MOH laboratories included 32 primary health care laboratories, one central laboratory, one

central blood bank and one public health (food and water) laboratory (Palestine, MOH, October, 2006).

Chapter Tow

Literature Review

2.1 Conceptual Framework for determinants of septicemia among infants

After reviewing the literature the researcher will describe the most common factors that could be associated with occurrence of septicemia among infants. These factors included socio-demographic, socio-economic factors, medical factors, and source of infection.

2.1.1 Socio-demographic factor

Some studies have explored the association of various sociodemographic factors with septicemia. These factors include age, sex, area of residency, family size, and income.

2.1.2 Medical history

Several published studies that provided the relationship between the patient medical health with septicemia as low birth weight, prematurity, Immunocompromize patient. Yancey et al (1996) reported demonstrated a progressive increase in risk for neonatal sepsis in general with decreasing gestational age or associated with low birth weight (Benitz, et al, 1999).

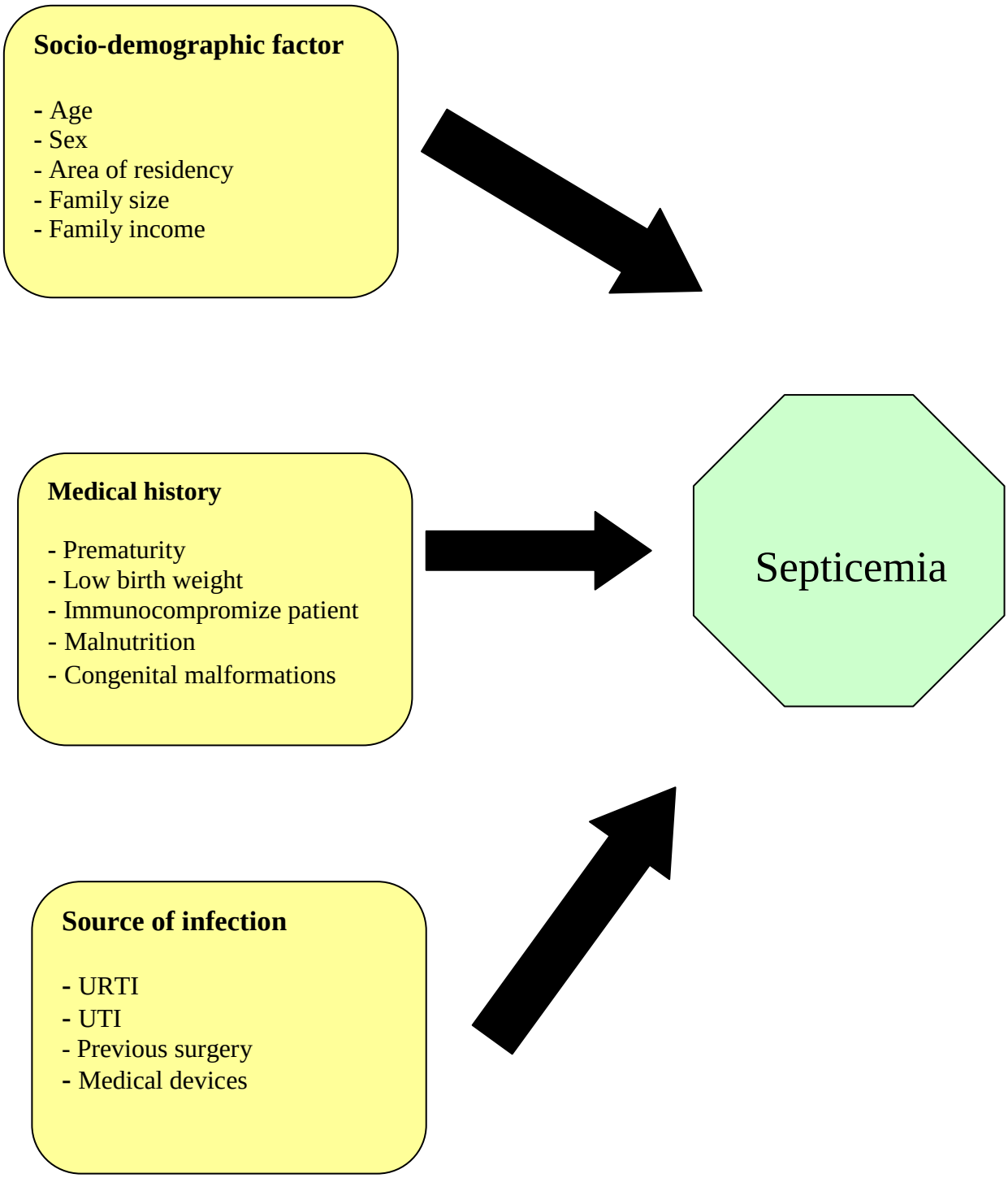
Behrman, and Kliegman, (2002) reported that immunocompromized patients with malignancy, AIDS, nephritic syndrome, Galactosemia, Diabetes, Systemic lupus erythrematosus (SLE), alcoholism, malnutrition or who are taking steroids are at increased risk for septicemia.

2.1.3 Source of infection

Some studies describe the major risk factors for septicemia from medical devices as indwelling intravascular catheters, indwelling urinary catheter, endotracheal intubation,

ventriculoatrial shunts, continuous peritoneal dialysis, prosthetic heart valves, and surgery (Behrman, and Kliegman, 2002). Sepsis may develop as a complication of a localized infection as urinary tract source is suggested by an antecedent history of pyelonephritis, stone disease, congenital abnormal collecting system, prostate enlargement, and previous prostate or renal surgery. Meningococcemia from a respiratory source also may result in sepsis (Burke, 2004).

2.2 Theoritical Diagram of Conceptual Framework



2.3 History of Septicemia

In 1914, Schottmueller wrote, "Septicemia is a state of microbial invasion from a portal of entry into the blood stream which causes sign of illness." The definition did not change significantly over the years because sepsis and septicemia were considered to refer to a number of ill-defined clinical conditions in addition to Bacteremia. In practice, the terms were often used interchangeably; however, less than one half of the patients who have signs and symptoms of sepsis have positive blood culture results. In the late 1960s, several reports appeared describing remote organ failure (eg, pulmonary failure, liver failure) as a complication of severe sepsis. In 1975, a classic editorial by Baue was entitled "Multiple, progressive or sequential systems failure, a syndrome of the 1970s." This concept was formulated as the basis of a new clinical syndrome. Several terms were cloned thereafter, such as multiple organ failure, multiple system organ failure, and multiple organ system failure, to describe this evolving clinical syndrome of otherwise unexplained progressive physiological failure of several interdependent organ systems. More recently, the term multiple organ dysfunction syndrome (MODS) has been proposed as a more appropriate description (Sharma, 2006).

2.4 Definition of Septicemia

Septicemia is a clinical term used to describe bacteremia with clinical manifestations of a severe infection, including chills, fever, malaise, toxicity, and hypotension, the extreme form in shock. Shock can be caused by toxins produced by Gram-negative rods or Gram-positive cocci (WHO,2003).

Over the last three decades the syndrome now commonly referred to as sepsis has alternately been called septicemia, sepsis syndrome, or simply sepsis. One definition of sepsis was described jointly with the closely related concept of systemic inflammatory response syndrome (SIRS) (Jaimes, 2005).

Bacteremia is a bloodstream infection and is documented by positive blood cultures. This is distinguished from sepsis, which is the systemic response to infection and includes tachypnea, tachycardia, hyperthermia or hypothermia, and neutropenia or leukocytosis (Behrman and Kliegman, 2002). Sepsis is an infection-induced syndrome defined as the presence of two or more of the following features of systemic inflammation: fever or hypothermia, leukocytosis or leucopenia, tachycardia, and tachypnea or supernormal minute ventilation. When an organ system begins to fail because of sepsis, the sepsis is considered severe (Wheeler and Bernard, 1999).

Severe sepsis is complicated by organ dysfunction. Septic shock (hypotension despite adequate fluid resuscitation) is a subcategory of severe sepsis. At the end of spectrum is multiple organ dysfunction syndrome (MODS), defined as the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention. Bacterial septicemia in ICD-10 codes: A41.0 to A41.9 (Aird, 2001).

Septicemia is a growing problem among low birth weight infants. Early identification and treatment of septicemia in these infants would help to reduce the high mortality and morbidity seen with this disorder (Horns, 2000).

Neonates are susceptible to infection because they have diminished nonspecific, specific immunity, and because the infants poor response to infectious agents (Whaley and Wong, 1997).

2.5 Magnitude of the problem

Epidemiological studies from the United State of America and from Europe have shown that sepsis is a widely prevalent syndrome, with either steady or slightly decreasing rates of morbidity and of mortality in recent decades. According to the Society of Critical Care Medicine, and the international Sepsis forum, estimates that the number of sepsis cases in

the world has reached 18 million annually. With a mortality rate of almost 30%, Sepsis is considered a leading cause of death worldwide (Jaimes, 2005).

The reported incidence of neonatal sepsis varies from 7.1 to 38.0 per 1000 live births in Asia, from 6.5 to 23.0 per 1000 live births in Africa, and from 3.5 to 8.9 per 1000 live births in South America and the Caribbean. By comparison, rates reported in the United State and Australasia rang from 1.5 to 3.5 per 1000 for Early Onset Septicemia (EOS) and up to 6.0 per 1000 live births for Late Onset Septicemia (LOS), a total of 6.0 to 9.0 per 1000 live births for neonatal sepsis (Vergnano, et al, 2005).

Each year, Sepsis develops in more than 500,000 patients in the United Stat, and only 55 to 65 percent survive (Burry and Wax, 2003).

2.5.1 International magnitude of Septicemia

Septicemia is still one of the most important cause of morbidity and mortality in infants especially in the neonatal period. Infection is responsible for approximately 2 million neonatal deaths per year in developing countries (Lanari et al, 2001).

According to study in the United State in 1995, a total of 9,675 children with sever sepsis. The incidence was highest in infants (5.16 per 1,000) and fell dramatically in older children (0.2 per 1,000), 48% were less than 1 year of age, and 55.1% of cases were male. The high rate of severe sepsis in infants was largely due to neonatal severe sepsis (69.7% of infants). Two-thirds (69.3%) of neonates were low birth weight (LBW) and half (52.7%) were very LBW (VLBW). The annual incidence of severe sepsis in newborns was 0.3 of 100 live births. Four-fifths (81.1%) of newborns were LBW, and nearly two-thirds (63.6%) were VLBW. Mortality of the 9,675 children with severe sepsis, 993 (10.3%) died before discharge. Hospital mortality generally varied little with age except for the significantly higher rate (13.5%) among non-neonatal infants (those 1–12 months old). Infant boys had a higher mortality rate than infant girls (63.9 versus 45.1 per 100,000).

Among newborns, LBW babies had a higher hospital mortality than babies of normal birth weight (11.0% versus 6.1%), and LBW boys had a higher hospital mortality than LBW girls (13.5% versus 7.8%). The most common infecting organism was Staphylococcus (17.5% overall), especially among neonates (25.7% of all neonatal infections). Meningococcal infections were uncommon (1.2% of all infections) and much less common in patients with comorbidity than without comorbidity (0.2% versus 2.2%, $p < 0.001$) (Scott Watson et al, 2003).

According to study in the United State, 2003 of children less than 19 years of age hospitalized with severe sepsis. There were 12604 cases, representing 21448 hospitalizations nationally in 2003. Over half (53%) of all hospitalized patients were male, and 58% were infants and children <5 years of age. Another peak in the frequency of hospitalizations (18%) was in children 15 to 19 years of age. Over half (59%) of hospitalizations were related to major or extreme illness severity, the overall in-hospital mortality rate was 4.2%. Nearly half of all fatalities occurred among children <5 years of age, and 25% occurred among children 15 to 19 years of age. There was no gender difference in mortality; however, patients with comorbid illness or extreme illness severity had higher mortality rates. Comorbid illness was present in 34% of all hospitalized children. Cardiac dysfunction occurred in 46.4% of the hospitalized children. Other dysfunctional organ systems were, in decreasing order of frequency: respiratory (39.2%), hematologic (19.5%), neurologic (8.1%), renal (7%), and hepatic (0.7%) (Odetola**,** Gebremariam**,** and Freed**,** 2007).

In the United State a study published by the centers for disease control and prevention (CDC) that indicate the incidence of septicemia had increased 139%, from 73.6 per 100,000 patients in 1979 to 175.9 per 100,000 patients in 1987 (Angus et al, 2001).

In 1990, the centers for disease control and prevention (CDC) reported an estimate of 450,000 cases of septicemia per year in the United Stat, with over 100,000 deaths. Other studies suggest that less than 28-day mortality rate of sever sepsis may be 50% or greater. (Aird, 2001). Estimated that 750,000 cases of sever sepsis occur per year, with mortality rate of 28.6% (Martin, Mannino, Eaton, and Moss, 2003), according to recent reports, the incidence is rising at rates between 1.5% and 8.0% per year (Riedemann, Feng Guo, and Ward, 2003).

According to study in the United State in 1990, the case fatality rates associated with early and late-onset septicemia, GBS septicemia were 4.7% and 2.8% respectively. Mortality is higher in premature infants, the study reported a case fatality rate of 30% in infants whose gestational age was <33 week and 2% in infant whose gestational age was 37 week or older. The case fatality rate in children aged 3 months to 14 years was 9% (Kliegman, et al, 2007).

According to Angus et al, 2001, the mortality rate due to sever sepsis represented 9.3% of all deaths in United Stat in 1995. Importantly, the incidence of severe sepsis was projected to increase by 1.5% per year (Angus et al, 2001).

In Spain a total of 30,993 admissions to the neonatal units of the participating hospitals, the nosocomial septicemia rate was 2.1% with an incidence rate of 0.89 per 1000 patient. The over all mortality rate was 11.8% (Sastre, Catallo, and Colomer, 2002).

In Stockholm the most common causative organism was Group B Streptococcus with incidence of 1.4 per 1000 live birth, in 17,586 live birth in the area and the incidence of neonatal septicemia was 2.6 per 1000 live birth (Faxelius and Ringertz, 1987).

In Norwegian National study of all infants with gestational age of <28 weeks or birth weight of <1500 g who were born in Norway in 1999–2000 was performed. The incidence

rate of septicemia within the first 3 days of life ranging between 1.5% and 2.7%, case fatality rates are high, ranging from 26% to 36% (Ronnestad et al. 2005).

According to study in Mexico from 1992 to 1996 among 945 newborn admissions, 103 septic patients with 147 episodes of Bacteremia were detected. Over all mortality rate was 34% but septicemia related mortality rate was 13% (Castorena, and Sierra , 1998).

In the Nigeria, the total number of live births in the Ilorin teaching hospital during the study period was 4118, the incidence of neonatal septicemia was 7.04 per 1000 for in-born patients, the male : female ratio was 1.2 to 1.0 respectively (Mokuolu, Jiya, and Adesiyun. 2002), and in the other study at the university of Benin teaching hospital (UBTH) of Nigeria the incidence of neonatal septicemia was 6.1 per 1000 live births, fifty five percent of the infants were low birth weight (Omene, 1997).

During 1995-1996 among 13367 live birth in the South India with 131 episodes of septicemia among 125 newborn infants, were 18 (14.4%) of whom died. Thirty (24%) had Early Onset Septicemia (EOS) (diagnosed within 48 hours after delivery), and 95 (76%) had Late Onset Septicemia (LOS) (diagnosed after 48 hours of age) (Anil, Pillai, Jesudason, and Kumar, 1989).

In Nairobi, Kenya, a total of 308 records of neonatal infants admitted to the general pediatric wards at Kenyata pediatric hospital during year 2000, the mortality rate was 315 per 1000 neonatal infants admitted. Of the 308 admission, 33.4% were have low birth weight (LBW), 5% being very low birth weight (VLBW). The common diagnosis at admission or discharge were suspected septicemia, 71% (confirmed septicemia 8.4%) (Simiyu, 2003).

2.5.2 Magnitude of Septicemia in neighboring countries

Asghar, (2006) reported that, study of 1626 septicemic cases in Saudi Arabia (in the 4 main hospitals in Makkah City) during April 2004 to March 2005. The result showed the

overall case fatality rate was 11.9%, the most age groups affected with septicemia were in infants and patients above 50 years old (Asghar, 2006). Five years from September 1983 to September 1988 were 61 cases of neonatal septicemia identified positive blood culture during surveillance of infection at King Fahd Hospital of the university in khobar Saudi Arabia, the incidence of neonatal septicemia was 4.9 per 100,000 live births among inborn infants, birth weight specific sepsis rate ranged from 2 per 1000 live births among infants with birth weight > or = 2500g to 150 per 1000 live births in those weighting < or = 1500g (Dawodu, Al-Ummran, and danso, 1997).

In Libyan Arab Jamahiriya, the study was conducted in the neonatal unit at Al-Fatah children's Hospital Benghazi. During the study period, October 1997 to March 1998, the total number of neonates with positive blood culture was 36, of the 36 infants, 12 died (fatality rate = 33%)(Misallati, El-Bargathy, and Shembash, 2000). In Iraq a study done by Al-zwani, September, 2002, 118 neonates admitted to the main referral hospital in Al-Anbar with positive blood cultures. The incidence of neonatal septicemia for babies born at this hospital was 9.2 per 1000 live births, and mortality was 28% (Al-Zwaini, 2002).

In Jordan a study by Nazer, 1981, 112 cases of neonatal septicemia were diagnosed at the Jordan University Hospital over the two years period (1977–1978). The mortality rate among all cases was 42% (42.8% for 1977 and 41.2% for 1978)(Nazer, 1981). In Jordan neonatal septicemia is a major cause of mortality and morbidity in newborn. The incidence of 2.3 per 1000 live births (Daoud et al, 1995).

In Israel a study done by Leibovitz, et al, 1997, during the four years period 1989–1992, 18,227 neonates were born at Kaplan Hospital and 614 (3.4%) were admitted to the neonatal intensive care unit. During this period, 120 episodes (6.6 per 1000 live births) of neonatal sepsis were recorded in 109 neonates (6.0 per 1000 live births). The incidence

rate of early onset septicemia was 19/109 (17%), the overall fatality rate due to septicemia was 14% (0.8 per 1000 live births) with early onset septicemia death rate of 37% (Leibovitz, et al, 1997).

2.5.3 Magnitude of Septicemia in Palestine

In Palestine infant septicemia is still considered one of main causes of morbidity and mortality in hospitalized newborn, and considered with other infectious diseases the 4th causes of death among infant in Palestine with proportion of 7.3%, the infectious diseases include: septicemia (6.2%), diarrhea and gastroenteritis (0.1%), meningococcal infection (0.4%) and other infectious disease (0.5%). In the comparison between rates of leading cause of infant deaths per 1000 live births in Palestine 1995 and 2005 showed that septicemia and others infectious diseases were reported at 0.9 per 1000 in 1995 and 1.1 per 1000 live births in 2005 (Palestine, MOH, October, 2006). In Palestine a study done by El-Jadba, (2005), of neonatal septicemia in Gaza city hospitals the study showed 2487 neonates admitted in one year to neonatal intensive care units, were analyzed microbiologically, out of 579 neonatal cases were positive for pathogenic bacteria by blood culture. The incidence rate of neonatal septicemia 12.8 per 1000 live births. And case fatality rate was 45.4% in neonatal septicemia (El-Jadba, 2005).

2.6 The Economic burden of Septicemia

According to Angus et al, 2001, in the United State The average cost per case due to sever sepsis represent 22,100 US$, with annual total coasts of 16.7 billion US$ nationally. Cost were higher in infants, nonsurvivors, intensive care unit patients, surgical patients, and patients with more organ failure. Sever sepsis is a common, expensive, and frequently fatal condition (Angus et al, 2001).

According to study in the United State in 1995 for children with sever sepsis. The mean length of stay (LOS) and cost were 31 days and $47,050, yielding national estimates of 1.3-million hospital days and $1.97 billion. Forty percent of the total hospital days and 31% of the costs were incurred by VLBW newborns, who had a much higher mean LOS and mean cost than other children (74 versus 24 days, $86,910 versus $35,340). The mean LOS and cost were also high in surgical patients (46 days, $80,070) and in patients with comorbidity (37 days, $56,550). Mean LOS and cost were similar between boys and girls. Non survivors had similar LOS, but higher costs, than survivors (30 versus 31 days; $63,730 vs. $45,190) (Scott Watson et al, 2003).

The report on sepsis in Nevada from 2001 to 2005 were showed in 2005 the average billed charges for septicemia, newborn septicemia, septic shock, and systemic inflammatory response syndrome were 118,494 US$, in 2001 the average billed charges were 91,350 US$(Gibbons, et al, 2007). In 2002 a Quebec study conducted by Letarte, et al, (2002), the mean cost for all patients abstracted was 11,474 US$ per episode of care (1,064 US$ /day). The survivors had a mean cost for their treatment of 16,228 US$ per episode of care (877 US$ /day). The total cost per episode was 7,584 US$ per nonsurvivor (1,724 US$/day). An average cost of 27,481 US$ for survivors after day 28 through 1 year was calculated. The burden of severe sepsis was estimated to be 36.4 to 72.9 million US$ per year, but higher if costs beyond day 28 are included (Letarte, et al, 2002). In 1999 a United Kingdom study conducted by Edbrooke, et al, (1999), the cost of treating an ICU patient with sepsis is six times greater than that of treating a patient without sepsis (Edbrooke, et al, 1999).

2.7 The Sources of infection

Sepsis or septic shock may be associated with the direct introduction of microbes into the blood stream via intravenous infusion (e.g. IV line, other device-associated infections). Suspect intravenous (IV)-line infections when other sources of sepsis are eliminated and the IV line has been in for a prolonged period, usually more than a week. Central IV lines are the lines most commonly associated with Bacteremia or sepsis. Peripheral venous lines are almost never involved, and arterial lines are rarely associated with Bacteremia although it can still occur.

Patients with an intra-abdominal or pelvic source of infection usually have a history of antecedent conditions predisposing to perforation or abscess (e.g. Chronic or retrocecal subacute appendicitis, diverticulitis, Crohn disease, previous abdominal surgery, cholecystitis). There may be perforations, compromise, or rupture of an intra-abdominal or pelvic structure.

The urinary tract source is suggested by an antecedent history of pyelonephritis, stone disease, congenital abnormal collecting system, prostate enlargement, and previous prostate or renal surgery. Meningococcemia from a respiratory source also may result in sepsis with or without associated meningitis. Sepsis may be caused by overwhelming pneumococcal infection in patients with impaired/absent splenic function. Sepsis is not a random occurrence and usually is associated with the aforementioned conditions (Burke, 2004).

Sepsis may develop as a complication of a localized infection or may follow colonization and mucosal invasion by virulent pathogens (Kliegman, et al, 2007).

2.8 The Microorganisms causing Septicemia

The infectious agent associated with infant septicemia have changed over the past 50 years (Hickman, et al,1999). The infectious agents associated with sepsis in pediatric patients vary with the patients age and immune status. In the neonatal age group, group B streptococcus, E.Coli, Listeria monocytogenes are the pathogens most commonly associated with sepsis. In older children Streptococcus pneumonia, Neisseria meningitides, H.influenzae, E.coli, Salmonella, S.pyogenes, S.agalactiae and Staphylococcus aureus are more common. Toxic shock syndrome from group A streptococcus or S. aureus can also be seen in older children (Kliegman, et al, 2007).

The spectrum of organisms that cause neonatal sepsis changes over time and varies from region to region. It can even vary from hospital to hospital in the same city. This is due to the changing pattern of antibiotic use and changes in life style. Gram negative organisms were the most common cause of neonatal sepsis in Europe and America in the 1960. It changed to group B streptococcus during the 1970s and coagulase negative staphylococcus during the late 1980 and 1990s (Rahman, Hameed, Roghani, and Ullah, 2002). In Europe and North America, group B streptococci and Escherichia coli contribute to 70%-75% of cases of neonatal septicemia (Gotoff, Behrman, Kliegman, and Arvin, 1996).

2.8.1 Gram-positive bacteria

Staphylococci (mainly Staphylococcus aureus and Coagulase negative Staphylococci) and Streptococci (Streptococcus pyogenes, Streptococcus viridans, and Streptococcus pneumonia) are the commonest causes of Gram-positive sepsis. They are usually responsible for infection of skin and soft tissue, infections associated with intravascular devices, primary bloodstream infections, or respiratory infections. Gram-positive organisms can cause sepsis by at least two mechanisms: by producing exotoxins that act as

super antigens and by components of their cell walls stimulating immune cells (Bochud, and Glandra, 2003).

S.aureus is the most common cause of pyogenic infection of the skin and soft tissue. Bacteremia (primary and secondary) is common and can be associated with or result in osteomyelitis, suppurative arthritis, deep abscesses, pneumonia, empyema, endocarditis, pyomyositis, pericarditis, and rarely meningitis (Kliegman, et al, 2007).

Staphylococcus aureus is responsible for several clinical syndromes (Howard and Kloos, 1993), and can become a serious cause of infection in immunosuppressed host, Bacteremia from Staphylococcus aureus is common and may be associated with acute mitral and aortic valve endocarditis (Elmer et al, 1994).

Staphylococcal bacteremia and sepsis may be primary or associated with any localized infection. The onset may be acute and marked by nausea, vomiting, myalgia, fever, and chills. Organisms may localize subsequently at any site (usually a single deep focus) but are found especially in the heart valves, lungs, joints, and bones. In some instances, especially in young adolescent males, disseminated staphylococcal disease occurs, characterized by fever, persistent bacteremia despite antibiotics, and focal involvement of 2 or more separate tissue sites (skin, bone, joint, kidney, lung, liver, heart). Endocarditis and septic thrombophlebitis must be ruled out.

Untreated staphylococcal septicemia is associated with a mortality rate of 80%. Mortality rates have been reduced significantly by appropriate antibiotic treatment (Kliegman, et al, 2007).

Coagulase negative staphylococcus (CONS) reported to be the third most common causative agent of nosocomial infections and the most frequent causative agent of nosocomial blood stream infections (Agvald-Ohman, lund, and Edlund, 2004). The most

frequently common factor among these patients is prolonged venous catheterization. Although Staphylococcus epidermidis is the major pathogen associated with central venous catheter infections, Staphylococcus hemolyticus, Staphylococcus warneri and Staphylococcus hominis have occasionally been implicated (Howard and Kloos, 1993).

CONS, specifically S. epidermidis, are the most common cause of nosocomial bacteremia, usually in association with central vascular catheters. In neonates, CONS bacteremia, with or without a central venous catheter, may be manifested as apnea, bradycardia, temperature instability, abdominal distention, hematochezia, meningitis in the absence of CSF pleocytosis, cutaneous abscesses, and persistence of positive blood cultures for as long as 2 weeks despite adequate antimicrobial therapy. CONS bacteremia in patients with bone marrow transplantation and malignancy (leukemia, lymphoma) is associated with neutropenia, central venous access (Hickman or Broviac catheters), and gastrointestinal colonization. In most circumstances, CONS bacteremia is indolent and is not usually associated with overwhelming septic shock.

Most episodes of CONS bacteremia respond successfully to antibiotics and removal of any foreign body that is present. Poor prognosis is associated with malignancy, neutropenia, and infected prosthetic or native heart valves. CONS increases morbidity, the duration of hospitalization, and mortality rates among patients with underlying complicated illnesses (Kliegman, et al, 2007).

According to a study conducted by Asghar, 2006 in Saudi Arabia out of the 1626 septicemic cases identified, gram-positive organisms were involved in 56.6% of these episodes. The most often pathogens isolated from blood cultures were staphylococci, which accounted for 43.3% of all isolates. The 2 most common bacterial organisms, were Coagulase negative staphylococci accounting for 24.7% of isolates and Staphylococcus aureus accounting for 18.6% of isolates (Asghar, 2006). In a study done by Radriguez-

cervilla, et al, 1998, Staphylococcus epidermidis was the most frequent agent isolated in blood cultures (38.1%). The highest incidence of sepsis caused by Staphylococcus epidermidis was observed in neonates below 1500g (12.1%) and less than 32 weeks gestational age (13.4%). Staphylococcus epidermidis and other Coagulase negative staphylococcus (CONS) are the main agents causing sepsis in hospitalized neonates (Radriguez-cervilla, et al,1998), According to a study conducted by Vergnano, et al, 2005 the pathogens most often implicated in neonatal sepsis in developing countries differ from those seen in developed countries.

The incidence of sever invasive group A streptococci infections, including bacteremia, streptococcal toxic shock syndrome and necrotizing facilities has increased in the past decade. The incidence appears to be highest in the very young and in older persons (Kliegman, et al, 2007).

Overall of the Gram-positive organisms, Staphylococcus aureus, Coagulase negative staphylococcus (CONS), Streptococcus pneumonia, and Streptococcus pyogenes are most commonly isolated (Vergnano, et al, 2005). In a study by Bindayna, et al, 2006, in Bahrain from 1991 to 2001 of all infants with positive blood culture from the neonatal intensive care unit were reviewed of the 7,978 neonates, Gram positive bacteria were isolated at constant rate over the 11 year period. The main agents isolated were Coagulase negative staphylococcus (CONS) in (41%) of cases, Staphylococcus aureus in (8%)and Group B Streptococcus (7.8%) of cases (Bindayna, et al, 2004).

S.pneumoniae is the most frequent cause of bacteremia, bacterial pneumonia, and otitis media, and the second most common cause of meningitis in children (Kliegman, et al, 2007).

In the United State, the most common manifestation of invasive pneumococcal disease among young children is bacteremia without a known site of infection, which accounts for

approximately 70% of invasive pneumococcal cases among children aged <2 years. Only 12-16% of patients with invasive pneumococcal disease among this age group have pneumonia. The highest rates of invasive pneumococcal disease (e.g., bacteremia, meningitis, or other infection of a normally sterile site) occur among young children, especially those aged <2 years. In 1998, estimated incidence in the United State of invasive pneumococcal infections among children aged <12 months and 12-23 months were 165 and 203 cases/100,000 population, respectively, with peak incidence occurring among children aged 6-11 months (235/100,000). In contrast, incidence among persons of all ages and among persons aged ≥65 years were 24 and 61/100,000, respectively (CDC, 2008).

Group B streptococcus (GBS), or Streptococcus agalactiae, has been a major cause of neonatal bacterial sepsis in the United State since the 1960s. While advances in prevention strategies have led to a recent decline in the incidence of neonatal disease, GBS remains a major pathogen for neonates, pregnant women, and Immunocompromize non pregnant adults (Kliegman, et al, 2007).

2.8.2 Gram-negative bacteria

In the developing world, Gram-negative organisms are more prevalent among the opportunistic of the mothers genital tract normal flora and ultimately these organisms are transferred to the newborns causing outbreaks of various infections (Orrett and Sherland, 2001), Gram negative infection were predominant in 1960s and early 1970s, while Gram positive infection and fungal infection have increased in the past two decades and now account for about half of cases of sever septicemia (Bochud et al, 2001). The spectrum of responsible microorganisms appears to have shifted from predominantly Gram-negative bacteria in the late 1970s and1980s to predominantly Gram-positive bacteria at present. In addition the rate of fungal infection is reported to have increased more than 200% during

the same period (Martin, Mannino, Eaton, and Moss, 2003). Enterobacteriaceae family of Gram-negative bacilli, Proteus organisms are implicated as serious causes of infections in humans, along with Escherichia, Klebsiella, Enterobacter, Neisseria meningitidis and Serratia species, Proteus found in multiple environmental habitats, including long-term care facilities and hospitals (Engle, and Schaeffer, 1998). Gram-negative bacilli (mainly Escherichia coli, Klebsiella species, and Pseudomonas aeruginosa) are the third commonest cause. Gram negative organisms isolated from patients with sever sepsis and septic shock Gram negative infections usually occur in the lung, abdomen, bloodstream, or urinary tract. Lipopolysaccharide is an important component of the outer membrane of Gram negative bacteria and a pivotal role in inducing Gram negative sepsis. Lipopolysaccharide binding protein in host cells binds to Lipopolysaccharide in the bacteria and transfers it to CD14. CD14 is a protein anchored in outer leaflet of the plasma membrane, although it also exists as a soluble plasma protein that attaches Lipopolysaccharide to CD14-negative cells, such as endothelial cells. CD14 is located in the extra cellular space and therefore cannot induce cellular activation without a transmembrane signal transducting coreceptor (Bochud, and Glandra, 2003).

Escherichia coli associated with a number of syndromes including diarrhea, gastroenteritis, cystitis, pyelophrities, septicemia, meningitis, and pneumonia (Weissfeld et al, 1993). In a study by Rahman, et al, 2002 at the Khyber Teaching Hospital in Pakistan a total of 1598 blood cultures were taken: 1003 were positive. Escherichia coli was the most common organism found (36.6%) (Rahman, et al, 2002).

Shigellae and sometimes other gram-negative entericbacilli are recovered from blood cultures in 1-5% of patients in whom blood cultures are taken; because patients selected for blood cultures represent a biased sample, the risk for bacteremia in unselected cases of

shigellosis is presumably lower. Bacteremia is more common with S.dysenteriae serotype 1 than with other shigella, the mortality rate is high (20%) when sepsis occurs (Kliegman, et al, 2007).

Neisseria meningitidis causes fulminant meningococcal sepsis that term used for an overwhelming meningococcal infection. That usually includes Bacteremia , particularly for patients whose infections are so sever that they are in shock, fulminant meningococcemia occurs in 5 to 15% of patients with meningococcal disease and has a high mortality rate. The disease rapidly progresses to septic shock characterized by hypotension, DIC, acidosis, adrenal hemorrhage, renal failure, myocardial failure, and coma (Behrman, et al, 2000).

Klebsiella species is the most encountered Gram-negative pathogen causing nosocomial infections of the lower respiratory tract and is second to Escherichia coli as a cause of primary Bacteremia by Gram-negative organisms (Volk, et al, 1991).

The rate of Pseudomonas aeruginosa bacteremia in children is 3.8/1,000 patients over 10 years with a 20% mortality rate, rates vary according to the prevalent underlying diseases (Kliegman, et al, 2007). Pseudomonas aeruginosa is frequently present in hospital environments, especially in moist places such as sinks, bowels, drains, cleaning buckets. It can also be found growing in eye drops, ointments and weak antiseptic solutions. Pseudomonas aeruginosa causes respiratory infections especially in patients with cystic fibrosis or conditions that cause immunosuppression, septicemia especially in persons already in poor health (Cheesbrough, 1989).

Serratia is an opportunistic Gram negative bacillus that is most often associated with infections of the respiratory tract, urinary tract, wounds and blood stream (Bremer, and

Darouiche, 2005). Serratia marcesens is a pathogen that sometimes causes nosocomial infection, S.marcesens is a well known pathogen that frequently, develops multidrug resistance (Shimizu, Kojima, Yoshida, 2003). Serratia marcesens does not constitute part of the intestinal bacterial flora of infants. This bacterium may be transmitted to neonates through feeding and use soap, contaminated antiseptics, breast pump and tocograph transducers, and it can be spread via contact with the patient (Fleischer, et al, 2002). In Palestine a study done by El-Jadba, 2005, of neonatal septicemia in Gaza city hospitals the Serratia species the second pathogenic microorganisms with percent of (27.5%) (El-Jadba, 2005).

Proteus mirbilis is the most frequent agent of proteus Bacteremia, perhaps because it produces as adhesion that binds to uroepithelial cells, Proteus providencia and Proteus morganella are most often encountered as nosocomial urinary tract infections, but septicemia, pneumonia, and wound infections also occur (Volk, et al, 1991). Proteus mirbilis cause 90% of Proteus infections and can considered a community-acquired infection (Engle, and Schaeffer, 1998).

Various species of Citrobacter may cause infections in neonates and immunocompromized hosts. Citrobacter koseri is best known as the cause of septicemia and meningitis leading to central nervous system (CNS) abscesses in neonates and young infants (Doran, 1999).

2.9 Clinical Manifestations

Bacterial septicemia can take many forms, varying in severity from sepsis, systemic inflammatory response syndrom (SIRS), sever sepsis to septic shock and multiple organ dysfunction syndrome. Septicemia or sepsis characterized by.

- General variables: including temperature (hyperthermia or hypothermia), tachycardia (heart rate > 90 beats/min), tachypnea (respiratory rate >20

breaths/min), chills, unexplained change in mental status, these are age dependent, usually higher in children.

- Inflammatory response variables: including alteration in white blood cells count, increased number of bands, plasma C-reactive protein more than 2 standard deviations above the normal value.
- Hemodynamic variables: including systolic blood pressure <90 mmHg or mean arterial blood pressure <70 mmHg.
- Organ dysfunction variables: including PaO2/FiO2 < 300, decreased urine output, international normalized ratio (INR) > 1.5 or activated partial thromboplastin time > 60 sec, decreased number of platelet , plasma total bilirubin > 4 mg/dl.
- Tissue perfusion variables: including hyperlactatemia >1 mmol/L, decreased capillary refill or mottling (Levy, et al, 2003).

2.10 Pathophysiology of sever sepsis

Severe sepsis associated with 3 integrated responses: 1) activation of inflammation, 2) activation of coagulation, and 3) impairment of fibrinolysis. These 3 responses are due to a variety of proinflammatory mediators, procoagulant factors, and inhibitors of fibrinolysis. Understanding the pathophysiology of severe sepsis and the network of cascading events that occur is important for management patients with severe sepsis (Van der poll, Van Deventer,1999)

2.10.1 Inflammation in severe sepsis

Inflammation is the body's normal response to infection. In response to infectious organisms and their products, white blood cells, specifically monocytes and macrophages, generate and release cytokines, proteins that act as nonspecific mediators of inflammation. Inflammatory cytokines, including tumor necrosis factor, interleukin-1 (IL-1), IL-6, and

platelet-activating factor, are released. Although these early-response cytokines play a critical role in host defense by attracting activated neutrophils to the site of infection, the entry of these cytokines and the products of pathogens into the systemic circulation is also associated with clinical manifestations of SIRS. As part of the host's attempt to reestablish homeostasis, anti-inflammatory cytokines such as IL-4 and IL-10 are also released (Van der poll, Van Deventer,1999). Release of both proinflammatory and anti-inflammatory cytokines may lead to a state of immune refractoriness (Kox, et al, 1997). In sepsis, continued activation of proinflammatory cytokines overwhelms the actions of counteractive anti-inflammatory cytokines, and excessive systemic inflammation results, contributing to impaired tissue function and organ damage (Aird, 2001).

2.10.2 Activation of coagulation

Several mechanisms activate the hemostatic pathway in patients with severe sepsis. Inflammation and coagulation are closely linked. The proinflammatory cytokines IL-1 and tumor necrosis factor stimulate the release of tissue factor, a cell-surface glycoprotein, from monocytes and endothelial cells. Tissue factor directly stimulates the extrinsic coagulation pathway. Stimulation of the intrinsic pathway can also occur in sepsis through cross-talk and feedback mechanisms (Aird, 2001). Regardless of the initiating pathway of coagulation, the result is the formation of the enzyme thrombin, which converts fibrinogen to fibrin, producing a clot. A state of enhanced coagulation occurs in sepsis not only through stimulation of the coagulation cascade but also through a reduction in the levels of protein C and antithrombin III, which are components of the normal anticoagulation system. These events lead to an attenuation in anticoagulant function, resulting in the generation of thrombin and a procoagulant state (Aird, 2001). Continued formation of thrombin leads to a prothrombotic diathesis with formation of microthrombi, which can impair blood flow and organ perfusion.

Alterations in coagulation that occur in sepsis can lead to sepsis-associated coagulopathy and death. The association between activation of coagulation and severe sepsis was delineated more than 30 years ago in patients with septic shock. Activation of coagulation is independent of the type of infectious microorganism, gram-positive bacteria, gram-negative bacteria, fungi, and parasites all can trigger this response. The sepsis-associated coagulopathy meets the criteria of overt disseminated intravascular coagulation in less than 20% of patients. However, a prothrombotic diathesis is almost universal in patients with severe sepsis. For example, in the Effects of Ibuprofen on the Physiology and Survival of Patients With Sepsis trial, (Yan, et al, 2001). Depressed concentrations of protein C and increased levels of D-dimers were detected in almost all enrollees. Abnormalities in fibrinolysis are also common in patients with sepsis (Mcgilvray, and Rotstein, 1998). Thrombocytopenia can also occur and is often due to disseminated intravascular coagulation, inhibition of thrombopoiesis, or increased destruction or margination of activated platelets into the peripheral circulation (Vincent, Yagushi, and Pradier, 2002).

2.10.3 Impairment of fibrinolysis

As part of the body's normal response to activation of the coagulation pathway, fibrinolysis is activated concurrently to promote clot breakdown. In sepsis, activation of the fibrinolytic system is followed by inhibition of the system because of the release of several mediators that suppress fibrinolysis. These include plasminogen activator inhibitor-1 and thrombin activatable fibrinolysis inhibitor. Plasminogen activator inhibitor-1 is produced by endothelial cells and platelets and is the major inhibitor of tissue plasminogen activator, which normally promotes the conversion of plasminogen to plasmin to break down clots. Although plasminogen activator inhibitor-1 and thrombin activatable fibrinolysis inhibitor have a protective function in limiting excessive fibrinolysis, increased levels of these 2 inhibitors suppress fibrinolysis to the point of creating a state of coagulopathy. The

imbalance between inflammation, coagulation, and fibrinolysis that occurs in severe sepsis results in systemic inflammation, widespread coagulopathy, and microvascular thrombosis, conditions that can lead to multiple organ dysfunction (Kleinpell, 2003).

2.11 Multiple organ dysfunction syndrome

As sepsis progresses, alterations in organ function may occur. The prognosis of patients with severe sepsis is related to the severity and duration of organ dysfunction (Lundberg, et al, 1998). Systemic inflammation and simultaneously occurring derangement of the coagulation system lead to the deposition of microvascular thrombin in various organs, a condition that may contribute to the pathogenesis of multiple organ dysfunction syndrome (Levi, et al, 1997). Multiple organ dysfunction syndrome is currently recognized as a major cause of mortality in patients with sepsis. A variety of potential pathophysiological mechanisms have been postulated to result in the syndrome. These include inadequate tissue/organ perfusion, cellular injury, ischemia, and diffuse endothelial cell injury (Balk, 2000).

2.12 The Protein C System in severe sepsis

Protein C is a vitamin K–dependent anticoagulation protease and is involved in regulating the formation of thrombin in the microvasculature and in preventing microvascular thrombosis. Protein C circulates in an inactive state. Activation of protein C requires binding of the protein to 2 endothelial cell-surface receptors: thrombomodulin and endothelial protein C receptor (Esmon, 2001). Activated protein C is a member of a group of natural anticoagulants that include tissue factor pathway inhibitor and antithrombin III. Activated protein C has antithrombotic, anti-inflammatory, and profibrinolytic properties and potentially can correct pathophysiological abnormalities associated with severe sepsis (Balk, and Goyette, 2002). Specifically, activated protein C inhibits cytokine release from

monocytes, reduces neutrophil rolling and subsequent adhesion to the endothelium, inhibits coagulation by inactivating factors VIIIa and Va of the coagulation cascade to prevent generation of thrombin, and stimulates fibrinolysis by reducing the concentration of inhibitors of fibrinolysis (Matthay, 2001). Activated protein C can inhibit plasminogen activator inhibitor-1, thus preventing the blockade of endogenous tissue plasminogen activator and facilitating fibrinolysis (Fisher, and Yan, 2000). Additionally, by limiting the formation of thrombin, activated protein C indirectly enhances endogenous fibrinolytic activity by preventing the activation of thrombin activatable fibrinolysis inhibitor (Fisher, and Yan, 2000). Abnormalities of the protein C system play an important role in patients with severe sepsis. Concentrations of protein C decrease before the onset of clinical manifestations of severe sepsis and septic shock (Mesters, et al, 2000). Low concentrations of protein C in patients with sepsis are associated with a poor clinical outcome, including lower survival rate, higher prevalence of shock, longer stays in the intensive care unit, and fewer days without mechanical ventilation, regardless of age, infectious causes, presence of shock, disseminated intravascular coagulation, or hyper-coagulation (Yan, et al, 2001). Experimentally, infusions of protein C prevented mortality and reversed the coagulopathy associated with the infusion of lethal doses of Escherichia coli. However, in order to obtain the benefits of this protein, the molecule must be activated. In severe sepsis, expression of thrombomodulin by endothelial cells is decreased. Consequently, activation of protein C is impaired, and patients cannot benefit from its protective properties. In recent studies (Bernard, et al, 2001), recombinant human activated protein C reduced the concentrations of markers of inflammation and sepsis-associated coagulopathy in patients with severe sepsis.

2.13 Septic shock

Shock is a state of circulatory dysfunction that occurs from:

1) Decreased cardiac output and/or maldistribution of regional blood flow.

2) Increased metabolic demands with or without impaired utilization at the cellular level despite adequate oxygen delivery. Cardiac output may be high, low, or normal. The body has compensatory mechanisms to maintain blood pressure through increase heart rate and peripheral vasoconstriction. Hypotension, a late finding in infants and children, occurs when the compensatory mechanisms are failing and cardiorespiratory arrest is imminent (Kliegman, et al, 2007).

Septic shock, a systemic response to infection, bacteria produce extracellular products (endotoxin) and cell wall components which can stimulate the immune system, producing the clinical feature of shock, that is marked by fever, tachycardia, tachypnea, and/or leukocytosis. Hypotention 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, and organ dysfunction may develop in the setting of septic shock (Bone, Balk, and Cerra, 1992).

2.14 Diagnosis

The diagnosis of sepsis is based on a variety of clinical and physiological signs and symptoms in addition to the results of diagnostic and laboratory tests. Changes in vital signs may be the first indication of an infectious process, with elevated body temperature and increased heart rate or respiratory rate occurring as subtle but key indicators of potential sepsis. Other clinical signs, including decreased skin perfusion, decreased urine output, and central nervous system alterations (eg, confusion, agitation, lethargy), may also be present. Suspicious wound drainage, redness or swelling at the insertion sites of

catheters. Results of diagnostic and laboratory tests, including abnormal findings on chest radiographs, (Wheeler, and Bernard, 1999).

2.14.1 Lab studies

Laboratory tests are useful in suspected sepsis or septic shock to assess the general hematologic and metabolic condition of the patient. The microbiologic studies provide results, which may indicate occult bacterial infection or bacteremia, and indicate the specific microbial etiology (Sharma, 2006). Elevated white blood cell count, and cultures positive for microorganisms, can provide evidence of infection (Wheeler, and Bernard, 1999).

2.14.1.1 Microbiological tests

Blood culture the mainstay of investigation of potential septicemia in infants and children, despite recent advances in the molecular diagnosis of bacterial and fungal septicemia (Corless, Guiver, and Borrow, 2001). Culture specimens should be obtained from peripheral veins and not from indwelling catheters. Most common pathogens can be detected when volumes of (0.5–1.5 ml) are inoculated into culture media, PCR molecular genetic technique also used for antigen detection in the blood, CSF and urine (Schelonka, et al, 1996).

2.14.1.2 Hematological tests

White blood cell count, total neutrophil count, band count, immature to total granulocyte ratio (I:T ratio) and platelet count are some of the hematological parameters used in assessing infants septicemia (Rodrigo, 2002).

WBC count: The white cell differential and the WBC count may predict the existence of a bacterial infection. In adults who are febrile, a WBC count greater than 15,000 cells/μL or

a neutrophil band count greater than 1500 cells/μL is associated with a high likelihood of bacterial infection (Sharma, 2006).

Neutropenia is an important early laboratory finding caused by infection-mediated neutrophil storage pool depletion and margination of cells (Behrman, and Kliegman, 2000).

Platelets: Acute phase reactants, platelets usually increase at the onset of any serious stress. The platelet count will fall with persistent sepsis, and DIC may develop (Sharma, 2006).

Thrombocytopenia is commonly observed in very low birth weight (VLBW) neonates with septicemia, thrombocytopenia was defined a platelet count < 100,000/mm (Guida, et al, 2003).

Prothrombin time (PT) and activated partial thromboplastin time (aPTT): Assess coagulation status with Prothrombin time (PT) and activated partial thromboplastin time (aPTT). Patients with clinical evidence of coagulopathy require additional tests to detect the presence of DIC (Sharma, 2006).

2.14.1.3 Clinical Chemistry tests

Measurement of serum lactate provides an assessment of tissue hypoperfusion, elevated serum lactate indicates that significant tissue hypoperfusion exists with the shift from aerobic to anaerobic metabolism, higher serum lactate indicates a worse degree of shock and a higher mortality (Sharma, 2006).

Perform metabolic assessment with serum electrolytes, including magnesium, calcium, phosphate, and glucose, at regular intervals. Assess renal and hepatic function with serum

creatinine, BUN, bilirubin, alkaline phosphate, and alanine aminotransferase (ALT) (Sharma, 2006).

Electrolyte abnormalities include hyperglycemia as a stress response or hypoglycemia if glycogen reserves are exhausted. Hypoalbuminemia, metabolic acidosis, and low serum bicarbonate and other electrolyte abnormalities include hypocalcemia (Kliegman, et al, 2007).

2.14.1.4 Serological tests

C-reactive protein (CRP) is an acute phase protein released by the liver as a consequence of inflammation. CRP is frequently used to assess the presence and severity of inflammatory response. Although CRP is often used as a marker of bacterial infection, it is induced by a variety of non-bacterial stimuli, e.g. after surgery, during autoimmune and rheumatic disorders, or even myocardial infarction and malignant tumors. Despite a relatively high sensitivity, its predictive value was less than cytokines for the diagnosis of infection in febrile patients with episodes of Gram-negative Bacteremia (Engel, et al, 1998). During septicemia, CRP concentration reach their maximum early in the inflammatory response, and cannot indicate any further increase in severity (Meisner, et al, 1999).

The function of CRP is felt to related to its role in the innate immune system. Similar to immunoglobulin IgG, it activates complement, binding to FC receptors and acts as an opsonin for various pathogens. Interaction of CRP with FC receptors lead to generation of proinflammatory cytokines that enhance inflammation response. Unlike IgG, which specifically recognizes distinct antigenic epitopes, CRP recognizes altered self and foreign molecules based on pattern recognition. Thus CRP thought to act as a surveillance molecule for altered self and certain pathogens. The recognition provides an early defense

and leads to a proinflammatory signal and activation of the humeral, adaptive immune system. Thus a number of functions have been described to CRP including initiation opsonization and phagocytosis and activation of complement, neutrophils, and monocytes-macrophage (Clos, and Terry, 2000).

2.14.1.5 Immunological tests

Neutrophils are inflammatory cells with potent oxidative and proteolytic potential are usually the first line of defense against invading pathogens. Activated neutrophils produce cytotoxic factors leading to deleterious inflammatory processes, including tissue injury while lymphoid cells are undergoing accelerated apoptosis, spontaneous neutrophil apoptosis associated with septicemia or SIRS is delayed (Oberholzer, et al, 2001).

Monocytes, tissue macrophages, other myeloid-derived cells, and some extent endothelial cells, are the cornerstones of the innate immune response. As a first line of defense, these cells recognize invading pathogens through pattern recognition receptors that interact with conserved microbial structures. The interaction between pathogens and host cells results in the initiation of inflammatory and coagulation cascades (Aird, 2003).

Bacterial products, including endotoxin, can activate the classical and alternative component pathways an important part of the normal host defense mechanism aimed at facilitating bacterial clearance. However, complement activation causes an increased release of interleukin (IL-1), tumor necrosis factor (TNF) and other inflammatory mediators, thus sustaining the Septicemia response. C5a is perhaps one of the most important complement factors in the pathogenesis of Septicemia, stimulating the adhesion and degranulation of polymorphonuclear and lymphocytes. Degranulation results in the release of proteases and reactive oxygen species causing endothelial damage (Czermak, et al, 1999).

2.15 Classification of neonatal sepsis

Classification of neonatal sepsis is useful as it facilitates consideration of common principles of causation, presentation and treatment. The most helpful classification is given below (Rodrigo, 2002).

2.15.1 Early-onset Septicemia (EOS)

Early-onset septicemia, presenting during the first few days of life, usually progresses rapidly and has multiorgan involvement. It is frequently associated with obstetric complications, such as premature rupture of membranes (PROM), premature onset of labor, chrioamnionitis, and peripartum maternal fever. The majority of affected newborns are premature or low birth weight (LBW) infants, and the pathogens are frequently acquired during passage through the birth canal. Mortality rang from 5 to 50% (Jiang, et al, 2004).

Early-onset septicemia is associated with acquisition of microorganisms from mother. Transplacental infection or an ascending infection from the cervix may be caused by organisms that colonize in the mother's genitourinary. The infant may acquire the microbe by passage through a colonized birth canal at delivery (Linda, and Bryan, 2003).

The pathogenic microorganisms which causing (EOS) including both aerobic and anaerobic organisms, most of which do not cause disease in the mother. Approximately 70% of causes of early-onset septicemia in the united state are caused by two organisms: group B streptococcus (GBS) and Escherichia coli. Other organisms that are less commonly cultured from newborn infants with septicemia in the first few days of life include:- Listeria monocytogenes, Enterococcus faecolis, Haemophilus influenza, Streptococcus viridans, Staphylococcus aureus, Streptococcus pneumonia, and Gram-negative enteric bacteria other than E. coli (Gladston, et al, 1990). In 1994 the incidence of

(EOS) appears to be declined group B streptococcus (GBS) and Escherichia coli, Listeria monocytogenes, Haemophilus influenza, Enterobacter spp, Klebsiella pneumonia, Pseudomonas aeruginosa and Staphylococcus aureus are the other microorganisms commonly isolated from infants with (EOS) (Philip, 1994).

2.15.2 Late-onset Septicemia (LOS)

Infections presenting after 48 hours of age are considered late-onset infections and are generally caused by microorganisms acquired from the environment rather than from the mother (Rodrigo, 2002). According to study done by Yurdakok, in 1998 late-onset disease is more commonly recognized after the first week of life. The mortality rate is lower than the early-onset septicemia (Yurdakok, 1998). Late-onset septicemia is less sever and less frequently associated with obstetric complications (Jiang, et al, 2004).

The infants skin, respiratory tract, conjunctive, gastrointestinal tract, umbilicus may become colonized from the environment leading to the possibility of late onset septicemia from invasive microorganisms (Linda, and Bryan, 2003).

Bacteria responsible for late-onset septicemia include those acquired from the maternal genital canal, and organisms acquired after birth from human contacts or from contaminated equipment or materials (Yurdakok, 1998). Organisms that have been implicated in causing late onset septicemia syndrome include, staphylococcus aureus, E. coli, Klebsiella, pseudomonas, Enterobacter, GBS, Serratia, Acinetobacter, and anaerobes (Linda, and Bryan, 2003). In general the organisms responsible for (LOS) are these nosocomially acquired from the environment. In the developed world coagulase negative Staphylococci (CONS) and Candida albicans are the leading cause of (LOS) (Rodrigo, 2002).

2.16 Risk factors of Septicemia

2.16.1 Maternal risk factors for neonatal Septicemia

Maternal risk factors for neonatal septicemia include spontaneous premature rupture of membranes, prolonged rupture of membranes (12-18 hours or more), maternal fever, maternal urinary tract infection, vaginal colonization with GBS, low levels of maternal antibody to GBS, and the presence of chorioamnionitis. In an otherwise healthy term baby, none of these factors individually should warrant a complete septic workup. However, the combination of these risk factors greatly increases the probability of infection and should heighten the clinical suspicion of sepsis. Furthermore, the presence of any single risk factor in a sick newborn should prompt an evaluation for sepsis (Rodrigo, 2002). The risk of neonates being infected by vertical transmission is directly related to absolute number of microorganisms in the birth canal during delivery. The neonate born of a colonized mother is more prone to develop invasive disease, however, only 1% to 2% of babies born of women with a positive vaginal/rectal swab develop neonatal septicemia (Hickman, et al, 1999 and Baker, 1997)

2.16.2 Prematurity and low birth weight risk factors

The excess risk in preterm and low birth weight infants (LBW) has been well recognized for many years. Early reports noted that preterm and LBW infants were overrepresented among infants with early onset disease. Yancey et al (1996) reported demonstrated a progressive increase in risk for neonatal sepsis in general with decreasing gestational age or associated with low birth weight < (2500g) (Benitz, et al, 1999).

Prematurity is the most important infant risk factor for infection. There is direct correlation between the degree of prematurity and the risk of infection. Infants born at less than 32 weeks gestation are 4 to 25 times more likely to develop (EOS) than their more

mature counterparts (Rodrigo, 2002). Delivery at less than 34 weeks was a significant risk factor among cases, and in addition five of the six infants who died were preterm (Oddie and Embleton, 2002). In this national study, greater than half of sepsis deaths occurred in neonates and infants who were born prematurely. This observation is consistent with a higher case-fatality rate for sepsis among low birth weight preterm infants (Stoll, Holman, Schuchat, 1998).

Premature delivery is the chief problem in obstetrics today, accounting for 70% of perinatal mortality and nearly half of long- term neuralgic morbidity. Approximately 10% of all births are preterm, but most of the 1 to 2 % of infants who are born at less than 32 weeks of gestation and who weight less than 1500 g (Robert, et al, 2000).

2.16.3 Medical instrumentation risk factors

The major risk factor for nosocomial septicemia is intravascular catheterization. Over 80% of infections occur among patients with intravascular lines (Pemberton, et al, 1984). The increasing incidence of blood stream infections appear to be related to the use of prolonged central and peripheral IV canulation. The initial step in the pathogenesis of catheter related infections is the formation of fibrin sheath around canula inserted into a vessel (Maki, 1981). Other medical instruments considered risk factors for septicemia as indwelling intravascular catheters, indwelling urinary catheter, endotracheal intubation, ventriculoatrial shunts, continuous peritoneal dialysis, prosthetic heart valves, and surgery (Behrman, and Kliegman, 2002).

2.16.4 Risk factors associated disease status

Immunocompromized Patients with Malignancy, AIDS, Nephritic syndrome, Galactosemia, Diabetes, Systemic lupus erythrematosus (SLE), Alcoholism, malnutrition

or who are taking steroids also are at increased risk for septicemia (Behrman, and Kliegman, 2002).

2.16.5 Other risk factors for septicemia

Other risk factors for sepsis include resuscitation at birth, ventilation, parenteral nutrition, prolonged courses of broad-spectrum antibiotics, race or ethnicity, maternal age (Rodrigo, 2002).

2.17 Antimicrobial resistance for Septicemia

The first major advance in the era of antimicrobial agents was made in 1910 by the German scientist Paul chrlich (Gould and Booker, 2000). The term antibiotic refer to substances product by living microorganisms to suppress the growth of other microorganisms. While the term antimicrobial agent is broader in meaning since it encompasses agents synthesized in the laboratory as well as those natural antibiotics produced by microorganisms (El-Mishad, 1997 and Wingard et al, 1991).

Antimicrobial-resistant infectious agents are an increasingly important public health concern. A key factor in development of antimicrobial resistance is the ability of infectious organisms to adapt quickly to new environmental conditions. A mutation that helps a microbe survive in the presence of an antibiotic drug will quickly become predominant throughout the microbial population. Microbes also commonly acquire genes, including those encoding for resistance, by direct transfer from members of their own species or from unrelated microbes. The innate adaptability of microbes is complemented by widespread and sometimes inappropriate use of antimicrobials (NIH, 2000).

Antimicrobial resistance of the causative organisms of septicemia is a rapidly emerging, potentially disastrous problem (Bax, Mullan, and Verhoef, 2000). Orrett and Shurland (2001) from Trinidad reported that 85% of staphylococcus aureus are resistant to ampicillin, and Pseudomonas had 76.6% resistance to cefotazidime and 72.1% resistance to gentamicin. The study of Joshi, et al (2000) from India shows a predominance of Gram-negative bacteria (67.2%) in their series, which had 25-75% resistance to cephalosporin's, 68-78% resistance to pipracilline, and 23-69% resistance to gentamicin (Joshi, et al, 2000).

Friedman, et al (2000) from Toronto isolated ampicillin resistant E. coli from 75% of infants with early onset neonatal sepsis and from a group with late onset neonatal sepsis. Gentamicin resistance was found in 50% of the early onset group and 16% of late onset group (Friedman, et al, 2000). Kaushik, et al (1998) reported their bacterial isolates to be resistant to penicillin, ampicillin, and gentamicin, but with good sensitivity to third generation cephalosporin's and netilmicin (Kaushik, et al, 1998). Leibovitz, et al (1997) reported the appearance of extremely virulent, multiresistant Klebsiella in their neonatal intensive care unit in Kaplan Hospital, Israel (Leibovitz, et al, 1997). Koksal et al (2001) from India, reported a series of 35 cases of sever Gram-negative neonatal sepsis, with all the organisms being resistant to ampicillin, amoxicillin, ticarcillin, cefazoline, cefotaxime, ceftazidime, ceftriaxone, and aminoglycoside. They treated these babies with meropenem and achieved 94.3% satisfactory clinical and bacterial response (Koksal et al, 2001). The routine use of intrapartum antibiotic prophylaxis for the prevention of group B streptococcus Septicemia in newborn babies has resulted in the appearance of ampicillin resistant Gram-negative neonatal sepsis in a large number of developed countries (Mercer, et al,1999).

2.18 Prevention of infection

Selective intrapartum administration of antibiotics to women in labour has been shown to be effective in preventing early-onset GBS septicemia (Ohlsson and Myhr, 1994). Intrapartum antibiotics are most effective when administrated at least 4 hours before delivery and when at least 2 doses have been given. Currently, two equally acceptable strategies (screening based and risk based) have been recommended by the Centers for Disease Control and Prevention (CDC,1996). If the mother has been given intrapartum antibiotic chemoprophylaxis for GBS, the neonates should be observed for a minimum of 48 hours after delivery. If signs of sepsis appear, a full diagnostic evaluation and empirical therapy should be initiated (Allen, 1997).

Nosocomial infections account for an increasingly large proportion of neonatal infections. Meticulous attention to hand washing is the most effective measure in reducing hospital infection (Raju and Kobler, 1991). Jewellery, wristwatches and all other ornaments should be removed and hands scrubbed from elbow downwards with an iodine containing solution before entering the neonatal unit. Hand washing should not only be done before and between handling infants, but also after handling potentially contaminated sites including one's face or hair, pens, bed head tickets, telephones etc. A written hand washing policy sited above the wash area may help the staff to adhere to correct technique. Proper staffing, adequate space in neonatal units, controlling admission, aseptic care of catheters and appropriate limitation of antibiotic usage, are some of other measures helpful in reducing hospital acquired infections. Wearing of protective clothing by parents and staff is not an effective method of infection reduction.

Communal equipment such as thermometers, stethoscopes and suckers are a major source of cross-infection. Ideally individual pieces of equipment should be provided. If equipment has to be shared it should be wiped clean between patients (Rodrigo, 2002).

2.18.1 Prevention by immunization

Infection control is a vital part of pediatric medicine. Such control requires an intact and active public health system, universal immunizations, optimal nutrition, and use of specific methods to prevent transmission of infection from child to child, child to adult, and adult to child. Infection control is the responsibility of every health care provider.

Immunization is one of the most beneficial and cost-effective disease prevention measures. As a result of effective and safe vaccines, smallpox has been eradicated, polio is close to worldwide eradication, and measles and rubella are no longer endemic in the U.S. The incidence of most other vaccine-preventable diseases of childhood has been reduced by >99% from the annual morbidity prior to development of the corresponding vaccine. An analysis of effective prevention measures recommended for widespread use by the U.S. Preventive Services Task Force reported that childhood immunization received a perfect score, based on clinically preventable disease burden and cost-effectiveness.

Immunization with the conjugate H. influenzae type b and S. pneumoniae vaccines is recommended for all infants. High-risk patients should also receive recommended immunizations. Penicillin prophylaxis to prevent pneumococcal infection is recommended for patients with splenic dysfunction (e.g., sickle cell disease) and those who are asplenic (acquired or congenital). Antibiotic prophylaxis is recommended for household and other close contacts of patients with invasive N.meningitidis or H. influenzae type b disease. There are recommended measures for prevention of nosocomial infections and sepsis in immunocompromised patients and neonates (Kliegman, et al, 2007).

2.18.2 Prevention by hand hygiene

The most important measure in any infection control program is hand hygiene. Although much attention is directed at the types of soap used, the important component of hand washing is placement of the hands under water and use of friction with or without soap. Studies show that a 15-second scrub removes the majority of transient flora but does not alter the permanent flora. A variety of hand gels and rubs can be used in place of hand washing. Waterless hand hygiene products increase compliance and save time, these agents are the preferred agents for routine hand hygiene. These products are effective in killing most microbes, they will not remove dirt or debris. Hands should be cleaned before and after every patient encounter. Studies in developing countries, child-care settings, homes, and schools have determined that hand washing with soap can be taught to families and children and that the rates of infection are decreased when children as well as caregivers regularly clean their hands (Kliegman, et al, 2007).

2.19 Treatment of Septicemia

Early administration of antimicrobial agents is associated with a reduction of mortality. The choice of antimicrobial agents is dependent on the predisposing risk factors and the clinical situation. Bacterial resistance patterns in the community should also be considered when selecting optimal antimicrobial therapy (Kliegman, et al, 2007).

The treatment of patients with Septicemia is becoming more complicated in an era of increasing antimicrobial resistance among frequently occurring pathogens (Biedenbach, et al, 2001). The type of organisms causing septicemia has also changed over the years, reflecting antibiotic usage at the time (Edgeworth, et al,1999). Particularly, gram-positive organisms have over taken gram-negative species in terms of prevalence (Karchmer, 2000). During the 1970, bloodstream infections were most commonly associated with

gram-negative organisms, but during the 1980s and 1990s, several gram-positive organisms began to emerge important Septicemic pathogens, including coagulase-negative Staphylococci, Staphylococcus aureus and Enterococci (Karchmer, 2000).

Septicemia is one of the most sever invasive bacterial infections and surveillance of antibiotic susceptibility of the organisms isolated from susceptibility of the organisms isolated from blood cultures is an important method of obtaining information on resistance patterns at the regional and national level (Asghar, 2006). The initial choice of antibiotics depends on the knowledge of prevalent organisms responsible for infection within a geographical area, as well as the pattern of specific antimicrobial susceptibility. Typically the initial therapy for suspected early-onset septicemia should include coverage of GBS and gram-negative enteric bacilli. The combination of C.Penicillin and an aminoglycoside (usually gentamicin) is usually adequate. The choice of antibiotic fore use in late-onset septicemia would depend on organisms generally responsible for such infections in individual units. The combination of an aminoglycoside with fluxacillin/cloxacilline has been the standard therapy for suspected late-onset septicemia. How ever, in most of the developed world (CONS) are the main organisms responsible for (LOS), and are often resistant to multiple antibiotics including methicillin. Therefore, an increasing tendency is seen to use vancomycin in combination with the aminoglycoside or cephalosporin as initial blind therapy. In addition, removal of indwelling intravenous catheters and other devices may be necessary to eradicate the infection if antibiotics alone are not successful. Several newer antibiotics are finding a place in difficult cases. Azetreonam and imipenem are valuable in the treatment of gram-negative sepsis, when necrotizing enterocolitis is suspected, it is usual to add metronidazole to cover anaerobes. When cultures are positive and sensitivities available, treatment should be modified to reflect the susceptibility of isolated organism (Rodrigo, 2002).

The choice of antimicrobial agents depends on the specific predisposing risk factors. Neonates should be treated with Ampicillin plus Cefotaxime or gentamycin. Child with cefotaxime or ceftriaxone and for Community acquired infections with N.meningitides, S. pneumoniae, Staphylococcal resistance to methacillin or cefotaxime. requires the addition of Vancomycin. Nosocomial sepsis should be treated with 3rd or 4th generation cephalosporin or an extended gram-negative spectrum penicillin (e.g., pirpracilline tazobactam) plus an aminoglycoside. Vancomycin should be added to the regimen if the patient has an indwelling medical device and gram-positive cocci are isolated from the blood, if methicillin-resistant S.aureus infection is suspected, and as empiric coverage for S. pneumoniae in patients with meningitis (Kliegman, et al, 2007).

An adequate hemoglobin concentration is necessary to ensure oxygen delivery in shock. Maintain the hemoglobin at a level of 8 g/dL (Sharma, 2006). The hematocrit level should be more than 30% (Stapczynski, 2002).

2.19.1 Overview of antimicrobial therapeutic drugs

2.19.1.1 Penicillins

Penicillins are beta lactam antibiotics, they are bactericidal, inhibiting formation of the cell wall. These group include ampicillin and amoxicillin, they are semi synthetic Penicillins which are slightly broader spectrum than penicillin-G. Penicillins are still effective against most of the common pathogens and are generally less toxic than many of the other antibiotics currently in clinical use (Gould and Booker, 2000). These agents are active against many gram-positive, gram-negative and anaerobic bacteria (Holton, 2000, Bush, 1999).

Penicillin G and gentamycin were being used to treat babies with suspected early onset septicemia (within 48 hours of birth), while flucloxacilline and gentamycin to treat suspected late onset septicemia (Isaacs and Wilkinson, 1987).

Pipracillin is an acylampicillin with excellent activity against Pseudomonas aeruginosa and effective against Klebsiella pneumonia, Proteus mirabilis, and many strains of Enterobacter. Pipracillin administered in combination with an aminoglycoside as synergistic therapy (Linda and Bryan, 2003).

2.19.1.2 Cephalosporins

Cephalosporin's differ structurally from Penicillins by having the B-Lactam ring as a 6 member ring, compared to the 5 member ring structure of the penicillin's (Kliegman, et al, 2007).

The first commercially available cephalosporin was introduced in 1962. the cephalosporins are chemically related to the penicillin's as they also contain the beta lactam ring (Holten and Onusko, 2000).

Cephalexine is one of the first generation cephalosporins antibiotic which is commonly used for management of skin and soft tissue infection caused by susceptible strains of S. aureus and group A streptococcus. The second generation cephalosporins include (Cefaclor, Cefuroxime) compared with first generation cephalosporins, these drugs have better activity against gram-negative infections than do 1st generation such as H. influenzae, N.meningitidis and M.catarrhalis (Kliegman, et al, 2007).

Third generation cephalosporins are broad spectrum antibiotics, such as Cefotaxime, Ceftriaxone, and Ceftazidime which are used for serious pediatric infections, including meningitides, and sepsis. Ceftazidime is highly active against most strains of

Pseudomonas aeruginosa, making this a useful agent for febrile, neutropenic oncology patients (Kliegman, et al, 2007). Cefotaxime is characterized with excellent in vitro activity against GBS and E. coli and other gram-negative enteric bacilli and has good serum and CSF concentration. (Linda and Bryan, 2003).

Ceftriaxone, a parenteral third generation cephalosporin, has become a frequent choice for empiric antimicrobial therapy in hospitals, emergency departments, and in ambulatory care setting (Adu and Armour, 1995). Ceftriaxone has a long elimination half-life which permits once-daily administration. It has good activity against Streptococcus pneumonia, methicilline-suseptible Staphylococci, Haemophilus influenzae, Moraxella catarrhalis and Neisseria spp. Also active against Enterobacteriaceae (Lamb, et al, 2002). Ceftriaxone is used for the treatment of meningococcemia and meningitis.

2.19.1.3 Aminoglycosides

Aminoglycoside antibiotics include streptomycin, kanamycin, gentamicin, tobramycin, netilmicin, and amikacin. The most commonly used aminoglycosides in pediatric practice are gentamicin and tobramycin. They exert their mechanism of action via inhibition of bacterial protein synthesis. Although they are most commonly used to treat gram-negative infections, the aminoglycosides are broad-spectrum agents and have activity against S. aureus and provide synergistic activity against group B streptococcus, L. monocytogenes, viridans streptococci, corynebacteria, Pseudomonas, Staphylococcus epidermidis, and Enterococcus when co-administered with a p-lactam agent. Aminoglycoside use has decreased with the development of newer alternatives, but they still play a key role in pediatric practice in the management of neonatal sepsis, urinary tract infections, gram-negative sepsis, and complicated intra-abdominal infections, infections in cystic fibrosis

patients (including both parenteral and aerosolized forms of therapy), and in oncology patients with fever and neutropenia (Kliegman, et al, 2007).

Gentamicin the most commonly used Aminoglycoside, but Amikacin may be particularly effective against resistant organisms. (Gonzalez and Spencer, 1998). Gentamicin isolated from Micromonospore in 1963, was a breakthrough in treatment of gram-negative bacillary infections, including those caused by pseudomonas aeruginosa (Gonzales and Spencer, 1998). It is effective against both gram-positive and gram-negative organisms and that is bactericidal for susceptible to E.coli and Pseudomonas, Proteus and Serratia species. Effective in combination with ampicillin for Group B Streptococcus and Enterococcus (Linda and Bryan, 2003).

Amikacin is a semisynthetic derivative of kanamycin, its less toxic than the parent molecule. It is resistant to many enzymes that inactivate gentamicin and tobramycin and therefore can be employed against some microorganisms resistant to the latter drugs. Many gram-negative enteric bacteria, including many strains of proteus and pseudomonas, are inhibited in vitro by Amikacin (Katzung, 1997). Amikacin is particularly effective when used against bacteria that are resistant to other aminoglycosides, since its chemical structure makes it less susceptible to inactive enzymes (Gonzales and Spencer, 1998).

2.19.1.4 Chloramphenicol

Chloramphenicol is a broad spectrum bacteriostatic antimicrobial agent against gram-positive and gram-negative organisms, it is an inhibitor of protein synthesis. Chloramphenicol rarely may cause a plastic anemia (Howard, 1994).

2.19.1.5 Glycopeptides

Glycopeptide antibiotics include Vancomycin and teicoplanin, the less commonly available analog. These agents are bacteriocidal and act via inhibition of cell wall biosynthesis. The antimicrobial activity of the glycopeptides is limited to gram-positive organisms, including S. aureus, coagulase negative Staphylococci, pneumococcus, Enterococcus, Bacillus, and Corynebacterium (Kliegman, et al, 2007). Vancomycin, a glycopeptide antibiotic licensed in 1956, increased in 1958 with the emergence of penicillinase-producing Staphylococci. Vancomycin use continued to increase in the1980s with the emergence of ampicillin-resistant Enterococci and Methicillin-resistant coagulase-negative Staphylococci, and in the 1990s with the emergence of penicillin resistant Pneumococci (Keyserling et al, 2003). Infants with suspected late-onset septicemia are typically treated with empiric antimicrobial therapy that often includes Vancomycin. However, there are national recommendations that vancomycin use in hospitals should be restricted because exposure of patients to vancomycin is a risk factor for emergence of vancomycin resistance Enterococci or vancomycin-intermediate Staphylococcus aureus (CDC, 1995 and McNeeley, et al, 1998). Vancomycin must be administered with care due to its propensity to produce red-man syndrome, which is a reversible adverse effect that is rare in young children and can typically be readily managed by slowing the rate of infusion of the drug (Kliegman, et al, 2007).

2.19.1.6 Quinolone

Quinolone antibiotics, available since 1960s. These early quinolones targeted gram-negative organisms including Escherichia coli, Klebsiella and Proteus species (Lee and Kanatani, 1999). Ciprofloxacin is an antibacterial agent with a broad spectrum of activity effective against various pathogens as Pseudomonas aeruginosa and Klebsiella pneumonia, Ciprofloxacin despite the risk of toxicity, the need for broad spectrum antibacterial made

the use of ciprofloxacin appealing for some patient populations. To date, in infants and children with multidrug resistant infections, have been successfully treated with ciprofloxacin (Echols, 1997). Ciprofloxacin was used in the treatment of multidrug resistant septicemia on a compassionate basis as a life saving drug (Chaudhari, et al, 2004).

2.19.1.7 Carbapenems

Carbapenems are synthetic beta-lactam antibiotics that differ from the penicillin's in that sulfur atom of the thiazolidinedione ring has been externalized and replaced by a carbon. Carbapenems include Imipenem and Meropenem (Gordana, et al, 2003).

Imipenem is the first of new beta-lactam antibiotics, its spectrum of activity includes most aerobic and anaerobic gram-positive and negative bacteria (Goldfarb, 1995).

Meropenem another Carbapenems seems to have some what broader gram-negating activity than imipenem (Blumer, 1995). Meropenem is antimicrobial agents used to treat a variety of serious infections when an organisms is resistant to the primary agent of choice (CDC, 1999).

Meropenem has been shown to possess invitro activity against many gram-positive organisms, including most Streptococci, Staphylococci and Enterococci species and Gram-negative includes E.coli, Haemophilus influenzae, Klebsiella pneumonia, Neisseria meningitides, Pseudomonas aeruginosa, and strains of Acinetobacter, Citrobacter, Shigella, Pasteurella, Proteus. Meropenem also have bactericidal activity against Moraxella catarrhalis, Morganella morganii, Serratia marcescens (Wiseman, et al,1995). Meropenem lacks the toxicity of seizure potentiation associated with imipenem. These agents are reasonable choice for empiric monotherapy in infants and children with serious infections (Arrieta, 1997).

2.19.1.8 Sulphonamides

Trimethoprime and the Sulphonamides are bacteriostatic agents that inhibit the bacterial folate synthesis pathway, in the process impairing both nucleic acid and protein synthesis. Sulfonamides interfere with the synthesis of dihydropteroic acid from para-aminobenzoic acid, whereas trimethoprim acts at a site further downstream, interfering with synthesis of tetrahydrofolic acid from dehydrated folic acid. The most important agent is the combination of trimethoprime-sulfamethoxazole, which is used to treat urinary tract infections (Kliegman, et al, 2007).

2.19.1.9 Macrolides

The macrolide antibiotics most commonly employed in pediatric practice include erythromycin and the newer agents clarithromycin and azithromycin. These agents bind to the 50s subunit of the bacterial ribosome and block elongation of bacterial polypeptides. The spectrum of antibiotic activity includes many gram-positive infections, including S.aureus and group A streptococcus, although resistance to these agents in now fairly widespread, limiting the usefulness of macrolides for skin and soft tissue infections and streptococcal pharyngitis. The newer macrolides, azithromycin and clarithromycin, have demonstrated efficacy for otitis media. All of the member of this class have an important role in the management of pediatric respiratory infections (Kliegman, et al, 2007).

Chapter Three

Methodology

3.1 Study Design

This study is descriptive analytical cross sectional design. It described the occurrence of Septicemia disease among infant children under (12 months) old in El-Nassr pediatric hospital.

3.2 Setting of the study

This study was carried out for every infant (under 12 months old) admitted to El-Nassr pediatric hospital and who had lab confirmed Septicemia disease.

3.3 Period of the study

Our study was conducted over twelve months (four seasons), starting in 1st October 2006 ending in 30th September 2007.

3.4 Study Population

The study population was all infant children under (12 months) old from both genders. Included all Septicemic disease cases among infant with confirmed diagnosis depending clinical laboratory result at El-Nassr hospital in Gaza Governorates during the period of the study, which were 366 subjects.

3.5 Selection criteria

A case of Septicemia disease was defined as each hospitalized case admitted with Septicemic disease manifestations and has laboratory confirmation by isolation of bacteria from blood culture with clinical manifestations of a severe infection.

The study investigated all cases occurring among infant (under 12 months) old at El-Nassr pediatric hospital during the period of the study.

3.6 Piloting

A pilot study is a basic component that should be undertaken before the major part of the study to be conducted which enable to identify any problem in the design of the research or in the questionnaire to be corrected in order to avoid biases and obstacles in implementation processes.

3.7 Ethical Consideration

1- Helsinki committee and ministry of health were approved.
2- Coordination will carry out with the concerned department in the ministry health including the director general of hospital affaires, the director general of public health and the director of laboratories and blood banks.
3- Explanation for parents will be done including explanation about the nature of the study, the purpose and the confidentiality of information. Consent will be obtained from parents of subjects verbally.
4- The researcher explained for all participants that participation in the study is optional and they have the right to refuse to participate or to drop out in any phase of the study, with emphasis on the confidentiality of information which was maintained all over the study.

3.8 Data Collection

Data collected by both direct and indirect methods. The indirect method included a structure interview questionnaire (Annex, 5), the direct method included laboratory results such as blood culture, blood glucose, CBC, ESR, serum CRP, serum electrolytes, PT, PTT,

blood gases. Trained persons such as laboratory director in El-Nassr hospital shared in data collection, after explanations by the researcher about the questionnaire items, how to fill it, how to carry out the interview and explanations about the laboratory examinations which included in the study with emphasis on the ethical and administrative considerations.

3.8.1 The Indirect method

This method was designed as face to face interview questionnaire (Annex, 4). The interview was carried out face to face with children's parents, also we taken the clinical assessment from doctors and files of the patient. In this study the interview took place after confirming the cases by laboratory results. The questionnaire main information areas included are:

1- Personal data.
2- Demographic data.
3- Socio-economic data of subjects and family.
4- Clinical assessment of the patient (Biomdeical measures and disease manifestation such as fever, blood pressure, weight, convulsion, coma and shock).
5- Prognosis and complication data to complete some biomedical information.

3.8.2 The Direct method

The direct method included blood samples collected from patients in the first day of admission for examination. The laboratory examinations were carried out in El-Nassr pediatric hospital laboratory using standard techniques as the following:

3.8.2.1 Blood culture

3.8.2.1.1 Collection of the Specimen

The collection of blood for culture was performed by experienced personnel under aseptic technique, the skin was disinfected with 70% alcohol and then 1% tincture iodine or povidone-iodine was applied. After the disinfectant has dried, the blood was withdrawn by vein puncture and directly inoculated into the blood culture bottles containing trypticase soy broth (TSB) for aerobic blood culture, and other bottles containing thioglycolate broth for anaerobic blood culture, the bottles were swirled several times. The diaphragm of the blood culture bottle was cleaned with 70% alcohol and povidone-iodine before inoculating the medium. Blood cultures from young children were diluted to 1-2 ml of blood in 20 ml of broth (1:10 to 1:20). Then blood culture bottles were labeled appropriately with patient identification and the date and time of blood collection. Blood culture bottles were transport to the laboratory immediately and processed for examination (Popovic, et al, 1999).

More than 3 ml blood cultures rarely are indicated, even in endocarditis. Whenever possible, at least 2-3 ml of blood should be obtained for culture before administration of antibiotics. Obtaining a large volume of blood is necessary to maximize yield from blood cultures, because children may have low-grade bloodstream infections (Kliegman, et al, 2007).

3.8.2.1.2 Culture procedure for blood

The blood culture bottles were incubated at 37°C, subcultures were performed after 14 to 17 hours of incubation, again at 48 hours, and at day 7 (Popovic, et al, 1999).

3.8.2.1.3 Subculture

Before subculturing, the bottles were swirled to mix the contents. Subcultures were made by first disinfecting the surface of the blood culture bottle rubber stopper with alcohol and a povidone-iodine swab, and then aspirating a small volume (0.5 ml) with a syringe and needle from the blood culture bottle and inoculating the agar media with the fluid. Ordinarily, Blood agar, MacConkey agar, Chocolate agar were used for subculture. The agar plates should be streaked, and incubated in 5 -10% CO2 atmosphere for up to 48 hours. When bacterial growth has been confirmed by subculture of the blood culture bottle, there is no need to continue to incubate the bottle (Popovic, et al, 1999).

3.8.3 Identification of organisms

The routine organisms are identified by their physical (morphology, oder, culture characters),Gram stain and biochemical tests.

3.8.3.1 Identification by Gram Stain

With the Gram stain , bacteria can be divided into two categories, Gram positive bacteria that retain the methyl violet-iodine dye complex and appear purple, and gram negative bacteria that destain with 95% alcohol, and appear pink due to counter-staining with basic function.

Assay procedure:

(a) Preparing a thin smear of material for study on the surface of slides and allow to air dry.

(b) The smear was fixed by passing the slide quickly through a flame 3 or 4 times.

(c) The slides were flood with ammonium oxalate-crystal violet and let stand for 1 minute, gently washed with water and drained.

(d) The slides were flood with Gram’s iodine solution and let stand for 1 minute, gently

washed with water and drained.

(e) Slides were decolorized with 95% ethyl alcohol (5-10 seconds enough).

(f) Slides were Counterstained with safranin for 20-30 seconds and washed with water·

(g) The stained smears were Blotted dry and examined using oil immersion microscopy.

(h) Gram positive bacteria stain dark- blue, and Gram negative bacteria appear pink-red (Popovic, et al, 1999) .

3.8.3.2 Identification by Biochemical Tests

3.8.3.2.1 Catalase Test

This test is used to differentiate those bacteria that produce the enzyme Catalase, such as Staphylococcus from non-Catalase producing bacteria such as Streptococcus. Catalase acts as a catalyst in the breakdown of hydrogen peroxide to oxygen and water.

Assay procedure:

(a) 2-3 ml of hydrogen peroxide solution 3% were poured into a test tube.

(b) A well separated representative colony was chosen on the primary isolation medium, put the colony by sterile wooden stick in the hydrogen peroxide solution.

(c) The active bubbling indicate positive result or Catalase produced but if no release of bubbles that negative result or no Catalase produced (Cheesbrough, 1989).

3.8.3.2.2 Coagulase test

This test is used to differentiate Staphylococcus aureus which produce the coagulase enzyme, from Staphylococcus epidermidis and Staphylococcus saprophyticus which do not produce coagulase.

Assay procedure:

(a) A drop of physiological saline 0.95% was placed on slide.

(b) The colony or the tested organism was emulsified.

(c) A drop of plasma was added to one of the suspensions, and mix gently. Look for clumping of the organisms within ten seconds.

(d) No plasma is added to the second suspension. This is used to differentiate any granular appearance of organism from true coagulase clumping.

(e) The clumping within ten seconds that indicate Staphylococcus aureus, no clumping within ten seconds indicate no bound coagulase produce (Cheesbrough, 1989).

3.8.3.2.3 Kovac's Oxidase Test

The oxidase test is an important and commonly used reaction for the screening and presumptive identification of microbial cultures. This test determines the presence of cytochrome oxidase. The reagent tetramethyl-p-phenylenediamine hydrochloride is turned into a purple compound by organisms containing cytochrome c as part of their respiratory chain such as Neisseria species, Pseudomonas (Popovic, et al, 1999). The used technique was the dry stick reagent (Identification Sticks Oxidase) (Oxoid, 2000). Formula: The tip of each stick is impregnated with a solution of N,N-dimehtyl-p-phenylenediamine oxalate, ascorbic acid and alpha-naphthol. The other end is colored red for identification and to ensure that the correct end is held (Oxoid, 2000).

Assay procedure:

(a) The container was removed from the refrigerator and allow it to stand for 5 minutes at room temperature.

(b) A well separated representative colony was chosen on the primary isolation medium.

(c) One stick (Color coded red) was removed from the container and holding it by the colored end, touch the colony with the impregnated end of the stick, rotate the stick, picking off a small mass of cells.

(d) The stick was placed between the lid and the base of the inverted plate.

(e) The impregnated end of the stick was examined after from 30 seconds to 3 minutes.

(f) A positive reaction was shown by the development of blue-purple color. No color change was observed with organisms that were oxidase negative (Oxoid, 2000).

3.8.3.2.4 API 20 E (Analytical Profile Index)

API 20 E is a commercial system (Biomerioux Company) (Biomerioux, 2000), used as a biochemical system for identification of gram negative rod bacteria (Enterobacteriace group).

The API 20 E strip consists of 20 micro tubes containing dehydrated substrates, these strips were inoculated with a bacterial suspension, which reconstitutes the media. They incubated at 37 C for 18-24 hours, during incubation , metabolism procedure colour change that are either spontaneous or revealed by the addition of reagents. The reaction were determined according to the reading table and the identification was obtained by referring to the API index (Biomerioux, 2000).

3.8.3.2.5 API NH (Analytical Profile Index)

API NH is a commercial system (Biomerioux Company) (Biomerioux, 2000), for the identification of Neisseria, Haemophilus and Moraxella catarhalis, which uses standardized miniaturized database. The species which may be identified by the system are indicated in the identification table at the end of the package insert.

The API NH strip consists of 10 micro tubes containing dehydrated substrates, which enable the performance of 12 identification tests (Enzymatic reactions or sugar fermentations). The reactions produces during incubation result in spontaneous color changes or are revealed by the addition of reagents. After the 2-hour incubation period at the temperature of 35-37Cº, in aerobic conditions, the reading of the reactions is performed visually and should be recorded as + or – on the result sheet. The identification is obtained

by consulting the profile list in the package insert or the corresponding identification software (Biomerioux, 2000).

3.8.3.3 Identification by Specific Antisera

3.8.3.3.1 Agglutinative Sera Test for Streptococci

Strep-cheek is a commercial kit (Lorne Company) (Lorne, 2002), for the identification of Streptococci, lance fields groups A,B,C,D,F and G. The different reagent are coated with the specific antibody and will agglutinate in the presence of enzymatically-extracted antigen.

Assay procedure:

(a) By a sterile loop pick 2-6 colonies of Streptococci on the blood agar plate.

(b) Colonies were emulsified in 0.4 ml of extraction enzyme.

(c) The mixture were incubated in a water bath at 37 Cº for 10 minutes, vigorously shacking the tubes after incubation.

(d) Dispense 1 drop of each latex reagent into the labeled test slide.

(e) Add one drop of the extract to each drop of latex reagent, and mix the contents of each circle with a separate mixing stick.

(f) Observe the agglutination after one minute.

(g) Strong agglutination of specimen with one latex reagent, indicates the presence of that specific Streptococci group, either A,B,C,D,F or G.

(h) No visible agglutination of latex particles. Indicates the absence of streptococci groups (Lorne, 2002).

3.8.3.3.2 Agglutinative Sera test for Staphylococci

Staphylase AVIPATH is a commercial kit (Omega diagnostic Company) (Omega, 1997), for the detection of Staphylococci. The latex particles are coated with human fibrinogen

and IgG. The fibrinogen will bind with coagulase and IgG will bind protein A. Both factors are associated with S.aureus.

Assay procedure:

(a) Add one drop of isotonic saline on the test circles.

(b) By a sterile loop, 2-4 colonies of suspected Staphylococcus bacteria were picked and picked and emulsified in the isotonic saline on the test circle.

(c) If agglutination or clumping occurs at this point it is anticoagulation and the sample is unstable for the test.

(d) The latex reagent was shacked vigorously, then using the dropper provided, add one drop of reagent to the circle.

(e) The reagent and culture emulsion using a disposable stirrer ensuring coverage of the test circle with the mixture.

(f) Gently and evenly, rock and rotate the test slide for one minute.

(g) A positive result was indicated by the obvious agglutination pattern of the latex in a clear solution.

(h) A negative result was indicated by no change in the latex suspension on the test Slide (Omega, 1997).

3.8.3.4 Antibiotic Susceptibility Tests

All the isolated and purified strains were tested for the antibiotic susceptibility test, to find out the susceptible or resistant strains for the antibiotics used in the treatment of Septicemia. The method used is the disk diffusion method which principally depends on the determination of minimum inhibition concentration. The diffusion method relies on the linear relationship that for most antimicrobials exists between the diameters of the zone of inhibition and the minimum inhibitory concentration (Henry,1996, Howard,1994).

Assay Procedure:

1) The inoculum: (Bacterial suspension):

By the inoculating loop, a portion of the isolated colonies was transferred into a tube containing 5 ml of sterile normal saline, the tubes were mixed well to make homogeneous suspension was adjusted by matching with turbidity standard developed by McFarland to approximate number of bacteria in solutions of equal turbidity as determined by colony counts. A standard inoculum of the microorganism (often 1 X 10^6 organisms per milliliter) 1:500 dilution of a suspension of turbidity equal to McFarland standard 1.0 was used. 1.0 McFarland standard was prepared by mixing 0.1 ml of the 1% BaCl2 (barium chloride) solution with 9.9 ml of 1% H2SO4 (sulfuric acid). The resulting mixture was placed in a tube (screwcapped) identical to that used for preparing the dilution of bacterial ID plate. The same size tube and volume of liquid were used and store in the dark at room temperature when not in use. A fresh standard solution was prepared every 6 months. McFarland standard density solution will precipitate and clump overtime, and it needs vigorous vortexing before each use. The tube was marked to indicate the level of liquid, and checked before use to be sure that evaporation has not occurred (Popovic, et al, 1999) .

2) Inoculating the culture media:

The media used was the Mueller Hinton agar contained 5% sheep blood. The plates of Mueller Hinton agar were inoculated carefully with standardized inoculum by using cotton wool swabs to give a confluent growth. The antibiotic discs were applied and placed on the surface of the inoculated plates. These discs were pressed gently to confirm complete contact with agar. The inoculated plates with antibiotic discs were incubated for 24 hrs at 30Cº and the zone of the inhibition of the bacterial growth around the antibiotic discs were measured with the calipers, and the results were reported for each isolate as sensitive,

intermediate or resistant, according to the diameters of the inhibition zone (Henry,1996, Howard,1994). Types of antibiotic discs were chosen according to disease treatment .

3.8.3.5 Quality Control of Media

Immediately after preparation, each medium was tested for proper growth characteristics. A record of all media preparation dates and quality control test results were reported and kept. Any unusual characteristic such as color of the medium or slow growth of test bacteria were noted (Popovic, et al, 1999).

3.8.3.6 CBC

Two ml of blood was withdrawn from peripheral circulation of each patient in EDTA tube to measure total hemoglobin concentration, WBCs total, differential and platelets count. These parameters were measured by using the automated cell counter "Cell DYN 1700 – ABBOTT Laboratories" (Abbott, 2001), which is available in El-Nassr pediatric hospital lab. The samples were labeled with patient names and sent immediately with hematology request to the laboratories and analyzed.

3.8.3.6.1 Total Hemoglobin Concentration

In this study the anemic persons were reported according to values of hemoglobin levels indicative of anemia in populations living at sea level (WHO 1996). Children 6 months to 5 years: Hemoglobin level <11 (gm/dl).

3.8.3.6.2 White Blood Cell Count (WBC) Total count:

This test measures the number of white blood cells in a liter of blood. Normal values of children 6 months to 6 years are 6-15 $x10^9$/ L, in adults male and female ranged from 5-10 $x10^9$ /L (Campbell & Mclntosh,1998).

3.8.3.6.3 Platelets Count

This test measures the number of platelets in a liter of blood. Normal values of children 1 month to 6 years are 150-450 $x10^9$/ L, in adults male and female ranged from 150-450 $x10^9$ /L (PMOH, 2005).

3.8.3.7 Prothrombin Time

It is the time, in seconds, required for clot formation after addition of calcium and thromboplastine, to evaluate the extrinsic pathway of coagulation system.

Assay Procedure:

(a) The specimen should be citrated plasma. As soon as the venous blood is drawn into a citrated tube ,gently invert at least 5 times, then as soon as possible, mix thoroughly, vigorous mixing must be avoided. Citrate tubes must be properly filled, 4.5 ml blood added to 0.5 ml citrate, the sample should be separated from cells as soon as possible and refrigerated if testing cannot be immediately performed, plasma is stable for 2 hours at room temperature, for 4 hours at refrigerator.

(b) Clot detection manually (visual) or, more commonly by an automated device for fibrin clot detection.

(c) Seconds along with the corresponding International Normalized Ratio (INR). The INR is derived by dividing the patient Prothrombin time by the mean Prothrombin time of the normal population. This result is raised to the power of value of the international sensitivity index (ISI) of the thromboplastine reagent used in the assay. The ISI is an indication of the sensitivity of the thromboplastine measured against the WHO reference. The higher the ISI, the less sensitive the thromboplastine.

(d) Reference values will vary with the type of thromboplastine. In general. 11-15 seconds for all ages, male and female. Critical value 51.6 seconds or higher. INR greater than 5.1

healthy premature newborns have prolonged PT by 3.5 seconds which return to normal adult values by day 3 or 4 (PMOH, 2005).

3.8.3.8 Partial Thromboplastin Time

APTT is used the most useful procedure for routine screening of coagulase disorders in the intrinsic pathway.

Assay Procedure:

(a) The specimen should be citrated plasma. As soon as the venous blood is drawn into a citrated tube, gently invert at least 5 times, then as soon as possible, mix thoroughly, vigorous mixing must be avoided. Citrate tubes must be properly filled, 4.5 ml blood added to 0.5 ml citrate anticoagulant 3.2%, the sample should be separated from cells as soon as possible and refrigerated if testing cannot be immediately performed, plasma is stable for 1 hours at refrigerator.

(b) detection manually (visual) or, more commonly by an automated device for fibrin clot detection.

(c) Reference range approximately 25 – 35 seconds for all ages, male and female. Critical values 70 seconds or higher (PMOH, 2005).

3.8.3.9 Electrolytes

Two to three ml of blood was withdrawn from peripheral circulation of each patient in plan tube to measure total calcium, sodium and potassium in blood, these parameters were measured by using the Nova 10 Analyzer which is available in El-Nassr hospital lab. The Nova 10 Analyzer is a machine used for quantitative determination of sodium, potassium, chloride, total calcium and lithium in serum and plasma; sodium, potassium, chloride and total calcium in urine and chloride in CSF. The ion selective electrode is a measuring device of this machine, where the ion exchange phenomena occur at the membrane of the

ion selective electrode (Nova, 1996). The blood samples were labeled with patient names and sent immediately to the laboratory. Serum separated by centrifugation from contact with cells as soon as possible to maximum time limit of one hour from the time of collection of blood specimens. Serum specimens were introduced to machine for analysis and the results were obtained within few minutes, then recorded for patients. Total calcium normal range in children 8.8 -10.7 mg/dl (McClatchey, 1994). Sodium normal range 135-150 m.Eq/L (Henry,1996).

3.8.3.10 Blood gases

Arterial blood is the preferred specimen for acid-base and blood gas studies, venous blood is affected by peripheral circulatory efficiency and cellular metabolic needs, but may used to reflect the patient acid-base status (PH, PCO2, and HCO3). One to two ml of arterial blood was withdrawn from peripheral circulation of each patient in syringe and mixing the blood with anticoagulant (heparin salt**)** to measure blood gases by Radiometer ABL-5 blood gas analyzer. The Blood gas analyzer directly measures, PH, PCO2, and PO2 by means of electrodes. And calculated or estimated HCO3, SO2, ABE, and other parameters. By mathematical equations. PH normal range in children normal range in children (7.35 - 7.45), blood PCO2 normal range (35 – 45) mm Hg, PO2 (85 – 105) mm Hg, Blood HCO3 (21 – 26) mmol / l, total CO2 (22 – 30) mmol/ l and Actual Base Excess ABE (0 to ± 2.5) mmol / l (Radiometer, 1994).

3.9 Data entry and statistical analysis

Statistical analysis and data entry will do on a computer basis, using the SPSS (statistical package for social sciences) software package version (11). Variables are defined and coded; data will entered by researcher.

Analysis of data was carried out using frequency tables; cross tabulation. Statistical relationship between variables are assessed by using chi square, T-Test in addition to correlation ® and regression, coefficient interval (CI) 95%, with p-value0.05.

3. 10 Limitation of the study

1- Lack of resources and materials and absence of funding.

Chapter Four

Results

4.1 Characteristic of study population

The study population consists of 366 infant children who were diagnosed Septicemia by blood culture positive results. Results of this study revealed that 59.6% of the cases were males and 40.4% of them were females (figure 4.1). The distribution of cases by governorates shows that 60.4% of cases were living in Gaza governorate, 33% in North governorate, and approximately 6.6% of them were living in southern governorates (Mid-zone, Khanyounis and Rafah) (figure 4.2).

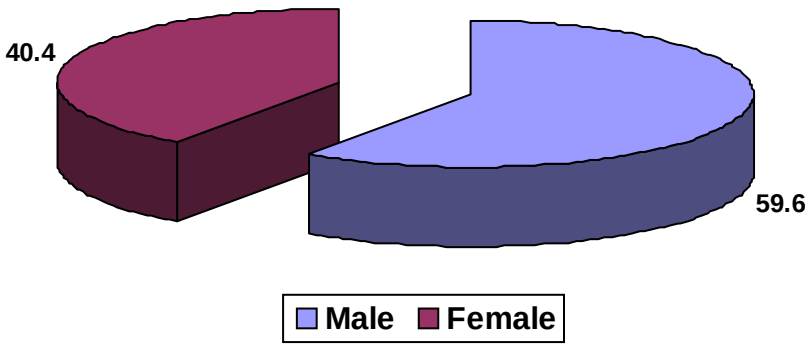


Figure (4.1) Distribution of Septicemia cases by sex

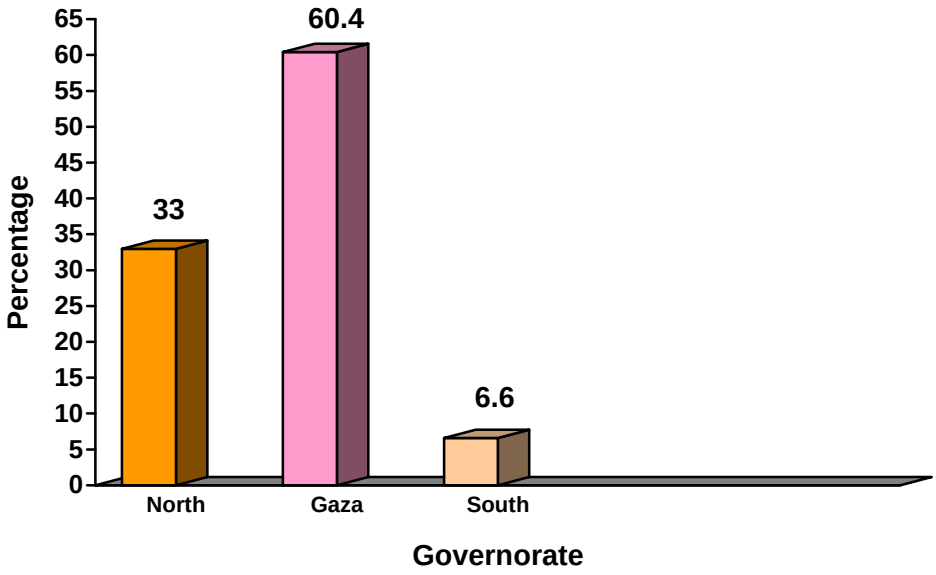


Figure (4.2) Distribution of cases by governorates

These findings that show 59.6% of the total cases were males and 40.4% of them were females, disagree with the Male: Female ratio with the general population male: female ratio in Gaza governorates which is (50.56 : 49.35) (Palestine, MOH, 2000).

Our results are consistent with the study of Scott Watson et al, (2003) that conducted in the United Stat and showed that 55.1% of sever sepsis children cases were male and 44.9% were females. Also, these results are in agreement with the findings of El-Jadba (2005) which were carried out in Palestine for neonatal Septicemia in Gaza city hospitals and demonstrated that 62% of cases were male and 38% were females.

In our study the highest incidence rate of Septicemia disease was found in Gaza governorate followed by North governorates, while the study revealed low incidence rates in southern governorates. This could be explained by the location of El-Nassr pediatric hospital which is between Gaza and North governorates, however, another hospitals in Gaza Strip also introduce the clinical services for others.

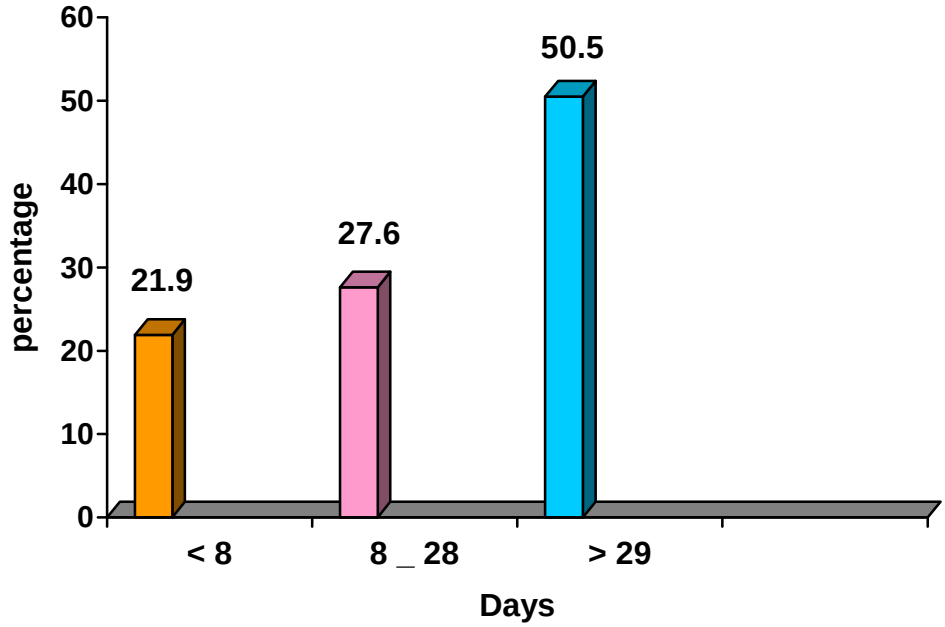


Figure (4.3) Distribution of Septicemia cases by age groups

The mean age of cases was 69.65 days (SD = ± 88.73, range 1 - 355 days). Age groups distribution shows that 49.5% of the cases were < 28 days old (neonates), 38.1% of them were females and 61.9% were males, however 21.9% of all cases were < 8 days old (early neonates), 38.7% of them females and 61.3% were males. 27.6% of all cases were 8 - 28 days old (late neonates), 37.6% of them females and 62.4% were males, and 50.5% of all cases were > 28 days old (post neonates), 42.7% of them females and 57.3% were males as shown in. (Figure 4.3) and (Table 4.1) (Kliegman, et al, 2007).

Table (4.1) Distribution of cases by age groups and sex

Age groups (Days)	Male		Female		Total	
	No	%	No	%	No	%
< 8	49	61.3	31	38.7	80	100
8 - 28	63	62.4	38	37.6	101	100
>28 - 365	106	57.3	79	42.7	185	100
Total	**218**	**59.6**	**148**	**40.4**	**366**	**100**

Findings show 49.5% of cases were neonates less than 28 days which indicated the risk of susceptibility to Septicemia during the first month of life. It was noticed that males in all age groups were more likely to have septicemia disease.

Table (4.2) Distribution of cases by crowding index

Crowding index	Frequency	Percent
< 2	87	31.2
2 - < 3	69	24.7
3+	123	44.1
Total	**279**	**100.0**

The results showed that 44.1% of cases with Septicemia were living in houses with crowding index three persons and more per room, while 31.2% of the cases were living in houses with crowding index less than two (Table 4.2). The average number of rooms were 3 rooms/house (SD = 1.52). Also, the average number of persons per house of the cases was 9.63 (SD = 6.24). These results are consistent with that of other studies which found that overcrowding was associated with increased risk for Septicemia disease, as it increases the risk of transmission of infectious organisms among people (Behrman, and Kliegman, 2002). It is clear that 67.5% of the cases were from low economic status according to income of the family (Table 4.3).

Table (4.3) Distribution of cases by family income

Income level	Frequency	Percent
High	11	3.9
Moderate	80	28.6
Low	189	67.5
Total	**280**	**100.0**

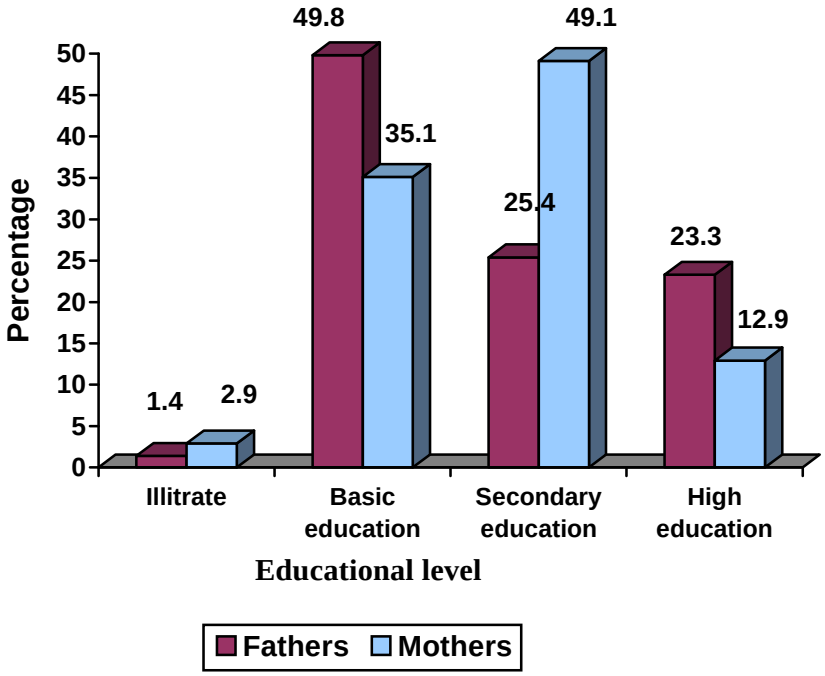


Figure (4.4) Distribution of cases by parents' education

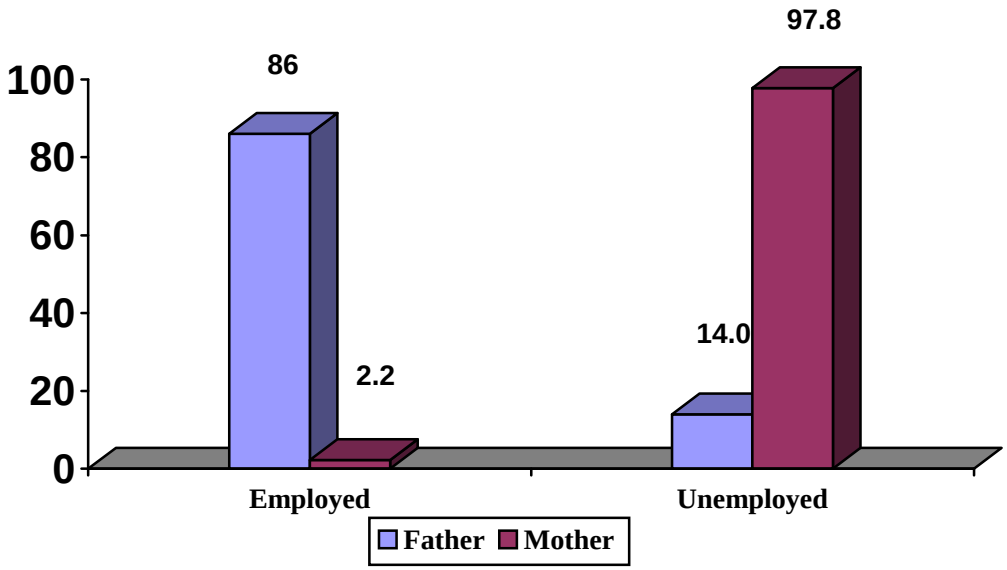


Figure (4.5) Distribution of cases by by fathers' occupation

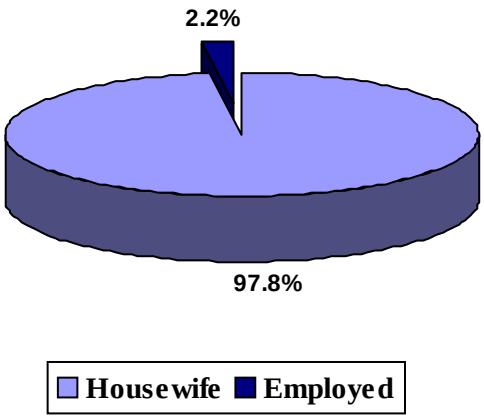


Figure (4.6) Distribution of septicemia cases by mothers occupation

The average years of education of fathers' cases was 10.26 years (SD = 3.94, range 0 - 22), compared to 10.42 years for their mothers (SD = 3.26, range 0 - 18). Interestingly the percentage of illiteracy were 1.4% among the fathers and 2.9% among the mothers of cases. About 49.8% of fathers had their basic education while 35.1% of mothers had their basic education. Mothers with high educational level represented 12.9%, while fathers of the same category represented 23.3% of cases (Figure 4.4).

In addition to that, 86% of cases' fathers were employed and 14% unemployed. However 97.8% of mothers were housewives while only 2.2% were employed (figures 4.5, 4.6).

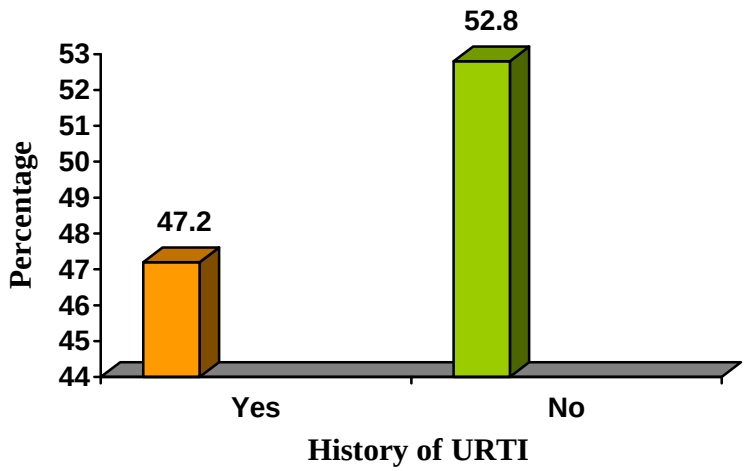


Figure (4.7) Distribution of cases by history of upper respiratory tract infection.

Approximately more than 47% of cases had a history of upper respiratory tract infections preceding the septicemia infection (figure 4.7). These result indicate that the risk factor of exposure to upper respiratory tract infections may be developed to Septicemia disease among infants. However, about 13.5% of the cases had congenital diseases while 2.5% of the cases had immunodeficiency diseases (figure 4.8). More studies are needed to investigate the relationship between congenital diseases and immunodeficiency as a risk factors of septicemia.

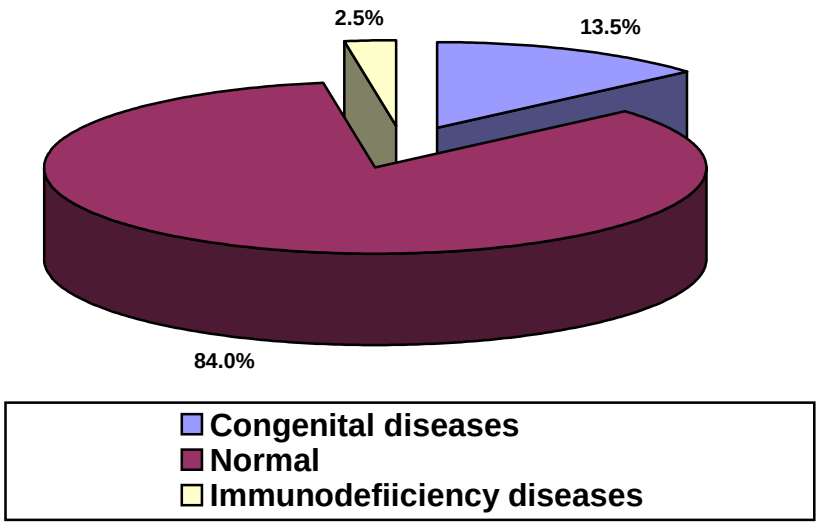


Figure (4.8) Distribution of cases by health status

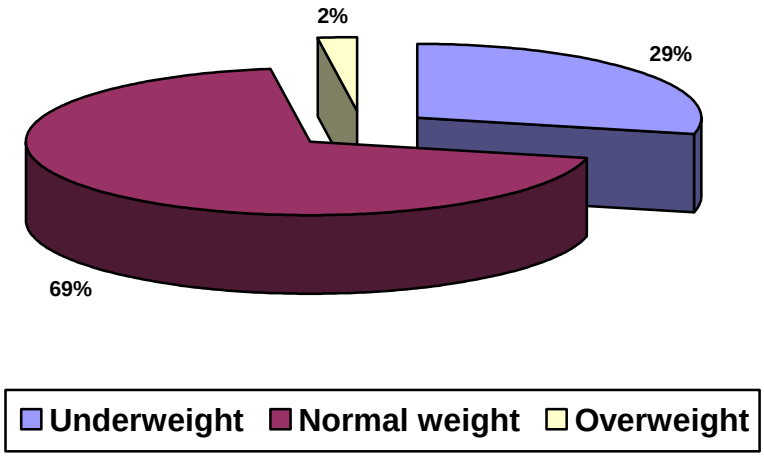


Figure (4.9) Distribution of cases by weight status

The study results reveal that 29% of cases were underweight, and 69% of them were within normal weight, this was calculated depending on WHO criteria as shown in (Figure 4.9), (Kliegman, et al, 2007). furthermor 53.2% of the cases were anemic, but 46.8% of them were none anemic (WHO 1996) (Figure 4.10).

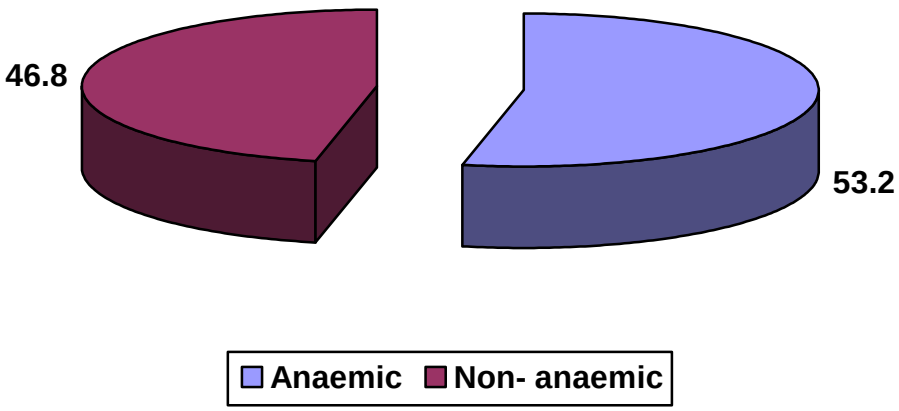


Figure (4.10) Distribution of cases by anemia status

Our study demonstrate that 29% of cases were underweight which is consistent with the study of Simiyu (2003) that conducted in Nairobi-Kenya about neonatal infants admitted to the general pediatric wards at Kenyata pediatric hospital during the year 2000, which showed that 33.4% were having low birth weight (LBW), and 5% being very low birth weight (VLBW).

This study showed that 53.2% of all cases is anemic but this result dose not representative in the same age group of population because all cases in the study were sick and collecting from the hospital departments. But, anemia is one of the manifestations of malnutrition (Kliegman, et al, 2007). Though anemia in children in Palestine is common, anemia in our study could be a manifestation of the disease process itself. Anemia might be due to the bad nutritional status which was found to be associated with Septicemia as a risk factor as indicated in the study by Rodrigo (2002).

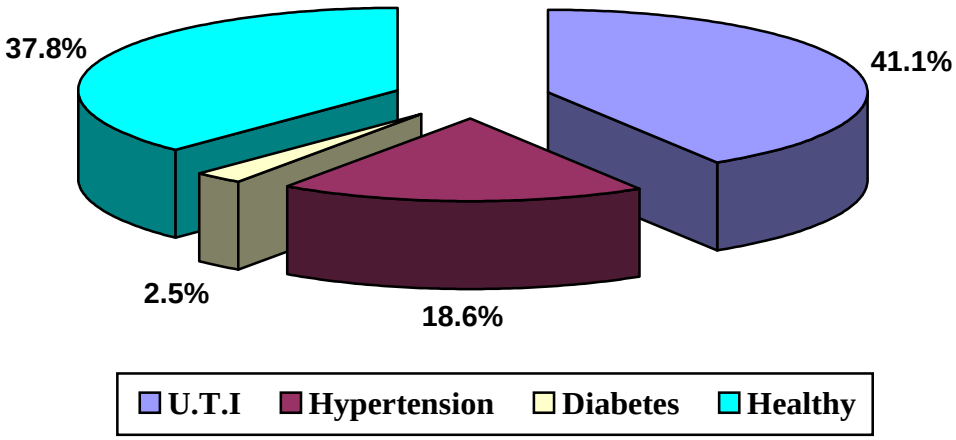


Figure (4.11) Distribution of cases by mother's medical history during pregnancy period

Table (4.4) Distribution of cases by mother's medical history during pregnancy period

Maternal status	Neonates < 28 day		Post neonates		Total	
	Freq.	%	Freq.	%	Freq.	%
U.T.I	53	42.1	62	40.3	115	41.1
Hypertension	20	15.9	32	20.8	52	18.6
Diabetes	3	2.4	4	2.6	7	2.5
Healthy	50	39.6	56	36.3	106	37.8
Total	**126**	**100**	**154**	**100**	**280**	**100.0**

The result showed that 41% of mothers' had a history of urinary tract infection during the pregnancy period (42.1% for neonates, 40.3% for post neonates mothers), 18.6% of mothers' cases had a history of hypertension (15.9% for neonates, 20.8% for post neonates mothers) and 2.5% of mothers' had a history of diabetes during the pregnancy period, (2.4% for neonates, 2.8% for post neonates mothers) as illustrated in (Table 4.4) and (Figure 4.11).

These findings are inconsistent with result of a study performed in the Gaza city hospitals of neonatal septicemia done by El-jadba, (2005) which showed that 28.6 of mothers had urinary tract infection (UTI), 33% had hypertension and 6.5% had diabetes mellitus. These findings and their association with infection in the post neonatal period is not explained, though it is well known in the neonate.

4.2 Incidence and case fatality of septicemia disease

The incidence rate of Septicemia disease among infants under 1 year old in El-Nassr pediatric hospital was 58 per 1000 children (366 of 6314), the incidence rate between neonates less than 28 days of age was 150 per 1000 children (181 of 1206), and the incidence rate between post neonates more than 28 days to 1 years old was 36.2 per 1000 children (185 of 5108). This means that the younger the infant the more liable he is to develop Septicemia.

Results showed that 37 out of 366 cases died from Septicemia diseases with case fatality rate 10.1%. It is important to mention that 18 out of 37 deaths were females with case fatality rate 12.2% (18 of 148), and 19 case was male with case fatality rate 8.7% (19 of 218) (figure 4.12). The case fatality surprisingly is lower for males than females though mortality in general for males are higher in males than females put reference from the Palestinian statistics of the Ministry of Health. 16 cases of all deaths were less than 8 days old (early neonates) with case fatality rate 20% (16 of 80), 6 cases of all deaths were 8 – 28 days old (late neonates) with case fatality rate 5.9% (6 of 101), and 15 cases of deaths were more than 28 to 365 days old (post neonates) with case fatality rate 8.1% (15 of 185). It was noticed that most the deaths were from North governorate with case fatality rate 14.3% (17 of 119), Gaza governorate (18 of 218) cases with case fatality 8.3% and south governorates (Mid-zone, Khanyonous and Rafah) with case fatality rate 6.9% (2 of 29) cases (Table 4.5).

Our findings of fatality rate are consistent with that reported by Kliegman, et al, (2007) that shown the case fatality rate in children aged 3 months to 14 years was 9%. However, our results are inconsistent with the study done by Ronnestad et al,(2005) who reported the case fatality rates were high, ranging from 26% to 36%.

Our results show lower case fatality than that of El-jadba (2005) who reported that the case fatality in Gaza city hospitals 45% and also lower than that in the study done by Leibovitz, et al, (1997) in Israel who reported that the overall fatality rate due to Septicemia was 14%, and also lower than that of Aird (2003) who reported that the case fatality in United State with sever sepsis was 50% or greater. This indicated that El-Nassr pediatric hospital provides high quality services in management of cases with early diagnosis and early effective therapeutic measures, which regards effective in treatment of the Septicemia disease cases and reducing the complications of the disease and consequently decreasing the case fatality rate.

In our study, we demonstrated that the incidence rate of Septicemia was 58 per 1000 infant less than 1 year old (366 of 6314), and the incidence rate between neonates less than 28 days of age was 150 per 1000 children (181 of 1206), these results are inconsistent with that of Scott Watson et al. (2003) who observed that the incidence was highest in infants by 5.16 per 1,000. The differences in results of our study about that obtained by Scott Watson et al. (2003) may be explained in that, this study was done in El-Nassr Pediatric hospital only, which could not be representative for all population.

Regarding to the incidence of Septicemia among infants which was shown to be high in this study this could be explained due to the crowded living condition and low socio-economic status of families and the high incidence of malnutrition (underweight) that might be associated with Septicemia disease.

Case fatality rate was considered the highest in North governorate with rate of 14.3%, this could be explained by high crowded, poverty and bad socio-demographic factor in the North governorate.

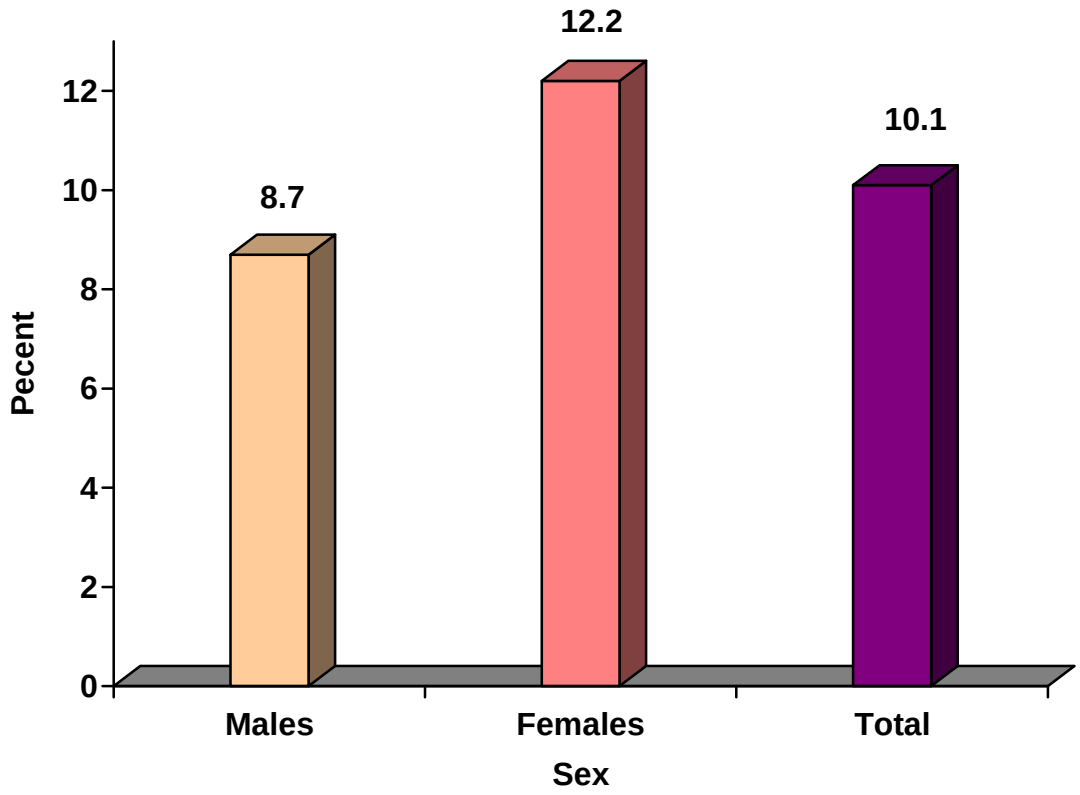


Figure (4.12) Distribution of cases by fatality rates

Table (4.5) Relationship between governorates and prognosis.

Governorates	Recovery		Death		Total		Chi-Square	P-value
	Freq.	%	Freq	%	Freq	%		
North	102	85.7	17	14.3	119	100	**3.007**	**0.222**
Gaza	200	91.7	18	8.3	218	100		
South	27	93.1	2	6.9	29	100		
Total	**329**	**89.9**	**37**	**10.1**	**366**	**100**		

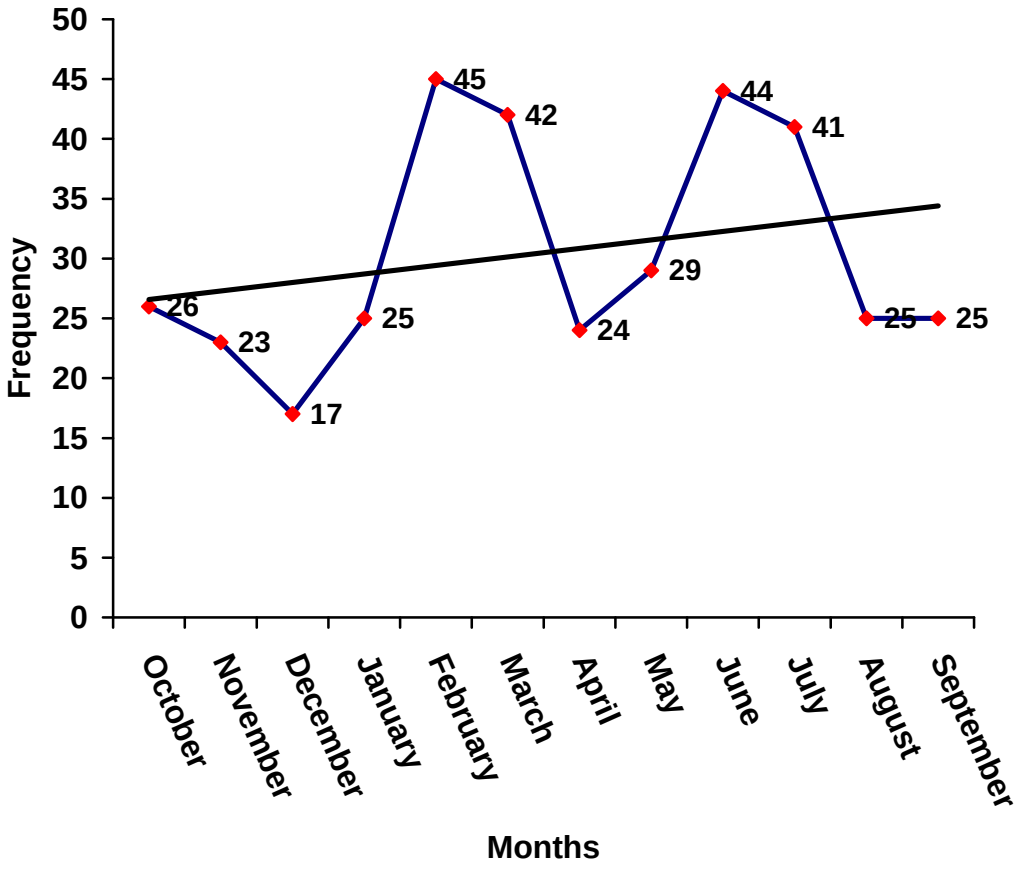


Figure (4.13) Trend of septicemia in El-Nassr hospital 2006-2007

The incidence of septicemia disease began to be increased in January and reach its peak in February and March, then return to reach its end in April. This curve increased again in June and July, then return to reach its end in August (figure 4.13).

The study showed seasonal variation occurrence, with the highest attack rates in February and reach its lowest incidence in April then increase in June and July in the peak of summer. This coincides with the respiratory infections in winter and diarrheal diseases in summer. This result is consistent with the study of Kennedy (1996) conducted in Australia which revealed that a seasonal upsurge in meningococcemia (septicemia disease) occurs in winter where viral infection increases. Alters of the integrity of noso-pharyngeal mucosa is also thought to increase susceptibility (Kennedy, 1996). It is well known that diseases

either communicable or non-communicable are present in a dynamic state and not in static state. There is some diseases disappear and others reemerge and that is what we call dynamic epidemiological transition, so not always we can predict or explain the variations which occurs in the occurrence of diseases and may be this is positive cases in our study.

4.3 Laboratory results and clinical manifestations of septicemia disease

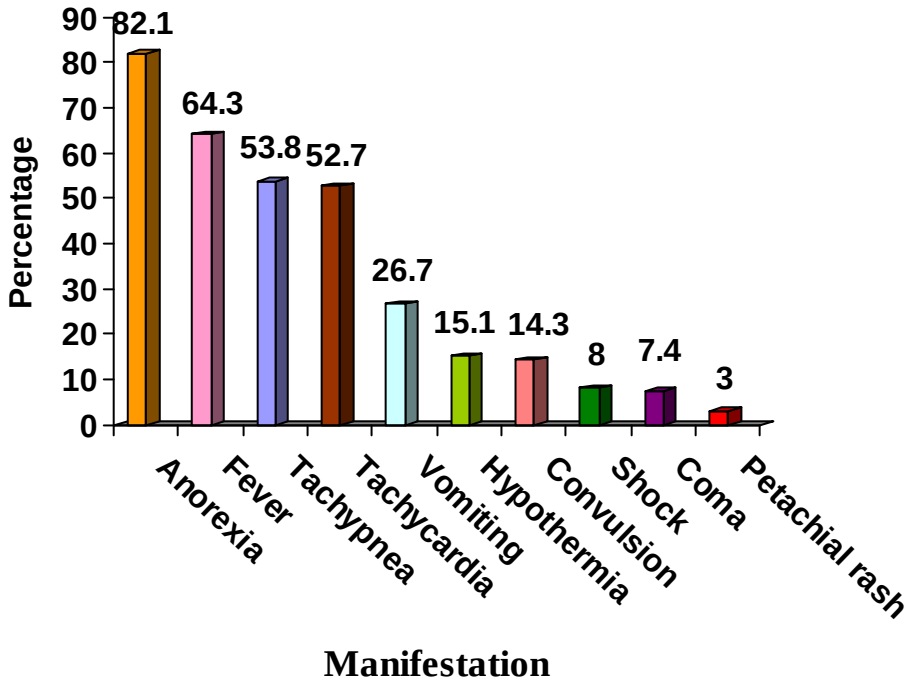


Figure (4.14) Distribution of cases by manifestations of Septicemia

According to the clinical manifestations of the Septicemia disease, 82.1% of cases were complaining of anorexia, where approximately more than 64% of cases were complaining of fever. Tachypnea and tachycardia were signs in more than half of the cases. In addition, 26.7% of the cases had vomiting, 15.1% were hypothermia as indicated by (Kliegman, et al, 2007), 14.3% of cases had attack of convulsion, 8% were shocked, 7.4

were comatosed and rashes were signs in 3% of cases (meningococcemia cases) (Figure 4.14). For blood pressure about 8% of all cases had been done in which 86.2% of these cases were low blood pressure and 13.8% of them were normal as shown by (Kliegman, et al, 2007) (Table 4.6). This high percentage because blood pressure is measured in selected group of patients who are clinically severely sick.

Our study results are agreement with Kliegman et al. (2007) who reported that Septicemia disease is associated with alterations in temperature regulation (hyperthermia or hypothermia), tachycardia, tachypnea and hypotension which were a late findings in children with sepsis and shock.

Table (4.6) Distribution of cases by measurement of blood pressure

Blood pressure	Frequency	Percentage
Hypotension	25	86.2
Normal	4	13.8
Hypertension	0	0
Total	**29**	**100**

Table (4.7) Distribution of cases according to the results of complete blood count

	Frequency	Percentage (%)
W.B.Cs		
Low	38	11.2
Normal	216	63.5
High	86	25.3
Total	**340**	**100**
HB		
Anemic	181	53.2
Normal	159	46.8
Total	**340**	**100**
Platelets		
Low	62	18.2
Normal	278	81.8
Total	**340**	**100**
Neutrophil		
Low	176	51.8
Normal	69	20.3
High	95	27.9
Total	**340**	**100**

For CBC Examination that had been done for 93% of the cases, from which W.B.Cs for 11.2% of these tests were low (leucopenia), 63.5% were normal and 25.3% were high (Leucocytosis) as demonstrated by (Campbell & Mclntosh,1998). On other hand, about 53.2% of these cases were anemic, 46.8% were normal Hb (WHO 1996). More over, 18.2% of these cases had low platelets count (thrombocytopenia) and 81.2% had normal platelets count (PMOH, 2005). Furthermore, approximately 52% of these cases were with low Neutrophil count (neutropenia) (Table 4.7).

This study showed that 63% of the patients were within the normal range of leucocyte count. These results are inconsistent with the previous study of Sharma (2006) that reported septicemia was associated with increased levels of leucocyte count in the majority of their study cases. This indicate that, we could not take leucocyte count as indication for Septicemia diagnostic tool in infants. Also, our study showed that 51.7% of cases had

Neutropenia, these findings agrees with Kliegman et al. (2007) that reported Neutropenia is an important early laboratory finding caused by infection-mediated neutrophil storage pool depletion and margination of cells and Neutropenia is an ominous sign of overwhelming sepsis.

Our study indicate that 18.2% of cases had thrombocytopenia, these findings are consistent with the study of Bone (1996) that reported thrombocytopenia and coagulation abnormalities were associated with Septicemia.

Table (4.8) Distribution of cases according to the results of C- Reactive Protein & Erythro Sedimentation Rate

Tests	Frequency	Percentage (%)
C.R.P		
Positive	81	65.3
Negative	43	34.7
Total	**124**	**100**
E.S.R		
Normal	7	11.7
High	53	88.3
Total	**60**	**100**

For C- Reactive Protein (C.R.P) examination, about 34% (124 of 366) of the cases that had been done from which 65.3% of these cases were positive. For Erythro Sedimentation Rate (ESR) investigation 16.4% (60 of 366) that had been done of the cases from which about 88.3 % of them was high (Table 4.8).

These findings are consistent with Peitola and Jaakkola, (1988) that reported C.R.P is another marker for neonatal Septicemia, and there was high significant statistical association between C- Reactive Protein positive and Septicemia. Our result also is agreement with the study done by El-jadba, (2005) that showed 72% of neonates cases had positive C.R.P, but in our series high ESR was more correlated with Septicemia than CRP.

Table (4.9) Distribution of cases according to the results of electrolytes

Electrolytes	Frequency	Percentage (%)
Na		
Low	55	17.8
Normal	241	78.0
High	13	4.2
Total	**309**	**100**
Ca^{+2}		
Low	87	35.7
Normal	146	59.8
High	11	4.5
Total	**244**	**100**

Regarding sodium electrolyte (Na) examination that had been done for 84% of the cases, 17.8% of them were low (hyponatremia), but 63.5% were normal and 25.3% were high (hyponatremia) as shown by Henry,(1996). Moreover, (Ca^{+2}) examination was done for 66.7% (244 of 366) of the cases and the results showed that 35.7% of them was low (hypocalcaemia), 59.8% were normal (Ca^{+2}) and 4.5% were high (Ca^{+2}) (hypocalcaemia) as indicated by McClatchey, (1994) (Table 4.9).

Results of this study are consistent with Kliegman et al. (2007) that reported the association between Septicemia and electrolyte abnormalities including hypocalcaemia.

Table (4.10) Distribution of cases according to the results of (PT, PTT) tests

	Frequency	Percentage (%)
P.T		
Normal	11	11.3
Prolonged	86	88.7
Total	**97**	**100**
P.T.T		
Normal	24	24.7
Prolonged	73	75.3
Total	**97**	**100**

Prothrombin time (P.T), Partial thromboplastine time (P.T.T) had been done for 26.5% (97 of 366) of the study cases. Our results show that 88.7% of these patients were having prolonged (P.T), while 75.3% were with prolonged (P.T.T) which is consistent with PMOH, (2005) (Table 4.10).

These results are also supported with those of Bone, (1996) who reported that thrombocytopenia and coagulation abnormalities are often seen in Septicemia and with that Kliegman et al. (2007) who reported the relationship between Septicemia and prolonged P.T , PTT. From our point of view, these findings demonstrated that PT, PTT, were very important and essential in diagnosis and treatment of Septicemia.

Table (4.11) Distribution of cases according to the results of blood gas

Blood gases	Frequency	Percentage (%)
PH		
Acidosis	110	47.2
Normal	90	38.6
Alkalosis	33	14.2
Total	**233**	**100**
HCO-3		
Low	114	48.9
Normal	86	36.9
High	33	14.2
Total	**233**	**100**
ABE		
Normal	95	40.8
Abnormal	138	59.2
Total	**233**	**100**

Blood gas examination identified that about 63.7% (233 of 366) of the cases that had been done, from which 47.2% were acidosis, 38.6% were normal and 14.2% had alkalosis. Results revealed that about 48.9% of those performed HCO-3 investigation had low levels, 36.9% were normal and 14.2% were with high HCO-3 levels as indicated by Radiometer, (1994) (Table 4.11).

Our study agreement with Kliegman et al. (2007) that concluded the association between metabolic acidosis and low serum bicarbonate with Septicemia. These results demonstrated that blood gases were important and essential in diagnosis of Septicemia and determined the severity of disease.

4.4 Relationship between laboratory results and prognosis of septicemia.

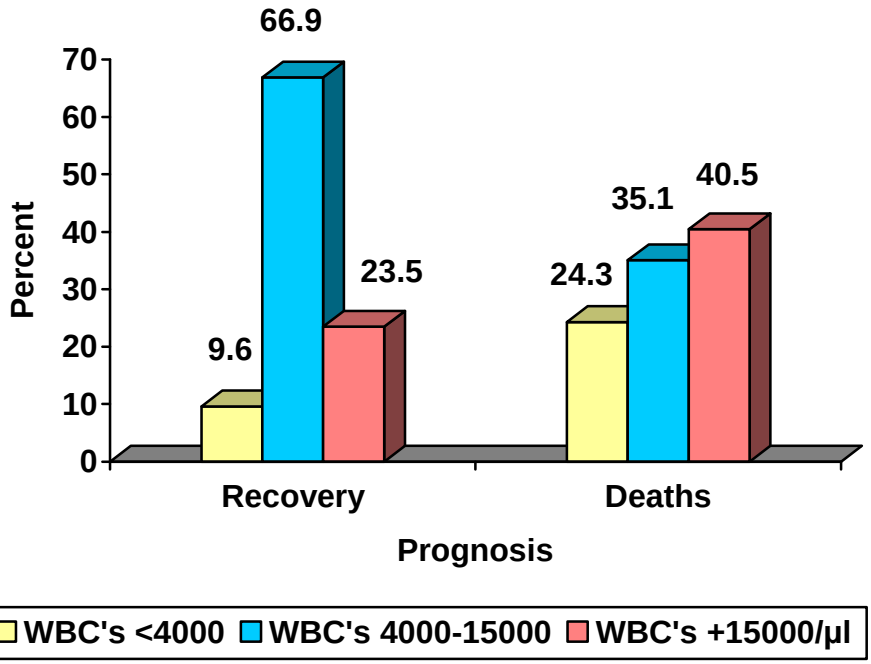


Figure (4.15) Distribution of cases by peripheral WBC's and prognosis

Table (4.12) Relationship between WBC's count and prognosis

	Recovery		Death		Chi-Square	P-value
	Frequency	Percent %	Frequency	Percent %		
W.B.CS						
Low	29	9.6	9	24.3		
Normal	203	67.0	13	35.1	**17.947**	**0.001**
High	71	23.4	15	40.5		
Total	**303**	**100.0**	**37**	**100.0**		

Average of leukocyte count of the study population was 12,497 cells /µl with range from 2,300 cells /µl to 83,100 cells /µl. Leukocytosis was found in 25.3% (86 of 340) of all Septicemia disease cases, while leucopenia was found in 11.2% (38 of 340) of all cases. Moreover leucopenia was associated with deaths, 24.3% (9 of 37) of died cases had leucopenia, compared to 9.6% recovered cases (Campbell & Mclntosh,1998). This reflects that there was high significant statistical association between leucopenia in blood and Septicemia diseases as bad prognosis *(*Chi-Square= *17.947, p-v= 0.001)* (Table 4.12). Also, leukocytosis was associated with deaths, 40.5% (15 of 37) of died cases were with leukocytosis, compared to 23.4% (71 of 303) that were recovered cases. (Figure 4.15).

Our study result is consistent with El-jadba, (2005) that showed Leukocytosis was found in more than 30% of neonatal with Septicemia and the neonates with Leukocytosis was more associated with death.

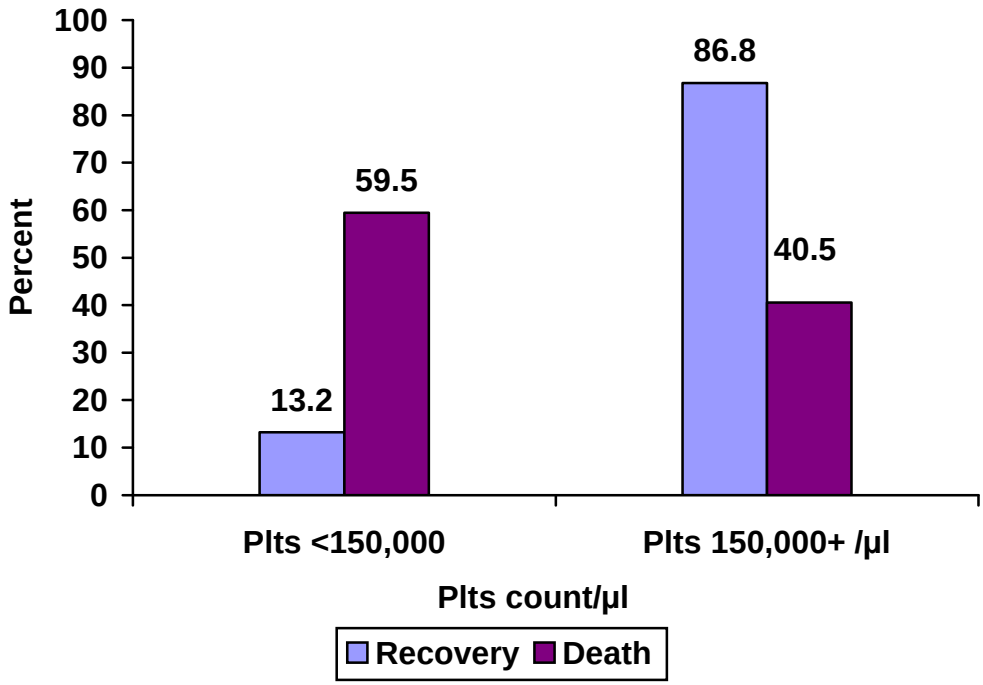


Figure (4.16) Distribution of cases by platelets count and prognosis

Table (4.13) Relationship between platelets count and prognosis

	Recovery		Death		Chi-Square	P-value
	Frequency	Percent %	Frequency	Percent %		
Platelet					47.353	0.001
Low	40	13.2	22	59.5		
Normal	263	86.8	15	40.5		
Total	**303**	**100.0**	**37**	**100.0**		

It is clear that thrombocytopenia was associated with Septicemia, about two third 59.5% (22 of 37) of died cases were with thrombocytopenia, while 40.5% (15 of 37) of died cases had normal platelets count as shown in (Figure 4.16). This reflects that there was high significant statistical association between thrombocytopenia in blood and septicemia diseases as bad prognosis *(*Chi-Square*= 47.353, p-v= 0.001),* (Table 4.13).

These findings are consistent with that of El-jadba, (2005) who demonstrated that 68.8% of patient with thrombocytopenia died compared to 31.2% of patient with normal platelet count who were died.

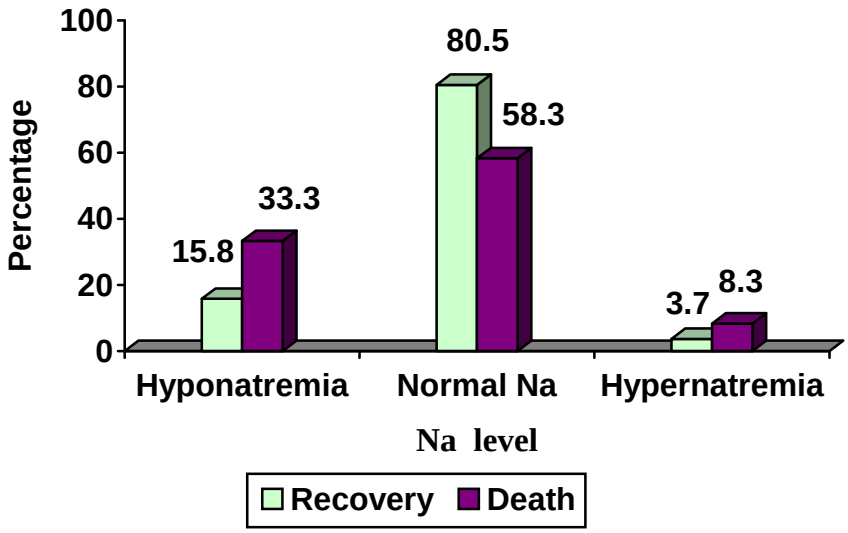


Figure (4.17) Distribution of Cases according to Na level and prognosis

Table (4.14) Relationship between (Na) level and prognosis

	Recovery		Death		Chi-Square	P-value
	Frequency	Percent %	Frequency	Percent %		
Na						
Low	43	15.8	12	33.3		
Normal	220	80.5	21	58.3	**9.109**	**0.011**
High	10	3.7	3	8.3		
Total	**273**	**100.0**	**36**	**100.0**		

Hyponatremia was associated with septicemia. About one third 33.3% (12 of 37) of died cases had hyponatremia, while 58.3% (21 of 37) of the died cases had normal (Na) level as shown in (Figure 4.17) which is consistent with Henry,(1996). This reflects that there was high significant statistical association between Hyponatremia in blood and Septicemia diseases *(*Chi-Square= *9.109, p-v= 0.011)* ,(Table 4.14).

These findings demonstrated the relationship between hyponatremia and mortality of Septicemia, and this result is agreement with the study of Faber, et al (1993) that show hyponatremia occurred frequently in patients with severe infections and though that its cause has not been established.

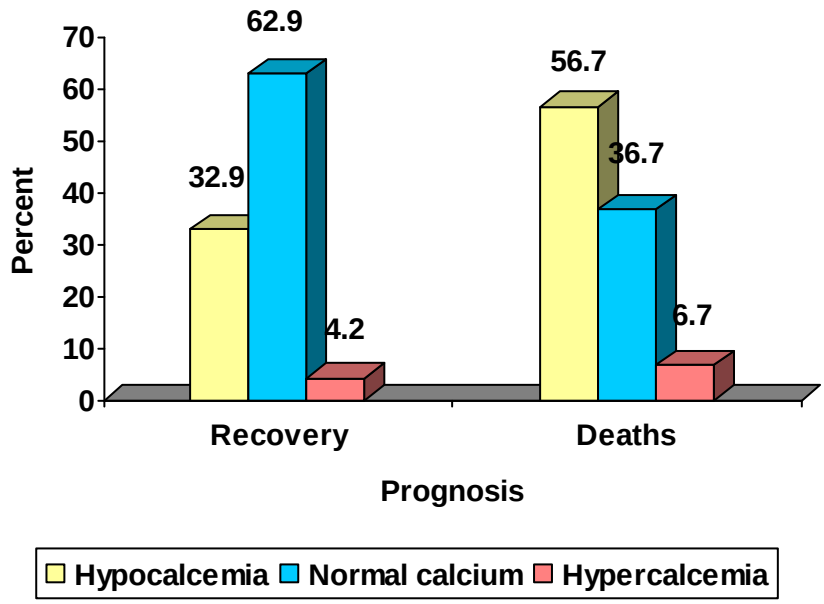


Figure (4.18) Distribution of cases according to blood (Ca^{+2}) level and prognosis

Table (4.15) Relationship between (Ca^{+2}) level and prognosis

	Recovery		Death		Chi-Square	P-value
	Frequency	Percent %	Frequency	Percent %		
(Ca^{+2})						
hypocalcaemia	70	32.7	17	56.7		
Normal	135	63.1	11	36.7	**7.543**	**0.023**
hypercalcaemia	9	4.2	2	6.7		
Total	**214**	**100.0**	**30**	**100.0**		

In septicemia cases 59.8% (146 of 244) had normal calcium level in blood, but most of the died cases who were 56.7% (17 of 30) had hypocalcaemia. This reflects that there was high significant statistical association between hypocalcaemia in blood and Septicemia diseases as bad prognosis *(*Chi-Square*= 7.543, p-v= 0.023)* (Table 4.15), (Figure 4.18).

Our study show the significant relationship between the died cases and hypocalcaemia and this is consistent with Kliegman et al. (2007) that reported an association between Septicemia and electrolyte abnormalities including hypocalcaemia as bad prognosis.

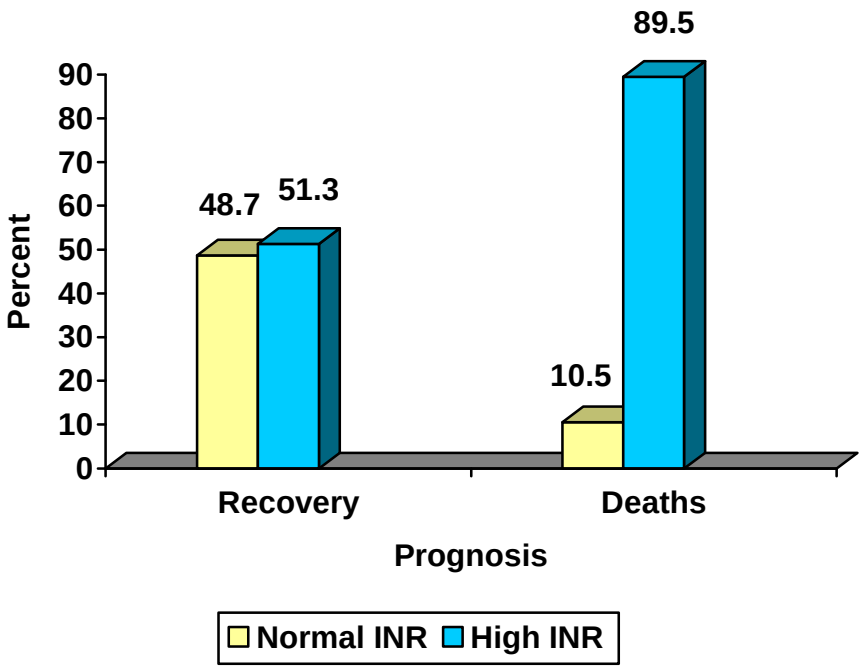


Figure (4.19) Distribution of cases by results of (P.T) by (INR) and prognosis

Table (4.16) Relationship between results of (P.T) by (INR) and prognosis

	Recovery		Death		Chi-Square	P-value
	Frequency	Percent %	Frequency	Percent %		
P.T					**9.110**	**0.011**
Normal	36	48.7	2	10.5		
High	38	51.3	17	89.5		
Total	**75**	**100.0**	**19**	**100.0**		

It is clear that International Normalized Ratio (INR) was associated with Septicemia. About 89.5% (17 of 19) of the died cases had high INR, while 10.5% (2 of 19) of the died cases had normal INR as shown in (Figure 4.19) (PMOH, 2005). This reflects that there was high significant statistical association between prolonged P.T (high INR) and Septicemia diseases *(*Chi-Square= *9.110, p-v= 0.011)* (Table 4.16).

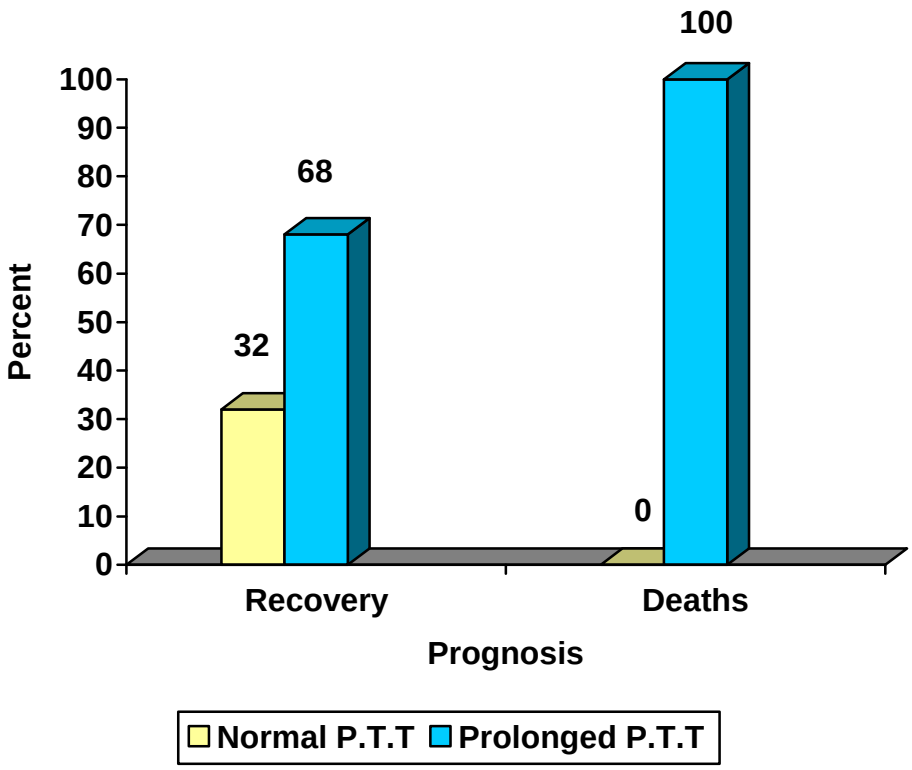


Figure (4.20) Distribution of Cases by results of P.T.T and prognosis

Table (4.17) Relationship between results of (P.T.T) and prognosis

	Recovery		Death		Chi-Square	P-value
	Frequency	Percent %	Frequency	Percent %		
P.T.T					**9.335**	**0.001**
Normal	24	32.0	0	0.0		
Prolonged	51	68.0	22	100.0		
Total	**75**	**100.0**	**22**	**100.0**		

For P.T.T examination that had been done for 26.5% (97 of 366) of the cases, from which 80.4% (78 of 97) of these tests were prolonged P.T.T. On other hand, all died cases (22 of 22) were had prolonged P.T.T, compared to recovered cases which were 68% (51 of 75) as shown in (Figure 4.20). This reflects that there was highly significant statistical association between prolonged P.T.T in blood and Septicemia diseases as bad prognosis *(*Chi-Square= *9.335, p-v= 0.001),* (Table 4.17). The most likely explanation for the prolonged PT and PTT may be attributed to the decrease in the synthesis of coagulating factors due to impaired liver synthetic function, and the consumption coagulopathy that accompanies Septicemia.

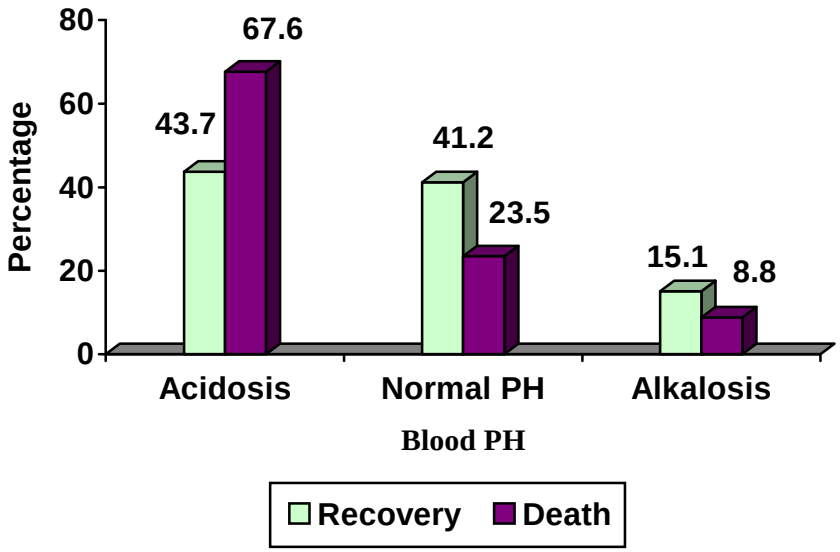


Figure (4.21) Distribution of Cases according to Blood PH and prognosis

Table (4.18) Relationship between blood PH and prognosis

	Recovery		Death		Chi-Square	P-value
	Frequency	Percent %	Frequency	Percent %		
PH						
Acidosis	87	43.7	23	67.6	**6.672**	**0.036**
Normal PH	82	41.2	8	23.5		
Alkalosis	30	15.1	3	8.8		
Total	**199**	**100.0**	**34**	**100.0**		

Acidosis was associated with Septicemia, about 67.6% (23 of 34) of died cases had acidosis compared to recovered cases 43.7% (87 of 199), while 23.5% (8 of 34) of died cases had normal PH as shown in (Figure 4.21) as shown by Radiometer, (1994). This reflects that there was significant statistical association between Acidosis in blood and Septicemia diseases as bad prognosis *(*Chi-Square*=6.672,pv=0.036)*, (Table 4.18).

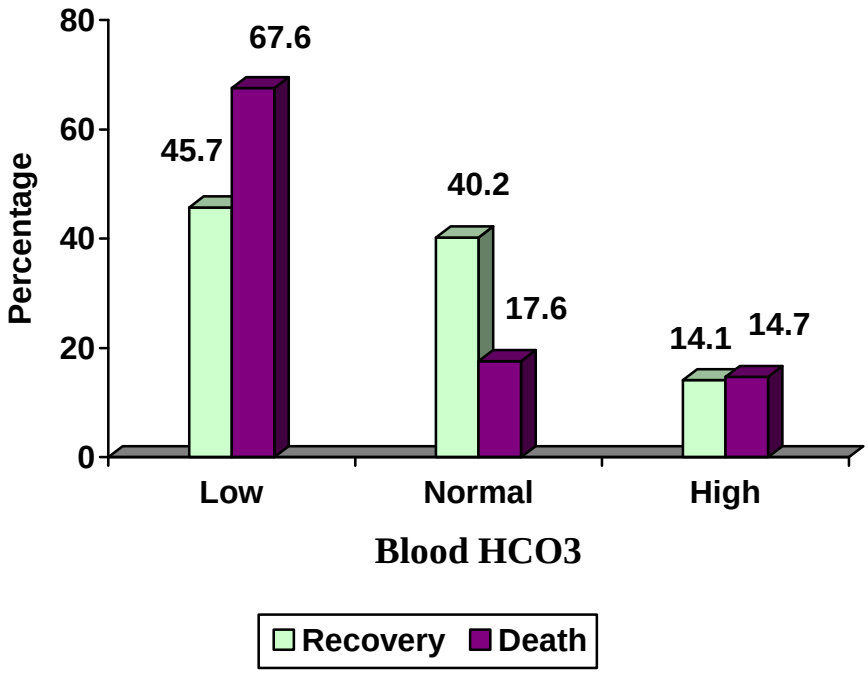


Figure (4.22) Distribution of cases according to blood HCO3 and prognosis

Table (4.19) Relationship between blood (HCO3) and prognosis

	Recovery		Death		Chi-Square	P-value
	Frequency	Percent %	Frequency	Percent %		
HCO3						
Low	91	45.7	23	67.6		
Normal	80	40.2	6	17.6	**6.682**	**0.032**
High	28	14.1	5	14.7		
Total	**199**	**100.0**	**34**	**100.0**		

For HCO3 that had been done for about 64% (233 of 366) of the cases, from which 48.9% (114 of 233) of these cases were low HCO3. On other hand, 67.6% (23 of 34) of died cases were had low HCO3, compared to 45.7% (91 of 199) recovered cases as shown in Figure (4.22). This reflects that there was significant statistical association between low HCO3 and Septicemia diseases *(*Chi-Square= *6.682, p-v= 0.032)* ,(Table 4.19) as indicated by Radiometer (1994).

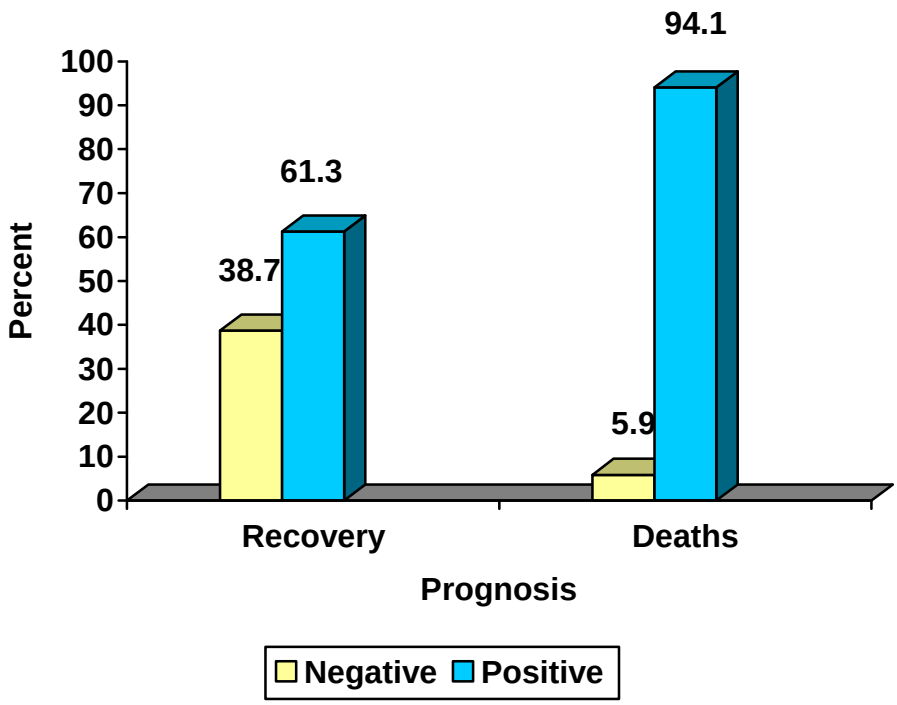


Figure (4.23) Distribution of cases by results of (CRP) and prognosis

Table (4.20) Relationship between results of (CRP) and prognosis

	Recovery		Death		Chi-Square	P-value
	Frequency	Percent %	Frequency	Percent %		
C.R.P					**7.008**	**0.005**
Negative	41	38.7	1	5.9		
Positive	65	61.3	16	94.1		
Total	**106**	**100.0**	**17**	**100.0**		

It is clear that C.R.P in blood was associated with septicemia. About 94.1% (16 of 17) of the died cases was positive C.R.P, while 5.9% (1 of 17) of died cases had negative C.R.P as shown in Figure (4.23). It could be found that there was high significant statistical association between positive C.R.P and septicemia diseases *(*Chi-Square= *7.008, p-v= 0.005)* ,(Table 4.20). More studies are required to investigate such association.

Table (4.21) Relationship between delivery weight and prognosis

Delivery weight	Recovery		Death		Total		Chi-Square	P-value
	Freq.	%	Freq	%	Freq	%		
Underweight	80	85.1	14	14.9	**94**	**100**	**4.306**	**0.116**
Normal weight	210	92.5	17	7.5	**227**	**100**		
Over weight	6	85.7	1	14.3	**7**	**100**		
Total	**296**	**90.2**	**32**	**9.8**	**328**	**100**		

Average of delivery weight of study population was 2893 gm with range from 1060 gm to 4700 gm. For delivery weight that taken for about 90.2% (328 of 366) of the cases, from which 28.7% (94 of 328) of these cases were underweight. On other hand, 14.9% of underweight cases were died, compared to 85.1% (80 of 94) recovered cases as shown in (Table 4.21). The relationship between delivery weight and prognosis is not statistical significant *(*Chi-Square= *4.306, p-v= 0.116),* which is different from all studies done in

neonate that show strong correlation between birth weight with mortality and morbidity (Kliegman, et al, 2007).

Table (4.22) Relationship between Age groups and prognosis

Age groups	Recovery		Death		Chi-Square	P-value
	Frequency	Percent %	Frequency	Percent %		
Early neonate	64	80	16	20	**10.275**	**0.006**
Late neonate	95	94.1	6	5.9		
Post neonate	170	91.9	15	8.1		
Total	**329**	**89.9**	**37**	**10.1**		

Early neonates (< 8 days old) was associated with Septicemia. About 20% (16 of 80) of early neonates cases were died compared to 80% (64 of 80) recovered cases, while 5.9% (6 of 101) of late neonates cases were died and 25.9% (22 of 181) of died cases were neonatal cases (<28 days old), while 8.1% (15 of 185) of died cases were post neonatal (>28-365 days old). This indicate that there was significant statistical association between age and Septicemia diseases *(*Chi-Square*= 10.275 p-v= 0.006)*, (Table 4.22) as shown in the study of Kliegman, et al, (2007). Moreover we observed that early neonate age group are more at risk to have Septicemia and incidence of death that required crucial therapeutic measures.

4.5 The most common types of bacteria isolated from blood

Table (4.23) The most common types of bacteria isolated from blood among infants.

Bacterial types	Frequency	Percentage
Coagulase negative staphylococcus (CoNS)	250	68.3
Klebsiella spp.	18	4.9
Pseudomonas spp.	17	4.6
E.coli spp.	16	4.4
Streptococcus viridance	14	3.8
Staphylococcus aureus	11	3.0
Neisseria meningitides spp.	10	2.7
Acinetobacter spp.	7	1.9
Group (D) Streptococcus	5	1.4
Group (B) Streptococcus	4	1.1
Streptococcus Pneumonia	3	0.8
Haemophilus influenza spp.	3	0.8
Citrobacter	2	0.5
Bacillus spp.	2	0.5
Salmonella spp.	1	0.3
Serratia	1	0.3
Moraxella	1	0.3
Proteus spp.	1	0.3
Total	**366**	**100**

The result of this study showed that, gram-positive bacteria caused septicemia with percentage about 79% (289 of 366), compared to gram-negative bacteria (21)% (77 of 366). The most common gram positive pathogenic microorganisms isolated was coagulase negative staphylococcus 250 cases (68.3%), followed by Streptococcus viridance 14 cases (3.8)%, Staphylococcus aureus 11 cases (3.0)%, Group (D) Streptococcus 5 cases, Group (B) Streptococcus 4 cases (1.1)%, Streptococcus Pneumonia 3 cases (0.8)%, and Bacillus Spp, two cases (0.5)%. However, the most gram negative pathogenic microorganisms isolated was Klebsiella Spp. 18 cases (4.9)%, followed by Pseudomonas Spp. 17 cases (4.6)%, E.coli Spp. 16 cases (4.4)%, Neisseria meningitides Spp.10 cases (2.7)%, Acinetobacter Spp. 7 cases (1.9)%, Haemophilus influenza Spp. Three cases (0.8)%, Citrobacter Spp. two cases (0.5)%, Salmonella Spp. one case (0.3)%,

Serratia one case (0.3)%, Moraxella one case (0.3)%, and Proteus Spp. one case (0.3)% (Table 4.23).

The study demonstrated that the dominant bacteria caused Septicemia among infants were gram-positive bacteria with percent of 79%, and the common bacteria isolated from blood was Staphylococcus of both Coagulase negative staphylococcus (CONS) and Staphylococcus aureus, other gram-positive organisms causes Septicemia as Streptococcus viridance, Group (D) Streptococcus**,** Group (B) Streptococcus**,** Streptococcus Pneumonia**,** and Bacillus spp**.**

These findings are consistent with that of the study of Bochud, and Glandra, (2003) that reported Staphylococci (mainly Staphylococcus aureus and Coagulase negative Staphylococci) and Streptococci (Streptococcus pyogenes, Streptococcus viridans, and Streptococcus pneumonia) are the commonest causes of gram-positive sepsis. Also, our result is consistent with the study result of El-jadba, (2005) that showed the most common gram-positive bacteria isolated from blood were Coagulase-negative Staphylococci followed by Staphylococcus aureus, Streptococcus viridance, Group (A) Streptococcus, Group (B) Streptococcus, Group (D) Streptococcus, and Streptococcus Pneumonia.

Our findings show that 21% of isolated bacteria from blood were gram-negative bacteria as Klebsiella spp, followed by Pseudomonas spp, E.Coli spp, Neisseria meningitides spp, Acinetobacter spp**,** Haemophilus influenza spp, Citrobacter**,** Salmonella spp**,** Serratia**,** and Proteus spp.

These results are consistent with those of Kliegmen et al. (2007) that reported the infectious agents were associated with sepsis in pediatric patients which were vary with the patients age and immune status**.** The most commonly organisms associated with gram-

negative sepsis in older children were Neisseria meningitides, H.influenzae, E.coli, and Salmonella.

Table (4.24) Relationship between bacterial types and prognosis

Bacterial types	Recovery		Death		Total		Chi-Square	P-value
	Freq.	%	Freq	%	Freq	%		
Coagulase negative staph.	233	93.2	17	6.8	250	100		
Klebsiella	16	88.9	2	11.1	18	100		
Pseudomonas	12	70.6	5	29.4	17	100		
E.coli	11	68.8	5	31.2	16	100		
Streptococcus viridance	13	92.9	1	7.1	14	100		
Staphylococcus aureus	11	100	0	0	11	100		
Neisseria meningitides	6	60	4	40	10	100		
Group (D) Streptococcus	5	100	0	0	5	100		
Group (B) Streptococcus	3	75	1	25	4	100		
Acinetobacter	7	100	0	0	7	100	**43.439**	**0.000**
Streptococcus Pneumonia	3	100	0	0	3	100		
Haemophilus influenza	3	100	0	0	3	100		
Citrobacter	1	50	1	50	2	100		
Bacillus	2	100	0	0	2	100		
Salmonella	1	100	0	0	1	100		
Serratia	1	100	0	0	1	100		
Moraxella	1	100	0	0	1	100		
Proteus	0	0	1	100	1	100		
Total	**329**	**89.9**	**37**	**10.1**	**366**	**100**		

In Table (4.24) which represents that gram-positive bacterial pathogens isolated from blood culture accounted for 79% (289 of 366) from cases. The died cases with gram-positive bacteria were 6.6% (19 of 289) and 93.4% (270 of 289) were recovered.

Coagulase Negative Staphylococcus (CONS) accounted of 250 cases. 6.8% (17 of 250) of cases were died. The second organism isolated was Streptococcus viridance 14 cases, in which 7.1%, (1 of 14) cases were died followed by Group (B) Streptococcus 4 cases, in which 25% (1 of 4) cases were died. However Staphylococcus aureus, Group (D) Streptococcus, Streptococcus Pneumonia and Bacillus Spp. were found in 11, 5, 3, and 2 cases respectively.

In 21% (77 of 366) of cases that were with gram-negative bacteria pathogens isolated, 23.4% (18 of 77) cases were died but 76.6% (59 of 77) were recovered. Neisseria meningitides accounted 10 cases with high fatality rate that estimated as 40% (4 of 10) cases died, this is different from previous study conducted by Abu Shaaban, (2003) to study meningococcal infection but his patient were older and this confirm our results the younger the age the more worse the prognosis, followed by E.coli 16 cases with fatality rate 31.3% (5 of 16) cases who were died. Furthermore, Pseudomonas Spp. was in 17 cases, 29.4% (5 of 17) cases who were died, while Klebsiella Spp. accounted of 18 cases. 11.1% (2 of 18) cases that were died. However, Acinetobacter Spp. were in 7 cases, but non of then died, Citrobacter Spp. was in 2 cases one of these cases died but the other was recovered. Haemophilus influenza was in 3 cases, without dying, Salmonella reported in 1 case, that was not died, Serratia Spp. was in 1 case, but did not dye. Moreover, Proteus Spp. reported in one died case, and Moraxella Spp. found in one case, that was not died. The relationship between bacterial types and prognosis was found to be statistical significant *(*Chi-Square= *43.439, p-v0.000).*

From the previous results, we indicate that the increase of mortality rate in cases infected with gram-negative pathogenic organisms more than those infected with gram-positive pathogenic organisms. Especially Neisseria meningitides, E.coli and Pseudomonas Spp.

were reported to be the most common gram-negative bacteria respectively which were associated with the lethality of infants with Septicemia.

Table (4.25) Relationship between types of bacterial and age groups.

Bacterial types	Neonates		Post neonates		Total		Chi-Square	P-value
	Freq.	%	Freq	%	Freq	%		
Coagulase negative staph .	120	48.0	130	52.0	250	100		
Klebsiella	11	61.1	7	38.9	18	100		
Pseudomonas	9	52.9	8	47.1	17	100		
E.coli	14	87.5	2	12.5	16	100		
Streptococcus viridance	7	50	7	50	14	100		
Staphylococcus aureus	4	36.4	7	63.6	11	100		
Neisseria meningitides	0	0	10	100	10	100		
Group (D) Streptococcus	3	60	2	40	5	100		
Group (B) Streptococcus	4	100	0	0	4	100		
Acinetobacter	4	57.1	3	42.9	7	100	**70.856**	**0.000**
Streptococcus Pneumonia	0	0	3	100	3	100		
Haemophilus influenza	0	0	3	100	3	100		
Citrobacter	1	50	1	50	2	100		
Bacillus	2	100	0	0	2	100		
Salmonella	0	0	1	100	1	100		
Serratia	1	100	0	0	1	100		
Moraxella	0	0	1	100	1	100		
Proteus	1	100	0	0	1	100		
Total	**181**	**49.5**	**185**	**50.5**	**366**	**100**		

Table (4.25) represents that neonates with Septicemia were 49.5% (181 of 366) cases but post neonates were 50.5% (185 of 366) cases. More bacterial type isolated from blood in both neonates and post neonates were Coagulase negative staphylococcus, with percent of

48.0% (120 of 250), 52% (130 of 250) cases respectively, followed by Klebsiella isolated from neonates 61.1% (11 of 18), and from post neonates 38.9% (7 of 18). Pseudomonas Spp. isolated from neonates with percent of 52.9% (9 of 17) and from post neonates by 47.1% (8 of 17). It is important to show that 14 of 16 neonates (87.5%) were associated with E.Coli spp. Streptococcus viridance isolated from two age groups (both neonates and post neonates) with equal percent of 50% (7 of 14). S. aureus more associated with post neonates, which isolated with percent of 63.6% (7 of 11), and 36.4% (4 0f 11) from post neonates and neonates respectively. Neisseria meningitides isolated only from post neonates with percent 100% (10 of 10) cases. Group B streptococcus isolated only from neonates with percent 100% (4 of 4) cases. However group D streptococcus was more associated with neonates also, which was isolated with percent of 60% (3 of 5) and 40% (2 0f 5) from neonates and post neonates respectively. Acinetobacter also was more associated with neonates, it was isolated with percent of 57.1% (4 of 7) and 42.9% (3 0f 7) in neonates and post neonates respectively. S. pneumonia and H. influenzae were both isolated only from post neonates with the same percent of 100% (3 of 3) cases. Bacillus was isolated only from neonates with percent of 100% (2 of 2) cases, Serratia and proteus both were isolated only from neonates with the same number, one case, Salmonella and Moraxella both isolated only from post neonates with the same number, one case. Citrobacter isolated from two age groups (both neonates and post neonates) with equal percent of 50% (1 of 2) cases. Finally, the relationship between bacterial types and age groups is statistical significant *(*Chi-Square= *70.856, p-v0.000).*

4.6 Antibiotics resistance for isolated bacteria among infants.

Table (4.26) Antibiotics resistance for isolated bacteria among all infants.

NO	Item	Sensitive		Intermed		Resist		Total	
		Freq.	%	Freq.	%	Freq.	%	Freq.	%
1.	Penicilline	36	90.0	1	2.5	3	7.5	**40**	**100**
2.	Ampicilline	85	23.6	10	2.8	265	73.6	**360**	**100**
3.	amoxycilline	1	33.3	0	0.0	2	66.7	**3**	**100**
4.	pirpracillin	5	48.5	2	18.2	4	36.4	**11**	**100**
5.	Erythromycin	4	25	1	6.3	11	68.8	**16**	**100**
6.	Cephalexine	129	35.6	12	3.3	221	61.0	**362**	**100**
7.	Cefuroxime	97	58.1	9	5.4	61	36.5	**167**	**100**
8.	Cefotaxime	133	73.5	5	2.8	43	23.8	**181**	**100**
9.	Ceftazidime	76	29.9	7	2.8	171	67.3	**254**	**100**
10.	Ceftriaxone	149	67.1	10	4.5	63	28.4	**222**	**100**
11.	Sulfamethazone trimethoprime	35	43.8	0	0.0	45	56.3	**80**	**100**
12.	Gentamycin	230	64.6	9	2.5	117	32.9	**356**	**100**
13.	Amikacin	299	86.2	6	1.7	42	12.1	**347**	**100**
14.	Chloramphinicol	169	71.6	7	3.0	60	25.4	**236**	**100**
15.	Vancomycin	138	69.7	28	14.1	32	16.2	**198**	**100**
16.	Cloxacilline	41	20.2	4	2.0	158	77.8	**203**	**100**
17.	Meropenem	6	75.0	1	12.5	1	12.5	**8**	**100**
18.	Ciprofloxacin	14	100.0	0	0.0	0	0.0	**14**	**100**
19.	Rifampicin	9	90.0	0	0.0	1	10.0	**10**	**100**

According to the blood culture and sensitivity test, the antimicrobial biogram shows that all types of bacteria were resistant in high percentage to Cloxacilline 77.8%, Ampicilline 73.6%, Ceftazidime 67.3%, Amoxycilline 66.7, Cephalexine 61%, and sulfonamide 56.3%. However, the antimicrobial biogram shows that other antibiotics were more effective against the majority of detected bacteria in the cultures such as Penicilline-G 90.0% Rifampicin 90.0%, Amikacin 86.2%, Meropenem 75.0%, Cefotaxime 73.5%, Chloramphenicol 71.6%, Vancomycin 69.7%, Ceftriaxone 67.1%, Gentamycin 64.6%, and Cefuroxime 58.1(Table 4.26). Our results could be explained in that the antibiotics such as Meropenem, Cefotaxime, and Ceftriaxon which are broad spectrum antibiotic were effective against all types of bacteria. These agents are active against many Gram-positive, Gram-negative and anaerobic bacteria (Arrieta, 1997, Lamb, et al, 2005).

In most of the developing countries, Gram-negative organisms remain the major cause of neonatal sepsis, particularly early onset neonatal sepsis. These organisms have developed increasing multidrug resistance over the last two decades, due to the indiscriminate and inappropriate use of antibiotics (Rahman, Hameed, Roghani, and Ullah, 2002). Thus, the antibiotics such as Rifampicin, Amikacin, Chloramphenicol and Gentamycin showed good antimicrobial therapeutic effect because they are effective against gram-negative which is the primary causative agent of Septicemia disease among infants.

Chapter Five

Conclusion and Recommendation

5.1 Conclusion

Our study described the incidence and case fatality rates of Septicemia disease according to sex, age groups, governorates , health status and nutritional status of the cases in El-Nassr pediatric hospital. Furthermore, the socio-demographic and economic status of infants' patients with Septicemia disease were studied. The relationship between laboratory results and prognosis has also been investigated. Moreover, the most common types of bacteria isolated from blood and antibiotic resistant has been identified.

Our results indicate that the Septicemia disease was more prevalent among neonates less than 28 day of age. The risk age group was less than 8 days. Male in all age groups were more susceptible to infection with Septicemia than female. The incidence rate of septicemia was higher in North and Gaza governorates than the Southern governorates. The difference in incidence rates according to governorates was attributed to location of El-Nassr hospital between North and Gaza governorates. Septicemia was more prominent in cases with low Socio-economic status, overcrowded areas and low family income. Furthermore approximately half of cases were had a history of URTI preceding the onset of the disease. We, also, found underweight, malnutrition and anemia play an important role in decreasing the innate immunity of the cases. The highest peak of incidence of disease was in winter and in summer, this coincides with the respiratory infections in winter and diarrhea in summer.

Findings of this study showed that the case fatality rate in females was more than that in males. It was noticed that most of the deaths were from North governorate.

Septicemia among infants in Gaza governorates was more manifested by anorexia, hyperthermia or hypothermia, tachypnea and tachycardia while in sever sepsis was more manifested by fever, coma and shock.

There was high significant association between Septicemia from one side and thrombocytopenia, hypocalcemia, and prolonged PT, PTT from other side, these disturbances were considered as indicators of bad prognosis.

Dominant bacteria causes Septicemia among infants were gram-positive bacteria but we showed the increase of case fatality rate in cases infected with gram-negative pathogenic organisms more than those infected with gram-positive pathogenic organisms. There were resistant bacteria with high percentage to Amoxycilline, Ampicilline, Cloxacilline, Ceftazidime, Cephalexine, and sulfonamide. On the other hand there were sensitivity with high percentage to Meropenem, Cefotaxime, Ceftriaxon, Rifampicin, Amikacin, Chloramphenicol and Gentamycin.

5.2 Recommendations

Findings of this study help the researcher to understand the problem and give him the chance to make number of recommendation that may assist policy makers in solving this problem and control and treat Septicemia as soon as possible.

5.2.1 General recommendations

1- Increasing health awareness of public about the causes, mode of transmission, manifestations, and complications of Septicemia.
2- High index of suspicion is needed among the medical staff for early diagnosis and treatment of Septicemia

3- Encourage breast feeding that help infants to still in good immunity and within good general condition.

4- Development and supporting the treatment plans and protocols which followed in MOH pediatrics hospitals.

5- Application of vaccination programs against some of bacterial types that causes Septicemia as H. influenzae type b, S. pneumoniae and N. meningitides serogroups W135 especially for infants.

6- Develop national communicable diseases control strategy.

7- Strength communicable diseases (related to Septicemia) information system

8- Training the medical staffs all the required preventive measurements as washing their hands before and after handling of our infants patients.

5.2.2 Future research recommendations

1- Further studies are warranted with larger sample as community based study to verify the finding of this study.

2- Independently study are necessary to investigate the relationship between Septicemia and the different age groups in children

3- More studies are needed to determine the economic cost of Septicemia and to evaluate its cost from the total health care system budget**.**

4- Follow-up research and prospective studies are required to study the outcomes of Septicemia disease among the recovered cases after the end of the treatment course.

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Annex (1)

Palestine map

Annex (2)

Gaza Governorates map

Annex (3)

بسم الله الرحمن الرحيم

تقديم من أجل الحصول على إجابات لاستبيان خاص حول مرض تسمم الدم البكتيري

عزيزي ولي أمر الطفل:

أقدم لكم نفسي أنا الطالب ***عميد عوني مشتهى*** أدرس بكلية الصحة العامة – جامعة القدس أبو ديس، أقوم بإعداد بحث بعنوان "**معدل حدوث مرض تسمم الدم البكتيري بين الأطفال الأقل من عمر عام في مستشفى النصر للأطفال**" باعتباره متطلب للتخرج والحصول على درجة الماجستير وحيث أن طفلكم أصيب بهذا المرض فقد تم اختياركم بناءُ على ذلك، ولكم كامل الحرية في الموافقة، أو عدم المشاركة، أو الانسحاب في أي مرحلة ومتى شئتم، وأن إجاباتكم سوف تكون في غاية السرية، وأن هدفنا هو البحث وإيجاد السبل للتغلب على المرض والحد من انتشاره.

وشكراً لكم على حسن تعاونكم

عميد عوني مشتهى
جامعة القدس
كلية الصحة العامة
ماجستير الصحة العامة

Annex (4)

Infant Septicemia a cross sectional Study Questionnaire in El Nassr pediatric Hospital

Name: ..... Serial No.: .....

Child I.D. : ..... Date .....

Father I.D.: ..... Department: .....

Age (day): ..... Gestational Age : .....

Address: ..... Tel. No.: .....

Sex : □ Male □ Female

Type of delivery: □ Cesarean □ Vaginal

Breast feeding : □ Exclusive □ Bottles □ Mixed

Weight At delivery : ..... kg Weight on admission: ..... kg

Past history of (URTI in the last week): □ Yes □ No

history of immunodeficiency diseases: □ Yes □ No

history of congenital diseases: □ Yes □ No

<u>Mother medical history:</u>

Diabetes .M : □ Yes □ No

Eclampsia : □ Yes □ No

UTI : □ Yes □ No

<u>Social and personal:</u>

Father Education(year) ..... Father occupation .....

Mother Education(years)..... Mother occupation .....

Including this child , How many persons are living in your house?.....

Birth order of this child? .....

Child attending nursery: □ Yes □ No

Number of rooms in this house? .....

Building area in square meter .....

Family income: □ High □Moderate □Low

Clinical Description:

Fever	□ Yes	□ No
Hypothermia	□ Yes	□ No
Anorexia (Reluctant to feed)	□ Yes	□ No
Vomiting	□ Yes	□ No
Tachycardia	□ Yes	□ No
Techypnea	□ Yes	□ No
Convulsion	□ Yes	□ No
Coma	□ Yes	□ No
Petechia	□ Yes	□ No
Shock	□ Yes	□ No

Blood pressure: .....

Diagnosis: □ Septicemia □Septicemia & meningitis

Laboratory Investigations:

Blood Examination

Glucose: ..... mg/dl

W.B.CS: ..... / ul HB: ..... g%

Platelet: ..... / ul Neutrophil: ..... / ul

Na: ..... mEq/L K: ..... mEq/L

Ca: ..... mEq/L ESR: ..... mm/1st hr.

PT: ..... sec INR: .....

PTT: ..... sec PH: .....

HCO_3: ..... ABE: .....

CRP: .....

Methods of microorganism's identification:

Blood culture:

Causative organism: .....

Skin direct smear : .....

Sensitivity test result:

1.	Penicilline:	□ sensitive	□ intermed	□ resist
2.	Ampicilline:	□ sensitive	□ intermed	□ resist
3.	Amoxycilline:	□ sensitive	□ intermed	□ resist
4.	Pipracilline:	□ sensitive	□ intermed	□ resist
5.	Erythromycine:	□ sensitive	□ intermed	□ resist
6.	Cephalexine:	□ sensitive	□ intermed	□ resist
7.	Cefuroxime:	□ sensitive	□ intermed	□ resist
8.	Cefotaxime:	□ sensitive	□ intermed	□ resist
9.	Ceftazidime:	□ sensitive	□ intermed	□ resist
10.	Ceftriaxone:	□ sensitive	□ intermed	□ resist
11.	Sulfamethazone trimethoprime:	□ sensitive	□ intermed	□ resist
12.	Gentamicin:	□ sensitive	□ intermed	□ resist
13.	Amikacin:	□ sensitive	□ intermed	□ resist
14.	Chloramphenicol	□ sensitive	□ intermed	□ resist

Prognosis: □ Recovery □ Death

Annex (5)

Palestinian National Authority
Ministry of Health
Helsinki Committee

السلطة الوطنية الفلسطينية
وزارة الصحة
لجنة هلسنكي

Date: 25 / 6 /2006

التاريخ: 2006/6 / 25

Mr./ Ameed Mushtaha

I would like to inform you that the committee has discussed your application about:

السيد: عميد مشتهى

نفيدكم علماً بأن اللجنة قد ناقشت مقترح دراستكم حول:-

Incidence of Septicemia Among Infant at El Nassr Hospital – Gaza Strip 2007.

In its meeting on June 2006
and decided the Following:-
To approve the above mention research study.

و ذلك في جلستها المنعقدة لشهر يونيو 2006
و قد قررت ما يلي:-
الموافقة على البحث المذكور عاليه.

Ministry of Health Helsinki Committee

Signature
توقيع

Member
عضو

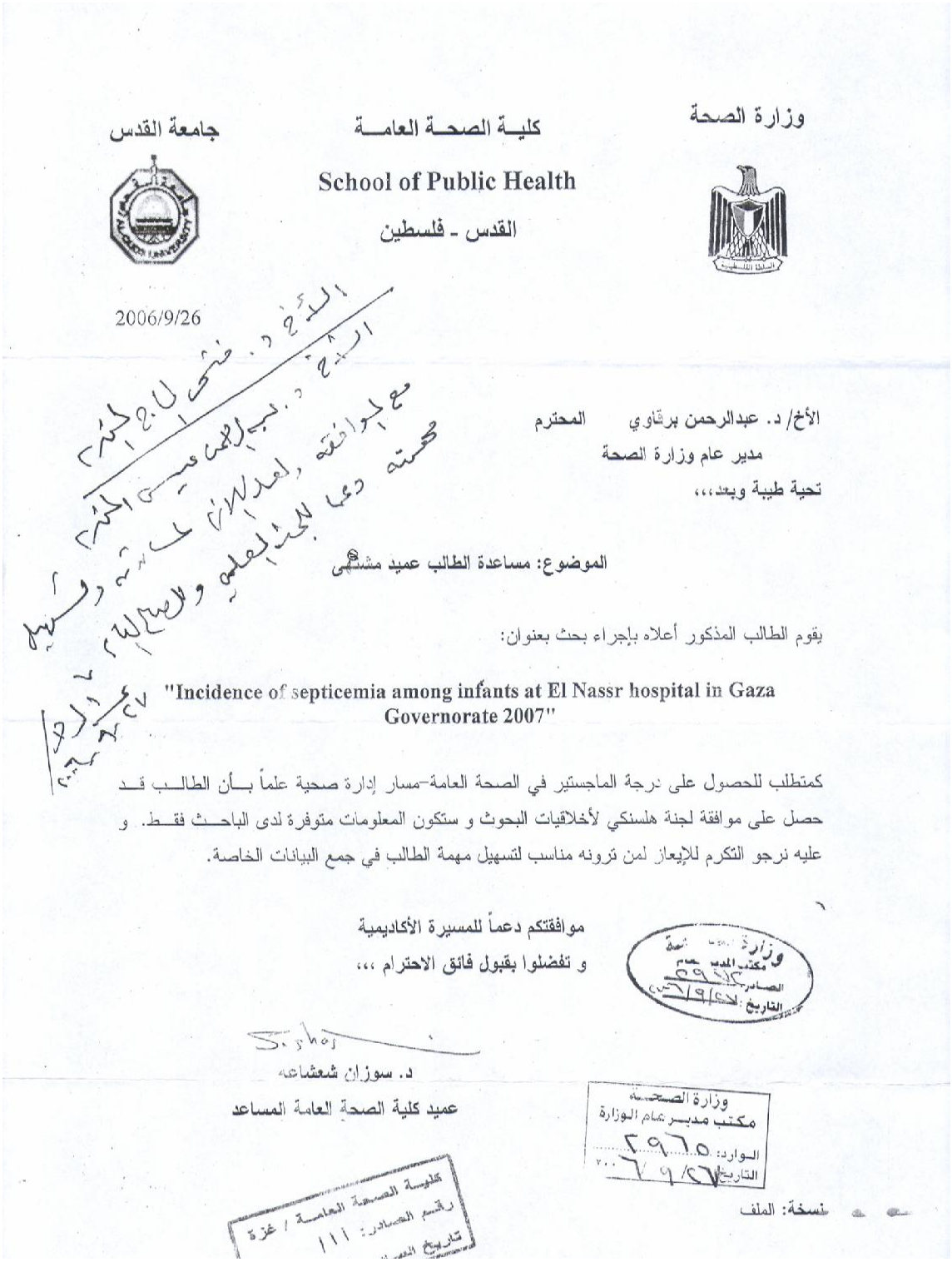
Member
عضو

Chairperson

Conditions:-
- Valid for 2 years from the date of approval to start.
- It is necessary to notify the committee in any change in the admitted study protocol.
- The committee appreciate receiving one copy of your final research when it is completed.

Gaza Etwam – Telefax 972-7-2878166

Annex (6)



وزارة الصحة

كليـة الصحـة العامـة

School of Public Health

القدس - فلسطين

جامعة القدس

2006/9/26

الأخ/ د. عبدالرحمن برقاوي المحترم

مدير عام وزارة الصحة

تحية طيبة وبعد،،،

الموضوع: مساعدة الطالب عميد مشعشعي

يقوم الطالب المذكور أعلاه بإجراء بحث بعنوان:

"Incidence of septicemia among infants at El Nassr hospital in Gaza Governorate 2007"

كمتطلب للحصول على درجة الماجستير في الصحة العامة-مسار إدارة صحية علماً بأن الطالب قد حصل على موافقة لجنة هلسنكي لأخلاقيات البحوث و ستكون المعلومات متوفرة لدى الباحث فقط. و عليه نرجو التكرم للإيعاز لمن ترونه مناسب لتسهيل مهمة الطالب في جمع البيانات الخاصة.

موافقتكم دعماً للمسيرة الأكاديمية

و تفضلوا بقبول فائق الاحترام ،،،

وزارة الصحة
مكتب المدير العام
الصادر: ٢٩٦٥
التاريخ: ٢٠٠٧/٩/٢٧

د. سوزان شعشاعه

عميد كلية الصحة العامة المساعد

وزارة الصحة
مكتب مدير عام الوزارة
الوارد: ٢٩٦٥
التاريخ: ٢٠٠٧/٩/٢٧

كلية الصحة العامة / غزة
رقم الصادر: ١١١
تاريخ

نسخة: الملف

Annex (7)

ملخص الدراسة

هدف الدراسة

الهدف من هذه الدراسة هو التعرف على مدى انتشار البكتيريا المسببة لمرض تسمم الدم البكتيري لدى الأطفال الذين أعمارهم أقل من 1 سنة وكذلك عوامل الخطر المؤدية إلى حدوث المرض، وعلاقة بعض نتائج الفحوصات المخبرية مع شدة المرض و تطور الحالة.

منهجية الدراسة

هذه الدراسة دراسة وصفية تحليلية تم إجراؤها في محافظة غزة عام 2006- 2007.

عينة الدراسة

تكونت العينة من 366 طفلاً ممن يبلغون من العمر أقل من عاماً واحداً والذين أدخلوا إلى مستشفى النصرللأطفال خلال عام كامل ابتداءً من بداية أكتوبر/2006م وحتى نهاية سبتمبر/2007م بسبب إصابتهم بمرض تسمم الدم الناتج عن أنواع مختلفة من البكتيريا المسببة للمرض و الذين تم توثيق تشخيصهم مخبرياً.

جمع المعلومات

جمعت المعلومات بواسطة استبانه خاصة تم تصميمها بواسطة الباحث وفحص مدى ثباتها من قبل محكمين من ذوي الاختصاص، كذلك جمعت المعلومات من الملفات الطبية للمرضى ومن تقارير المختبرات.

النتائج

أظهرت الدراسة أن معدل حدوث مرض تسمم الدم في مستشفى النصر للأطفال لمن تقل أعمارهم عن عام واحد بلغ 1000/58 طفل. وأن هناك فروقات في معدل الانتشار بحسب الجنس و المجموعات العمرية والمحافظات والحالة الإقتصادية والإجتماعية وأنواع البكتيريا المسببة للمرض والبكتيريا المقاومة لأنواع مختلفة من المضادات الحيوية. ولقد كان المرض أكثر انتشاراً بين الأطفال الأقل من28 يوم (49.5%) و أن الأطفال الأقل من 8 أيام هم الأكثر معدل للوفاة بالمرض (20%) وأظهرت الدراسة أن هناك ارتباطاً بين الحالة الإقتصادية الاجتماعية المنخفضة وحدوث المرض وأنه ينتشر لدى العائلات ذوي الإكتظاظ العالي، و أن هناك ارتباطاً مع مستوى تعلم الآباء والدخل. لقد كانت هناك فروقات واضحة في معدلات حدوث المرض بسب اختلاف فصول السنة حيث وصل المرض ذروة حدوثه في فصل الشتاء والصيف.

وقد كان مرض تسمم الدم أكثر انتشاراً بين الذكور (59.6%) بينما بلغ معدل الوفاة الكلى بالمرض 10.1% و بلغ معدل الوفاة بنفس المرض تسمم الدم الناتج عن الإصابة بنفس الميكروبات أعلى بين الإناث (12.2%) مقارنةً مع الذكور 8.7%، وكذلك أظهرت الدراسة أن انخفاض كرات الدم البيضاء وانخفاض الصفائح الدموية و ارتفاع زمن البروثرومبين والثرومبوبلاستين كذلك انخفاض معدل الصوديوم في الدم لدى المريض هي من المؤشرات الخطرة للمرض وأظهرت الدراسة أن تسمم الدم كان مرتبطاً بنقص الكالسيوم في الدم (إختبار كاي 7.543 ، القيمة المعيارية 0.023). وكان هناك فروقات في معدلات الوفاة بين المحافظات.حيث كانت أعلى معدلاً في محافظات الشمال وغزة بينما كانت أقل معدلاً في المحافظات الجنوبية.

كذلك أظهرت الدراسة بأن البكتيريا الموجبة لصبغة غرام هي البكتيريا السائدة بنسبة 79% بينما البكتيريا الموجبة لصبغة غرام بلغت نسبة 21% فقط. بينما كانت معدلات الوفاة بسبب البكتيريا السالبة لصبغة غرام أعلى حيث بلغت 23.4% في حين بلغت نسبة 6.6%مع البكتيريا الموجبة لصبغة غرام.

وأظهرت الدراسة أن هناك العديد من البكتيريا المقاومة للأمبيسلين (73,6%) والكلوكساسيلين (77.8%) والسيفوتازديم (67.3%) والأموكساسيلين (66.7%) و سيفالكسين (61%) و مجموعة السلفا (56.3) و السيفياروكسيم (41.9%) و الجنتاميسين (35.4) و السيفترياكسون (32.9%) و الكلورامفنيكول (68.6%) و الفانكوميسين (30.3%) و السيفوتاكسيم (26.5%) و الميروبنيم (25%)، بينما كانت هناك أنواعاً أخرى حساسة للسبروفلوكساسين (100%) و للبنسلين (90%) و الأميكاسين (86.2%) و الميروبنيم (75%) و السيفوتاكسيم (73.5%) و السفترياكسون (67.1%) و الكلورامفنيكول (71.6%) و الفانكوميسين (69.7%) والجنتاميسين (64.6%).

التوصيات

- زيادة وعي الجمهور حول أسباب وطرق انتشار وأعراض وعواقب مرض تسمم الدم البكتيري.
- تعزيز ودعم الخطط العلاجية الخاصة بالمرض والمتبعة في مستشفيات وزارة الصحة.
- تطبيق برامج تطعيم ضد العديد من أنواع البكتيرية المختلفة خاصة للأشخاص الأكثر عرضة للإصابة بالمرض.
- وضع بروتوكول عمل موحد ذو جودة عالية لتشخيص وتسجيل حالات تسمم الدم البكتيري وكيفية التعامل معها في المراكز والمختبرات الصحية التابعة لوزارة الصحة.
- تعزيز ودعم الخطط العلاجية الخاصة بالمرض والمتبعة في مستشفيات وزارة الصحة.
- عمل دراسات مستقبلية عن وبائية المرض في المجتمع بالكامل.

- تطوير دراسة مستقلة لمعرفة العلاقة بين المرض والفئات العمرية المختلفة.
- عمل دراسة لتحديد التكلفة الاقتصادية للمرض وتقييم الكلفة الإجمالية للمرض من الميزانية العامة للنظام الصحي