# EPIDEMIOLOGICAL SURVEILLANCE OF POSITIVE BLOOD AND CEREBRO-SPINAL FLUID CULTURES IN THE NEONATAL UNIT OF BARAGWANATH'S MATERNITY HOSPITAL OVER A TWO YEAR PERIOD (1989-1990)

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## ABSTRACT

The aims of this study were to establish the incidence of perinatally and nosocomially acquired bacteraemia and fungaemia as determined by blood and cerebrospinal fluid (CSF) isolates in the neonatal population seen at the Baragwanath Neonatal Unit; to identify risk factors for infection and record the outcome. Other aims were to analyze the susceptibility patterns of the organisms isolated with respect to changing antimicrobial policies and to compare these with previously reported studies.

Data recorded prospectively on all blood and CSF isolates obtained from babies admitted to the Unit during the period January 1989 to December 1990 were analyzed, as were the computerized clinical records of all the admissions over this period.

Group B Streptococci (GBS) were the most common cause of congenital bacteraemia having been recovered from 141 babies during the two year study period (1,9 cases per 1 000 live births). Just over 25% of these babies required admission to the Intensive Care Unit (ICU) and 10% were well babies with prolonged rupture of membranes (PROM) sent to their mothers on antimicrobials. The remainder were babies with mild to moderate respiratory distress not requiring ventilation. Risk analysis identified birth asphyxia as significantly associated with this infection.

Gram negative bacteria (GNB) were isolated at birth from 147 babies during these two years. The most common isolates were, however, those due to Psaudomonas and Serratia spp, both considered to be contaminants. The majority of GNB isolates were obtained from babies admitted to the high care areas.

Klebsiella spp was the most important cause of nosocomial sepsis accounting for nearly half of all hospital acquired GNB isolates followed by Pseudomonas and Serratia spp. A total of 222 babies developed a nosocomial GNB septicaemia during the two year study period, that is, 3,5% of the babies admitted to the Unit that survived beyond three days of age. Babies with birth weights <1500g had the highest incidence of Klebsiella bacteraemia. There was a strong correlation between GNB sepsis and necrotising enterocolitis (NEC). Klebsiella and Serratia infections were further associated with parenteral nutrition. Over half of the babies with nosocomial GNB sepsis died; in fact, deaths due to nosocomial GNB sepsis accounted for 25% of all deaths occurring after three days of age.

Increasing resistance of GNB to third generation cephalosporins led to restricted use of these antimicrobials. Nevertheless, resistance to both cefotaxime and ceftazadime increased significantly, from 36% to 58% (p=0,0009) and from 7% to 23% (p=0,0005) respectively during this period. A policy change to amikacin as sole aminoglycoside resulted in a significant increase in its resistance, from 9% to 25% (p<0,0001). Such a dramatic increase in amikacin resistance following the

increased use of this drug has not been reported previously.

There were 112 cases of hospital acquired systemic fungal infections during the study period, all but one case had been acquired in the high care areas. Babies admitted to the ICU and those with birth weights <1500g had the highest incidences. Once again, there was a strong correlation between babies with systemic fungal infection, parenteral nutrition and NEC. Just under a half of the babies with systemic fungal infections died.

Infections thus are an important cause of morbidity and mortality amongst the babies admitted to Baragwanath's Neonatal Unit. As the susceptibility patterns of the organisms are constantly changing, it is imperative that up to date records are kept in order to facilitate the formulation of antimicrobial policies. The relationship between nosocomial infections and NEC needs to be further defined.

**DECLARATION**

I declare that this dissertation is my own, unaided work. It is being submitted for the degree of Master of Medicine in Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

5th day of May 1992

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Antimicrobials: amikacin (ak)
ampicillin (am)
cefotaxime (cf)
ceftazadime (ct)
chloramphenicol (ch)
ciprofloxicin (ci)
cotrimoxazole (co)
gentamicin (g)
imipenem (i)
penicillin (p)
pipericillin (pi)
tobramycin (t)

Cerebrospinal Fluid (CSF)

Confidence Limits (C.L.)

C-reactive Protein (CRP)

Erythrocyte Sedimentation Rate (ESR)

Full Blood Count (FBC)

Gram Negative Bacteria (GNB)

Gram Positive Bacteria (GPB)

Group B Streptococci (GBS)

Intensive Care Unit (ICU)

Labour Ward (LW)

Low Birth Weight (LBW)

Minimum Bactericidal Concentration (MBC)

Minimum Inhibitory Concentration (MIC)

Necrotising Enterocolitis (NEC)

Odds Ratio (O.R.)

Prolonged Rupture of Membranes (PROM)

Transitional Care Unit (TCU)

Wards (Wds)

White Cell Count (WCC)

# CHAPTER 1: INTRODUCTION: NEONATAL SEPSIS

## 1. BACKGROUND

Infections are an important cause of morbidity and mortality in the neonatal period as the newborn is particularly predisposed to infections, their immunological system being immature. This is especially true for the low birth weight (LBW) neonate.

### 1.1 T Cell Functions

Total T cell numbers are decreased in the premature neonate. They are normal in the term neonate, though the suppressor T cells are more numerous and more functional than the helper T cells.[1,2] Neonatal T cells suppress B cell differentiation to plasma cells and immunoglobin synthesis. Antigen stimulated proliferation of T cells is depressed in the neonate, but they are capable of a stronger proliferative response to mitogens compared to those of adults. Production of certain lymphokines by neonatal T cells is decreased; lymphotoxin production is less than half of that of adult T cells and migration inhibition factor is also decreased.[3] Some workers have shown that levels of immune interferon in cord blood are diminished but that those of leukocyte inhibitory factor are normal.[4] Neonatal T cells also demonstrate depressed cytotoxicity. Infants thus show nonreactive skin tests to common antigens used to assess T cell function, even after deliberate sensitization.[5]

## 1.2 B Cell Functions

As already mentioned, neonatal B cells show a limited capacity to differentiate into plasma cells and produce immunoglobins. This is not only due to excessive T cell suppressor activity, but also because of the poor development of lymphoid tissue and plasma cells in the neonate, a sterile in utero environment, presence of immunosuppressive quantities of transplacental antibodies and intrinsic B cell hyporesponsiveness.[6] Some IgM synthesis, however, does begin at 30 weeks gestation; synthesis of the other classes of immunoglobulins only commencing well after birth.[7,8] IgM synthesis is especially active during the first week of extrauterine life due to stimulation by antigens in the neonatal gastrointestinal tract regardless of the gestational age of the infant. Only IgG is transferred across the placenta to the foetus, beginning at 8 weeks gestation. By term the IgG level in the foetus exceeds the maternal level.[8,9] Neonates are thus protected against infections with organisms to which their mothers have high levels of circulating IgG. As maternal antibodies to GNB are predominantly of the IgM class, the newborn is susceptible to infections due to these organisms.[10] IgG levels fall off rapidly having a half life of 25 days resulting in a physiologic hypogammaglobulinaemia by 4 months of age.[9] Premature neonates have lower levels of IgG at birth because of decreased maternal transfer and thus an earlier and more severe physiologic hypogammaglobulinaemia. IgA levels do not reach adult values till adolescence but IgD and IgE levels rise sig-

nificantly during the first year of life.[11] Secretory IgA is passively ingested by breast fed infants, inhibiting the growth of certain organisms. As breast milk also has various other immunological properties, a decreased intake might predispose to neonatal sepsis.[12]

### 1.3 Monocyte and Macrophage Functions

Antigen processing by neonatal monocytes and macrophages is depressed, as is monocyte chemotaxis and macrophage phagocytosis.[13] Poor bactericidal and viricidal capabilities may result in increased susceptibility to infection from intracellular organisms. Bactericidal activity is especially compromised in babies with sepsis, meconium aspiration, respiratory distress, hyperbilirubinaemia and PROM. Cytotoxic response to antibody-coated cells by monocytes and killer cells appears to be normal in newborns.[14]

### 1.4 *Complement System*

Synthesis of complement components start at 5 weeks gestation. There is no placental transfer of maternal complement. Levels of the individual components and total haemolytic activity is significantly decreased at birth, especially in the premature newborn, resulting in deficient opsonic and chemotactic activity.[15]

## 2. PATHOGENESIS OF NEONATAL INFECTIONS

Host susceptibility, socioeconomic factors, obstetric and nursery practices and the health and nutrition of mothers are all considered important in the pathogenesis of neonatal

sepsis.[16] Infection may occur at any time following conception and during the first month of life.

## 2.1 Intrauterine Infection

A foetus may become infected while still in utero either from organisms present in the genital tract that have invaded the amniotic fluid or via the transplacental route following invasion of the maternal bloodstream. The foetal membranes need not have ruptured for organisms to gain access to the amniotic fluid, microscopic defects in the membranes providing a pathway for such spread.[17] Invasion of the maternal bloodstream by microorganisms is not uncommon, yet in most cases neither foetal nor placental infection results. However, the developing foetus may be affected without direct microbial invasion of the placenta or foetal tissues due to high fever, circulating toxins or metabolic derangements resulting in embryonic death and resorption, abortion, stillbirth or premature delivery.[18] Actual infection of a foetus may result in a similar outcome or developmental anomalies including intrauterine growth retardation, congenital disease or persistent postnatal infection, though many neonates appear asymptomatic. Viral infections, especially those due to rubella and cytomegalovirus, have been shown to cause teratogenesis as well as intrauterine growth retardation. Babies with congenital disease may present with a variety of signs including jaundice, anaemia, skin rashes, hepatosplenomegally, respiratory distress, skeletal, cardiac and nervous system involvement. Organisms that may produce chronic infection

when acquired later in life such as syphilis, tuberculosis, cytomegalovirus, herpes and other viral infections, may also cause persistent postnatal infections.

## 2.2 Infection Acquired During Birth

The foetus is protected from the microbial flora of the maternal genital tract by the foetal membranes, but once these have ruptured, the vaginal flora may ascend and invade the foetus especially if delivery is delayed. In addition, the amniotic fluid is thought to be bacteriostatic, containing lysozyme, bactericidin, transferrin, peroxidase, immunoglobins of the IgA and IgG classes and a zinc-protein complex with antibacterial properties.[19] Amniotic fluid has been shown to inhibit the growth of E. coli and other bacteria.[20] However, the presence of meconium in amniotic fluid diminishes this effect.

In the absence of intrauterine infection, the newborn's first exposure to microorganisms is to those of the maternal cervix and vagina. A variety of organisms may be found in the maternal genital tract including GPB, GNB, anaerobes, viruses, fungi, chlamydia, mycoplasmas and protozoa. Some of these organisms are significantly associated with disease in the newborn, whereas others rarely if ever involve the neonate (see table 1.1).[21] This may depend on the virulence of the organism and the size of the innoculum. Interestingly enough, the organisms responsible for maternal pelvic infections are usually polymicrobial with anaerobes isolated in the majority

**Table 1.1 The Association of Neonatal Disease with Microorganisms Prese in the Maternal Birth Canal**

| Microorganism | Association with Neonatal Disease | | |
|---|---|---|---|
| | Significant | Uncommon | Rare or none |
| Bacteria | | | |
| Lactobacillus | | | + |
| *S. epidermidis* | | | + |
| *S. aureus* | | + | |
| α haem Streptococci | | + | |
| Group A Streptococci | + | | |
| Group B Streptococci | + | | |
| Group D Streptococci | | + | |
| *E. coli* | + | | |
| Proteus spp | | + | |
| Klebsiella spp | | + | |
| Pseudomonas spp | | + | |
| Salmonella spp | | + | |
| Shigella spp | | + | |
| *Neisseria meningitidis* | | + | |
| *Neisseria gonorrhoeae* | + | | |
| Haemophilus spp | | + | |
| *Listeria monocytogenes* | + | | |
| *Campylobacter foetus* | | | + |
| Saccharomyces spp | | | + |
| Corynebacterium spp | | | + |
| *Bacillus subtilis* | | | + |
| Bacteroides spp | | | + |
| Peptostreptococcus spp | | | + |
| Veillonella spp | | | + |
| Clostridium spp | | | + |
| Bifidobacterium spp | | | + |
| Eubacterium spp | | | + |
| Viruses | | | |
| Cytomegalovirus | + | | |
| Herpes simplex | + | | |
| Hepatitis | + | | |
| HIV | | + | |
| Fungi | | | |
| Candida | + | | |
| Torulopsis | | + | |
| *Chlamydia trachomatis* | + | | |
| Mycoplasma | | | |
| *Mycoplasma hominis* | | + | |
| *Ureoplasma hominis* | | + | |
| Protozoa | | | |
| *Toxoplasma gondii* | | + | |
| *Trichomonas vaginalis* | | + | |

of case, whereas anaerobes infrequently result in infections of the newborn which are usually caused by single species of aerobic bacteria.[22,23]

The newborn is initially colonized on the skin and mucosal surfaces and in most cases the organisms proliferate at these sites without causing illness. However, a few infants become infected by direct extension from these sites and in others invasion of the bloodstream may occur especially via the umbilicus or abrasions on the skin. Certain risk factors are associated with the development of sepsis, notably LBW, PROM, traumatic delivery, asphyxia, the use of invasive monitoring techniques, maternal peripartum infection and possibly maternal use of steroids.

## 2.3 Postnatal Infection

Babies may become colonized after birth by various means involving either human carriers or contaminated materials or equipment. Hands of hospital personnel are a significant means of transmission of microorganisms as is droplet spread from the respiratory tract. Neonates may thus then develop infection endogenously from invasion of acquired flora of the skin, respiratory tract and gut or from exogenously acquired microorganisms. Infection is especially likely if the newborn's flora is altered, antimicrobial therapy having been shown to be largely responsible for this alteration.[24] Babies who maintain "normal" flora rarely become infected. In addition, intense antimicrobial pressure such as is found in an

ICU encourages selection of resistant organisms. Disruption of natural barriers by catheterization of vessels and the passage of endotracheal or nasojejenal tubes predispose babies to nosocomial infections, as does placement of scalp electrodes and skin incisions.[25,26] Transient bacteraemia has been shown to occur in babies who received endotracheal suctioning. Contaminated solutions have often been implicated in nursery outbreaks especially in those involving GNB such as Pseudomonas, Serratia and Flavobacterium, other resident bacteria and fungi. Furthermore, any baby whose naturally immature immune system is further compromised, for example, by a pre-existing congenital infection, hypoxia, acidosis, skin or mucosal lesions, is at risk for developing a nosocomial infection.

There also appears to be an association between NEC, an extensive inflammation of the bowel wall of unknown aetiology with a high mortality occurring mainly in premature babies, and the isolation of nosocomially acquired organisms.[27] NEC is associated with the typical X-ray finding of pneumatosis intestinalis. If this is absent, but the baby has clinical signs in keeping with a diagnosis of NEC, a diagnosis of suspected NEC is made. Though bacteraemia is commonly observed amongst babies with NEC, it is unclear whether this represents a primary event or secondary invasion of a compromised intestinal epithelium. As the organisms isolated are also often inhabitants of the enteric flora, it has been proposed that the presence of these bacteria represent secondary

bacterial invasion. However, there is other evidence that implicates a causal relationship between bacteria and NEC;[28] cases of NEC often occur in epidemics and the clinical presentation of NEC mimics septicaemia with bacteraemia, neutropaenia, shock and disseminated intravascular coagulation. Alterations in the faecal flora of patients with NEC have been reported with an imbalance between pathogenic and endogenous bacteria, the use of broad spectrum antimicrobials being implicated as they often suppress normal aerobic faecal bacteria resulting in emergence of resistant organisms and anaerobic bacterial overgrowth.[29] NEC also has certain similarities with the enterotoxemias produced by Clostridial spp.[30] Babies with other forms of bowel pathology necessitating parenteral nutrition are also at an increased risk of acquiring an hospital infection. In fact, organisms harbored in the gastrointestinal tract of patients are thought to be the main source of nosocomial infections in ICU's.[31]

Acquired infections may result in severe systemic disease that lead to death or, if not fatal, additional morbidity and prolonged hospital stay of the neonate.

## 2.4 Clinical Presentation

An infected neonate may present with "early" or "late" onset disease. The former presents often as an fulminant, multisystemic illness during the first few days of life. Bacteria responsible for early onset disease are acquired *in utero* or during delivery from the birth canal whereas those responsible

for late onset disease include those from the vaginal tract and organisms acquired after birth from human contact or contaminated equipment or materials. Thus some organisms, such as E. coli and GBS, may be responsible for both early and late onset disease, whereas others such as S. aureus and Pseudomonas spp, are usually only associated with late onset disease. Infants with late onset disease may have an history of obstetric complications but this is not as common as in those with early onset disease. They also have a lower mortality rate than infants with early onset disease, 10% to 20% vs. about 5%, premature babies and those with meningitis having a worse prognosis.[32]

## 3. EPIDEMIOLOGY

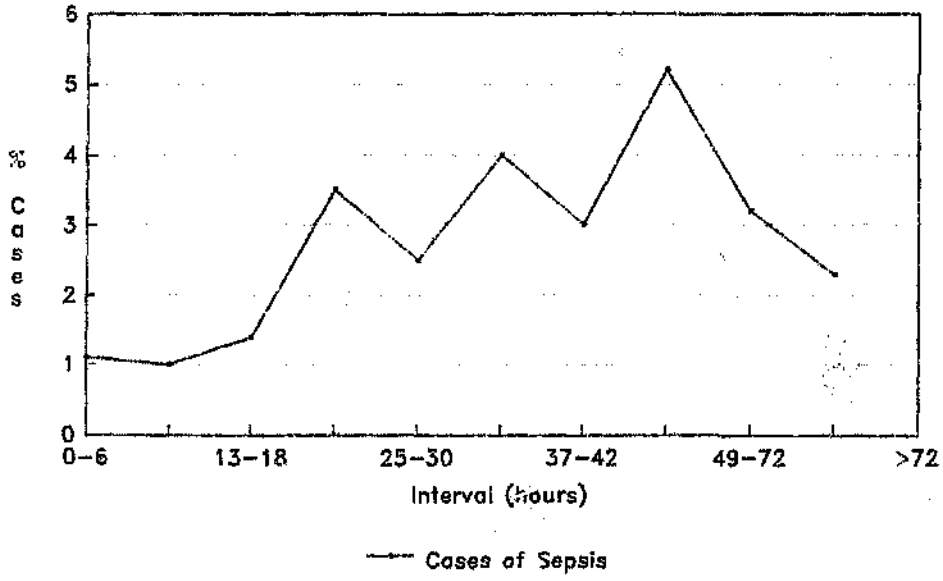
### 3.1 Occurrence

It is estimated that as many as 2% of foetuses are infected in utero and up to 10% of infants are infected during delivery or in the first few months of life, though nosocomial infection rates as high as 25% have been reported from some neonatal ICU's.[33] The incidence of bacterial sepsis varies from less than 1 to 8,1 cases per 1 000 live births, meningitis being present in about a third of these cases.[21] LBW babies have an increased incidence of sepsis compared to larger babies. In one study, babies with birth weights of 1000g to 1500g had twice the rate of infection compared to those with birth weights of 1500g to 2000g and eight times that of infants weighing 2000g to 2500g.[34] The incidence of sepsis is also increased in babies born to mothers with peripartum fever,

chorioamnionitis or PROM and in babies with asphyxia.[35] There is an increased incidence of bacterial sepsis acquired during delivery or in the nursery amongst male infants, though there is no such sex difference amongst those babies with intra-uterine infections.[36] Black infants are more predisposed to sepsis but whether this is a reflection of the increased rate of prematurity found amongst this population or their generally lower socioeconomic status is not clear.[16]

**3.1.1** Prolonged Rupture of Membranes Prolonged interval between rupture of membranes and birth is associated with an increased incidence of infection in both the mother and her newborn infant, and with an increased perinatal mortality rate (see fig. 1.1).[37] However, the vast majority of babies at risk do not develop any clinical evidence of infection. Only 1% to 6% of babies born to mothers with not just PROM, but also clinical chorioamnionitis become infected.[38] In fact, the majority of women who deliver babies who develop infection have no clinical evidence of infection themselves during labour. Further analysis of the subpopulations of women with PROM whose babies develop sepsis suggest that in these cases the amniotic fluid was already contaminated prior to the membranes having ruptured and that delayed delivery per se was not the cause of infection.[39] Similarly, tocolytics used in premature rupture of membranes to delay delivery of an immature foetus may result in the newborn being infected, but this probably only occurs in the woman who already had bacterial contamination of the amniotic fluid. Certainly,

Fig.1.1 Perinatal Infection Rate
Associated with PROM



bacteria in the amniotic fluid or endocervical canal may be responsible for the initiation of premature labour via the release of phospholipase A2 which results in the production of prostaglandins.

"Offensive" babies without PROM have not been shown to be at increased risk for infection in the newborn, the odour merely reflecting the presence of anaerobes in the amniotic fluid.[40]

A five minute Apgar score less than 6 in the presence of PROM is a strong predictor for neonatal infection. One study showed that 27% of premature babies with PROM and asphyxia were septic.[35] However, other obstetric causes of asphyxia must be ruled out.

3.1.2 Necrotising Enterocolitis NEC is reported to occur most commonly amongst premature babies nursed in high care areas with an average birth weight of 1400g to 1500g and gestational age of 30 to 32 weeks.[41] Incidences vary from hospital to hospital ranging from 2% to 7% with an overall mortality of 20% to 40%. Bacteraemia has been documented in about 30% of babies with NEC, the most common organisms recovered including E. coli, Klebsiella spp, S. aureus or S. epidermidis, E. faecalis, Clostridial and Pseudomonas spp.[28]

3.2 Organisms Involved

The types of bacteria responsible for neonatal sepsis have been changing with time; prior to the advent of sulphonamides, Gram positive cocci caused most neonatal sepsis.[42] With the

advent of antimicrobial agents, Gram negative enteric bacilli, especially E. coli, became the predominant cause of neonatal sepsis. In the 1960's, GBS became an important cause of neonatal infections in developed countries, accounting for up to a third of bacterial sepsis with an attack rate of 2,0 to 3,7 per 1 000 live births.[43] With the advent of sophisticated life-support systems in neonatal ICU's, Staphylococci and GNB together with fungi have again become important causes of nosocomial infections. Epidemics associated with contaminated solutions and equipment due to Proteus, Klebsiella, Serratia, Pseudomonas and Flavobacteria spp have been of increasing concern. Recently S. epidermis has been implicated as an important cause of nosocomial sepsis.[44] The bacterial aetiology of neonatal sepsis also varies from hospital to hospital and from one country to another. In Nigeria, for example, Salmonellae and S. pneumoniae are the most important causes of neonatal meningitis, and Klebsiella spp and S. aureus of bacteraemia.[21] While infections due to GBS are a major cause of neonatal morbidity and mortality in developed countries, it is uncommonly found amongst babies born to mothers in third world countries.[45] In addition, new strains of bacteria may appear spontaneously in the same hospital without there having been any change in nursery practices or antimicrobial usage.

## 4. DIAGNOSIS

The diagnosis of systemic infection in the newborn is difficult to establish on the basis of clinical findings alone. A history of risk factors associated with the pregnancy or

delivery may be present. Clinical signs of sepsis are often subtle and nonspecific initially but may rapidly progress to more obvious signs. Isolation of microorganisms from a significant source such as the blood, CSF, urine, other body fluids or tissues remains the most valid method of diagnosing bacterial sepsis. Organisms isolated from other sites such as the pharynx, stool or umbilicus, indicate colonization and do not establish the presence of active systemic disease.

### 4.1 Blood and CSF Cultures

Cultures obtained from blood or CSF are a reliable means of identifing the neonate with sepsis, one study giving a sensitivity of 87% and specificity of 96%.[46] The frequency with which organisms are isolated in newborns with unequivocal signs of sepsis may be decreased though if the mother was on antimicrobials prior to or during labour, if the baby was already partially treated and if techniques used to obtain the cultures were suboptimal. It has been suggested that two specimens of blood of at least 0,2mls should be obtained in the neonate suspected of being septic.[47] Cultures of blood taken from the umbilical vessels are not reliable as they are often positive when those obtained simultaneously from peripheral veins are negative.[48] Bacteraemia may occur in some newborns without signs of sepsis. The incidence of this asymptomatic transient bacteraemia is not known as blood cultures are rarely taken from well babies.

Blood cultures may be negative in up to 15% of babies with

culture proven bacterial meningitis; a lumbar puncture should thus be performed in all cases of suspected sepsis especially as babies seldom manifest with clinical signs of meningitis.[49] The cell count and protein level in the CSF's of normal newborns is higher and the glucose level lower than that of older children making the diagnosis of meningitis using these parameters difficult.[50] In addition, microorganisms have been cultured from the CSF in the absence of pleocytosis.

### 4.2 Laboratory Aids

White blood cell counts (WCC's) are of limited value in the diagnosis of septicaemia of the newborn. Total leukocyte counts are normal in a third of infants with culture proven bacteraemia and conversely less than half of those with low or elevated cell counts (normal=5 000-30 000/ml) are ultimately identified as being infected.[46,51] The neutrophil count, especially neutropaenia, though more reliable than the total WCC, is not an infallible predictor of sepsis either. While very specific, immature neutrophil counts (bands & metamyelocytes) are not sensitive in identifying the infected neonate.[52] However, ratios of immature to mature neutrophils of greater than 0,3 have shown excellent correlation with serious bacterial disease with a 93% sensitivity and 95% specificity. Reduction in the number of platelets (normal= 100 000-400 000/ml) has been shown to be an insensitive, nonspecific and relatively late indicator of bacterial infection in the newborn period, only half of newborns with culture proven bacteraemia developing thrombocytopaenia often one to

three days after serious illness is already apparent.[53] Other conditions such as birth asphyxia, maternal hypertension and meconium aspiration, may also be associated with depressed platelet counts.

Acute phase reactants such as C-reactive protein (CRP), fibrinogen, haptoglobin and orosomucoid have been evaluated in neonatal sepsis. Though the reliability of CRP as an indicator of neonatal infection is increasing with improved laboratory techniques, about 15% of cases would be missed when used alone as a test for sepsis.[54] It is thus most useful when used together with other laboratory tests in identifying the infected neonate. The microerythrocyte sedimentation rate (ESR) though elevated in most case of infants with systemic infection and normal in noninfected cases, may be falsely raised in infants with Coombs positive haemolytic disease and falsely low in cases of septicaemia associated with disseminated intravascular coagulopathy.[55] Fibrinogen, haptoglobin and orosomucoid levels have not proven to be very reliable in identifying the infected neonate.[51]

New techniques for detecting the presence of microorganisms in body fluids such as the limulus-lysate assay for endotoxin and counterimmunoelectrophoresis for bacterial antigens are being evaluate in the newborn.[56]

5. RESISTANCE PATTERNS

Extensive use of antimicrobials as found in an ICU results in elimination of susceptible strains and allows proliferation of

resistant ones. Thus there is a selective pressure towards colonization by microorganisms that are resistant not only to the antimicrobial agents used in the unit but, because of cross resistance patterns, to other similar drugs. These changes in antimicrobial susceptibility are usually plasmid mediated and have occurred notably with aminoglycosides.[57,58] Resistance in these cases is usually due to specific aminoglycoside inactivating bacterial enzymes, those that, for example, hydrolize tobramycin not being effective against gentamicin. Amikacin is a poor substrate for these enzymes but outbreaks due to amikacin-resistant enteric organisms are being increasingly reported. Resistance to cephalosporins due to β-lactams is also of increasing concern. Once entrenched, these resistant bacteria can be exceedingly difficult to eliminate from the environment.[59,60] The principle receivoir of infection is thought to be the faecal flora of infants; colonization rates with resistant organisms approaching 100% in ICU's during epidemics have been reported.[61]

## CHAPTER 2: THE STUDY

### 1. BACKGROUND

#### 1.1 Baragwanath's Neonatal Unit

Baragwanath Hospital serves the area of Soweto, which has an estimated population of two million. There are approximately 22 000 births per year at Baragwanath's Maternity Hospital. An additional 12 000 babies are delivered at the Soweto Clinics every year, and there are some 2 000 home deliveries. Thus, altogether there are about 36 000 deliveries per year in the greater Soweto area, for which Baragwanath is the only hospital. Approximately 2 000 neonates per year are referred to the Baragwanath Maternity Hospital after delivery, the vast majority being from the clinics and from home deliveries but a small number are referred from elsewhere.

About 14 000 babies are seen and assessed by the Paediatric medical staff (registrars or medical officers) in the labour ward (LW) every year. Well babies with birth weights >2000g are transferred with their mothers to the postnatal wards. Babies with birth weights <2000g and all sick babies are admitted to either:-

a) the Intensive Care Unit if requiring ventilation (ICU)
b) the high care area (Transitional Care Unit) (TCU)
c) the intermediate care areas, wards 66 or 67.

The ICU has facilities for 12 ventilated babies and runs at 100% occupancy most of the time. The TCU is in the same area and has 20 to 35 babies in it at any one time, with a daily

average of 24 babies. The official bed status is 18. At the other end of the maternity hospital are wards 66 and 67. They officially have 30 and 25 beds respectively, but on occasions more than 50 babies can be found in either ward, with a daily average of 40 per ward. There are two additional neonatal wards in the main section of the hospital, wards 40 and 42, to which stable premature infants are sent from wards 66 and 67 solely for weight gain.

Approximately 3 500 babies (a quarter of all those seen) are admitted per year to the Neonatal Unit. An additional 4 750 babies per year sent to their mothers are continued to be seen by the neonatology staff. In addition, there are about 100 deaths in the LW per year of neonates considered to be viable.

1.2 Antimicrobial Policies

Indications for initiation of antimicrobials in this Unit during the first 72 hours of life following a septic work-up are:-

a) respiratory distress
b) babies born following prolonged rupture of membranes (>24 hours)
c) babies with offensive liquor at birth
d) other clinical signs suggestive of infection.

If a congenitally acquired bacterial infection is suspected, first line antimicrobials consisting of penicillin (200 000U/Kg/day) and an aminoglycoside are used. Prior to July 1989 the aminoglycoside used was gentamicin (5mg/Kg/day) but once

it was established that there was a high rate of gentamicin resistance amongst the congenitally acquired GNB (see below), amikacin (15mg/kg/day) was introduced as first line therapy for all babies admitted to the ICU and TCU. By October 1989, it was the only aminoglycoside in use in the Neonatal Unit. If a nosocomially acquired infection is suspected, the baby is put onto second line antimicrobials. Prior to 1989 this consisted of amikacin and cefotaxime (100mg/kg/day) but with the advent of cefotaxime-resistant GNB (see below) the cephalosporin used was changed to ceftazadime (100mg/Kg/day). By April 1989, GNB resistant to all cephalosporins were emerging and it was decided to change the second line antimicrobials to amikacin and vancomycin (15mg/Kg/day), the latter to cover for methicillin-resistant Staphylococci and multiresistant E. faecalis (see below). However, ceftazadime would still be used if a CSF result was indicative of meningitis as aminoglycosides do not penetrate the blood-brain-barrier well. It was hoped that by restricting the use of cephalosporins for a period, susceptibility to them would be restored. Imipenem (60mg/Kg/day) was introduced to cover GNB sepsis if the baby was not improving on amikacin alone. With the emergence of amikacin resistance (see below), it was decided in April 1990 to use the cephalosporins more liberally again i.e. when the organism isolated was shown to be susceptible to them. Antifungal therapy was only instituted once a blood, CSF or suprapubic urine culture confirmed the presence of a fungus. It was never used on purely clinical suspicion.

Some 2 600 babies per year (nearly 80% of the admissions) are suspected of having a congenital bacterial infection, cultured and put onto first line antimicrobials. Approximately 550 of these babies are admitted to the ICU, 850 to the TCU and 1 200 to wards 66/67. In addition, about 400 babies per year with prolonged rupture of membranes or offensive liquor but otherwise well are cultured, put onto antimicrobials and sent to the postnatal wards to room in with their mothers.

Approximately another 1 500 blood cultures per year are sent on babies suspected of having nosocomial infections, about 500 from babies in the ICU, 400 from the TCU and 600 from wards 66/67.

About 800 CSF cultures are done per year, mostly on babies suspected of having nosocomial infections; 250 come from babies in the ICU, 200 from the TCU and 300 from wards 66/67.

The origins of these figures are explained below in section 3.4 under "METHODS".

## 2. AIMS OF THE STUDY

The incidences of perinatal bacteremia and nosocomial infections amongst the neonates admitted to Baragwanath's Neonatal Unit had not previously been documented; nor had the frequencies of the various organisms, susceptibility patterns or outcome of these patients been recorded. The aims of this thesis thus were:-

1) to establish the incidences of perinatally and nosocomially

acquired infections in this population.

2) to identify the weight categories at risk for infection and other clinical factors that predispose to septicaemia, and to ascertain the frequency of meningeal involvement. Morbidity and mortality associated with these infections were also examined.
3) to analyze the organisms involved, their susceptibility patterns and seasonal variations, and to postulate on possible mechanisms for changing antimicrobial susceptibilities.
4) to review the literature on the experiences of other neonatal units and to compare them with these data from Baragwanath Hospital.

The information from this epidemiological report should prove to be valuable in enabling logical antimicrobial policies to be formulated in view of ever changing susceptibility patterns of organisms especially as are found in ICU's and other high care areas.

## 3. METHODS

### 3.1 Ethical Committee Approval

The study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand. No. 3/10/90

### 3.2 Specimen collection

Blood and CSF cultures taken from babies suspected of being infected were taken at the attending doctor's discretion together with full blood counts (FBC's), following which anti-

microbials currently recommended were commenced. Only if organisms were isolated with susceptibility patterns not covered by the present treatment or the infant's condition deteriorated was the antimicrobial therapy altered.

### 3.3 Laboratory Methods

Blood culture bottles were processed by using radioactive Bactec 660 instrumentation (Becton Dickinson) (Johnston Laboratory Incop. Cockeysville, Maryland) following recommended procedures. Cultures that gave a positive signal were Gram stained, subcultured onto 5% horse blood, chocolate and MacConkey agar, incubated for a week and inspected daily for bacterial growth. Bacterial colonies were identified using standard methods and resistance patterns established by the Kirly-Bauer disc diffusion technique.[62] Minimum inhib-itory (MIC's) and minimum bacteriocidal concentrations (MBC's) were obtained on resistant organisms when possible. These assays were performed using NCCLS criteria.[62a]

### 3.4 Data Collection

Data on all positive blood and CSF cultures with their resistance patterns were collected prospectively from January 1989 to December 1990. If an organism was isolated more than once from the same site at different times from a patient, only the first culture was recorded, unless different resistance patterns were demonstrated when they would be counted as separate strains. This, together with details of the babies from whom these cultures were obtained i.e. date of

birth, birth weight, sex, ward admitted to and outcome, were entered into a computer data base using the "dBASE III PLUS" program (Ashton Tate Corporation, Torrence, California, 1988). Cultures obtained before 72 hours of life were considered to be congenitally acquired or "early onset" infections and those obtained later nosocomially acquired or "late onset" infections except for those of GBS when the internationally accepted definition of 7 days was used. Further information such as the total number of babies admitted to the unit, their birth weights, wards admitted to, disease profile, antimicrobials used and outcome was obtained from the data base on which all admissions to the unit are being routinely entered. As this system was only fully operational from October 1989, some patient details are however unfortunately missing. Information required on those relatively well babies not admitted to the Unit but seen by the neonatal staff in their mothers' wards was obtained from another data base.

The number of babies estimated to be born in the Soweto clinics and the number of home deliveries are taken from the annual figures supplied by the Medical Officer of Health for Soweto. As there are no official records on the number of babies delivered at Baragwanath Hospital and not admitted to the Unit, such figures are taken from the Matrons' annual reports, as are the number of babies referred to the Hospital and all those seen by the medical staff in LW. The number of blood cultures taken from babies in the LW suspected of having a congenital infection was derived from the number of babies

started on first line antimicrobials (see below). The total number of blood and CSF cultures sent from babies in the Unit was obtained by counting the entries in the laboratory's file but is only an estimate as the total was calculated from the results obtained from counting the entries for only six of the 24 months. The number of cultures taken from babies suspected of having a nosocomial infection would thus be the total number of cultures sent minus the number of babies started on first line antimicrobials. These figures were thought to be important as the yield of positive cultures could then be determined.

### 3.5 Data Analysis

The computer program "Epi Info" (USD Incorporated, Stone Mountain, Georgia, 1990) was used to analyze the data. Statistical analysis of the data was performed by using chi-squared analysis or Fisher's exact test when appropriate. A significance level of $P<0,05$ was used.

## CHAPTER 3: RESULTS

### 1. PATIENT POPULATION

#### 1.1 Admissions

Table 3.1 shows the total number of admissions to the Unit and deaths, including those that died in the LW, according to birth weight during the two year study period. Babies are categorized in 500g weight categories up to 2500g, those below this weight being, by definition, of LBW. In 1989 there were 3 553 admissions and the following year 3 386. The male to female ratio was 1,2:1. The monthly numbers of admissions are reflected in fig. 3.1.

The breakdown of admissions to the individual wards according to birth weight for the two years is given in table 3.2. Wards 66 and 67 are considered together as there were no significant differences with respect to the number of admissions, duration of stay, birth weight or severity of illness amongst babies admitted to these wards. These figures do not include the deaths in LW as these babies died there before they could be transferred to a ward.

It should be mentioned here, that any individual baby may be admitted from one ward to another; for example, a baby who survives ventilation would be discharged from the ICU to the TCU and from there to wards 66/67. Equally, a baby in ward 66/67 whose condition deteriorates would be transferred to the TCU or ICU.

**Table 3.1 Admissions and Deaths by Birth Weight**

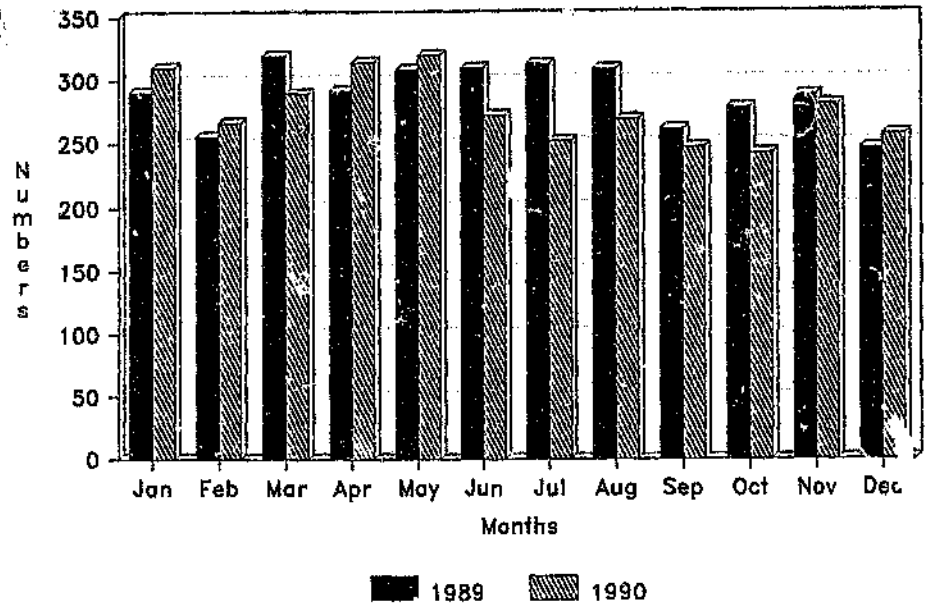
| | Birth Weights | | | | | |
|---|---|---|---|---|---|---|
| | <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
| a)1989 | | | | | | |
| Total | 124 | 580 | 1031 | 573 | 1245 | 3553 |
| Deaths(%) | 86(69,4) | 195(33,6) | 78(7,6) | 59(10,6) | 140(11,2) | 558(15,7) |
| b)1990 | | | | | | |
| Total | 116 | 569 | 908 | 562 | 1231 | 3386 |
| Deaths(%) | 82(70,7) | 187(32,9) | 69(7,6) | 42(7,5) | 141(11,5) | 521(15,4) |

**Table 3.2 Admissions to Wards by Birth Weight**

| | Birth Weights | | | | | |
|---|---|---|---|---|---|---|
| Wards | <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
| a)1989 | | | | | | |
| ICU | 10 | 217 | 122 | 66 | 145 | 560 |
| TCU | 101 | 403 | 366 | 190 | 394 | 1454 |
| 66/67 | 39 | 402 | 950 | 513 | 1079 | 2983 |
| Total* | 107 | 560 | 1025 | 557 | 1212 | 3461 |
| b)1990 | | | | | | |
| ICU | 4 | 226 | 129 | 81 | 150 | 590 |
| TCU | 102 | 440 | 338 | 214 | 404 | 1498 |
| 66/67 | 33 | 424 | 859 | 524 | 1109 | 2949 |
| Total* | 102 | 548 | 898 | 558 | 1205 | 3311 |

*These are the overall numbers of babies admitted to the unit and will thus correspond to the sum of the admissions to ICU, TCU and Wds 66/67 since transferred babies would otherwise be counted more than once

Fig 3.1 Monthly Admissions to the Unit



An average of 575 babies per year were admitted to the ICU, 1 476 to the TCU and 2 966 to wards 66/67. LBW babies made up 64,3% (4355/6772) of the total admissions to the Neonatal Unit, with those having birth weights of 1500g to 1999g making up the largest single category. LBW babies constituted an even higher proportion of admissions to the ICU accounting for 74,3% (855/1150) of the admissions there. The largest weight category there was the 1000g to 1499g category The bigger, more stable babies with weights >2499g were usually admitted to wards 66/67.

Table 3.3a shows the mean durations of stay in the various wards by weight category of all babies, including those that died, over the two year period, and table 3.3b of the survivors. The babies with the longest average stay in the unit were those with birth weights of 1000g to 1499g, staying a mean of 35,0 days. However, if one only looks at the survivors, babies with birth weights of <1000g stayed the longest, an average of 69,5 days vs. 46,7 days for survivors with birth weights of 1000g to 1499g. The average stay of survivors with birth weights of <1000g in the TCU was also much longer if the deaths are excluded (33,1 days vs. 16,9 days).

1.2 Deaths

The numbers of babies in the different weight categories who died are reflected in table 3.1. Table 3.4 shows where these babies actually died during the two years. Once again, a baby

**Table 3.3 Average Duration of Stay in Days by Birth Weight**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g |
|---|---|---|---|---|---|
| a)All babies | | | | | |
| ICU | 11,9(3-35) | 9,5(0-64) | 7,9(0-48) | 5,3(0-36) | 3,6(0-25) |
| TCU | 16,9(0-71) | 7,8(0-59) | 4.3(0-37) | 3,1(0-18) | 4,4(0-97) |
| 66/67 | 17,7(5-38) | 18,8(1-79) | 9,6(0-59) | 7,5(0-77) | 6,0(0-103) |
| Total | 27,0(0-98) | 35,0(0-211) | 19,8(0-128) | 10,9(0-97) | 8,7(0-153) |
| b)Survivors | | | | | |
| ICU | 11,4(3-35) | 11,7(4-64) | 9,0(3-48) | 5,9(3-36) | 6,0(2-25) |
| TCU | 33,1(3-71) | 8,4(1-59) | 4,4(1-37) | 3,0(0-35) | 4,6(0-97) |
| 66/67 | 18,1(5-38) | 19,2(1-79) | 9,6(1-59) | 7,5(1-77) | 6,1(2-103) |
| Total | 59,5(48-98) | 46,7(14-211) | 20,5(1-128) | 11,3(1-97) | 9,0(2-153) |

Figures in parenthesis = range of stay in days

**Table 3.4 Deaths per Ward by Birth Weight**

a) 1989

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | 5(0) | 123(50) | 47(25) | 18(9) | 67(49) | 260(133) |
| TCU | 62(34) | 45(15) | 23(8) | 18(7) | 26(16) | 174(80) |
| 66/67 | 2(0) | 7(0) | 2(0) | 5(2) | 12(1) | 28(3) |
| LW | 17(17) | 20(20) | 6(6) | 16(16) | 33(33) | 92(92) |
| Misc.* | - | - | - | 2(0) | 2(0) | 4(0) |
| Total | 86(51) | 195(85) | 78(39) | 59(34) | 140(99) | 558(308) |

b) 1990

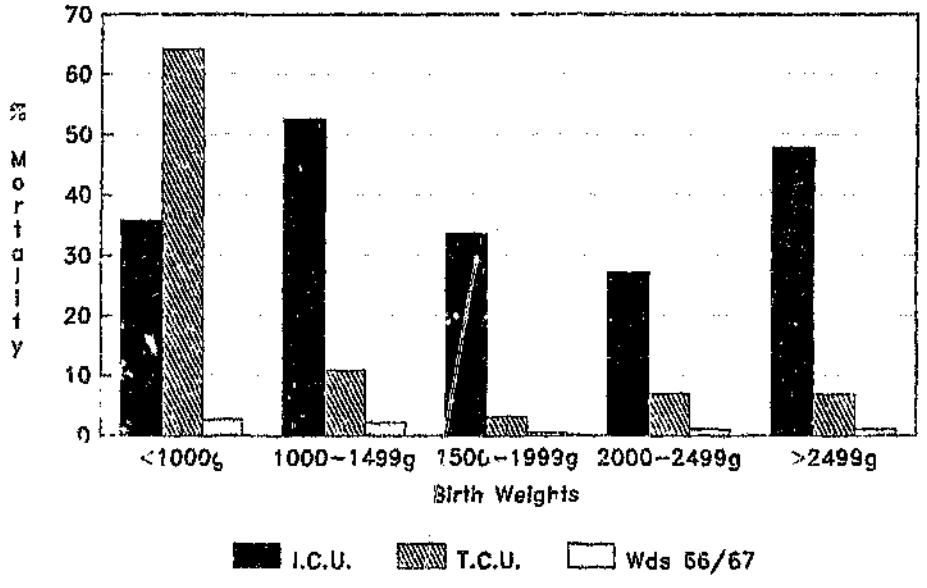
| Wards | Birth Weight 1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | - | 110(42) | 37(18) | 22(8) | 74(50) | 243(118) |
| TCU | 68(35) | 46(18) | 17(6) | 10(3) | 28(16) | 169(78) |
| 66/67 | - | 10(0) | 5(0) | 5(3) | 11(8) | 31(11) |
| LW | 14(14) | 21(21) | 10(10) | 4(4) | 26(26) | 75(75) |
| Misc.* | - | - | - | 1(0) | 2(0) | 3(0) |
| Total | 82(49) | 187(81) | 69(34) | 42(18) | 141(100) | 521(282) |

*Babies dying in other wards e.g. wards 40 or 42
Figures in parenthesis = deaths before 3 days of age

who is admitted to, for example, the TCU but then requires ventilation and dies would be recorded as an admission to both the TCU and ICU and a death in the latter unit. The numbers of babies who died before three days of age are also shown in parenthesis. Of the total number of deaths amongst babies admitted to the unit during the two year study period, 46,4% (423/912) died in the first three days of life i.e. 6349 babies survived beyond three days. These figures are important when analyzing nosocomial infections as these are, by definition, acquired by babies older than three days. The mortality rates for the individual wards according to birth weights are shown in fig. 3.2.

The average mortality of babies admitted to the ICU was 43,7% (503/1150), with another 5,6% (64/1150) of these babies dying after discharge from the ICU. This means that 49,3% (567/1150) of the babies requiring ventilation ultimately died. Similarly, 11,6% (343/2952) of all babies admitted to the TCU died there, most of them being babies with birth weights of <1000g as they are not routinely ventilated; another 9.1% (270/2952) died elsewhere bringing the total mortality to 20,8% (613/2952). Few babies died in wards 66/67. These were largely babies with lethal congenital abnormalities or babies with severe brain damage following asphyxia. On average, 70,0% (168/240) of babies with birth weights <1000g and 33,2% (382/1149) with birth weights of 1000g to 1499g died, the mortality rates for the remaining weight categories ranging

Fig 3.2 Ward Mortalities by Birth Weight



babies with birth weights >2499g requiring ventilation had an higher morality than would be expected (see fig. 3.2). The total mortality of admissions to the Neonatal Unit for the two years was 15,5% (1079/6939). This translates to a mortality of about 2,5% (1079/44000) of the total neonatal population at the Baragwanath's Maternity Hospital or 1,5% (1079/72000) of all births in the greater Soweto area.

### 1.3 Antimicrobials

Table 3.5 shows the number of babies put onto the various antimicrobials over the two year period. In order not to include a baby several times in the analysis, once counted under one ward's admission they are excluded from another ward's admission. The total number of babies on an antimicrobial are only given for 1990 as the data for 1989 is incomplete. The number of babies treated with penicillin during the two years was used as an indicator of the number suspected of having a congenital infection. The number of babies in 1990 put onto vancomycin was used to determine the number suspected of having developed a nosocomial infection.

Thus, 90,7% (1043/1150) of ICU admissions, 82,4% (1152/1397) of babies admitted to the TCU and not requiring ventilation at any stage and 71,4% (1747/2446) of babies only admitted to wards 66/67 were put onto first line antimicrobials. 27,9% (165/590) of babies admitted to the ICU (35,0% (165/472) of those that survived for more than three days) were suspected at some point of having a nosocomial infection and put onto

**Table 3.5 Number of Babies on Antimicrobials**

| Drug | Wards | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1989 ICU n=560 | TCU n=381* | 66/67 n=741* | 1990 ICU n=590 | TCU n=1016 | 66/67 n=1705 | Total n=3311 |
| Penicillin | 512 | 318 | 528 | 531 | 834 | 1219 | 2584 |
| Gentamicin | 276 | 83 | 364 | 11 | 0 | 0 | 11 |
| Amikacin | 386 | 246 | 197 | 561 | 364 | 1278 | 2703 |
| Vancomycin | 119 | 42 | 47 | 165 | 118 | 119 | 402 |
| Cefotaxime | 27 | 8 | 4 | 18 | 10 | 18 | 46 |
| Ceftazadime | 42 | 7 | 2 | 97 | 56 | 78 | 231 |
| Imipenem | 18 | 1 | 0 | 39 | 2 | 19 | 60 |

* Only data for September to December available for TCU and Wds 66/67

second line antimicrobials. Of those babies admitted to the TCU but never requiring ventilation at any time and surviving beyond three days, 12,6% (118/938) were suspected of having a nosocomial infection. Only 7,0% (119/1694) of babies admitted solely to wards 66/67 were commenced on second line antimicrobials.

### 1.4 Summary

Table 3.5 is a summary of the relevant features of the three main neonatal wards as mentioned above. The proportion of babies admitted to the ICU or TCU who were of LBW were significantly greater than that of the babies admitted to wards 66/67 ($P<0,0001$). Not unexpectedly, the mortalities in these wards were significantly higher than that in wards 66/67, and so were the proportions of babies that died before reaching three days of age ($P<0,0001$). Even though most of the babies were admitted directly from the LW, babies admitted to wards 66/67 were significantly older than those admitted to the ICU or TCU ($P<0,0001$). The percentages of babies on both first and second line antimicrobials decreased significantly amongst babies admitted to the ICU or TCU or wards 66/67 ($P<0,0001$). Babies admitted to the TCU stayed there for a significantly shorter time than babies admitted to the ICU or wards 66/67 ($P<0,0001$).

## 2. NECROTISING ENTEROCOLITIS

### 2.1 Occurrence

During the two years of study there were 123 cases of proven

**Table 3.6 Comparison of the Neonatal Wards**

| | ICU | TCU | Wds. 66/67 |
|---|---|---|---|
| Av. daily bed status | 12 | 24 | 40 |
| Av. admissions/year | 575 | 1476 | 2966 |
| M:F | 1,2:1 | 1,2:1 | 1,3:1 |
| Mean age (range) | 3,5(0-134) days | 4,0(0-89) days | 4,4(0-120) days |
| % LBW | 74,3 | 72,9 | 63,1 |
| Birth weight(mean+/-SD) | 1955+/-830g | 1978+/-860g | 2267+/-800g |
| Mean duration of stay: | | | |
| all babies (range) | 8,9(0-64) days | 6,1(0-97) days | 9,4(0-103) days |
| survivors (range) | 9,6(2-64) days | 6,3(1-97) days | 9,4(1-103) days |
| Total deaths (%) | 503 (43,7) | 343 (11,6) | 59 (1,0) |
| % Deaths <3 days | 49,9 | 46,1 | 23,7 |
| % on 1st line A/M | 90,7 | 82,4 | 76,8 |
| % on 2nd line A/M | 34,9 | 12,6 | 7,0 |

NEC, an incidence of 1,9% (123/6349) of all babies admitted to the Unit surviving beyond three days. There were also 197 cases of clinically suspected NEC, an incidence of 3,1%. The data in table 3.7 shows that the highest incidence of proven NEC occurred in the babies with birth weights of 1000g to 1499g, 7,4% (73/983). The highest incidence of suspected NEC, 15,0% (21/140), occurred in the babies with birth weights <1000g who survived beyond three days .

**2.2** Mortality

Babies with proven NEC had a mortality of 74,0% (91/123) and those with suspected NEC a significantly lower mortality of 40,6% (80/197) (P<0,0001). As seen from table 3.8, babies who developed proven NEC and had birth weights <1000g had the highest mortality, 80,0% (4/5) and those with birth weights >2499g the lowest, 33,3% (2/6). The mortalities of babies with suspected NEC showed a similar trend i.e. decreasing with increasing birth weights.

**2.3** Parenteral Nutrition

In addition to those babies with NEC, several other babies with gut pathology, such as congenital lesions, and babies with a prolonged ileus as found in those with severe lung disease requiring high pressure ventilation, were placed on parenteral nutrition. There were an additional 69 such babies during the two year study period on parenteral nutrition.

## 3. CONGENITAL GRAM POSITIVE INFECTIONS

**3.1** Group B Streptococci

**Table 3.7 Babies with Necrotising Enterocolitis by Birth Weight**

| NEC | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| Proven | 5(3,6) | 73(7,4) | 30(1,6) | 9(0,8) | 6(0,2) | 123(1,9) |
| ? NEC | 21(15,0) | 85(8,6) | 41(2,2) | 20(1,9) | 30(1,3) | 197(3,1) |

Figures in parenthesis = % babies surviving beyond 3 days who develop NEC

**Table 3.8 Deaths from Necrotising Enterocolitis by Birth Weight**

| NEC | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| Proven | 4(80,0) | 57(78,1) | 23(76,6) | 5(55,6) | 2(33,3) | 91(73,9) |
| ? NEC | 10(47,6) | 47(55,2) | 11(26,8) | 7(35,0) | 5(16,7) | 80(40,6) |

Figures in parenthesis = % mortality of babies with NEC

3.1.1 Occurrence There were 141 babies with culture proven early onset GBS bacteremia during the two year study period; 139 positive blood and 11 CSF cultures, two of the CSF cultures not having an associated positive blood culture. All except three of these cultures were obtained at birth. The number of cases per month are reflected in fig. 3.3. There were 74 cases in 1989 and 67 in 1990. Even though it appeared that there was an increase in the number of patients with early onset GBS infections during the winter months (83/141) (63,4%), this was not confirmed statistically probably because an unusually high number of cases occurred in November 1990. As there are about 36 000 deliveries in the Soweto area per year, this would give an annual incidence of GBS bacteremia of 1,9 cases per 1 000 live births.

There were equal numbers of males to females. The mean birth weight of babies from whom GBS were isolated early on was 2458 +/-877g (median 2500g, range 770-4800g). The breakdown of the wards to which these babies were admitted according to their birth weights is shown in table 3.9. 35,5% (50/141) of the cases were babies admitted to wards 66/67 with mild respiratory signs, 26,2% (37/141) necessitated admission to the TCU and 22,7% (32/141) had such severe respiratory distress that they required ventilation. The remaining cases were well babies with PROM or offensive liquor that were sent to their mothers (12,8%) (18/141) or babies that died in the LW ward prior to admission (2,8%) (4/141). GBS were isolated early on

Fig 3.3 Group B Sreptococci

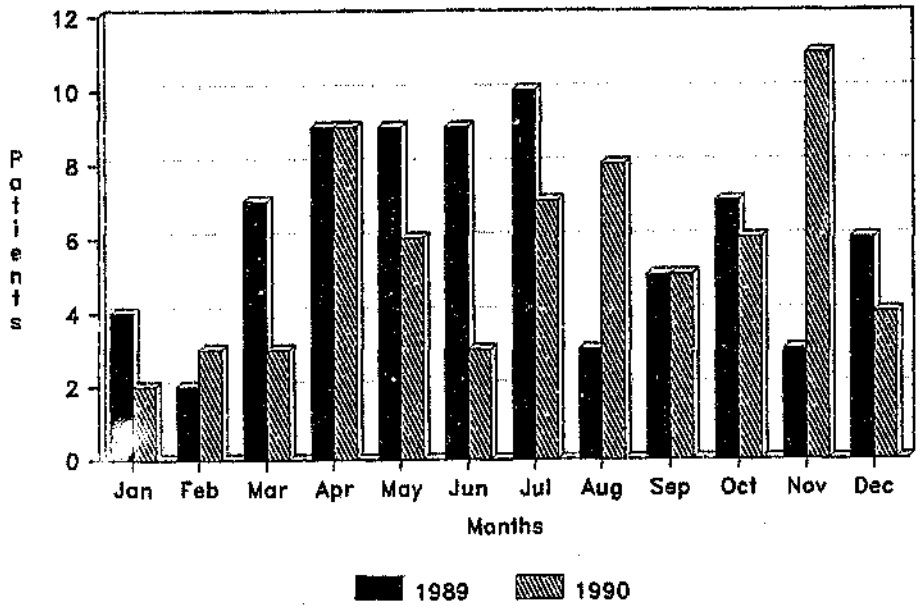


**Table 3.9 Patients with Early Onset Group B Streptococcal Bacteremia**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | - | 9(2,0) | 6(2,4) | 4(2,7) | 13(4,4) | 32(2,8) |
| TCU | 3(1,5) | 9(1,1) | 7(1,0) | 3(,7) | 15(1,9) | 37(1,2) |
| 66/67 | - | 1(,1) | 5(,3) | 16(1,5) | 28(1,3) | 50(,8) |
| LW | 1(3,2)* | 2(4,8%)* | 1(6,2)* | 3(?)** | 15(?)** | 22(?) |
| Total | 4(1,6) | 21(1,8) | 19(1,0) | 26(?) | 71(?) | 141(?) |

Figures in parenthesis = % admissions with early onset GBS bacteremia
* = babies that died in LW
** = exact denominator not known as these are babies sent to their mothers

**Table 3.10 Risk Factors for Developing Group B Streptococcal Bacteremia**

| | Total (1990) n=3386 | With GBS(%) n=67 | P value | O.R. | 95% C.L. |
|---|---|---|---|---|---|
| Maternal age: <20y | 584 | 12(2,1) | 0,88 | 1,05 | 0,53-2,03 |
| " >30y | 1034 | 10(1,0) | 0,005 | 0,39 | 0,19-0,80 |
| Gravidity: G1 | 1077 | 23(2,1) | 0,65 | 1,12 | 0,65-1,92 |
| >G3 | 843 | 11(1,3) | 0,14 | 0,59 | 0,29-1,16 |
| NVD | 2745 | 56(2,0) | 0,59 | 1,19 | 0,60-2,42 |
| Asphyxia | 698 | 31(4,4) | <0,0001 | 3,42 | 2,65-5,72 |
| PROM/offensive | 704 | 15(2,1) | 0,74 | 1,10 | 0,59-2,03 |

addition, GBS were isolated from 4,5% (4/88) of babies with birth weights <2000g who were seen in LW but died there before having been admitted and from 2,3% (18/800) of the well babies with birth weights >1999g cultured for PROM or offensive liquor and sent to their mothers on antimicrobials. These organisms accounted for 2,8% (32/1150) of the admissions to the ICU, 1,3% (37/2952) of those to the NICU and they were only isolated from 0,8% (50/5932) of babies admitted to wards 66/67. More importantly, GBS were only isolated in 2,7% (141/5200) of babies cultured for suspected congenital infections, the highest yield being amongst babies admitted to the ICU with suspected congenital sepsis, 3,1% (32/1043). GBS appeared to be a more common cause of illness amongst the bigger babies, 4,4% (13/295) of the babies with birth weights >2499g admitted to the ICU having GBS septicaemia compared to 2,2% (19/855) of babies with birth weights <2500g (P=0,05). However, if all births in Soweto are analyzed then GBS were isolated significantly more frequently from babies with birth weights <2000g compared to bigger babies, 44/3328 (1,3%) vs. 77/68672 (0,1%), there having been about 72 000 deliveries in the Soweto area during the two year study period (P<0,0001, O.R.=9,47, 95% C.L.=6,52-13,74). As the exact number of babies with birth weights between 1999g and 2500g born in Soweto is not known because only babies with birth weights <2000g are routinely admitted for weight gain, the incidence of GBS for LBW babies defined as a birth weight <2500g could not be determined.

3.1.2 Risk Factors Further clinical data were available on the 67 babies that had GBS bacteremia during 1990. The mother's age and gravidity, the mode of delivery, whether there was PROM or offensive liquor and the baby's apgar score were noted. Compared to the data available for the rest of the admissions to the Neonatal Unit, the only predictor for the presence of GBS infection was the presence of asphyxia, 46,3% (31/67) of the babies from whom GBS were isolated were asphyxiated compared to 20,1% (667/3319) of those without GBS (p<0,001). The latter percentage would, of course, be much lower if all the uncomplicated deliveries that occurred in Soweto during that year were included, i.e. 1,9% (667/35933), making asphyxia an even more significant association with GBS sepsis (P<0,0001, O.R.=65,03, 95% C.L.=38,81-108,84). Also, older mothers were less likely to deliver a baby with such an infection (see table 3.10). Neither the presence of PROM or offensive liquor, vaginal delivery vs. delivery by Caesarian section, nor the mother's gravidity were predictors of GBS bacteremia in a baby requiring admission to the Unit. However, if one included all the other deliveries that occurred in Soweto during that year in the analysis and assuming that all babies with PROM or offensive liquor were referred to Baragwanath Hospital, then the presence of these conditions is associated with an increased risk of the baby having early onset GBS sepsis; 15/704 (2,1%) vs. 52/35296 (0,1%) (P<0,0001, O.R.=14,76, 95% C.L.=7,92-27,12). Similarly, GBS sepsis also occurred much more frequently amongst babies born by Caesarian

section than vaginally, 11/641 (1,7%) vs. 56/35359 (0,1%) (P<0,0001, O.R.=11.04, 95% C.L.=5,42-21,81), as deliveries occurring outside the hospital must have been vaginal.

3.1.3 Mortality Thirty-three babies with GBS bacteremia died, a mortality of 23,4%. This organism was responsible for 3,1% (33/1079) of all the deaths in the Neonatal Unit. The wards in which the babies died according to their birth weights are reflected in table 3.11. The highest mortality was amongst babies admitted to the ICU, 65,6% (21/32) of those with GBS bacteremia died. Babies with birth weights <2000g had a significantly higher mortality than larger babies, 22/44 (50,0%) vs. 11/97 (11,3%) (P<0,0001). This is also confirmed by the fact that the mean birth weight of babies that died from GBS infection was significantly less than that of babies that survived, 1847+/-742g (median 1629g, range 770-3384g) vs. 2644+/-831g (median 2662g, range 850-4800g) (P<0,0001). The contributions to the mortality amongst the various wards by GBS infections according to birth weight is shown in fig. 3.4. It can be seen that GBS infection is a less important cause of death at both extremes of birth weight, accounting for only 1,2% (2/168) of the deaths amongst babies with birth weights <1000g and 3,8% (8/281) amongst those with birth weights >2499g vs. 6,1% (9/147) amongst those with birth weights between 1500 to 1999g (p=0,007). It was responsible for 4,2% (21/503) of the deaths in the ICU, 2,0% (7/343) of those in the TCU, 1,6% (1/59) of those in wards 66/67 and 2,4% (4/167)

**Table 3.11 Deaths due to Group B Streptococci by Birth Weight**

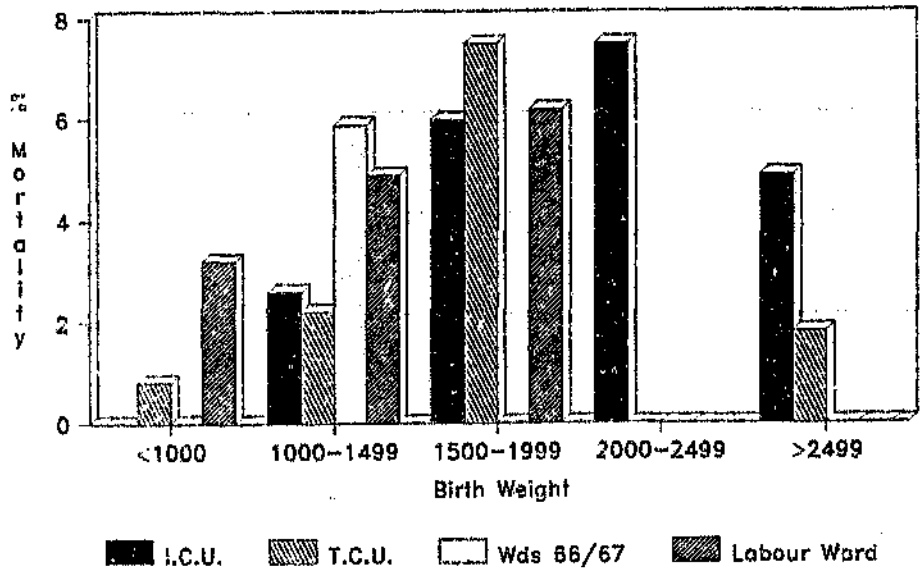
| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | - | 6(66,7) | 5(83,3) | 3(75,0) | 7(53,8) | 21(65,6) |
| TCU | 1(33,3) | 2(22,2) | 3(42,9) | - | 1(6,7) | 7(18,9) |
| 66/67 | - | 1(100) | - | - | - | 1(2,0) |
| LW | 1(100) | 2(100) | 1(100) | - | - | 4(18,2) |
| Total | 2(50,0) | 11(52,4) | 9(47,4) | 3(11,5) | 8(11,3) | 33(23,4) |

Figures in parenthesis = % mortality of babies with early onset GBS

**Table 3.12 Early Onset Group B Streptococcal Meningitis**

| Pt | Weight | Sex | Ward | Spec.date | B/C | CSF Micro | Died |
|---|---|---|---|---|---|---|---|
| T.K. | 2260 | M | ICU | 17/04/89 | Y | no cells prt 0,9 glu 5,0 | Y |
| X.M. | 3024 | F | 67 | 15/05/89 | Y | N400 L40 prt 2,6 glu <1 | N |
| S.M. | 3340 | F | TCU | 03/06/89 | Y | bloody | Y |
| M.L. | 1300 | M | ICU | 13/06/89 | Y | N30 L10 prt 1,7 glu 3,6 | N |
| J.M. | 3350 | F | TCU | 13/07/89 | N | N5 L7 R7260 prt 1,9 glu 4,8 | N |
| M.C. | 2300 | F | ICU | 04/10/89 | Y | bloody | Y |
| T.M. | 1920 | M | ICU | 10/10/89 | Y | N20 L30 R3 prt 3,2 glu <1 | Y |
| N.M. | 3500 | F | TCU | 16/12/89 | Y | N1200 L4 R0 prt 2,2 glu <1 | N |
| T.L. | 3710 | M | 66 | 22/12/89 | Y | N1430 L0 R4660 prt 2,5 glu 3,6 | N |
| M.N. | 1619 | M | 67 | 30/07/90 | N | no cells prt 1,4 glu 3,2 | N |
| S.M. | 3185 | F | 66 | 10/11/90 | Y | N401 L160 R0 prt 2,0 glu <1 | N |

Fig 3.4 % Mortality due to Group B Steptococcal Infection

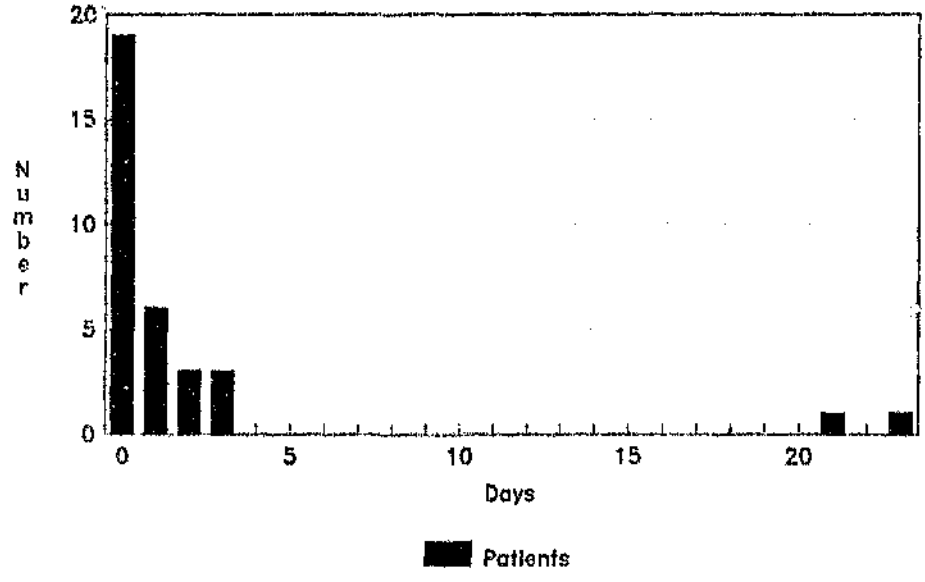


Most of the babies died within the first 24 hours of admission, 25/33 (75,8%) (see Fig. 3.5). The baby who died at three weeks of age died from severe brain damage following asphyxia and the other baby who died after three weeks died from nosocomial Klebsiella septicaemia.

3.1.4 Meningitis There were 11 babies (7,8% of the total) with GBS meningitis. Relevant clinical details together with the CSF cell count and biochemistry are given in table 3.12. Interestingly enough, a cellular response was not present in two of the CSF taps from which GBS were isolated. Four of the babies died, a mortality of 36,3%, not significantly higher than that of the babies with GBS infection without meningitis.

3.1.5 Associated Cultures A S. aureus, S. epidermidis, Klebsiella spp, Serratia spp and two E. coli were isolated at the same time as the GBS from 5 patients (3,5%). In addition, 13 of the 88 babies with GBS bacteremia that survived beyond three days (14,7%) developed apparent nosocomial infections; S. aureus was isolated 5 times, Klebsiella spp 3 times, candida spp, E. faecalis and S. epidermidis twice and Pseudomonas spp, Serratia spp and an anaerobic bacteria once from these babies after three days of age. This was not a significantly higher rate of nosocomial infection compared to babies admitted without a GBS infection as far as the nosocomial GNB and fungal infections were concerned, 5/88 (5,7%) vs. 215/6261 (3,4%) and 2/88 (2,3%) vs. 110/6261 (1,8%) respectively, there having been 6349 babies admitted to the

Fig 3.5 Interval Between Diagnosis of Group B Strep. and Death



Unit that survived for more than three days (see below).

3.1.6 Haematology The mean WCC of the 127 babies with early onset GBS infection on whom FBC's were done was 10 615 +/- 5 840/ml (range 1 300-27 200/ml) and their mean platelet count was 225 000+/-79 690/ml (range 51 000-451 000/ml). The mean WCC of babies that died was significantly lower than that of those that survived, 8 771+/-6 100/ml (range 1 300-23 500/ml) vs. 11 137+/-5 700/ml (range 2 200-27 200/ml) (P=0,04). There was no significant difference between the mean platelet count of those that survived compared to those that died, 232 200+/-79 240/ml vs. 199 000+/-77 412/ml respectively. Ten (35,7%) of 28 babies that died had WCC's <5 000/ml and 14 of 99 babies (14,4%) that survived (P=0,02). A low platelet count on the other hand was not a prognosticating feature. Only 2 babies that died had platelet counts <100 000/ml and 5 that survived.

3.2 Miscellaneous Congenital Gram Positive Isolates

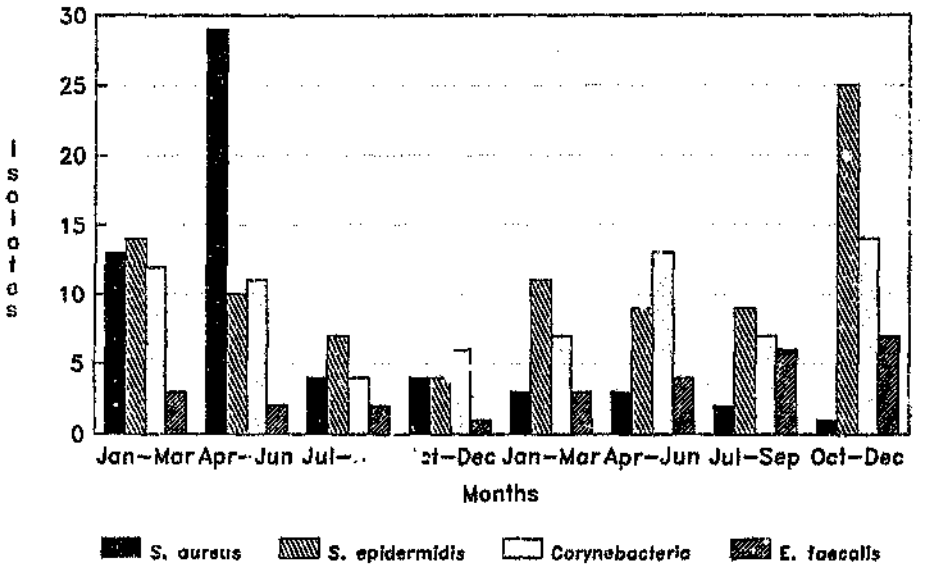
3.2.1 Occurrence Other GPB were isolated at birth during the two year study period as reflected in table 3.13. The numbers isolated every month are shown in fig. 3.6. Both the numbers of S. aureus and S. epidermidis appeared to reach "epidemic" proportions at times, 17 isolates of S. aureus occurring in June 1989 and 13 of S. epidermidis in October 1989. The mean birth weight of the babies from whom these organisms were cultured was 2362+/-882g (median 1947g, range 810-5340g) and the male to female ratio 1,5:1. There were no differences amongst the babies from whom the various different GPB were

**Table 3.13 Miscellaneous Gram Positive Isolates**

| Organism | Blood | CSF | Patients | ICU | TCU | 66/67 | LW |
|---|---|---|---|---|---|---|---|
| S. epiderm | 80 | 10 | 89 | 11 | 31 | 37 | 10 |
| c haem Strep | 74 | - | 74 | 9 | 23 | 30 | 12 |
| S. aureus | 57 | 2 | 59 | 14 | 27 | 13 | 5 |
| Corynebact | 38 | - | 38 | 2 | 15 | 17 | 4 |
| Bacillus | 27 | 1 | 28 | 5 | 12 | 7 | 4 |
| E. faecalis | 25 | 3 | 28 | 4 | 8 | 14 | 2 |
| Listeria | 2 | 1 | 2 | 2 | - | - | - |
| Total | 303 | 17 | 310* | 46* | 115* | 112* | 37 |

* Not equal to the sum of the figures above as some patients had multiple cultures

Fig 3.6 Miscellaneous Gram Positive Isolates (Jan1989–Dec1990)



isolated with respect to their mean birth weights or the wards to which they were admitted. Most of these miscellaneous GPB isolates were obtained at birth from babies admitted to the TCU or wards 66/67 (73,2%). However, this was probably just a reflection of the larger numbers of babies on whom blood cultures were taken as these GPB were isolated from 4,4% (46/1043) of the babies admitted to the ICU with suspected congenital infection, and in 6,8% (115/1700) of those admitted to the TCU, 4,6% (112/2400) of those admitted to wards 66/67 and 3,8% (37/970) of those who died in the LW or were cultured for PROM or offensive liquor but sent to their mothers. The latter three figures are estimates as the exact numbers of these babies suspected of having a congenital infection for 1989 are not known. The two patients from whom Listeria Monocytogenes were isolated both required admission to the ICU and demised.

**3.2.2** Associated Cultures Eleven (18,6%) of the patients from whom S. aureus was isolated, 16 (17,9%) of those with S. epidermidis, 8 (10,8%) with α haemolytic Streptococci, 8 (27,5%) with E. faecalis and 3 (7,9%) with Corynebacteria spp had other organisms isolated from them at the same time. None of the babies from whom Bacillus spp were isolated had another organism cultured at the same time. These other organisms were cultured from 28 patients and consisted of 8 isolates of Pseudomonas spp, 7 of E. coli, 4 anaerobic bacteria, 2 each of Acinetobacter spp, Serratia spp and GBS, and one each of

was isolated at the same time from an additional 9 babies. Thus, 37/310 (11,9%) of the babies from whom these miscellaneous GPB were cultured at birth grew other organisms from the same specimen, a significantly higher proportion than that of the babies with GBS isolated at birth (5/141) (P=0,02).

3.2.3 Mortality Seventeen (19,1%) of the babies from whom S. epidermidis was isolated died, 9 (12,2%) of those with α haemolytic Streptococci, 8 (13,5%) with S. aureus, 1 (2,6%) with a Corynebacteria spp, 6 (21,4%) with Bacillus spp and 3 (10,7%) with E. faecalis. Only 2 (3,3%) of the S. aureus and 12 (20,3%) of the S. epidermidis isolates were susceptible to penicillin, the antimicrobial with which these babies were treated. All of the other GPB isolates except two of the Bacillus spp and α haemolytic Streptococci, and 7 of the E. faecalis were susceptible to penicillin. They were all susceptible to vancomycin. Forty-nine (86,0%) of the 57 babies from whom penicillin-resistant S. aureus was isolated at birth survived despite only receiving that drug; 62 (80,5%) of the 77 babies from whom penicillin-resistant S. epidermidis was isolated and 6 (85,7%) of the 7 from whom penicillin-resistant E. faecalis was isolated also survived.

## 4. CONGENITAL GRAM NEGATIVE INFECTIONS

### 4.1 Occurrence

The number of GNB isolates obtained from babies within the first three days of life and the wards into which these babies were admitted are shown in table 3.14. None of the organisms

**Table 3.14 Congenital Gram Negative Isolates**

| Organism | Blood | CSF | Patients | ICU | TCU | 66/67 | LW |
|---|---|---|---|---|---|---|---|
| Serratia | 42 | - | 42 | 19 | 20 | 3 | - |
| Pseudomonas | 34 | - | 34 | 10 | 18 | 6 | - |
| Klebsiella | 27 | 1 | 28 | 11 | 15 | 2 | - |
| E.coli | 27 | 1 | 28 | 9 | 11 | 7 | 1 |
| Enterobacter | 6 | 1 | 7 | 2 | 3 | 1 | 1 |
| Acinetobact. | 5 | 1 | 6 | 3 | 3 | - | - |
| Proteus | 3 | - | 3 | - | 2 | 1 | - |
| Total | 144 | 4 | 147* | 53* | 72 | 20 | 2 |

* Not equal to the sum of the figures above as more than one organism isolated from one patient

**Table 3.15 Congenital Escherichia Coli Bacteraemia by Birth Weight**

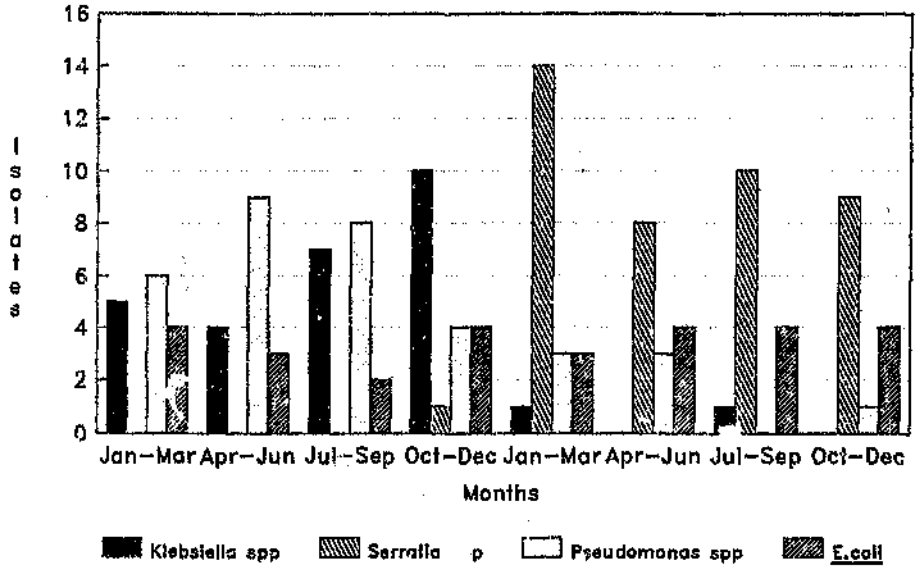
| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | - | 4(,9) | - | - | 5(1,6) | 9(,8) |
| TCU | - | 5(,6) | 3(,4) | 1(,2) | 2(,3) | 11(,4) |
| 66/67 | - | - | 3(,2) | 2(,2) | 2(,2) | 7(,1) |
| LW | - | - | - | - | 1(,05) | 1(,6) |
| Total | - | 9(,8) | 6(,3) | 3(,3) | 10(,4) | 28(,4) |

Figures in parenthesis = % admissions which had E. coli bacteremia at birth

cultured from the CSF had a corresponding positive blood culture. Once again, there appeared to be "epidemics" in the number of isolates obtained of the various organisms (see fig. 3.7). All the Klebsiella isolates obtained at birth except for two occurred in 1989; all the Serratia isolates except one occurred in 1990, coinciding with an outbreak of nosocomially acquired Serratia septicaemia; 79,4% (27/34) of the Pseudomonas isolates occurred in 1989, surprisingly not coinciding with an outbreak of nosocomial Pseudomonas septicaemia (see below). Isolates of E. coli, however, were obtained regularly throughout the two year study period and the numbers of the remaining GNB organisms were too small to note any changes in incidence.

The mean birth weight of babies from whom GNB were isolated at birth was 2146+/-850g (median 2063g, range 880-4770g) and the male to female ratio 1,5:1. Unlike the GPB isolated from cultures taken at birth, most (125/147) (85,0%) of the GNB isolates were obtained from babies admitted to the high care areas cf. 162/311 (52,1%) (P<0,0001). In fact, GNB were isolated from 5,1% (53/1043) of babies admitted to the ICU with suspected congenital infection, from 4,2% (72/1700) of those admitted to the TCU and only 0,8% (20/2400) of those admitted to wards 66/67 (P<0,001). Very few GNB were isolated at birth from babies that died in LW or from those cultured at birth for PROM or offensive liquor but who were otherwise well and sent to their mothers.

Fig 3.7 Congenital Gram Negative Isolates (Jan1989–Dec1990)



Other organisms were cultured at the same time as the GNB from 4 of the babies with Klebsiella isolates (14,3%), from 3 with Serratia (7,1%), 9 with Pseudomonas (26,4%), 9 with E. coli (32,1%), 2 of the 3 with Proteus and 2 of the 6 with Acinetobacter isolates. These other organisms consisted of 7 isolates each of S. aureus and S. epidermidis, 6 of E. faecalis, 4 of GBS, 3 of α haemolytic Streptococci and one Corynebacteria spp from amongst 26 babies. Two GNB organisms were isolated at the same time from one other baby. Thus, 27/147 (18,4%) of the babies from whom GNB organisms were cultured had multiple isolates, a similar proportion as found with the miscellaneous GPB obtained at birth (37/311) (11,9%) and also significantly higher than that found in the babies from whom GBS were isolated (5/141) (3,5%) (P=0,0001).

## 4.2 Congenital E. coli Septicaemia

The wards to which the babies from whom E. coli were cultured at birth were admitted are reflected in table 3.15. E. coli was isolated from only 0,4% (28/6939) of the admissions to the Unit, the highest incidences being amongst babies with birth weights <1500g and babies admitted to the ICU. Eleven of the babies from whom E. coli were cultured died giving a mortality of 39,3%. All, except for two, were babies with birth weights below 2000g.

## 4.3 Susceptibility Patterns

As can be seen from table 3.16, most of the GNB organisms cultured at birth were multiresistant organisms, especially

**Table 3.16 Percentage Resistance of Congenital Gram Negative Organisms**

| Organism | am | t | g | ak | cf | ct | ch | co | pi | i |
|---|---|---|---|---|---|---|---|---|---|---|
| Klebsiella | 100,0 | 85,7 | 78,5 | 3,6 | 64,2 | 32,1 | 46,4 | 46,4 | 96,4 | 3,6 |
| Pseudomonas | 100,0 | 88.2 | 91,2 | 73,5 | 97,1 | 35,3 | 76,5 | 97,1 | 38,2 | 26,5 |
| Serratia | 100,0 | 97,6 | 9,5 | 14,3 | 95,2 | 9,5 | 7,1 | 95,2 | 92,8 | 0 |
| E. Coli | 60,7 | 7,1 | 17,8 | 0 | 3,6 | 0 | 7,1 | 7,1 | 53,8 | 0 |
| Enterobacter | 100,0 | 57,1 | 57,1 | 14,2 | 57,1 | 14,3 | 71,4 | 57 1 | 57,1 | 0 |
| Acinetobacter | 83,3 | 83,3 | 33,3 | 50,0 | 66,6 | 16,6 | 50,0 | 100,0 | 16,6 | 16,6 |
| Proteus | 33,3 | 0 | 0 | 0 | 33,3 | 33,3 | 33,3 | 33,3 | 0 | 0 |
| Total | 90,5 | 46,6 | 45,9 | 22,3 | 62,8 | 25,6 | 35,8 | 66,9 | 67,6 | 6,8 |

the Pseudomonas isolates. Only the E. coli and Proteus isolates showed some susceptibility to ampicillin. 54,1% (80/148) of the GNB isolates were susceptible to gentamicin, the antimicrobial that used to be prescribed for suspected congenital infections, though 82,2% (23/28) of the E. coli isolates were susceptible to this drug. There was a 24,3% (36/148) resistance to amikacin, the antimicrobial used at present to cover for GNB organisms.

### 4.4 Mortality

In addition to the deaths of the babies from whom E. coli was isolated at birth, 11 (39,3%) of the babies with Klebsiella, 9 (21,4%) with Serratia, 10 (29,4%) with Pseudomonas, and 2 (28,6%) with Enterobacter spp died. One of the three babies with Proteus isolated at birth died and two of the six with Acinetobacter. Interestingly, more babies died who were on appropriate than inappropriate therapy; 57,1% (4/7) from whom Pseudomonas and 46,1% (6/13) from whom Klebsiella was cultured and on appropriate therapy vs. 22,2% (6/27) and 33,3% (5/15) respectively on inappropriate antimicrobials (P=N/S). None of the 6 from whom Serratia was cultured who were not treated with appropriate antimicrobials died. Only one of the patients with E coli bacteraemia was on inappropriate antimicrobials and he died.

## 5. CONGENITAL ANAEROBIC BACTERIA

### 5.1 Occurrence

Anaerobic bacteria were isolated 42 times from the blood, the

**Table 3.17 Babies with Anaerobes Isolated at Birth by Birth Weight**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | - | 1(1) | 1(1) | - | 2(1) | 4(3) |
| TCU | 2(1) | 5(3) | 3 | 1 | 2 | 13(4) |
| 66/67 | - | 1 | 2 | 2 | 6 | 11 |
| LW | - | 1(1) | - | - | 13 | 14(1) |
| Total | 2(1) | 8(5) | 6(1) | 3 | 23(1) | 42(8) |

Number in parenthesis = number of babies that died

wards to which the babies from whom these cultures were obtained were admitted being depicted in table 3.17 together with the number that died in parenthesis.

The mean birth weight of the babies from whom anaerobic bacteria were isolated at birth was 2415+/-976g (median 2014g, range 580-4570g) and the male to female ratio 1,3:1. Most of the anaerobic bacteria cultured at birth were from babies with birth weights >2499g, 23/42 (54,8%) and, as babies with this birth weight only made up 35,7% (2476/6939) of the total number of babies admitted, this finding is significant (P= 0,01). Equally, a significantly larger proportion of the isolates were obtained from well babies cultured for PROM or offensive liquor and sent to their mothers, 13/42 (31,0%), as there were only about 400 of these babies per year (P<0,0001).

Another organism was cultured at the same time as the anaerobe in five (11,9%) of these babies, a similar proportion as that found for the GNB isolated at birth (see above) and higher than that found for the GBS, 5/141 (3,5%) (P=0,05). These other organisms consisted of 2 isolates of S. epidermidis and one each of S. aureus, $\alpha$ haemolytic Streptococci and Pseudomonas spp.

## 5.2 Mortality

Eight of the babies from whom anaerobic bacteria were cultured died, a mortality of 19,0%. The mortality amongst the babies admitted to the ICU was 75,0% (3/4), significantly higher than that for the remaining babies, 5/38 (13,2%) (P=0,02).

Equally, that for babies with birth weights <1500g was 60,0% (6/10), also significantly higher than that for the bigger babies, 6,3% (2/32) (P=0,0009).

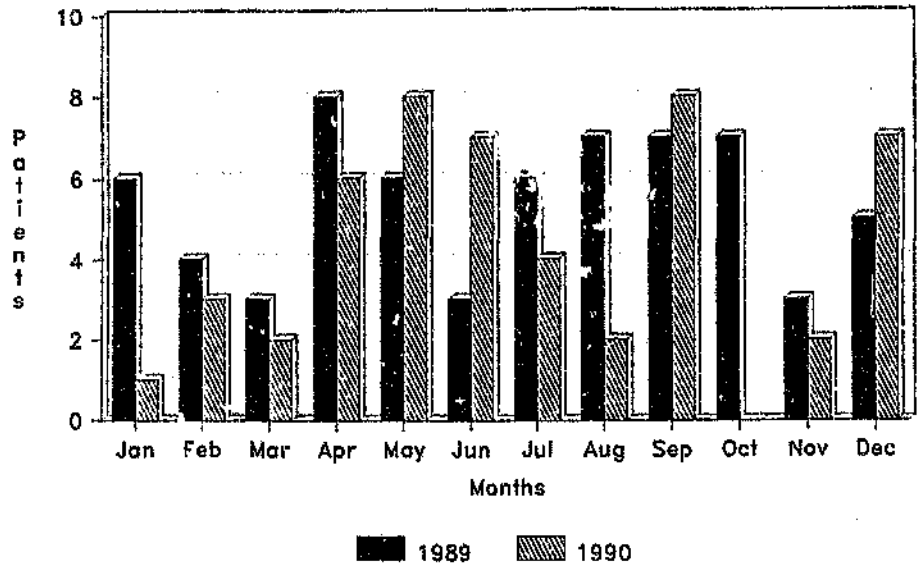
## 5. GRAM NEGATIVE NOSOCOMIAL INFECTIONS

### 6.1 Klebsiella spp

**6.1.1** Occurrence Klebsiella septicaemia was the most common cause of nosocomial GNB infection in the Neonatal Unit making up 46,1% of all hospital acquired GNB isolates (see below). Ther . were 122 isolates of Klebsiella spp from the blood taken from babies older than three days over the two year period, and 14 from the CSF, 5 of them occurring in patients without a positive blood culture. Thus, there were a total of 131 individual episodes of nosocomial Klebsiella septicaemia during the two years of study occurring in 115 patients, 14 patients having Klebsiella spp with different susceptibility patterns isolated from them more than once.

The male to female ratio was 1:1,1. As can be seen from fig. 3.8, there appeared to be a seasonal variations; 72 (62,6%) of the 115 babies with nosocomial Klebsiella septicaemia developed their infection during the winter months. This was significant, as the admission numbers to the unit showed no such seasonal variations, 3 457 (51,0%) of the total of 6 772 admissions occurring during the winter months (P=0.02). There were fewer patients with nosocomial Klebsiella septicaemia in 1990 than 1989, 50 vs. 65 cases respectively, but this difference was not significant. The mean age at which the babies

Fig 3.8 Nosocomial Klebsiella Septicaemia

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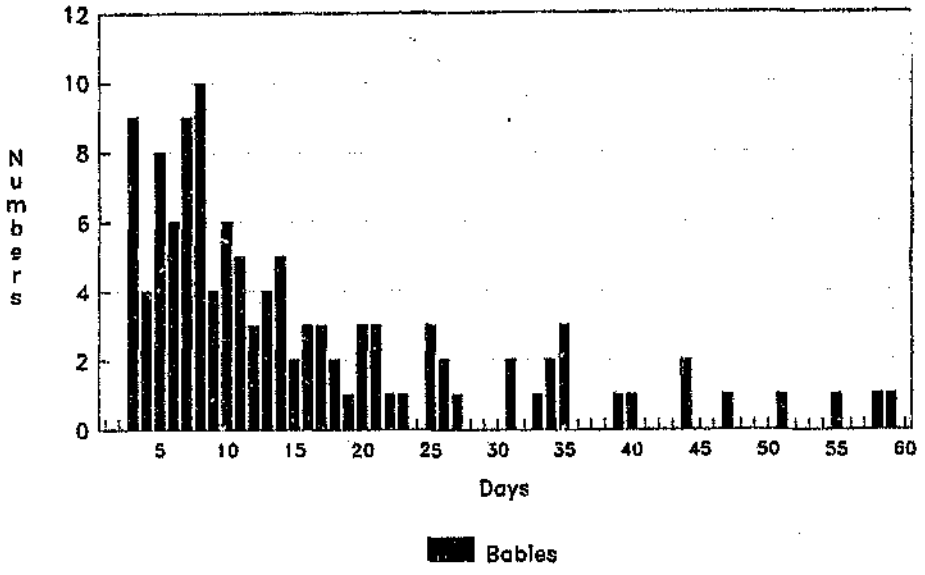
acquired Klebsiella septicaemia was 15,0+/-12,4 days (median 11 days, range 4-58 days) (see fig.9). The mean birth weight was 1591+/-715g (median 1350g, range 720-4000g). Table 3.18 shows the number of patients with acquired Klebsiella septicaemia in each weight category over the two year period, and the wards in which they became infected. It also shows in parenthesis the percentage of babies in each ward that survived for more than three days and then developed nosocomial Klebsiella septicaemia according to birth weight. 1,8% (115/6349) of all the admissions to the Unit older than three days developed Klebsiella septicaemia, the babies with the lower birth weights and those admitted to the ICU having the higher incidences; 10,0% (14/140) of babies with birth weights <1000g and 4,9% (44/899) of all ventilated babies developed Klebsiella bacteraemia. Most of the babies (85,2%) (98/115) with nosocomial Klebsiella septicaemia acquired their infections in the ICU or TCU. Babies admitted to wards 66/67 seldom acquired Klebsiella septicaemia.

There was a strong association between nosocomial Klebsiella infections and NEC, 22 babies with nosocomially acquired Klebsiella septicaemia (19,1%) had suspected and 32 (27,8%) had proven NEC; 9 (7,8%) additional babies had been put onto parenteral nutrition, 4 for other surgical abdominal problems and 5 for other reasons. As there were only 114 cases of proven and 197 cases of suspected NEC over this two year period amongst the 6 349 babies that survived beyond three days, and an additional 69 babies placed on parenteral

Fig 3.9 Age of Babies with Nosocomial Klebsiella Septicaemia




57f

**Table 3.18 Patients with Nosocomial Klebsiella Septicaemia by Birth Weight**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | 2(14,3) | 18(5,1) | 14(6,7) | 6(4,6) | 4(2,6) | 44(4,9) |
| TCU | 12(8,9) | 22(2,7) | 13(1,9) | 1(,2) | 6(,8) | 54(1,9) |
| 66/67 | - | 8(1,0) | 5(,2) | 1(,1) | 3(,1) | 17(,3) |
| Total | 14(10,0) | 48(4,9) | 32(1,7) | 8(,7) | 13(,6 ) | 115(1,8) |

Figures in parenthesis = % survivors after 3 days who developed Klebsiella septicaemia

**Table 3.19 Risk Factors for Acquiring Klebsiella Septicaemia**

| | Data | P value | O.R. | 95% C.L. |
|---|---|---|---|---|
| Sex: M vs. F | 55/3463:60/2886 | 0,14 | 0,76 | 0,52-1,12 |
| Seasons: Winter vs. Summer | 72/3457:43/3315 | 0,02 | 1,61 | 1,09-2,40 |
| Weight: <1,5Kg vs. 1,5-2,5Kg | 62/1123:40/2949 | <0,0001 | 4,25 | 2,79-6,49 |
| " 1,5-2,5Kg vs. >2,5Kg | 40/2949:13/2277 | 0,005 | 2,39 | 1,24-4,72 |
| Wards: ICU vs. TCU | 44/899:54/2794 | <0,0001 | 2,61 | 1,71-3,99 |
| " TCU vs. 66/67 | 54/2794:17/5918 | <0,0001 | 6,84 | 3,85-12,28 |
| NEC: Proven vs. suspected | 32/114:22/197 | 0,0002 | 3,10 | 1,63-5,93 |
| " Suspected vs. none | 22/197:61/6038 | <0,0001 | 12,32 | 7,16-21,06 |
| Parenteral nutrition vs. none | 63/380:52/5969 | <0,0001 | 22,61 | 15,14-33,80 |
| Fungal infection vs. none | 25/112:90/6237 | <0,0001 | 19,63 | 11,65-32,89 |

nutrition for other reasons, the association of Klebsiella septicaemia with these conditions was significant (P<0,0001).

A summary of the risk factors for acquiring Klebsiella septicaemia in Baragwanath's Neonatal Unit is shown in table 3.19. There was no difference in the incidences amongst the sexes but there was an increased risk of developing Klebsiella septicaemia the lower the birth weight and the higher the level of care the baby required. There was also a high risk amongst babies with NEC especially if this condition was proven, and amongst babies on parenteral nutrition even if not given for bowel pathology.

Other nosocomially acquired organisms were isolated from 48 (41,7%) of the patient with hospital acquired Klebsiella septicaemia: 25 (20,8%) patients had had or developed a fungaemia; 11 S. epidermidis, 7 Pseudomonas spp, 6 S. aureus and E. faecalis, 5 Enterobacter spp, 4 E. coli, 3 Citrobacter and Serratia spp, and 1 S. viridans were in addition isolated at some stage. In fact, 10 of the 131 Klebsiella isolates (7,6%) had other organisms isolated at the same time. Twenty-eight (60,8%) of the babies with multiple isolates were babies receiving parenteral nutrition (P=N/S).

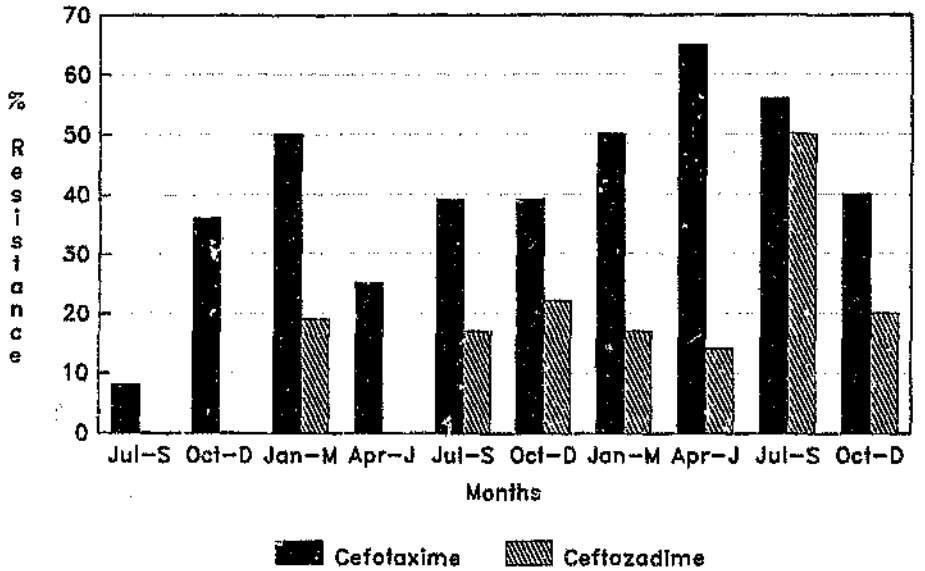
### 6.1.2 Susceptibility Patterns

a) The Cephalosporins: Resistance to cefotaxime amongst hospital acquired Klebsiella spp in Baragwanath's Neonatal Unit first appeared in the second half of 1988. Within the first three months of 1989, resistance to ceftazadime had also

developed, 3 of the 16 isolates being ceftazadime-resistant. Fig. 3.10 shows the percentage resistance amongst the Klebsiella isolates to these two cephalosporins over this time period. Data from the later half of 1988 are also included. As can be seen from this graph, no improvement ocurred in the susceptibility patterns of the Klebsiella spp to the cephalosporins despite withdrawing their use over a one year period from April 1989 to April 1990. Nine months prior to the change in antimicrobial policy, 20 of the 59 isolates (33,8%) were resistant to cefotaxime and 3 (5,1%) to ceftazadime; during the next year, 24 of the 67 (35,8%) isolates were resistant to cefotaxime and 9 (13,4%) to ceftazadime. These differences are not statistically significant. During the remaining nin months of 1990 when cephalosporins were used in selected cases, 25 of the 48 (52,1%) nosocomial Klebsiella isolates were resistant to cefotaxime and 13 (27,1%) to ceftazadime. The resistance to ceftazadime thus in fact increased significantly (P=0.003).

b) The Aminoglycosides: Only one Klebsiella isolate was identified as resistant to amikacin prior to the change to amikacin as sole aminoglycoside used in the Neonatal Unit. After the change, 25 of the 72 (34,7%) isolates were amikacin resistant (P<0,0001). The MIC's and MBC's of amikacin for these resistant Klebsiella isolates were >64µg/ml. Fig. 3.11 shows the changing susceptibility patterns of the nosocomial Klebsiella isolates to the two aminoglycosides. Though it appears that the resistance to gentamicin improved, this was

Fig 3.10 Cephalosporin Resistance
(Jul 1988–Dec 1990)



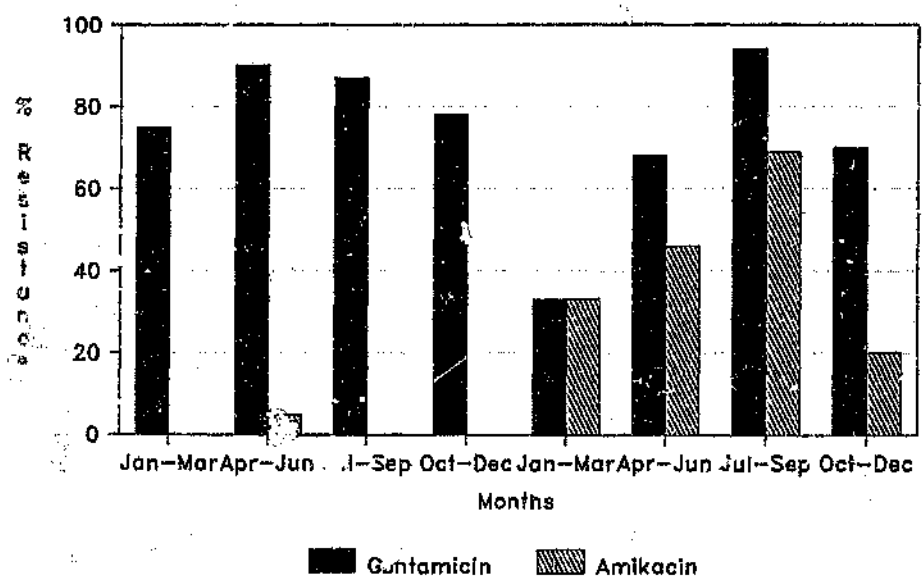
not confirmed statistically. In the first period 50 of the 59 (84,7%) Klebsiella isolates were resistant to gentamicin and in the second period 53 of the 72 (73,6%). The resistance to tobramycin, an aminoglycoside never used in the unit, prior to the change was significantly less than that due to gentamicin, 39/59 (66,1%) (P=0,02). The resistance to tobramycin during the second period did not change significantly, 41/72 (56,9%); in addition, the organisms still remained significantly more resistant to gentamicin than tobramycin (P=0,03).

The 26 Klebsiella isolates resistant to amikacin were generally multiresistant organisms: 8 (30,7%) were susceptible to cefotaxime, 14 (53,8%) to ceftazadime, 19 (73,1%) to chloramphenicol, 3 to tobramycin, and 2 each to gentamicin, piperacillin and cotrimoxazole. All however were susceptible to imipenem.

c)Other Antimicrobials: Sixty-two of the 131 nosocomial Klebsiella isolates were susceptible to chloramphenicol (47,3%), 23 to cotrimoxazole (17,6%) and 6 to piperacillin (4,6%). Three were resistant to imipenem and all except one to ampicillin.

**6.1.3** Mortality Sixty-five (56,5%) of the babies who had a nosocomial Klebsiella septicaemia died. However, it is often impossible to determine the exact cause of death in view of the multiple isolates in many of the patients and the co-existing medical conditions, for example, NEC, chronic lung disease, etc., which may have contributed to the patient's demise. Nevertheless, Klebsiella septicaemia almost certainly

Fig 3.11 Aminoglycoside Resistance
(Jan 1989–Dec 1990)



was a contributing factor in almost all of the deaths. The number of deaths for each weight category in the different wards are shown in table 3.20, as are these figures expressed as a percentage of the babies with nosocomial Klebsiella septicaemia in parenthesis. The highest mortality was amongst babies with birth weights <1000g, nearly all of those with Klebsiella septicaemia dying. Babies with birth weights of 1000g to 1499g requiring ventilation who developed nosocomial Klebsiella septicaemia had the second highest mortality of 66,6% (12/18). In fact, the mean birth weight of babies with nosocomial Klebsiella septicaemia that died was significantly lower than that of babies that survived, 1413+/-579g (median 1600g, range 720-3500g) vs. 1830+/-812g (median 1210g, range 780-4000g) respectively (P=0,0009).

Altogether, nosocomial Klebsiella septicaemia accounted for 13,3% (65/489) of all the deaths occurring after three days of age in the Neonatal Unit. It was responsible for a greater percentage of deaths amongst babies with lower birth weights, 16,2% (58/358) of deaths after three days of age amongst babies with birth weights <2000g vs. 5,3% (7/131) amongst the bigger babies (P=0,005). It was also responsible for a significantly smaller percentage of deaths amongst babies in the ICU compared to those in the TCU, 25/252 (9,9%) vs. 33/185 (17,8%) respectively (P=0,01). Even though deaths due to nosocomial septicaemia also appeared to account for a higher proportion of deaths after three days of age amongst babies in wards 66/67 compared to those in the ICU (7/45) (15,5%), this

**Table 3.20 Deaths due to Nosocomially Acquired Klebsiella by Birth Weight**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2500g | Total |
|---|---|---|---|---|---|---|
| ICU | 2(100) | 12(66,6) | 7(50,0) | 3(50,0) | 1(25,5) | 25(56,8) |
| TCU | 11(91,6) | 14(63,6) | 6(46,1) | 0 | 2(33,3) | 33(61,1) |
| 66/67 | 0 | 4(50,0) | 2(40,0) | 0 | 1(33,3) | 7(41,2) |
| Total | 13(92,8) | 30(62,5) | 15(46,8) | 3(37,5) | 4(30,7) | 65(56,5) |

Figures in parenthesis = % mortality of babies with Nosocomial Klebsiella Septicaemia

**Table 3.21 Percentage Deaths after Three Days due to Klebsiella**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2500g | Total |
|---|---|---|---|---|---|---|
| ICU | 40,0 (n=5) | 8,5 (n=141) | 17,1 (n=41) | 13,0 (n=23) | 2,4 (n=42) | 9,9 (n=252) |
| TCU | 18,0 (n=61) | 24,1 (n=58) | 23,1 (n=26) | 0 (n=18) | 9,1 (n=22) | 17,8 (n=185) |
| 66/67 | 0 (n=2) | 23,5 (n=17) | 28,6 (n=7) | 0 (n=5) | 7,1 (n=14) | 15,5 (n=45) |
| Misc. | - | - | - | 0 (n=3) | 0 (n=4) | 0 (n=7) |
| Total | 19,1 (n=68) | 13,8 (n=216) | 20,3 (n=74) | 6,5 (n=49) | 5,1 (n=82) | 13,5 (n=489) |

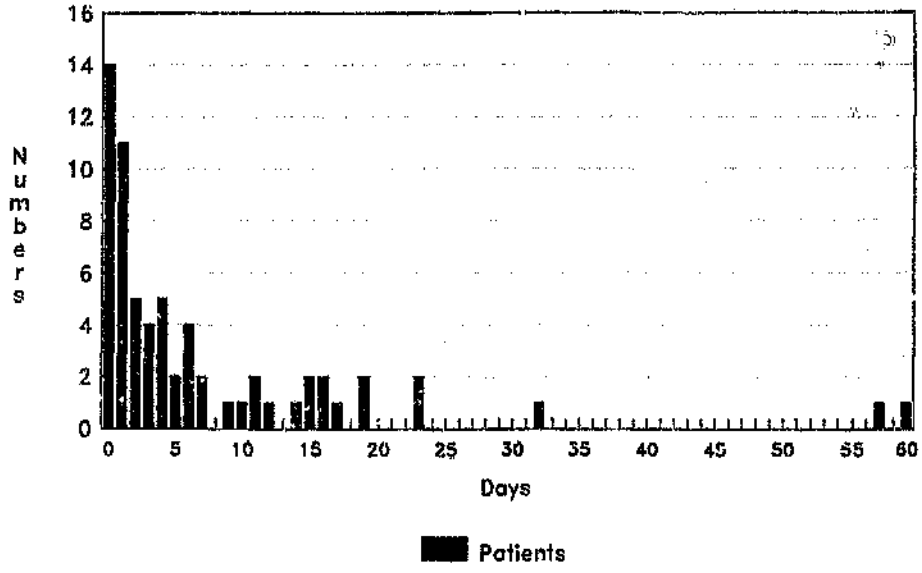
Figures in parenthesis = number of babies dying after 3 days of age

was not confirmed statistically (see table 3.21).

Klebsiella septicaemia can be a rapidly fatal disease, 25 (38,5%) of the deaths occurred within a day of the baby having been cultured for suspected sepsis (see Fig. 3.12). The mean interval from when Klebsiella spp was first isolated till the baby died was 7,6 days (range 0-66 days). The two babies that died 2 months after Klebsiella spp was isolated from them were babies with chronic lung disease following ventilation.

The association of NEC with nosocomially acquired Klebsiella septicaemia had a significantly higher mortality than in those babies without clinical bowel disease; of the 54 babies with either proven or suspected NEC who in addition had a nosocomially acquired Klebsiella septicaemia, 39 (72,2%) died, a significantly higher mortality than that of the remaining patients with nosocomial Klebsiella septicaemia and no bowel disease, 26/60 patients (43,3%) (P=0,005). However, if one analyses separately those babies with Klebsiella septicaemia and suspected or proven NEC, it is only in the latter where the death rate is significantly higher when compared to that of infected babies without bowel disease (P=0,002); 14 of the 22 (63,6%) babies with suspected NEC and Klebsiella septicaemia died, while 25 of the 32 (78,1%) babies with proven NEC and Klebsiella septicaemia died, these mortalities not being significantly different. The number of babies on parenteral nutrition for other reasons was too small to analyze. The percentage of babies with multiple nosocomial infections

Fig 3.12 Interval between Diagnosis of Klebsiella Septicaemia and Death



in addition to septicaemia due to Klebsiella spp who died appeared to be lower than that of babies who only had nosocomial Klebsiella septicaemia, 23/48 (47,9%) vs. 42/67 (62,6%) respectively. This difference however was not significant.

The mortality from nosocomial Klebsiella septicaemia prior to the change to amikacin as sole aminoglycoside used was 33/49 (67,3%) and following the change 32/66 (48,5%) (P=0.04). This decrease in mortality occurred despite an increase in amikacin resistance, the antimicrobial which was initiated in cases of suspected nosocomial sepsis. Of the 24 babies from whom amikacin-resistant Klebsiella spp was isolated who therefore would not have been commenced on appropriate antimicrobials, 15 died (62,5%). This was not statistically different from the mortality amongst babies with amikacin-susceptible Klebsiella isolates, 50/91 (54,9%).

There was no significant difference in the mortality after changing the empirical antimicrobial policy from amikacin and a cephalosporin to amikacin and vancomycin for suspected nosocomial infections. Of the 13 babies with nosocomial Klebsiella septicaemia prior to the change, 8 died (61,5%), whereas 52 of the 102 babies (55,8%) with the same infection died after the change. As the resistance to both amikacin and the cephalosporins increased during the study period, the original combination of amikacin and ceftazadime with which babies suspected of having a nosocomial infection were treated would not have been appropriate therapy in many. If one analyses

those patients in whom this combination would have been appropriate then 8/11 (72,7%) died prior to the change in policy and 33/69 (47,8%) after (P=0,2).

6.1.4 Meningitis Klebsiella spp was isolated from the CSF of 14 babies, i.e. 12,2% of those with nosocomial Klebsiella septicaemia had a meningitis due to that organism. The relevant patient details are given in table 3.22. Five of the babies with Klebsiella meningitis did not have a concomitant positive blood culture. The mortality for babies with nosocomial Klebsiella meningitis was 9/14 (64,2%), not significantly different when compared to the mortality of babies with nosocomial Klebsiella septicaemia without meningitis.

6.1.5 Multiple Isolates As mentioned previously, there were several patients with multiple Klebsiella isolates with different susceptibility patterns (see table 3.23). It appears that, on the whole, the organisms became more resistant as the antimicrobials failed to eradicate them; of the 11 patients with repeat isolates from the blood, 6 became more resistant to the cephalosporins and one less, 4 more resistant to aminoglycosides and 2 less. Klebsiella spp isolated from the CSF also often had different susceptibility patterns compared to that isolated from the blood; all four of the isolates from the CSF showing less resistance than those obtained from the blood.

6.1.6 Haematology The average WCC of the babies with nosocomially acquired Klebsiella septicaemia was 14 000+/-12 850/

**Table 3.22 Nosocomial Klebsiella Meningitis**

| Pt | Weight | Sex | Ward | Spec.date | Age(d) | B/C | Resistance | Died |
|---|---|---|---|---|---|---|---|---|
| T.M. | 1710 | M | ICU | 08/01/89 | 8 | Y | Ap,G,T,Co,Pi | Y |
| T.M. | 1530 | F | TCU | 22/01/89 | 51 | N | Ap,Co,Pi | Y |
| S.M. | 3660 | M | TCU | 08/03/89 | 14 | N | Ap,G,T,Cf,Pi | N |
| S.B. | 950 | M | TCU | 15/05/89 | 10 | Y | Ap,G,T,Co,Ch,Pi | Y |
| S.M. | 750 | F | TCU | 22/05/89 | 10 | Y | Ap,G,T,Co,Ch,Pi | Y |
| M.S. | 2900 | M | TCU | 30/05/89 | 40 | N | Ap,G,T,Co,Pi | N |
| T.M. | 1250 | F | TCU | 20/08/89 | 9 | Y | Ap,G,T,Co,Ch,Pi | Y |
| N.K. | 1950 | M | 66 | 02/12/89 | 34 | N | Ap,Co,Ch,Pi | N |
| L.T. | 1760 | M | 67 | 10/04/90 | 10 | N | Ap,Co,Pi | N |
| T.M. | 1950 | F | ICU | 08/06/90 | 17 | Y | Ap,G,Co,Ch,Pi | N |
| S.N. | 1320 | F | 66 | 09/06/90 | 6 | Y | Ap,Co,Pi | Y |
| T.T. | 880 | F | TCU | 29/06/90 | 7 | N | Ap,G,T,Ak,Co,Pi | Y |
| J.Z. | 820 | F | TCU | 25/07/90 | 13 | Y | Ap,G,Ak,Co | Y |
| P.M. | 1529 | M | ICU | 28/11/90 | 40 | Y | Ap,G,T,Ak,Cf,Ct,Co,P | Y |

**Table 3.23 Patients with Multiple Klebsiella Isolate**

| Pt. | Weight | Sex | Ward | Spec.date | Age(d) | Site | Resistance | Died |
|---|---|---|---|---|---|---|---|---|
| T.M. | 1710 | M | ICU | 04/01/89 | 4 | B | Ap,Co,Ch (Ak,Ct) | Y |
| " | " | " | " | 06/01/89 | 6 | B | Ap,G,T,Cf,Co,Ch,Pi | " |
| " | " | " | " | 08/01/89 | 8 | C | Ap,G,T,Co,Pi | " |
| I.S. | 2850 | M | ICU | 04/02/89 | 6 | B | Ap,G,T,Cf,Ct,Pi (Ak,Ct) | N |
| " | " | " | " | 12/02/89 | 14 | B | Ap,G,T,Cf,Ct,Co,Pi | " |
| N.B. | 1000 | F | TCU | 02/05/89 | 10 | B | Ap,G,Co,Pi (Ak,Ct) | Y |
| " | " | " | " | 08/05/89 | 16 | B | Ap,G,Co,Ch,Pi | " |
| " | " | " | " | 10/05/89 | 18 | B | Ap,G,T,Cf,Co,Ch,Pi | " |
| T.B | 1250 | M | TCU | 05/06/89 | 14 | B | Ap,G,T,Co,Ch,Pi (Ak,Ct) | N |
| " | " | " | " | 12/06/89 | 21 | B | Ap,Co,Ch,Pi | N |
| T.M. | 1250 | F | TCU | 20/08/89 | 9 | B | Ap.G,T,Cf,Co,Pi (Ak,Ct) | Y |
| " | " | " | " | 20/08/89 | 9 | C | Ap,G,T,Co,Ch,Pi | " |
| A.M. | 3010 | M | Wd66 | 24/08/89 | 8 | B | Ap,G,Co,Pi (Ak) | Y |
| " | " | " | " | 30/08/89 | 14 | B | Ap,G,T,Cf,Ct,Co,Pi | " |
| S.N. | 1750 | M | ICU | 29/08/89 | 8 | B | Ap,G,T,Cf,Ct,Ch,Pi (Ak) | N |
| " | " | " | " | 21/09/89 | 11 | B | Ap,G,T,Cf,Ch,Pi | " |
| T.G. | 1690 | M | ICU | 29/09/89 | 16 | B | Ap,T,Co,Pi (Ak,Ct) | Y |
| " | " | " | " | 02/10/89 | 19 | B | Ap,Cf,Co,Pi | " |
| S.M. | 1794 | M | ICU | 07/10/89 | 21 | B | Ap,G,T,Cf,Ch,Pi (Ak) | Y |
| " | " | " | " | 10/10/89 | 24 | B | Ap,G,T,Cf,Ct,Pi | " |
| D.M. | 1500 | F | TCU | 16/10/89 | 9 | B | Ap,G,T,Co,Ch,Pi,I (Ak) | N |
| " | " | " | " | 18/10/89 | 11 | B | Ap,G,T,Co,Ch,Pi | " |
| S.N. | 1320 | F | Wd66 | 09/06/90 | 6 | B | Ap,G,T,Ak,Cf,Co,Pi (Ct) | Y |
| " | " | " | " | 09/06/90 | 6 | C | Ap,Co,Pi | " |
| J.Z. | 820 | F | TCU | 25/07/90 | 13 | B | Ap,G,Ak,Co,Ch,Pi (Ak,Ct) | Y |
| " | " | " | " | 25/07/90 | 13 | C | Ap,G,Ak,Co,Pi | " |
| A.B. | 983 | F | TCU | 11/09/90 | 8 | B | Ap,G,T,Ak,Cf,Ct,Co,Pi (Ak,I) | Y |
| " | " | " | " | 20/09/90 | 17 | B | Ap,G,T,Ak,Cf,Ct,Co,Ch,Pi | " |
| M.C. | 2200 | M | ICU | 02/12/90 | 4 | B | Ap,G,T,Co,Ch,Pi (Ak) | Y |
| " | " | " | " | 31/12/90 | 33 | B | Ap,G,T,Ak,Cf,Ct,Ch,Pi | " |

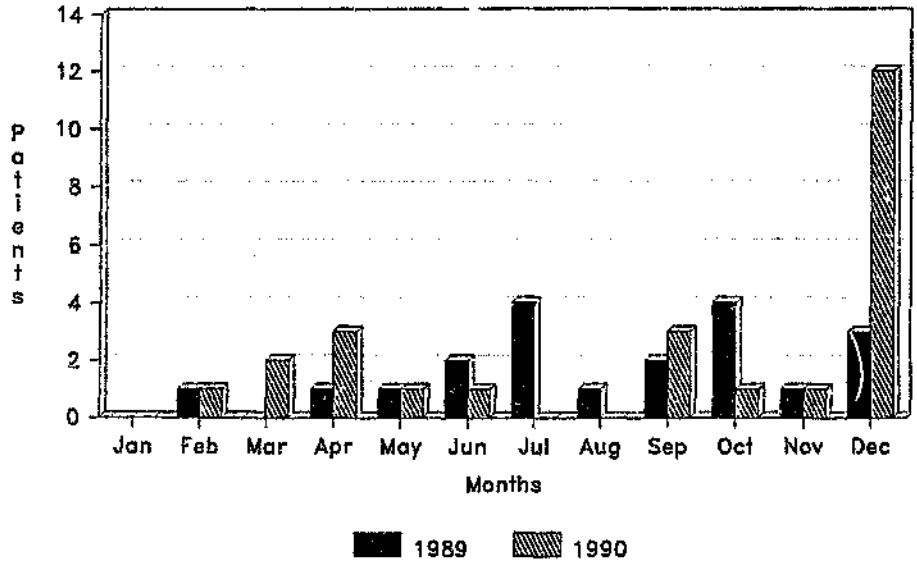
Letters in parenthesis = antimicrobials with which patient treated

ml (range 1 700-85 700/ml) and the platelet count 127 050+/-99 800/ml (range 3 000-471 000/ml). Only twenty (18,2%) of the 110 babies on whom FBC's were available had WCC's <5 000/ml and 13 (11,8%) >25 000/ml; 51 (46,4%) of these babies had platelet counts <100 000/ml. There were no significant differences when comparing the mean WCC's or platelet counts of babies with nosocomial Klebsiella septicaemia who survived to those that died (12 819+/-7 427/ml vs. 15 081+/-15 846/ml and 138 271+/-103 761/ml vs. 118 355+/-96 574/ml respectively).

**6.2** Pseudomonas spp

**6.2.1** Occurrence In contrast to nosocomial septicaemia due to Klebsiella spp, that due to Pseudomonas spp had a low background prevalence with only a few cases a month (see fig. 3.13). However, an outbreak of hospital acquired Pseudomonas septicaemia in December 1990 made it the second most common cause of nosocomially acquired GNB infections accounting for 17,9% of these isolates. Altogether there were 48 Pseudomonas isolates obtained from the blood of patients greater than three days old over the two year study period. It was also isolated from the CSF 4 times, 3 of them with concomitant blood cultures but only one of these having the same susceptibility pattern as that of the Pseudomonas spp isolated from the CSF. Three patients had Pseudomonas spp isolated from the blood more than once with different susceptibility patterns

Fig 3.13 Nosocomial Pseudomonas Septicaemia



(see below). Thus, 45 babies had Pseudomonas spp cultured from their blood/CSF over the two years with a total of 51 individual isolates.

The mean age of the babies from whom Pseudomonas spp was cultured was 13,8+/-10,9 days (median 11 days, range 4-44 days). The male to female ratio was 1:1,4 and the mean weight 1472+/-658g (median 1260g, range 760-3950g). Table 3.24 shows where the babies were thought to acquire Pseudomonas sepsis according to their birth weights together with the numbers of babies that died reflected in parenthesis.

Most of the babies who apparently developed nosocomial septicaemia due to Pseudomonas spp were in the 1000g to 1499g weight category and from the ICU, the latter accounting for 28/45 (62,2%) of the cases. This is significantly higher than the proportion of Klebsiella septicaemia acquired in that unit, 44/115 (38,3%) (P=0,006). Pseudomonas spp was cultured from 0,7% (45/6349) of the admissions to the ICU who survived for more than three days.

A significantly smaller proportion of babies from whom Pseudomonas spp was cultured had associated proven NEC compared to those from whom Klebsiella spp was isolated, 2/45 (4,4%) vs. 32/115 (27,8%) (P=0,002). Eight (17,7%) had suspected NEC, a similar proportion as was found with the babies who acquired Klebsiella septicaemia, 22/115 (19,1%). In addition, 6 (13,3%) of the babies from whom Pseudomonas spp was isolated were on parenteral nutrition for reasons not related to

**Table 3.24 Patients with Nosocomial Pseudomonas Septicaemia by Birth Weight**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | - | 21(12) | 4(4) | 1(1) | 2(2) | 28(19) |
| TCU | 4(3) | 6(3) | 2(1) | - | 3(1) | 15(8) |
| 66/67 | - | 2(1) | - | - | - | 2(1) |
| Total | 4(3) | 29(16) | 6(5) | 1(1) | 5(3) | 45(28) |

Figures in parenthesis = number of babies who died

**Table 3.25 Patients with Multiple Pseudomonas Isolates**

| Pt. | Weight | Sex | Ward | Spec.date | Age(d) | Site | Resistance | Died |
|---|---|---|---|---|---|---|---|---|
| N.M. | 1250 | F | ICU | 26/07/89 | 6 | B | Ap,G,T,Ak,Cf,Ct,Co,Ch,Pi,I | N |
| " | " | " | " | 04/08/89 | 9 | B | Ap,G,T,Cf,Ct,Co,Ch,Pi,I (Ak,I) | " |
| K.H. | 1585 | M | ICU | 22/10/90 | 11 | B | Ap,G,Cf,Co,Ch | N |
| " | " | " | " | 27/10/90 | 16 | B | Ap,Cf,Ct,Co,Ch,Pi (Ak,Ct,I) | " |
| J.M. | 3950 | M | ICU | 29/11/90 | 4 | B | Ap,G,Cf,Co,Ch | Y |
| " | " | " | " | 30/11/90 | 5 | B | Ap,G,Cf,Co,Ch,Pi | " |
| " | " | " | " | 05/12/90 | 10 | B | Ap,Cf,Co,Ch,Pi (Ak,Ct) | " |
| B.M. | 1220 | F | ICU | 11/12/90 | 4 | B | Ap,Cf,Co,Ch | Y |
| " | " | " | " | 11/12/90 | 4 | C | Ap,G,Cf,Co,Ch (Ak,Cf) | " |
| K.M. | 1650 | M | ICU | 20/12/90 | 4 | B | Ap,G,T,Cf,Co,Ch | Y |
| " | " | " | " | 20/12/90 | 4 | C | Ap,G,T,Co,Ch (Ak) | " |

Letters in parenthesis = antimicrobial with which patient treated

gastrointestinal pathology, a higher proportion than that of those babies with nosocomial Klebsiella septicaemia (5/115) (4,3%) (P=0,07).

Twenty-two babies (48,8%) with bacteraemia due to Pseudomonas spp also had other nosocomially acquired organisms isolated from them at some stage. There were 8 isolates of a yeast, 7 of Klebsiella spp, 5 of S. aureus, 4 of S. epidermidis, 3 of other GNB and 2 each of Serratia spp and E. faecalis cultured amongst these patients. Of these, 4 were isolated from the same specimen as the Pseudomonas isolate, a similar proportion of multiple isolates as that observed for nosocomial Klebsiella isolates, 4/51 (7,8%) vs. 10/131 (7,6%) respectively.

6.2.2 Susceptibility Patterns Prior to the change in antimicrobial policy with respect to the aminoglycosides, 1/13 (7,7%) nosocomial Pseudomonas isolates was susceptible to gentamicin and 7 (53,8%) to amikacin. Following the change, 10/38 (26,3%) were susceptible to gentamicin and 32 (84,2%) to amikacin. As these changes are not significantly different, withholding the use of gentamicin did not seem to improve the susceptibility to that aminoglycoside and resistance to amikacin was apparently not induced. If anything, the susceptibility to amikacin appeared to have improved. If one adds data available from the second half of 1988, 14/27 (51,8%) Pseudomonas isolates were susceptible to amikacin prior to the policy change. The apparent improvement in amikacin susceptibility now becomes significant (P=0,01). However, there

still was no significant change in gentamicin susceptibility.

As expected, the nosocomial Pseudomonas isolates were very resistant to cefotaxime, only 4 of the 51 (7,8%) isolates being susceptible. The susceptibility to ceftazadime was much greater, 33 (64,7%) being susceptible. If data from the latter half of 1988 are included, resistance to ceftazadime increased significantly during the period when no cephalosporins were used, 2/15 (13,3%) vs. 12/23 (52,2%) (P=0,03). However, this resistance improved significantly during the remaining 9 months of the study period when only 6 of the 27 isolates (22,2%) were resistant to ceftazadime (P=0,02). The resistance patterns to cefotaxime did not change significantly during these different periods.

32/51 (62,7%) of the Pseudomonas isolates were susceptible to piperacillin but only 2 of them to chloramphenicol. None were susceptible to ampicillin or cotrimoxazole. Of the 12 isolates resistant to amikacin, 7 were susceptible to ceftazadime, piperacillin and imipenem, 4 to chloramphenicol and 2 to cefotaxime. There was a high degree of resistance to imipenem, 12/51 (23,5%); 7 of these were susceptible to amikacin and all were susceptible to ciprofloxicin. Five isolates were multiresistant being susceptible only to ciprofloxicin.

**6.2.3** Mortality Once again, it is difficult to know how many deaths were due to Pseudomonas septicaemia, especially in view of the fact that some of the cultures may have been contamin-

ants. Certainly, 3 of the babies from whom Pseudomonas spp susceptible only to ciprofloxicin was isolated survived despite never receiving ciprofloxicin. Also, one patient with a complex cyanotic congenital heart and in whom Pseudomonas spp was isolated from the blood probably died from the cardiac lesion rather than an acquired infection. Twenty-eight (62,7%) of all the babies from whom Pseudomonas spp was isolated died, see table 3. 24. However, the mortality was much higher if one only looks at the babies involved in the outbreak in December 1990 who were obviously septic, 10 of the 12 babies dying (83%), and this when the Pseudomonas isolates were all susceptible to amikacin! There were no significant differences in the mortalities of babies from whom Pseudomonas spp was isolated who had and those who did not have gastrointestinal pathology; 1 of 2 babies with proven NEC died and 6 of the 8 (75,5%) with suspected NEC vs. 21/35 (60,0%) of the remainder. Nor was there any difference in the mortalities of babies from whom only Pseudomonas spp was isolated or from whom multiple organisms were isolated in addition to Pseudomonas spp, 16/24 (66,6%) vs. 12/21 (57,1%) respectively.

**6.2.4** Meningitis All of the 4 babies with Pseudomonas spp isolated from the CSF died, 3 of the babies having been amongst those involved in the outbreak. However, only one of the spinal taps was associated with inflammatory cells, and the one in which there was a concomitant positive blood culture with the same resistance pattern was in fact a bloody tap.

**6.2.5** Multiple Isolates Clinical details of the 5 patients from whom Pseudomonas with different susceptibility patterns was isolated more than once are shown in table 3.25. Repeat isolates from the blood were obtained from 3 babies, all showed decreasing resistance to the aminoglycosides, and one increasing resistance to the cephalosporins. The isolate from the CSF of one of the babies who also had one from the blood showed less resistance to the cephalosporins, and another increased resistance to the aminoglycosides.

**6.2.6** Haematology The mean WCC of babies with acquired Pseudomonas septicaemia was 11 490+/-8 780/ml (range 1 000-37 300/ml) and the mean platelet count 146 120+/-117 400/ml (range 10 000-456 000/ml). Seven (16,3%) of the 43 babies from whom FBC's were available had a WCC <5 000/ml and 4 (9,3%) >25 000/ml. Twenty-one (48,8%) of these babies had platelet counts <100 000/ml. There was no difference in the WCC's between babies who died compared with those who survived. However, babies who died of nosocomial Pseudomonas septicaemia had a significantly lower mean platelet count than those that survived, 107 154+/-101 649/ml vs. 205 706+/-117 464/ml (P=0,005). Equally, those with platelet counts < 100 000/ml had a higher mortality rate, 18/26 (69,2%) vs. 3/17 (17,6%) of those with platelet counts >100 000/ml (P=0,005).

**6.3** Serratia spp

**6.3.1** Occurrence Serratia spp had been a rare isolate in the Neonatal Unit, only having been reported once in July 1988.

However, shortly after changing to amikacin as sole aminoglycoside, an outbreak of Serratia septicaemia occurred, see fig. 3.14. The index case was a premature baby in ward 66 who had spent some time in the TCU. He developed a fulminant septicaemia in October 1989 and was dead within 24 hours. This was followed in November 1989 by two cases of NEC in the ICU both of whom died of Serratia septicaemia. Altogether, Serratia spp was isolated 28 times from the blood and 4 times from the CSF, the latter occurring with concomitant blood cultures but different susceptibility patterns. These were isolated from 26 patients as there were 2 from whom Serratia spp, with different susceptibility patterns, was isolated from the blood twice, in both cases the second isolate having gained amikacin susceptibility (see below). Thus, there were 32 separate Serratia isolates over the two year period, accounting for 11,3% of the nosocomial GNB isolates. The majority of the cases occurred in the first half of 1990. The occurrence of an outbreak of apparent congenital Serratia bacteraemia coinciding with the outbreak of nosocomial Serratia septicaemia has already been alluded to (see above).

The male to female ratio of the babies who developed nosocomial Serratia septicaemia was 1,4:1 and the mean age was 19,6+/-12,9 days (median 20 days, range 4-58 days). The mean birth weight of these babies was 1519+/-1230g (median 1230g, range 944-4140g). The wards in which these babies according to their birth weights were thought to acquire their Serratia infection are depicted in table 3.26 together with

Fig 3.14 Nosocomial Serratia Septicaemia

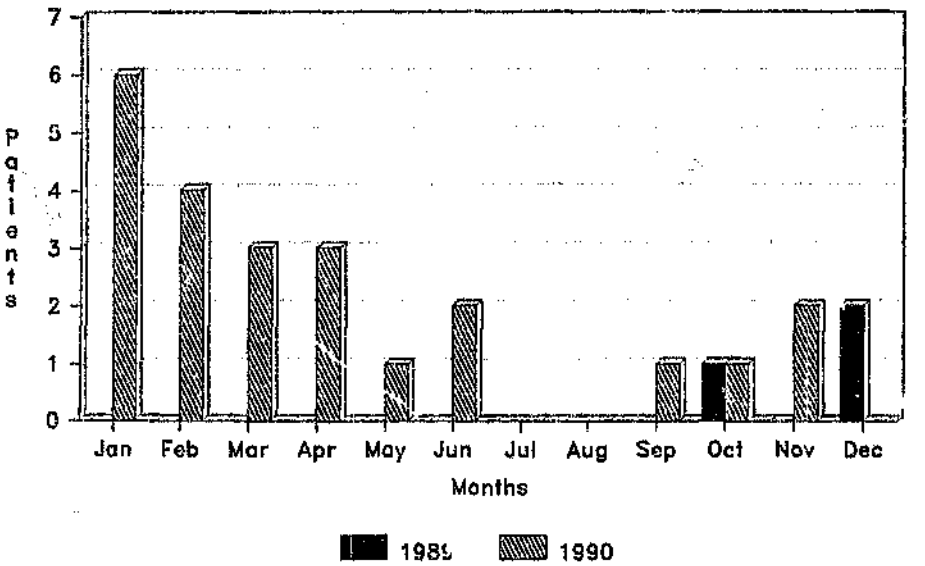


**Table 3.26 Patients with Nosocomial Serratia Septicaemia by Birth Weight**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | - | 11(6) | 5(1) | - | - | 16(7) |
| TCU | 2 | 2(1) | 1(1) | 1 | 2 | 8(2) |
| 66/67 | - | 2(1) | - | - | - | 2(1) |
| Total | 2 | 15(8) | 6(2) | 1 | 2 | 26(10) |

Figures in parenthesis = number of babies that died

**Table 3.27 Patients with Multiple Nosocomial Serratia Isolates**

| Pt. | Weight | Sex | Ward | Spec.date | Age(d) | Site | Resistance | Died |
|---|---|---|---|---|---|---|---|---|
| J.M. | 1500 | F | ICU | 11/01/90 | 9 | B | Ap,T,Ak,Co,Ch,Pi | Y |
| " | " | " | " | 11/01/90 | 9 | C | Ap,T,Ak, | " |
| T.D. | 1250 | F | ICU | 13/01/90 | 20 | B | Ap,T,Ak,Cf,Co | Y |
| " | " | " | " | 15/01/90 | 22 | C | Ap,G,T,Cf,Co,Ch,Pi | " |
| O.S. | 1020 | M | ICU | 07/02/90 | 35 | B | Ap,T,Ak,Cf,Co,Ch | N |
| " | " | " | " | 12/02/90 | 40 | B | Ap,T,Cf, | " |
| S.M. | 1100 | M | ICU | 10/04/90 | 24 | B | Ap,T,Cf,Ct,Co,Pi | Y |
| " | " | " | " | 26/04/90 | 40 | C | Ap,T,Co | " |
| J.B. | 3500 | M | TCU | 07/05/90 | 26 | B | Ap,T,Ak,Cf,Co,Ch,Pi | N |
| " | " | " | " | 21/05/90 | 50 | B | Ap,T,Cf,Ct,Co,Ch,Pi | " |
| V.K. | 1713 | M | ICU | 14/06/90 | 6 | B | Ap,T,Cf,Co,Pi, | N |
| " | " | " | " | 14/06/90 | 6 | C | Ap,G,T,Cf,Co,Pi | " |

the numbers that died. Most of the babies developed Serratia septicaemia in the ICU, 16/26 (61,5%). This is again a significantly higher proportion than that for nosocomial Klebsiella septicaemia, 38,2% (44/115) of which were acquired in the ICU (P=0,03). However, as with the nosocomial Klebsiella septicaemias, the babies were mostly in the 1000g to 1499g weight category. Altogether, 1,7% (16/899) of the babies aditted to the ICU who survived for more than three days developed nosocomially acquired Serratia septicaemia.

Once again, there appeared to be an association with bowel disease and hospital acquired Serratia septicaemia; 5 (19,2%) of the 26 patients had proven and 5 suspected NEC, and 2 (7,6%) were on parenteral nutrition for other reasons, similar proportions as were found amongst the babies with nosocomial Klebsiella septicaemia (see above).

Half of the babies with nosocomial Serratia septicaemia also had other nosocomial organisms cultured from them at some stage. There were 5 isolates of S. epidermidis, 3 each of Klebsiella spp and E. faecalis, 2 each of Pseudomonas spp, yeasts and Enterobacter spp, and 1 each of Acinetobacter spp, α haemolytic Streptococci, Citrobacter spp and Bacillus spp amongst these babies. Other organisms were cultured from the same specimen as 3 (9,3%) of the 32 Serratia isolates, a similar rate as that for other nosocomial GNB isolates.

**6.3.2** Susceptibility Patterns Of the 32 nosocomial Serratia isolates, 6 (18,7%) were susceptible to cefotaxime and 29

(91%) to ceftazadime. They showed a high degree of amikacin resistance, only 20 (62,5%) being susceptible; all were resistant to tobramycin. However, 28 (87,5%) were susceptible to gentamicin. All of the 12 isolates resistant to amikacin were susceptible to both gentamicin and ceftazadime and in addition, 3 were susceptible to cefotaxime. As far as the susceptibility to other antimicrobials was concerned, 16 (50,0%) of the Serratia isolates were susceptible to chloramphenicol, 6 to piperacillin and 4 to cotrimoxazole. All were susceptible to imipenem and none to ampicillin.

6.3.3 Mortality Ten (38,4%) of the babies with nosocomial Serratia septicaemia died, a lower mortality than that due to nosocomial Klebsiella septicaemia but not significantly so. Most of the deaths occurred amongst the babies with birth weights of 1000g to 1499g, 8 (53,3%) of the 15 dying. Seven (43,8%) of the 16 babies admitted to the ICU who developed nosocomial Serratia septicaemia died. All of the babies with proven NEC and Serratia septicaemia died and 3 of the 5 with suspected NEC. Once again, this difference in mortality amongst babies with nosocomial Serratia septicaemia and bowel disease as compared to the same infection but without bowel disease is significantly higher, 8/10 vs. 2/16 (P=0,001). The mortality of those from whom more than one organism was isolated was not significantly different from those from whom only Serratia spp was isolated, 4/13 vs. 6/13 respectively. There was no significant difference between the mortalities of babies with amikacin-resistant compared to those with amikacin

susceptible nosocomial Serratia isolates, i.e. between those commenced on inappropriate and those on appropriate therapy, 5/11 vs. 5/15 respectively. Of the 11 patients with amikacin-resistant nosocomial Serratia septicaemia, 4 died before their antimicrobials could be changed appropriately, 1 died despite changing the therapy and the remaining 6 survived once they had been put onto appropriate treatment.

**6.3.4** Meningitis As already mentioned, there were 4 cases of nosocomial Serratia meningitis over the two years, the details of these patients appearing in table 3.27, the susceptibility patterns of the organisms isolated from the CSF being different from those isolated from the blood. Three of the patients with nosocomial Serratia meningitis died.

**6.3.5** Multiple Isolates Table 3.27 displays some relevant details of those patients in whom Serratia spp was isolated after three days of age more than once with different susceptibility patterns. Repeat isolates from the blood occurred in two patients, one showed increasing resistance to the cephalosporins and both decreasing resistance to the aminoglycosides. All three CSF isolates were less resistant than those from the blood.

**6.3.6** Haematology The mean WCC of babies who developed Serratia septicaemia was 13 310+/-9 410/ml (range 3 300-39 200 /ml) and the mean platelet count 172 380+/-157 24 (range 9 000 -567 000/ml). Six babies (23,1%) had a WCC <5 000/ml and 3 > 25 000/ml, 12 (46,2%) had a platelet count <100 000/ml. Those

babies who died had a significantly lower mean platelet count than those that survived, 62 400+/-70 278/ ml vs. 241 125+/-158 561/ml respectively (P=0,01). Seven of the 12 babies with platelet counts <100 000/ml died. There was no difference between those that survived and those that died with regard to their WCC's.

6.4 Enterobacter spp

6.4.1 Occurrence Enterobacter spp was isolated 28 times from the blood and once from the CSF in 25 babies older than three days during the two year study period. The positive CSF culture was associated with two positive blood cultures but they all had different susceptibility patterns. Enterobacter spp with different susceptibility patterns were also isolated from blood from two additional babies. It accounted for 10,2% of all nosocomial GNB isolates.

There was no difference in the number of males who developed Enterobacter septicaemia compared to females. The mean age at which they became infected was 16,7+/-12,2 days (median 14 days, range 4-46 days). Their mean birth weight was 1595+/-654g (median 1600g, range 780-3230g). The incidence of GNB septicaemia due to Enterobacter spp was usually very low, though there appeared to be a small outbreak in December 1989 (see fig. 3.15). The wards in which the babies developed Enterobacter septicaemia according to their weight categories and the numbers that died are shown in table 3.28. 52% of the Enterobacter isolates were obtained from babies admitted to

Fig 3.15 Nosocomial Enterobacter Septicaemia

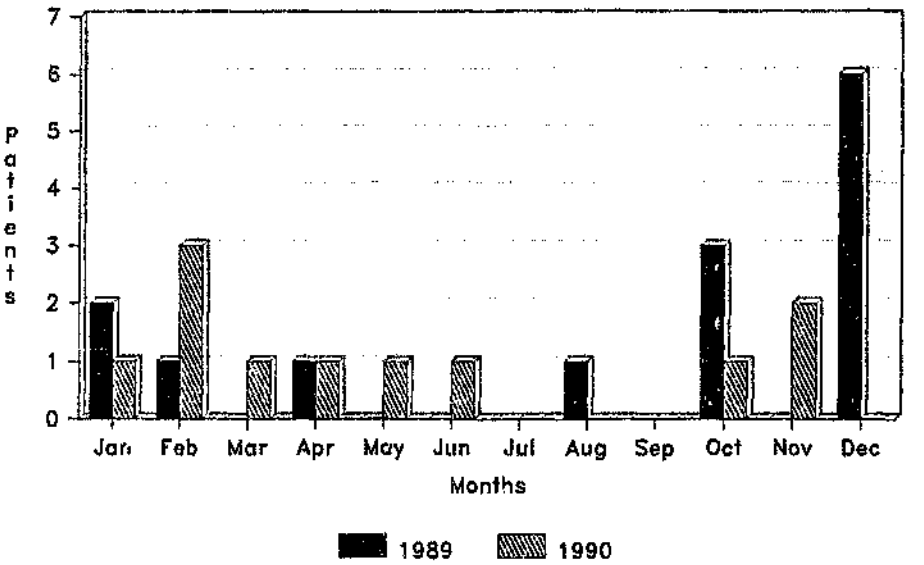



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**Table 3.28 Patients with Nosocomial Enterobacter Septicaemia by Birth Weigh**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2500g | Total |
|---|---|---|---|---|---|---|
| ICU | 1(1) | 6(5) | 4(4) | 1 | 1 | 13(10) |
| TCU | 2 | 3(3) | 1 | - | 2(1) | 8(4) |
| 66/67 | - | - | 3(1) | - | 1 | 4(1) |
| Total | 3(1) | 9(8) | 8(5) | 1 | 4(1) | 25(15) |

Figures in parenthesis = number of babies who died

**Table 3.29 Patients with Multiple Enterobacter Isolates**

| Pt. | Weight | Sex | Ward | Spec.date | Age(d) | Site | Resistance | Died |
|---|---|---|---|---|---|---|---|---|
| .M. | 1000 | M | ICU | 20/10/89 | 4 | B | Ap,G,T,Ak,Co,Ch | Y |
| " | " | " | " | 21/10/89 | 5 | B | Ap,G,T,Ak,Cf,Co,Ch | " |
| " | " | " | " | 21/10/89 | 5 | C | Ap,G,T,Pi | " |
| .M. | 1030 | M | ICU | 11/12/89 | 16 | B | Ap,T,Cf,Ct,Ch,Pi | Y |
| " | " | " | " | 11/12/89 | 16 | B | Ap,Co | " |
| .M. | 1390 | M | ICU | 29/12/89 | 31 | B | Ap,T,Co,Ch,Pi | N |
| " | " | " | " | 30/12/89 | 32 | B | Ap,T,Ak,Co,Ch,Pi | " |

the ICU; 1,4% (13/899) of the babies in that unit who survived for more than three days developed Enterobacter septicaemia.

There was a strong correlation between babies with nosocomial Enterobacter septicaemia and NEC, 9 of them (36,0%) having proven and 6 (24,0%) suspected NEC, similar proportions as those found amongst the babies with nosocomial Klebsiella septicaemia. In addition, one baby was on parenteral nutrition for an exomphalos post surgery.

In a high proportion of these babies other nosocomially acquired organisms were cultured at some stage, 17/25 (68,0%). Six isolates of yeast, 5 of Klebsiella spp, 4 of S. epidermidis, 2 each of Citrobacter spp, Serratia spp and S. aureus, and 1 E. faecalis, Acinetobacter spp and α haemolytic Streptococci occurred in these patients. In fact, other organisms were isolated at the same time as 10 (34,5%) of the 29 Enterobacter isolates. This is a significantly higher proportion when compared to all the previously mentioned nosocomially acquired GNB infections; 7,6% (10/131) of the nosocomial Klebsiella isolates grew other organisms at the same time (P=0,0002), 7,8% (4/51) of the Pseudomonas (P=0,005) and 9,3% (3/32) of the Serratia isolates (P=0,03).

**6.4.2** Susceptibility Patterns There were only 5 isolates of nosocomial Enterobacter spp during the study period prior to the change in antimicrobial policy with respect to the use of aminoglycosides, one of which was resistant to amikacin and two to gentamicin. The change in policy did not result in a

significant change in resistance pattern, 4 (16,7%) of the 24 isolates being resistant to amikacin and 8 to gentamicin. There still appeared to be no difference even if data from the second half of 1988 was included. Thus, altogether 17,2% (5/29) of the nosocomial Enterobacter spp were resistant to amikacin and 34,5% (10/29) to gentamicin.

Only 3 nosocomial Enterobacter isolates occurred before the change in cephalosporin usage. Using the data from the second half of 1988, none of the 15 isolates before April 1989 were resistant to either cefotaxime or ceftazadime. However, despite not using any of the cephalosporins from then on for a year, 8 of the 26 (30,7%) isolates obtained during the remainder of the study period were resistant to cefotaxime (P=0,02) and 6 (23,1%) to ceftazadime (P=0,04).

Nine (31,0%) of the isolates were susceptible to cotrimoxazole and piperacillin, 3 to ampicillin and 8 to chloramphenicol. All were susceptible to imipenem. Of the 5 Enterobacter isolates resistant to amikacin, all were susceptible to ceftazadime, 4 to cefotaxime, 3 to piperacillin and 1 each to cotrimoxazole and chloramphenicol. In addition, one isolate was resistant to amikacin but susceptible to gentamicin.

6.4.3 Mortality The mortality rate for babies with hospital acquired Enterobacter septicaemia was 60,0% (15/25), all the babies with bowel pathology and associated Enterobacter septicaemia except for one with suspected NEC dying. Thus, as none of the Enterobacter septicaemia without bowel disease

died, the correlation of bowel pathology with this infection and death was significant (P<0,0001). It is difficult to be certain that Enterobacter septicaemia was implicated in all the deaths in view of the fact that from so many of these babies other organisms were isolated in addition to the Enterobacter spp. Nevertheless, 8 of these babies were dead within a day of them having been cultured for suspected septicaemia. There was no significant difference in the mortalities between babies who only had Enterobacter spp isolated from them and those from whom more than one organism was isolated, 6/8 (75,0%) vs. 9/17 (52,9%) respectively. Nor was there any difference in the mortalities if the Enterobacter spp isolated was susceptible or resistant to amikacin, i.e. whether the baby was commenced on appropriate or inappropriate antimicrobials, 3/5 vs. 12/20. The one baby with Enterobacter meningitis died.

**6.4.4** Multiple Isolates Table 3.29 shows some relevant clinical details of the babies from whom Enterobacter spp with different susceptibility patterns was isolated more than once. Two isolates were obtained from the same specimen from one baby; in the remaining two babies the repeat isolates from the blood showed increasing resistance and the one isolate obtained from the CSF less resistance than that obtained from the blood.

**6.4.5** Haematology The mean WCC of the patients with acquired Enterobacter septicaemia was 10 750+/-6 270,/l (range 1 400-

25 500/ml) and their mean platelet count 92 730+/-92 730/ml (range 4 000-358 000/ml). Three of the 22 babies (13,6%) in whom FBC's were available had WCC's <5 000/ml and one >25 000/ml. Sixteen of these babies (72,7%) had platelet counts < 100 000/ml. There were no significant differences amongst those babies that died or those that survived with respect to their WCC's and platelet counts.

6.5 Escherichia coli

6.5.1 Occurrence There were 28 isolates of E. coli from the blood and 4 from the CSF in babies who survived for more than three days over the two year study period. Two of the CSF cultures also had concomitant blood cultures with the same susceptibility patterns. There were no patients in whom E. coli with different susceptibility patterns had been cultured more than once. Fig. 3.16 shows when the 30 babies developed their E. coli septicaemia. As can be seen, it was an uncommon cause of GNB nosocomial infections accounting for only 10,5% of these isolates. There were only one or two cases a month, but at the beginning of the second half of 1990 there appeared to be a small outbreak.

There were equal numbers of males to females. The mean age at which the babies developed nosocomial E. coli septicaemia was 15,3+/-10,8 days (median 10 days, range 4-52 days), and their mean birth weight 1893g (median 1599g, range 780-3900g). The wards where the babies were thought to acquire their E. coli septicaemia are depicted in table 3.30 together with the

Fig 3.16 Nosocomial E. Coli Septicaemi

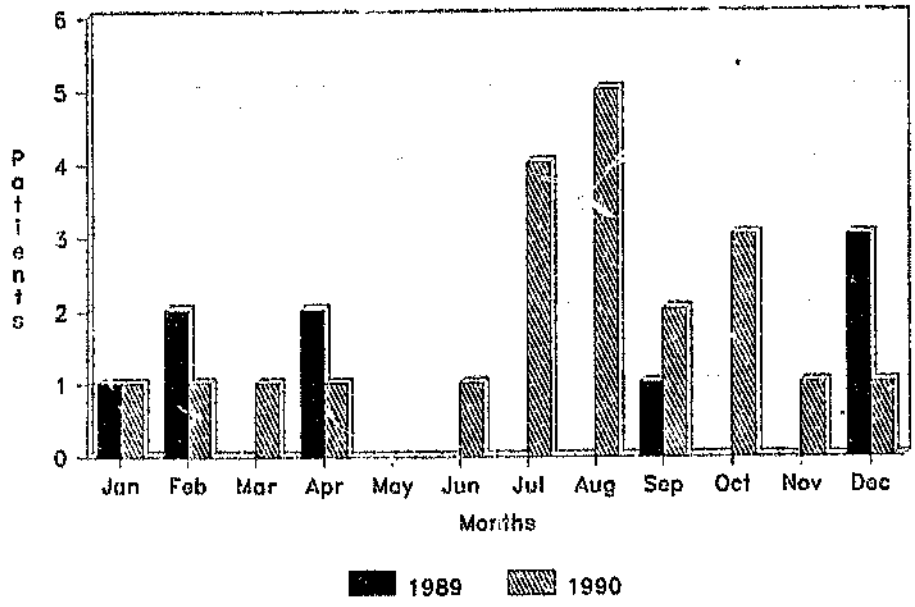


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**Table 3.30 Patients with Nosocomia. E. Coli Septicaemia by Birth Weight**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | - | 3(2) | 1(1) | - | - | 4(3) |
| TCU | 1 | 3(2) | 3(3) | 1 | 3(2) | 11(7) |
| 66/67 | - | 6(2) | 2 | 2 | 5(1) | 15(3) |
| Total | 1 | 12(6) | 6(4) | 3 | 8(3) | 30(13) |

Figures in parenthesis = number of babies that died

numbers that died. Once again, the highest number of nosocomial E. coli isolates occurred in babies with birth weights of 1000g to 1499g accounting for 40,0% (12/30) of all these infections. However, half of the babies appeared to acquire their infection in wards 66 or 67. This is not in keeping with the other hospital acquired GNB infections, the highest proportions of them occurring in babies admitted to the ICU. The proportion of babies who acquired E. coli septicaemia in the ICU, 4/30 (13,3%), is significantly less than the proportion of those who acquired Klebsiella sepsis in that ward, 44/115 (38,3%) (P=0,007).

Seven of the babies with nosocomial E. coli bacteraemia (23,3%) had proven and 2 suspected NEC; 1 was on parenteral nutrition following surgery for an exomphalos and 3 for other reasons.

Twelve (40,0%) of these babies had isolates of other organisms at some stage: 4 Klebsiella spp isolates, 3 each of a yeast, S. epidermidis and α haemolytic Streptococci, 2 E. faecalis and 1 each of S. aureus and Acinetobacter spp. Four of these (13,3%) were from the same specimen from which the E. coli was isolated.

5.5.2 Susceptibility Patterns Only one of the 30 nosocomial E. coli isolates was resistant to amikacin and that was isolated after the change in antimicrobial policy with regard to aminoglycoside usage. It was susceptible to the cephalosporins. There were 12 isolates (40,0%) resistant to genta-

micin, 10 of them occurring after gentamicin was no longer prescribed. Thus it would appear that nosocomial E. coli isolates were becoming more resistant to gentamicin. The numbers prior to the change in policy were too small to analyze, but using the data from the second half of 1988, 2 of the 16 nosocomial E. coli isolates (12,5%) were resistant to gentamicin prior to its withdrawal and 10/24 (41,6%) after (P=0,05).

Nosocomial E. coli isolates remained very susceptible to the third generation cephalosporins. Only two isolates were resistant to both cefotaxime and ceftazidime, one occurring before and one after the change in cephalosporin usage.

Six of the nosocomial E. coli isolates were susceptible to all antimicrobials including ampicillin, an additional 3 were susceptible to chloramphenicol, piperacillin and cotrimoxazole. All were susceptible to imipenem.

**6.5.3** Mortality Thirteen (43,3%) of the babies with nosocomial E. coli septicaemia died; 5 of them were babies with proven NEC. The two with suspected NEC also died. The mortality was thus significantly higher if the baby with nosocomial E. coli septicaemia also had bowel pathology (7/9) compared to babies with the same infection but without bowel disease (6/21) (P=0,02). Though it is impossible to be certain that the E. coli septicaemia was directly responsible for the deaths, 8 of the babies died within a day of the

E. coli septicaemia.

There was no difference in the number of babies who died from whom only E. coli was isolated compared to those from whom multiple organisms were isolated, 5/13 vs. 7/17 respectively. None of the four babies from whom E. coli was isolated in the CSF died.

**6.5.4** Haematology The mean WCC was 11 410+/-7 990/ml (range 1 800-29 000/ml) and platelet count 204 000+/-131 540/ml (range 17 000-509 000/ml). Eight of the 28 babies (28,5%) on whom FBC's were available had WCC's <5 000/ml and one >25 000/ml. Platelet counts <100 000/ml were obtained from 6 (21,4%) of these babies. There were no differences in the WCC's or platelet counts amongst babies who died compared with those who survived.

**6.6** Miscellaneous Nosocomial GNB Infections

A further 11 miscellaneous GNB were isolated over the study period from the blood of babies older than three days and 1 from the CSF, the latter having a concomitant blood culture. Relevant patient details and outcome are shown in table 3.31.

Two of these babies had proven and two suspected NEC; they all died. One was on parenteral nutrition for an exomphalos post surgery (the same baby from whom Klebsiella spp and E. coli were also isolated) and one for other reasons.

Other organisms were isolated from all except one of these babies at some stage, 5 (45,4%) from the same specimen, a

**Table 3.31 Patients with Miscellaneous Nosocomial GNB Septicaemia**

| Pt. | Weight | Sex | Ward | Spec.date | Age(d) | Site | Resistance | Died |
|---|---|---|---|---|---|---|---|---|
| a)Citrobacter spp | | | | | | | | |
| T.M. | 1650 | M | ICU | 20/10/89 | 4 | B | Ap,G,T,Ch,Pi | Y |
| M.M. | 1510 | F | TCU | 25/11/89 | 11 | B | Ap,Cf,Ct,Pi | N |
| J.B. | 3500 | M | TCU | 07/05/90 | 26 | B | Ap,G,T,Cf,Co,Ch,Pi | N |
| B.M. | 2310 | F | TCU | 02/09/90 | 23 | B | Ap,Ch | N |
| N.M. | 780 | F | TCU | 23/10/90 | 8 | B | Ap,Cf,Ct,Pi | N |
| b)Acinetobacter spp | | | | | | | | |
| K.M. | 1560 | M | ICU | 04/08/89 | 16 | B | Ap,G,T,Cf,Ct,Co,Ch,Pi,I | Y |
| T.M. | 1080 | F | ICU | 13/12/89 | 22 | B | Ap,Ak,Cf,Co,Ch,Pi | Y |
| c)Flavobacter spp | | | | | | | | |
| S.M. | 1000 | M | ICU | 07/11/89 | 13 | B | Ap,G,T,Co,Ch | Y |
| P.D. | 1080 | F | TCU | 29/12/89 | 10 | B | nil | Y |
| d)Proteus spp | | | | | | | | |
| S.M. | 2700 | F | ICU | 28/11/89 | 5 | B/C | nil | Y |
| T.M. | 1050 | M | ICU | 17/04/90 | 11 | B | Ap,G,T,Co,Ch,Pi | Y |

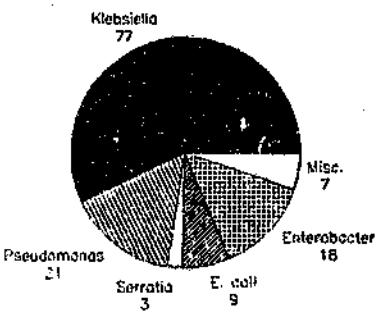
significantly higher proportion than amongst any of the other acquired GNB except Enterobacter spp. Only 10 (6,8%) of the 131 Klebsiella spp isolates had another organism cultured from the same specimen (P=0,0008). There were 3 isolates each of Enterobacter spp, Klebsiella spp and S. epidermidis, 2 each of Pseudomonas and Serratia spp, and 1 each of a yeast, E. coli and E. faecalis amongst these patients.

**6.7** Summary

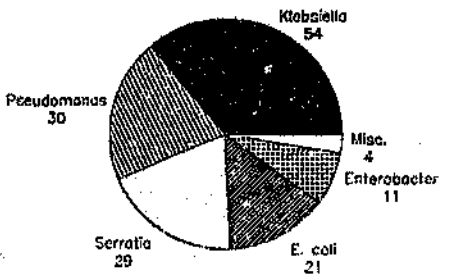
**6.7.1** Occurrence Thus, a total of 265 nosocomially acquired GNB isolates were obtained from the blood and 28 from the CSF during the two year period. Excluding CSF cultures that had matching blood cultures, there were a total of 284 GNB isolates from babies older than three days. As approximately 1500 blood cultures per year are sent from babies who have suspected nosocomial infections, this gives a yield of 8,8%. The yield is even lower (1,7%) for the CSF's sent for culture in that about 800 are sent per year. The breakdown of these organisms is given in table 3.32. As already mentioned, the most common cause of nosocomial GNB infections is that due to Klebsiella spp accounting for 46,1% (131/284) of all the isolates followed by Pseudomonas spp (51/284) (17,9%) with Serratia spp, E. coli and Enterobacter spp making up the remaining third.

As can be seen from fig. 3.17, Klebsiella spp became a less important cause of nosocomial infections accounting for 36,2% (54/149) of these isolates in 1990 compared to 57,0% (77/135)

## Fig 3.17 Nosocomial Gram Negative Septicaemia




1989




1990

**Table 3.32 Nosocomial GNB Isolates**

| Organism | Blood | CSF | Total | Patients |
|---|---|---|---|---|
| Klebsiella | 122 | 14 | 131 | 115 |
| Pseudomonas | 48 | 4 | 51 | 45 |
| Serratia | 28 | 4 | 32 | 26 |
| E. Coli | 28 | 4 | 30 | 30 |
| Enterobacter | 28 | 1 | 29 | 25 |
| Miscellaneous | 11 | 1 | 11 | 11 |
| Total | 265 | 28 | 284 | 222* |

* This does not equal the sum of the patients with individual organisms as more than one nosocomial GNB was isolated from 26 patients.

**Table 3.33 Patients with Nosocomial GNB Infections**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | 1(7,1) | 54(15,4) | 27(13,0) | 6(4,6) | 7(3,6) | 96(10,7) |
| TCU | 20(14,9) | 36(4,4) | 17(2,5) | 2(,5) | 14(1,8) | 88(3,1) |
| 66/67 | - | 17(2,1) | 10(,5) | 2(,2) | 9(,4) | 38(,6) |
| Total | 21 (15,0) | 107(9,7) | 54(2,9) | 10(,9) | 30(1,3) | 222(3,5) |

Figures in parenthesis = % survivors beyond 3 days with nosocomial GNB sepsis

in 1989 (P=0,0006), as did Enterobacter spp, 7,4% (11/149) vs. 13,3% (18/135) (P=N/S). Serratia spp became a common isolate in the second year accounting for 19,5% (29/149) of isolates in 1990 vs. 2,2% (3/135) in 1989 (P=<0,0001). E. coli accounted for 6,7% (3/135) of isolates in 1989 and 14,1% (21/149) in 1990 (P=0,0007).

These isolates occurred in 222 babies older than three days, 26 (11,7%) babies having more than one GNB isolated from them. This means that 3,5% (222/6349) of the babies admitted to the Neonatal Unit that survived for more than three days had culture proven nosocomial GNB septicaemias. The breakdown of the wards where these babies were thought to acquire these infections according to their birth weights is shown in table 3.33. These figures expressed as percentages of the admissions to a particular ward that survived for more than three days are also shown. If a baby had more than one nosocomial GNB infection, data for the first episode was analyzed. The babies with the highest number of nosocomial GNB cultures were those with birth weights of 1000g to 1499g admitted to the ICU, 54 of which became infected. These babies were also amongst those with the highest incidence of nosocomial GNB infections, together with babies <1000g, 15,4% (54/351) and 15,0% (21/140) respectively. Babies with birth weights of 1500g to 1999g admitted to the ICU also had a high incidence of acquired GNB infection of 13,0% (27/208). 48,4% (107/221) of all those babies with nosocomial GNB infections were those with birth weights of 1000g to 1499g. Babies with birth

weights >2400g seldom developed nosocomial GNB infections. 10,7% (96/899) of babies admitted to the ICU developed GNB septicaemia and 3,1% (88/2794) of those admitted to the TCU. Few babies acquired GNB septicaemia in wards 66/67.

The ratio of males to females was equal. The mean age at which these babies developed their hospital acquired GNB infection was 14,2+/-11,1 days (range 4-60 days), babies who developed Serratia septicaemia being older than those with Pseudomonas septicaemia, mean of 19,7+/-13,2 days vs. 13,5+/-11,0 days (P=0,02). The mean weight was 1606+/-727g (range 720-4140g), babies with acquired E. coli septicaemia being heavier than those with Klebsiella or Pseudomonas septicaemia, 1913+/-842g vs. 1594+/-718g and 1499+/-687g (P=0.02).

6.7.2 Association with Necrotising Enterocolitis The proportion of babies with proven NEC that also had proven GNB sepsis was much higher than that of those with suspected NEC, 40,6% (50/123) vs. 20,3% (40/197) respectively (P=0,001) (see table 3.34). These rates though are much higher than that of neonates without bowel disease, 132/6029 (2,2%) (p<0,0001). The proportion of babies with suspected NEC from who GNB were also isolated was greater the smaller the baby, 33,3% (7/21) of those with birth weights <1000g also having GNB sepsis and 6,7% (2/30) of those with birth weights >2499g (P=0,03). as for the babies with proven NEC, those with birth weights between 1500g to 1999g had the highest incidence of proven GNB sepsis, 53,3% (16/30).

**Table 3.34 Babies with Necrotising Enterocolitis and Nosocomial GNB Sepsis**

| NEC | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| Proven | 1(25,0) | 32(43,8) | 16(53,3) | 1(11,1) | 0 | 50(40,6) |
| ?NEC | 7(33,3) | 20(23,5) | 9(21,9) | 2(10,0) | 2(6,7) | 40(20,3) |

Figures in parenthesis = % babies with NEC that also have GNB

**Table 3.35 Patients with Bowel Disease and Gram Negative Infections**

| Organism | Total | Proven NEC n=123 | Suspected NEC n=197 |
|---|---|---|---|
| Klebsiella | 115 | 32 | 22 |
| Pseudomonas | 45 | 2 | 6 |
| Serratia | 26 | 5 | 5 |
| E. coli | 30 | 7 | 2 |
| Enterobacter | 25 | 9 | 6 |
| Miscellaneous | 11 | 2 | 2 |
| Total | 222* | 50* | 40* |

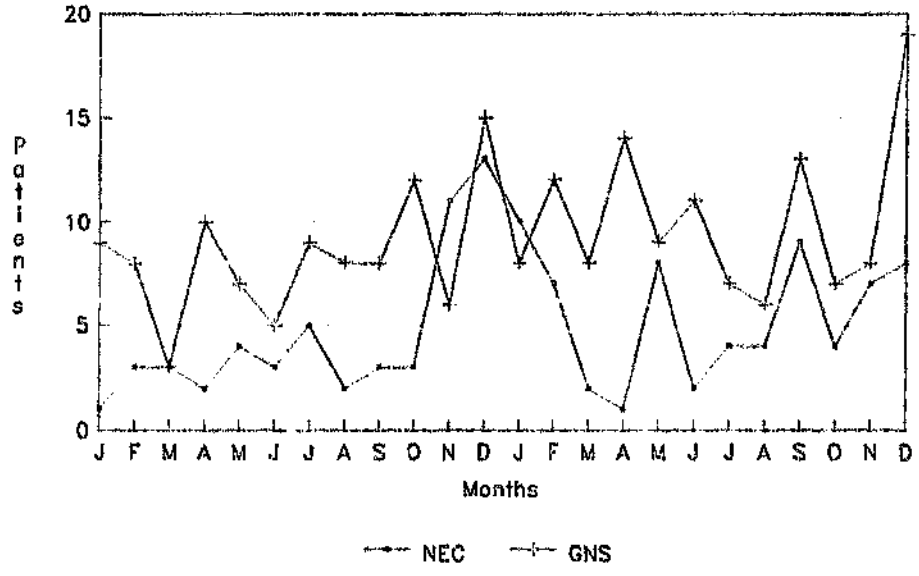
* This does not equal the sum of the individual organisms as more than one GNB was isolated from several patients

Table 3.35 shows the organisms that were isolated from these babies. Klebsiella spp were the most common, being isolated in 26,0% (32/123) of the cases of proven and 11,2% (22/197) of suspected NEC. The highest proportion of a nosocomial GNB infections associated with bowel disease was that due to Enterobacter spp, 36,0% (9/25) of patients with this infection having proven and 24,0% (6/25) suspected NEC, but this was not significantly higher than was found in patients with Klebsiella septicaemia, 27,8% (32/115) having proven and 19,1% (22/115) suspected NEC.

The number of cases of proven NEC and acquired GNB sepsis each month over the two year study period is shown in fig. 3.18. This shows a peak in the number of babies with NEC during December 1989 associated with an increase in GNB sepsis. The peak in the number of babies with GNB sepsis in December 1990 was mainly due to an outbreak of Pseudomonas septicaemia and was not associated with an obvious increase in cases of proven NEC.

There were no significant differences in the mean birth weights of those babies that had only proven NEC compared to those with the same pathology but with associated nosocomial GNB septicaemia, though the latter tended to be smaller (1574+/-621g vs. 1394+/-298g respectively). Likewise, those with suspected NEC and nosocomial GNB infection were also smaller, 1367+/-483g vs. 1728+/-805g (P=0,01), than those without an associated positive culture.

Fig 3.18 Proven NEC and
Nosocomial Gram Negative Septicaemia



6.7.3 Multiple Organisms More than one type of nosocomial GNB was isolated from 26 (11,7%) of the patients with acquired GNB septicaemia, 6 of them at the same time (involving 5 isolates of Klebsiella and Enterobacter spp, 3 of Citrobacter spp and 1 each of Pseudomonas spp, E. coli, Serratia and Acinetobacter spp). Other acquired organisms such as yeasts and GPB were also isolated, 2 at the same time as the GNB, from 11 of these patients. Another 61 patients had other organisms isolated from them as well as the one GNB, 17 at the same time. Thus, in 87 (39,2%) patients with nosocomial GNB septicaemia other hospital acquired organisms were also isolated at some stage; in fact, in 26 (11,7%) from the same specimen. These other organisms consisted of: 36 isolates of yeast, 20 of S. epidermidis, 13 of E. faecalis, 11 of S. aureus, 6 of α haemolytic Streptococci and one Bacillus spp. Those which grew from the same specimen as the GNB are reflected in table 3.36. Babies who acquire GNB sepsis in the Unit appeared to be at increased risk for developing a second episode of GNB sepsis, 18/222 (8,1%) had another GNB isolated from them which is 2,3 times the general incidence of GNB sepsis seen in the Unit (P= 0,001). They are also at a much greater risk of having a systemic fungal infection, 36/222 (16,2%) vs. 76/6027 (1,3%) amongst babies that never had a hospital acquired GNB septic episode (P<0,0001).

6.7.4 Susceptibility Patterns

a)The Cephalosporins: A summary of the susceptibility patterns of the various hospital acquired GNB during the periods of

**Table 3.36 Organisms Isolated from the same Specimen as the Gram Negative**

| | Klebsiella | Enterobacter | E. Coli | Pseudomonas | Serratia | Total |
|---|---|---|---|---|---|---|
| Yeast | 2 | 2 | | | | 4 |
| S. epiderm | 2 | 1 | | | | 2* |
| S. aureus | | 1 | | 2 | | 3 |
| E. faecalis | 2 | 1 | 1 | 1 | 2 | 7 |
| α haem.Strep | | 1 | 2 | | | 3 |
| Total | 6 | 6 | 3 | 3 | 2 | 19 |

*Klebsiella spp, Enterobacter spp and S. epidermidis isolated same time from one patient

liberal cephalosporin usage and limited use is shown in table 3.37. Data available on 92 cultures obtained in the latter half of 1988 are included. As can be seen, cefotaxime susceptibility of all the hospital acquired GNB infections obtained during the two year study period was 48,9% (139/284), whereas that of ceftazadime 79,9% (227/284). E. coli isolates had the highest susceptibility to both cephalosporins, 93,4% (28/30), and Pseudomonas spp the least, 7,8% (4/51) for cefotaxime and 64,7% (33/51) for ceftazadime. Serratia isolates were also very resistant to cefotaxime but susceptible to ceftazadime. Despite restricted use of the cephalosporins, the resistance overall to both cefotaxime and ceftazadime increased significantly, from 35,7% (41/115) to 57,8% (67/116) (P=0,0009) and 7,0% (8/115) to 23,3% (27/116) (P=0,0005) respectively. This was mainly due to increasing resistance amongst the Klebsiella, Pseudomonas and Enterobacter spp.

b)The aminoglycosides: A summary of the resistance patterns of all the nosocomial GNB isolates to the two aminoglycosides used in the unit before and after changing to first line amikacin usage is shown in table 3.38. The resistance to amikacin increased significantly once this policy was adopted, from 9,5% (8/84) to 24,5% (49/200) (P<0,0001). This deterioration in susceptibility was mainly due to the Klebsiella isolates becoming increasingly resistant and to the emergence of Serratia spp as an important cause of nosocomial septicaemia, isolates of which were largely amikacin resistant but gentamicin susceptible.

**Table 3.37 Percentage Cephalosporin Resistance**

| Organism | Liberal Use Jul 88-Mar 89 n=115 | | No Usage Apr 89-Apr 90 n=145 | | Limited Use May 90-Dec 90 n=116 | | Total Jan 89-Dec 90 n=284 | |
|---|---|---|---|---|---|---|---|---|
| | Cefo | Ceft | Cefo | Ceft | Cefo | Ceft | Cefo | Ceft |
| Klebsiella | 33.9 | 5,1 | 35,8 | 13,4 | 52,1 | 27,1* | 43,5 | 19,1 |
| Pseudomonas | 73,3 | 13,3 | 91,2 | 52,2* | 92,6 | 22,2 | 92,2 | 35,3 |
| Serratia | - | - | 79,0 | 0,0 | 84,6 | 23,1 | 81,3 | 9,4 |
| E. coli | 7,6 | 7,6 | 0,0 | 0,0 | 5,6 | 5,4 | 6,6 | 6,6 |
| Enterobacter | 0,0 | 0,0 | 25,0 | 15,0 | 50,0* | 50,0* | 27,6 | 20,7 |
| Miscellaneous | 66,6 | 8,3 | 42,9 | 28,6 | 50,0 | 25,0 | 45,5 | 27,3 |
| Total | 35,7 | 7,0 | 46,9 | 18,0* | 57,8* | 23,3* | 51,1 | 20,1 |

* p=<0,05 when compared to previous % resistance

**Table 3.38 Percentage Aminoglycoside Resistance**

| Organism | Gent 1st line Jan 89-Sep 89 n=84 | | Ami 1st line Oct 89-Dec90 n=200 | | Total n=284 | |
|---|---|---|---|---|---|---|
| | Gent | Ami | Gent | Ami | Gent | Ami |
| Klebsiella | 84,4 | 1,7 | 75,6 | 34,7* | 78,6 | 19,8 |
| Pseudomonas | 92,3 | 46,2 | 73,7 | 15,8 | 78,4 | 23,5 |
| Serratia | - | - | 12,5 | 37,5 | 12,5 | 37,5 |
| E. coli | 33,3 | 0,0 | 41,7 | 4,2 | 34,5 | 3,4 |
| Enterobacter | 40,0 | 20,0 | 33,3 | 16,7 | 40,0 | 17,3 |
| Miscellaneous | 100,0 | 0,0 | 40,0 | 10,0 | 45,5 | 9,1 |
| Total | 79,8 | 9,5 | 53,5* | 24,5* | 61,3 | 20,1 |

*p=<0,05

The resistance to gentamicin of the nosocomial GNB appeared to improve significantly after this drug's withdrawal from the unit; from 79,8% (67/84) to 53,5% (107/200) (P=0,007). However, this was not due to any improvement in the susceptibility amongst the established GNB, but rather due to the emergence of Serratia spp during the second period, 87,5% (28/32) of which were susceptible to gentamicin.

Altogether, amikacin susceptibility of all hospital acquired GNB infections was 79,9% (227/284) and that for gentamicin 38,7% (110/284). Klebsiella and Pseudomonas isolates were the most resistant to gentamicin, Serratia isolates the most susceptible. E. coli isolates were the most susceptible to amikacin and Serratia spp the least. The susceptibility to tobramycin, an aminoglycoside that had never been used in the Unit, was much better than that due to gentamicin for all GNB isolates except Serratia spp of which only one of the 32 isolates was susceptible and Enterobacter spp of which 41,4% (12/29) were resistant. 90,0% (27/30) of the E. coli isolates were susceptible to tobramycin, significantly more than were susceptible to gentamicin (P=0,02). Likewise, Klebsiella and Pseudomonas isolates were more susceptible to tobramycin than gentamycin, 38,9% (51/131) vs. 21,4% (28/131) (P=0,003) and 35,3% (18/51) vs. 21,6% (11/51) respectively (P=N/S).

c) Other antimicrobials: Chloramphenicol susceptibility of all nosocomial GNB isolates was 35,9% (102/284), that for piperacillin 23,2% (66/284) and cotrimoxazole 18,0% (51/284). Only

4,2% (12/284) of these isolates were susceptible to ampicillin. Sixteen (5,6%) were resistant to imipenem. A summary of the individual organisms' resistance patterns to these antimicrobials is given in table 3.39. The highest resistance to imipenem was found amongst Pseudomonas isolates which were also very resistant to ampicillin, chloramphenicol and cotrimoxazole, but relatively susceptible to piperacillin. Half of the Serratia spp and 47,3% (62/131) of the Klebsiella isolates were susceptible to chloramphenicol.

**6.7.5** Mortality 124 of the 222 babies with culture proven hospital acquired GNB septicaemia died, a mortality of 55,8%. The breakdown of the babies who died of nosocomial GNB septicaemia according to their birth weights and the wards where they were thought to develop their infection is shown in table 3.40. The highest mortality was amongst babies with birth weights <1000g, 71,4% (15/21) of those who developed a GNB nosocomial infection died. The lowest mortality was amongst babies with birth weights >2500g who developed GNB septicaemia in wards 66/67, 22,2% (2/9). In fact, death due to nosocomial GNB septicaemia accounted for 25,4% (124/489) of all deaths after three days of age. It made up the highest proportion of deaths after three days of age amongst babies with birth weights of 1500g to 1999g in whom it accounted for 40,5% (30/74) of these deaths (see fig. 3.19), cf. babies with birth weights <1000g who had the highest mortality but amongst whom it accounted for only 22,1% (15/68) of the deaths after three days of age (P=0,02).

**Table 3.39 Percentage Resistance of Nosocomial Gram Negative Organisms**

| Organism | Ampi | Chlor | Cotri | Pip | Imip |
|---|---|---|---|---|---|
| Klebsiella | 99,2 | 52,7 | 82,4 | 95,4 | 2,3 |
| Pseudomonas | 100,0 | 96,1 | 100,0 | 37,2 | 23,5 |
| Serratia | 100,0 | 50,0 | 87,5 | 81,2 | 0,0 |
| E. Coli | 80,0 | 70,0 | 70,0 | 70,0 | 0,0 |
| Enterobacter | 89,6 | 72,4 | 68,9 | 68,9 | 0,0 |
| Miscellaneous | 81,8 | 54,5 | 45,4 | 63,6 | 9,1 |
| Total | 95,8 | 64,1 | 82,1 | 76,8 | 5,6 |

**Table 3.40 Deaths due to Nosocomial Gram Negative Septicaemia**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | 1(100) | 35(64,8) | 15(55,5) | 3(50,0) | 3(42,8) | 57(59,3) |
| TCU | 14(70,0) | 22(61,1) | 12(70,6) | 0 | 6(42,8) | 54(61,3) |
| 66/67 | - | 7,1) | 3(30,0) | 0 | 2(22,2) | 13(34,2) |
| Total | 15(71,4) | 65(60,7) | 30(55,5) | 3(30,0) | 11(36,6) | 124(55,8) |

Figures in parenthesis = % of babies with GNB that died

**Table 3.41 Nosocomial Gram Negative Meningitis**

| Organism | Patient | Meningitis(%) | Associated Blood Culture | | Death |
|---|---|---|---|---|---|
| | | | Same | Different | |
| Klebsiella | 115 | 14(12,2) | 5 | 4 | 5 |
| Pseudomonas | 45 | 4(8,9) | 1 | 2 | 4 |
| Serratia | 26 | 4(15,3) | - | 4 | 3 |
| E. coli | 30 | 4(13,3) | 2 | - | 0 |
| Enterobacter | 25 | 1(4,0) | - | 1 | 1 |
| Miscellaneous | 11 | 1(9,1) | 1 | - | 1 |
| Total | 222* | 28(12,6) | 9 | 11 | 14 |

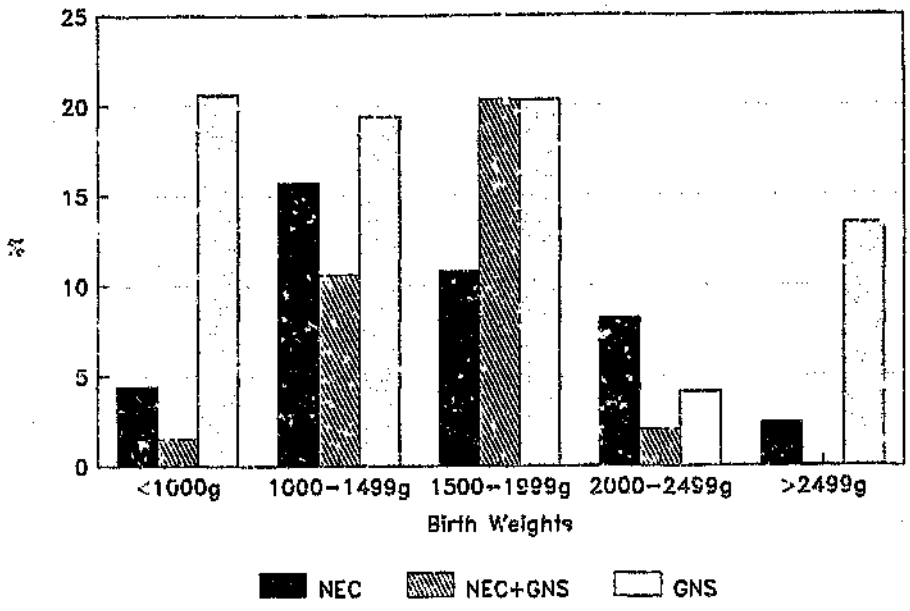
* This does not equal the sum of the individual organisms as several patients had more than one GNB organism isolated from them

a)Mortality with bowel disease: The mortality from proven NEC was not worse if there was or was not an associated culture proven nosocomial GNB infection, 40/50 (80,0%) vs. 51/73 (69,8%) respectively. However, the mortality of babies with suspected NEC was significantly worse if there was an associated GNB septicaemia, 52/105 (49,5%) vs. 28/40 (70,0%) (P<0,0001).

As mentioned before, the mortality due to hospital acquired GNB infection was significantly increased if the baby also had suspected or proven NEC with respect to those babies from whom Klebsiella spp, Serratia spp, Enterobacter spp or E. coli were isolated. Of the 132 babies with nosocomial GNB septicaemia but neither proven or suspected NEC, 56 (42,4%) died. This is significantly lower than the mortalities of the babies with nosocomial GNB infection and proven NEC (80,0%) (40/50) (P< 0,0001), or suspected NEC (70,0%) (28/40) (P=0,004).

Fig 3.18 shows the percentage deaths after three days of age due to proven NEC alone, together with proven GNB sepsis and due to acquired GNB sepsis alone. As can be seen, these conditions accounted for a substantial proportion of deaths after three days of age in the weight categories 1000g to 1499g and 1500g to 1999g, 45,8% (99/216) and 51,4% (38/74) of the deaths respectively. Deaths due to these conditions are much less important in the babies with birth weights >2499g accounting for only 15,8% (13/82) of deaths after three days of age. Nosocomial GNB sepsis was an important cause of death amongst

Fig 3.19 Deaths after 3 Days of Age




1051

babies with birth weights <1000g accounting for 15/67 (22,4%) of the deaths occurring after three days, but proven NEC was not, accounting for only 4 of these deaths (6,0%) (P=0,009).

b)Mortality with multiple isolates: There were no significant differences between the mortalities of the babies from whom more than one different GNB organism was isolated (12/26) (46,1%) compared to that of the babies in whom more than one type of organism was isolated (45/87) (51,7%) or that of the babies in whom only the one GNB organism was isolated (79/135) (58,5%).

c)Mortality with changing antimicrobial policies: Even though it appeared that the mortality due to nosocomial Klebsiella septicaemia improved after switching to amikacin as the sole aminoglycoside in use, the overall mortality due to nosocomial GNB septicaemia was not changed either adversely or for the better; 47 of the 74 babies (63,5%) with acquired GNB sepsis died before the change and 77/148 (52,0%) afterwards (P=0,1).

Nor did the mortality due to GNB septicaemia increase after changing from amikacin and ceftazadime to vancomycin and amikacin for suspected nosocomial sepsis as might have been anticipated. Sixteen of the 24 patients (66,7%) with acquired GNB septicaemia died before the new policy was implemented and 108/198 (54,5%) afterwards (P=0,25).

**6.7.6** Meningitis There were altogether 28 isolates of GNB organisms from the CSF of babies older than three days of age

during the two year study period. Most of these isolate were of Klebsiella spp but that is not surprising as that was the most common cause of nosocomial GNB septicaemia. In fact, 12,2% (14/115) of the babies with nosocomial Klebsiella septicaemia had an associated meningitis. Babies with nosocomial Serratia septicaemia had the highest rate of associated meningitis of 15,4% (4/26) and those with Enterobacter spp the lowest, 4,0% (1/25) (See table 3.41). Twenty (71,4%) of these cases of meningitis had associated positive blood cultures but only 9 of them had the same susceptibility patterns as the isolate from the blood.

Fourteen of the babies with nosocomial GNB meningitis died giving a mortality of 50,0%, not any higher than the mortality of babies with GNB infection but without culture proven meningitis.

6.7.7 Haematology FBC's were available on 211 of the 222 patients with nosocomial GNB septicaemia. The mean WCC of these babies was 12 590+/-11 030/ml (range 1 000-85 700/ml) and the mean platelet count was 145 120+/-118 120/ml (range 3 000-509 000/ml). Forty-two (19,9%) of the babies had WCC's <5 000/ml and 13 (6,2%) >25 000/ml. Ninety-six (45,7%) had platelet counts <100 000/ml. Only the platelet counts of babies with Pseudomonas or Serratia septicaemia were significantly different between babies that survived and those that died. If all the babies with nosocomial GNB septicaemia are analyzed, there is still a significant difference in the

mean platelet counts between babies that survived and those that died; 175 530+/-130 880/ml (range 9 000-509 000/ml) vs. 120 470+/-100 600/ml (range 3 000-432 000/ml) respectively (P= 0,03). In addition, 35/95(36,8%) of the babies that survived had platelet counts <100 000/ml compared to 61/116 (52,5%) of the babies that died (P=0,03). There were no significant differences between the WCC's of the babies that survived compared to those that died either for the individual organisms or for the whole population of babies with nosocomial GNB septicaemia.

## 7. NOSOCOMIAL SYSTEMIC FUNGAL INFECTIONS

### 7.1 Occurrence

During the two years of study, Candida spp were isolated from the blood of 92 babies older than three days and from the CSF of 6 babies, only one of them not having a concomitant blood culture. Torulopsis glabrata was cultured from the blood of 16 babies and concomitantly from the CSF of two of them. In addition, other fungi were isolated from the blood of 3 babies. Thus, 112 babies acquired a systemic fungal infection during their stay in the Neonatal Unit. There appeared to be an epidemic of systemic fungal infections due to Candida spp in 1989, 58 of the cases occurring then and only 35 the next year. Most of the latter occurred during the first three months of 1990. As there were 3 245 babies that survived beyond three days in 1989 and 3 104 in 1990, this decrease in the numbers was significant (P=0,03). All but two of the 16 Torulopsis glabrata isolates occurred in 1990, 13 during

November and October (see fig. 3.20).

The breakdown of where these babies were thought to acquire their systemic fungal infection according to birth weights is given in table 3.42. These figures expressed as the percentage of survivors beyond three days that developed a systemic fungal infection are given in parenthesis. All but one of the cases came from the high care areas; the highest incidence occurring amongst babies admitted to the ICU, 56/899 (6,2%) vs. 55/2794 (2,0%) of the admissions to TCU (P<0,0001). The highest number of cases was amongst babies with birth weights 1000g to 1499g, but the highest incidence was amongst babies with birth weights <1000g, 11/140 (7,9%) of them developed a systemic fungal infection. Babies with birth weights >1499g had a significantly lower incidence of systemic fungal infection than those with lower birth weights, 1,0% (51/5226) vs. 5,4% (61/1123) (P<0,0001).

The male to female ratio was 1,5:1. The mean birth weight of the babies with systemic fungal infections was 1607+/-687g (range 740-3900g), and the mean age at which they acquired this infection 22,0+/-15,0 days (range 4-90 days). The ages at which these babies became infected are shown in fig. 3.21.

Twenty-four (21.4%) of the babies with a systemic yeast infection also had proven NEC, 25 (22,3%) suspected NEC and 9 (8,0%) were on parenteral nutrition for other reasons. This was as strong an associatior with bowel pathology as that shown by babies with nosocomial Klebsiella septicaemia

Fig 3.20 Nosocomial Fungal Infections

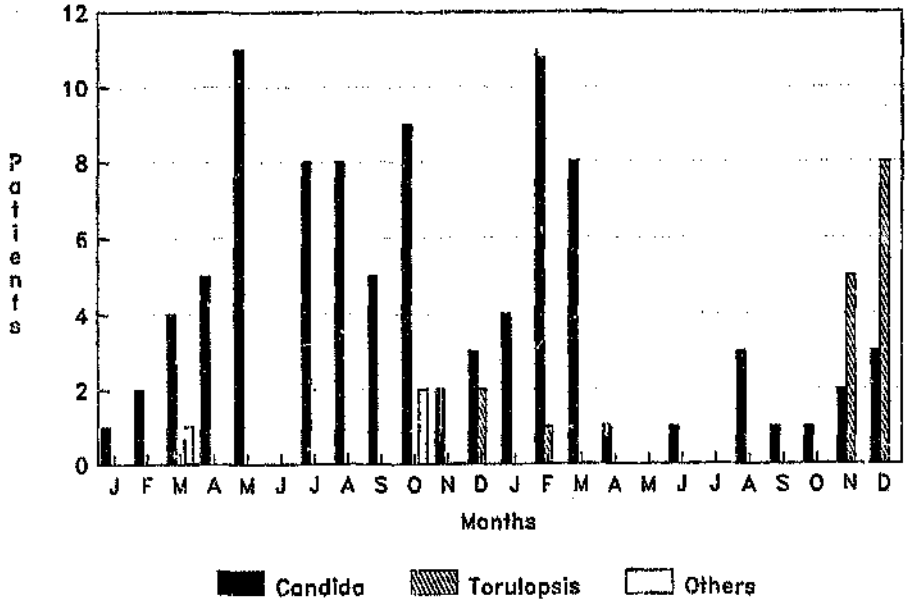



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**Table 3.42 Nosocomial Systemic Fungal Infections by Birth Weight**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | 4(28,6) | 26(7,4) | 14(6,7) | 4(3,1) | 8(4,1) | 56(6,2) |
| TCU | 7(5,2) | 24(2,9) | 12(1,7) | 7(1,8) | 5(,6) | 55(2,0) |
| 66/67 | - | - | 1(,05) | - | - | 1(,02) |
| Total | 11(7,9) | 50(5,1) | 27(1,4) | 11(1,0) | 13(,6) | 112(1,7) |

Figures in parenthesis = % of babies older than 3 days with fungaemia

**Table 3.43 Risk Factors for Acquiring Systemic Fungal Infection**

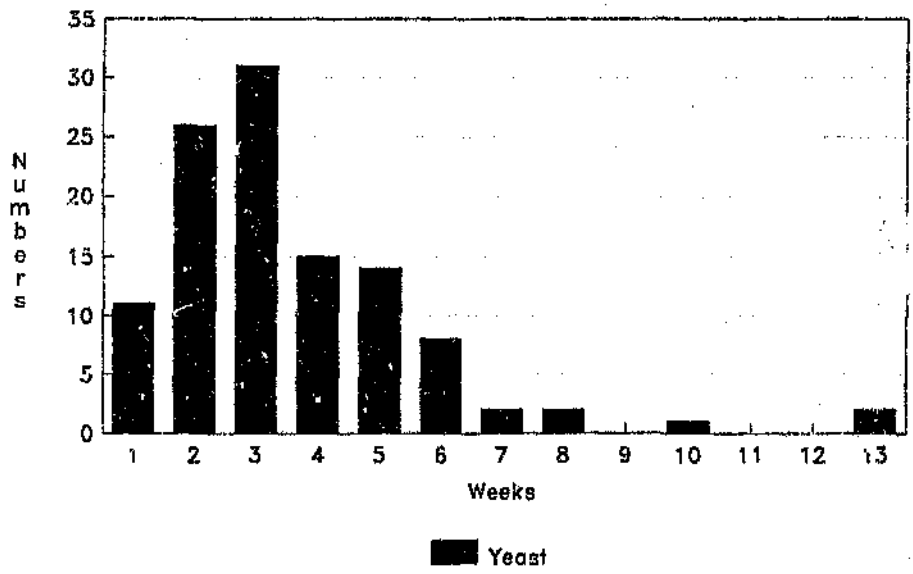
| | Data | P value | O.R. | 95% C.L. |
|---|---|---|---|---|
| Sex: M vs. F | 67/3463:45/2886 | 0,3 | 1,25 | 0,84-1,86 |
| Weight: <1,5Kg vs. 1,5-2,5Kg | 61/1123:38/2949 | <0,0001 | 4,40 | 2,86-6,77 |
| " 1,5-2,5Kg vs. >2,5Kg | 38/2949:13/2277 | 0,01 | 2,27 | 1,17-4,50 |
| Wards: ICU vs. TCU | 56/899:55/2794 | <0,0001 | 3,31 | 2,22-4,92 |
| " TCU vs. 66/67 | 55/2794:1/5918 | <0,0001 | 118,82 | 17,81-2314,0 |
| NEC: Proven vs. suspected | 24/114:25/197 | 0,07 | 1,83 | 0,95-3,55 |
| " Suspected vs. none | 25/197:63/6038 | <0,0001 | 13,79 | 8,22-23,00 |
| Parenteral nutrition vs. none | 58/380:54/5969 | <0,0001 | 19,7 | 13,16-29,58 |
| Klebsiella sepsis vs. none | 25/115:87/6234 | <0,0001 | 19,63 | 11,65-32,89 |

**Table 3.44 Deaths due to Systemic Fungal Infections**

| Wards | Birth Weights <1000g | 1000-1499g | 1500-1999g | 2000-2499g | >2499g | Total |
|---|---|---|---|---|---|---|
| ICU | 3(75,0) | 16(61,5) | 6(42,8) | 2(50,0) | 6(75,0) | 33(56,9) |
| TCU | 2(28,6) | 9(37,5) | 2(16,6) | 4(57,0) | 0 | 12(21,8) |
| 66/67 | - | - | 0 | - | - | 0 |
| Total | 5(45,5) | 25(50,0) | 8(29,6) | 6(54,5) | 6(46,1) | 50(44,6) |

Figures in parenthesis = % mortality of babies with systemic fungal sepsis

Fig 3.21 Age of Babies with Systemic Fungal Infections

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A summary of the risk factors for developing a systemic fungal infection is given in table 3.43. As was found for nosocomial Klebsiella septicaemia, sex was not a risk factor but decreasing birth weight and increasing level of care required by a baby were; babies admitted to wards 66/67 having a very low risk of developing a systemic fungal infection. However, unlike with nosocomial Klebsiella septicaemia, there was not a greater risk in developing a fungal infection if the baby had proven as opposed to suspected NEC.

Other nosocomially acquired organisms were isolated from 63 (56,2%) of the babies with systemic fungal infections at some stage, 13 (11,6%), in fact, from the same specimen as the fungus. Klebsiella spp was cultured from 25 (22,3%) of these babies, S. epidermidis from 18, S. aureus from 10, Pseudomonas spp from 8, E. faecalis from 7, Enterobacter spp from 6, E. coli from 3 and Serratia spp, Bacillus spp, α haemolytic Streptococci and anaerobic bacteria from 2. Acinetobacter spp was isolated from one baby prior to the fungus. Of these, 3 isolates of S. aureus and E. faecalis, 2 of S. epidermidis, Enterobacter and Klebsiella spp, and one Pseudomonas spp were cultured at the same time as the yeast. Of the remainder of the 25 babies from whom a Klebsiella spp was also cultured, the yeast was isolated prior to the Klebsiella spp in 8 babies and after in 15. Altogether, there were 38 babies from whom a yeast and at least one nosocomially acquired GNB were isolated at some stage, and of these 7 had NEC, 9 suspected NEC and 5 were on parenteral nutrition.

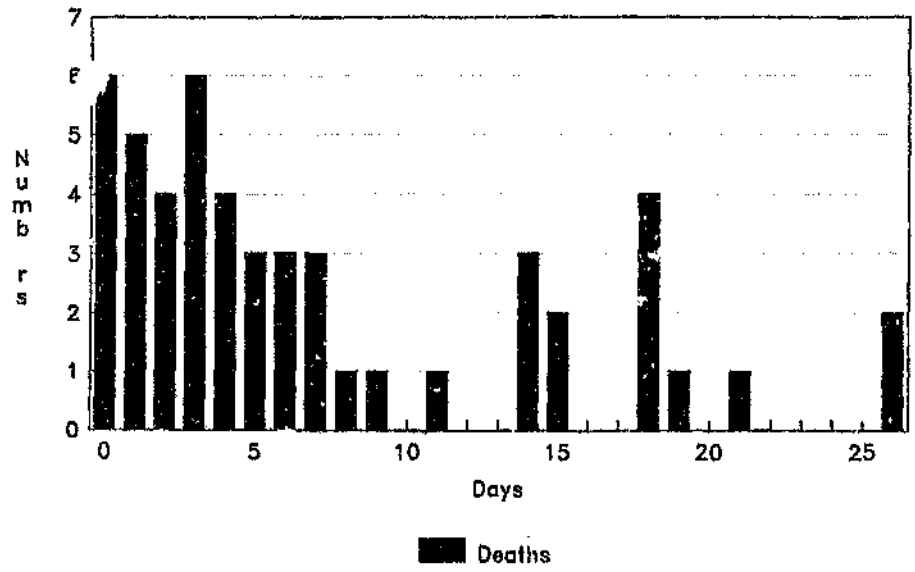
## 7.2 Mortality

Fifty (44,6%) of the babies with a systemic fungal infection died, a similar mortality as that found amongst babies with nosocomial Klebsiella septicaemia. Nine of these babies had Torulopsis glabrata, thus the mortalities for the various fungi were similar. The wards in which these babies died are reflected in table 3.44 together with the percentage mortality for the individual weight categories in parenthesis. Deaths due to fungal infections accounted for 10,2% (50/489) of all deaths after three days of age. The mortality of babies who acquired their fungal infection in the ICU was much higher than that of babies in the TCU, 33/56 (56,9%) vs. 12/55 (21,8%) (P=0,0001), but, unlike what is seen with the nosocomial GNB infections, the mortality from systemic fungal infections was not higher in the babies with the lower birth weights, the mean birth weight of babies that survived being 1603+/-614g (range 830-377g) vs. 1611+/-775g (range 1050-3900g) of those that died.

The time intervals between the culture of the yeasts and the babies' deaths are shown in fig. 3.22. Eleven (22,0%) died within a day of having been cultured for suspected sepsis, a smaller fraction than is found with babies with nosocomial Klebsiella septicaemia, 25/65 (38,5%) (P=0,6).

Thirty-four (58,6%) of the 58 babies with bowel pathology or on hyperalimentation for another reason plus a systemic yeast infection died, a significantly higher mortality than was

Fig 3.22 Duration of Systemic Fungal Infection till Death

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found amongst the remainder of the babies with this infection but without bowel involvement, 16/54 (29,6%) (P=0,003). However, if one analysed the mortalities of the babies with proven and suspected NEC individually, 12/ 24 (50,0%) and 16/ 25 (64,0%) respectivelv, it was only the latter that was significantly higher than that of babies with systemic fungal infection but without bowel disease (P=0,008), though these two mortalities are not themselves significantly different.

Thirty (47,6%) of the babies from whom multiple organisms were isolated died, a similar mortality as that of the remaining babies with systemic fungal infection only, 20/49 (40,8%).

Six (75,0%) of the babies with a fungal meningitis died, the numbers being too small to determine if having a fungal meningitis carried a higher mortality than fungaemia alone.

### 7.3 Treatment

Twenty-eight (25,0%) babies with systemic fungal septicaemia died before their culture results were available without having been on antifungal therapy. The remainder were treated with amphotericin B; 20 in addition were put onto 5-fluro-cytosine and ketoconozole was used in 3. The mortality amongst the treated babies was thus 26,2% (22/84), 14 (22,9%) of the babies on amphotericin B alone dying compared to 6 (26,0%) on additional antifungal therapy (P=N/S).

### 7.4 Haematology

The mean WCC of the 108 babies with systemic fungal infections

on whom a FBC was available was 12 650+/-10 260/ml (range 1 400-68 800/ml) and the mean platelet count 134 310+/-156 440 /ml (range 3 000-834 000/ml). There was a significant difference between the mean platelet counts of those babies that died compared to those that survived, 107 460+/-140 900/ml (range 3 000-634 000/ml) vs. 155 800+/-165 800/ml (range 7 000 -834 000/ml) (P=0,01). However, of the 63 babies with platelet counts <100 000/ml, 32 survived and 31 died. There was no difference in the mean WCC's of those babies that died and those that survived, 12 830+/-8 650/ml (range 1 110-45 200/ml) vs. 12 510+/-11 590/ml (range 2 000-68 800/ml). Sixteen babies had WCC's <5 000/ml of whom 10 died and 11 had WCC's >25 000/ml of whom 5 died.

## 8. GRAM POSITIVE NOSOCOMIAL ISOLATES

### 8.1 *Occurrence*

GPB were isolated from the blood 200 times and from the CSF 47 times from 208 babies older than three days, several babies having more than one isolate. None of the CSF's had a concomitant positive blood culture with the same susceptibility patterns, except for the GBS. The breakdown of the types of organisms involved and where the babies were thought to acquire them is shown in table 3.45. The most common isolates were *S. epidermidis,* as was found with the miscellaneous congenital GPB isolates (see above), occurring in 99 (47,6%) of these babies. However, unlike the congenital GPB isolates, α haemolytic Streptococci and Corynebacteria spp were not common isolates from babies older than three days, 19/208

**Table 3.45 Gram Positive Nosocomial Isolates**

| Organism | Blood | CSF | Patients | ICU | TCU | 66/67 | Other Wds |
|---|---|---|---|---|---|---|---|
| S. epiderm | 90 | 23 | 99 | 31 | 27 | 39 | 2 |
| S. aureus | 46 | 8 | 50 | 16 | 20 | 13 | 1 |
| E. faecalis | 32 | 10 | 40 | 13 | 10 | 11 | 6 |
| α haem Strep | 13 | 3 | 16 | 4 | 6 | 6 | - |
| Bacillus | 11 | - | 11 | 4 | 3 | 4 | - |
| Late GBS | 5 | 3 | 5 | 2 | 1 | 1 | 1 |
| Corynebact | 3 | - | 3 | - | 2 | 1 | - |
| Total | 200 | 47 | 208* | 64* | 64* | 73* | 7* |

* Not equal to the sum of the figures above as some patients had multiple isolates

**Table 3.46 Patient with Bowel Disease and Nosocomial Gram Positive Isolates**

| Organism | Total | Proven NEC n=123 | Suspected NEC n=197 |
|---|---|---|---|
| S. epiderm | 99 | 7 | 9 |
| S. aureus | 50 | 5 | 5 |
| E. faecalis | 40 | 5 | 5 |
| α haem Strep | 16 | 3 | 0 |
| Bacillus | 11 | 0 | 4 |
| Corynebact | 3 | 0 | 0 |
| Total | 204* | 18* | 21* |

* This does not equal the sum of the individual organisms as several patients had more than one GPB isolated from them

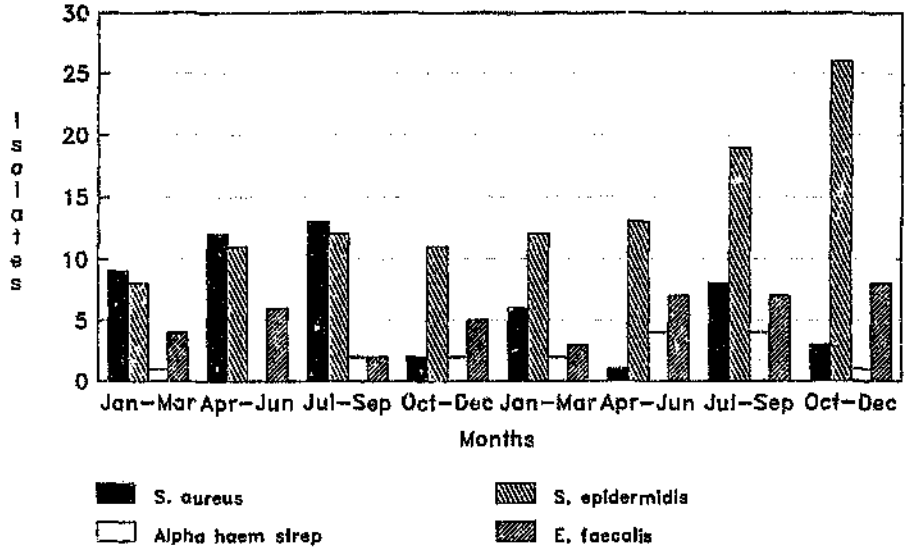
(9,1%) vs. 112/310 (36,1%) (P<0,0001). There were also few babies with late onset GBS, babies with this condition usually being admitted to the Paediatric wards. The number of babies from whom GPB were isolated after three days of age was similar to the number of those from whom GNB were isolated.

An equal number of these organisms were isolated from babies in TCU, ICU and wards 66/67. This was probably just a reflection of the number of babies cultured for suspected nosocomial infections; GPB being isolated from 12,8% (64/500) of the specimens sent from babies in ICU, 16,0% (64/400) from those in TCU and 12,1% (73/600) from those in wards 66/67.

The frequency of the four most common GPB obtained from babies older than three days is shown in fig. 3.23. The numbers of these organisms isolated monthly did not vary significantly throughout the two years studied except for those of S. epidermidis which increased steadily throughout this period.

Of the 204 babies who survived beyond three days from whom a GPB other than GBS was isolated, 18 (8,8%) had proven and 21 (10,3%) suspected NEC. These were significantly smaller proportions than were found amongst babies with nosocomial GNB septicaemia, 50/222 (22,5%) (P=0,0001) having proven and 40/222 (18,1%) (P=0,02) suspected NEC, and than were found amongst babies with fungal infections, 24/112 (21,4%) (P= 0,002) and 25/112 (22,3%) (p=0,006) respectively. Another 15 (7,4%) babies from whom nosocomially acquired GPB were isolated were on parenteral nutrition for other reasons, a

Fig 3.23 Miscellaneous Nosocomial
Gram Positive Isolates (Jan1989–Dec1990)



similar proportion as was found amongst those from whom other acquired organisms were cultured. Nevertheless, babies with bowel pathology were still more likely to have GPB isolated from them than those without: GPB were isolated from 18/123 (14,6%) babies with proven and from 21/197 (10,6%) babies with suspected NEC compared to 165/6029 (2,7%) of those without these conditions (P<0,00001). In total, 54 (13,9%) of the 389 babies on parenteral nutrition developed GPB bacteraemia compared to 150/5960 (2,5%) who never received parenteral nutrition. The various GPB isolated in babies with bowel pathology are displayed in table 3.46.

Other nosocomially acquired organisms were isolated in 40 (40,4%) of the babies from whom S. epidermidis was cultured, 6 (6,1%) at the same time, and in 24 (48,0%) of the babies with S. aureus isolates, 9 (18,0%) at the same time. Twenty-two (55,0%) of the babies from whom E. faecalis was cultured had other nosocomially acquired organisms isolated, of which 13 (32,5%) were from the same specimen as the E. faecalis, a much higher proportion than found amongst those with S. epidermidis isolates (P<0,0001). Seven (43,7%) of the babies from whom α haemolytic Streptococci were isolated and 3 (27,3%) from whom Bacillus spp were isolated had other organisms cultured at some stage; 2 (12,5%) from the same specimen as the α haemolytic Streptococcus. One of the babies with late onset GBS infection also had a S. epidermidis cultured earlier on. Thus, in 78 (38,2%) of the 204 babies with nosocomially acquired GPB isolates besides GBS other organisms or another

GPB were cultured at some stage after three days of age, 28 (13,7%) from the same specimen. These were similar proportions as found amongst the babies with nosocomial GNB isolates. GNB were cultured from 45 (57,7%) of these babies, yeasts from 35 (44,9%), anaerobic bacteria from 3 and more than one GPB from 17 (21,8%). Thirty-four (43,6%) of these babies with other isolates in addition to the one GPB were on parenteral nutrition, including 12 with proven and 12 with suspected NEC.

### 8.2 Mortality

It is difficult to ascertain if nosocomially acquired GPB were responsible for any deaths, as many were isolated together with other organisms. However, 22 (22,2%) of the babies from whom S. epidermidis was cultured died, 15 (30,0%) of those with S. aureus, 11 (27 5%) with E. faecalis, 4 (25,0%) with α haemolytic Streptococci and 1 (9,1%) with a Bacillus spp. Two (40,0%) with late onset GBS septicaemia died and none from whom Corynebacteria spp were isolated. As some babies had more than one GPB cultured from them, this translates to 50 (24,5%) of the 204 babies with nosocomial GPB isolates, excluding those with only late onset GBS, died. However, if one excludes all babies with bowel pathology or isolates of organisms other than only GPB, then 13/114 (11,4%) died. This is a significantly lower mortality than that of the remaining babies with nosocomial GPB isolates with bowel pathology and/or isolates of other organisms, 37/90 (41,1%) ($P<0,0001$). In fact, 12 (66,6%) of the babies with proven and 10 (47,6%) with

suspected NEC and nosocomial GPB isolates died, significantly higher mortalities than those of babies with nosocomial GPB isolates but no bowel disease, (P<0,0001 and P=0,002 respectively). Seven (46,7%) of the babies on parenteral nutrition for other reasons and with nosocomial GPB isolates died, also significantly higher than babies with these isolates but not on parenteral nutrition, 21/150 (14,0%) (P=0,004). Likewise, the mortality of the babies from whom multiple organisms were isolated was much higher compared to those from whom only the one GPB was cultured, 31/78 (39,7%) vs. 19/126 (15,1%) (P<0,0001).

### 8.3 Susceptibility patterns

Ninety-five (84,1%) of the S. epidermidis and 42 (77,7%) of the S. aureus were methicillin-resistant; 22 (55,0%) of the E. faecalis isolates were ampicillin-resistant. They were all susceptible to vancomycin. All except two of the α haemolytic Streptococci were susceptible to penicillin (87,5%); the two resistant isolates being susceptible to erythromycin. The Bacillus isolates were susceptible to penicillin (72,7%) except for three which were susceptible to chloramphenicol only. The few Corynebacteria spp and GBS isolates were susceptible to penicillin.

### 8.4 Meningitis

Only five (21,7%) of the 23 CSF's from which S. epidermidis were cultured had a cellular response in keeping with a diagnosis of meningitis; not one from which E. faecalis or

Corynebacteria spp were isolated. A higher proportion of CSF's from which S. aureus was isolated had a cellular response, 5/8 (62,5%), but the numbers were too small for this to be significant. One of the 3 babies from whom GBS was isolated from the CSF did not have a cellular response.

Fiv (21,7%) of the babies with S. epidermidis cultured from the CSF died, one of them with cells suggestive of a meningitis, 4 of the 8 with S. aureus, 3 of them with cells, and none of those with E. faecalis or Corynebacteria spp. Both of the GBS meningitis with a cellular response in the CSF died.

9. NOSOCOMIAL ANAEROBIC BACTERIA

Anaerobic bacteria were isolated from 12 babies older than three days during the two year study period. Only one of the babies was in the ICU, 5 in the TCU and 6 in wards 66/67. Three of the babies had NEC, 2 of which had perforated bowel, and 2 had suspected NEC. Four of the babies died, 3 of them having bowel pathology. Another organism was cultured at the same time as the anaerobic bacteria in 2 of these babies, a S. epidermidis and an E. faecalis.

## CHAPTER 4: DISCUSSION

Baragwanath's Neonatal Unit is responsible for the care of a large number of babies born to mothers who are often unbooked and of low socioeconomic status, with around 3 500 admissions and another 4 750 neonates observed with their mothers annually. Nearly two thirds of the actual admissions are LBW babies, these making up an even higher proportion of the babies admitted to the ICU. Half of the admissions require nursing in a high care area at some stage of their stay, of which 550 to 600 per year need ventilation. The neonatal wards are thus chronically overloaded with a rapid turnover of patients, the average duration of stay or the bigger babies, for example, being 4 to 6 days in any one ward, though very LBW babies stay much longer in the Unit. This, together with the fact that a very large percentage of babies are treated with antimicrobials during their hospital stay, makes it not surprising that infections play a major role in the morbidity and mortality amongst the admissions to this unit.

### 1. CONGENITAL INFECTIONS

GBS were the most common isolates obtained during the study period from babies admitted to Baragwanath's Neonatal Unit suspected of having a congenital bacterial infection. This organism was isolated in 2,7% of babies cultured for suspected sepsis in the first few days of life, giving an incidence of 1,9 per 1 000 live births. This is a similar incidence to that reported from developed countries, figures quoted in the

literature ranging from 2,0 to 3,7 per 1 000 live births, and much higher than that observed in developing countries.[21,43,45] The genital carriage rate of GBS amongst women in Soweto as determined in a previous study is 10,3%.[63] Thus, only 1,8% of babies born at Baragwanath Hospital to culture positive mothers develop GBS bacteraemia. These are similar figures as reported in the literature; maternal colonization rates of 4,6% to 40,6% have been reported with a transmission rate to the baby of 42% to 72%, though most babies remain asymptomatic and only 1% to 2% of babies born to culture positive mothers developing early onset septicaemia.[64,65,66,67] Babies born to heavily colonized women have a higher rate of colonization themselves and of developing systemic infection.[68] Though transmission rate is not influenced by the duration of labour or rupture of membranes, there is an association with these together with prematurity and the development of symptomatic infection; 15,2% of premature babies and 10,7% of babies with PROM born to culture positive mothers have been shown to develop sepsis. The genital carriage rate of GBS of women with premature ruptured membranes at Baragwanath Hospital has previously been found to be 9,7%, therefore, 7,5% of babies born to culture positive women in premature labour become systemically infected, as 1,3% of premature babies were found to have GBS bacteraemia in this study.[63]

Asphyxia was a significant risk factor in our study, babies with congenital GBS infection having a three to six fold increased chance of being asphyxiated than babies admitted

for other reasons. Put another way, babies born in Soweto with early onset GBS sepsis are 40 to 110 times more likely to be asphyxiated than babies without this infection. This is not an unexpected finding as it is likely that a baby with a congenital infection would have a poor apgar score. One report showed that 84% of babies with congenital GBS pneumonia following intrauterine exposure had one minute apgar scores of <6;[69] 46% of our study babies with GBS bacteremia were asphyxiated. Prematurity was also a significant risk factor as has been found in other studies, where rates 10 to 15 times higher than in term babies have been documented.[35] Babies with birth weights <2000g in our study were found to have an incidence of 1,3% compared to 0,1% amongst bigger babies; also a ten fold increased incidence. The higher incidences observed amongst the bigger babies that required admission, up to 4,4% for those needing ventilation, reflects the relative importance of GBS as a cause of morbidity in the bigger babies compared to in premature infants. Some investigators have suggested that the increased incidence of infection seen amongst premature babies is a reflection of their impaired immunity rather than of chorioamnionitis due to GBS causing premature delivery.[67] For example, babies born prematurely would not have received their full compliment of maternal antibodies against GBS since nearly 60% of maternal derived IgG is transported to the foetus in the last ten weeks of gestation. Though the presence of PROM was not a helpful feature in trying to determine if an admitted baby was likely to have GBS sepsis in our study,

babies with PROM or offensive liquor did have an 8 to 27 times increased chance of having GBS bacteremia when compared to babies born to mothers without these conditions. Nevertheless, the incidence of GBS amongst babies with PROM is still very low; for example, GBS were isolated from only 2,3% of babies with PROM or offensive liquor sent to their mothers on antimicrobials. GBS cultured from these well babies may even have been contaminants due to poor blood culturing techniques practised by the medical staff in LW, the organisms really just being present on the skin. This seems to be a likely explanation as these babies did well on a few doses of intramuscular penicillin, an unlikely event if these babies were systemically infected with GBS, though it is possible that this treatment might have prevented overt clinical infection developing later on in these babies. In fact, high dose ampicillin given to a mother just prior to delivery has been shown to decrease the incidence of symptomatic infection in babies as has a single dose of penicillin given to neonates at risk though it is thought not to be sufficient to treat established bacteremia.[70,71,72] It would, however, be interesting to determine if there is a difference in the strains of GBS isolated from ill babies compared to those isolated from well babies as type III organisms are known to be more virulent than the other two strains.[21] This difference in virulence seems to be related to the organisms ability to produce high levels of neuramidase, though levels of extracellular protease and type-specific polysaccharide are also high in this strain

making the precise function of these substances as virulence factors difficult to ascertain. Babies born to older mothers seemed to be protected from developing GBS septicaemia; a not unexpected finding as some investigators have shown a higher genital carriage rate amongst women less than 20 years old and in those with low parity, the latter, however, not appearing to be a risk factor in our study.[73] Birth by Caesarian section was not protective for developing GBS infection compared to vaginal delivery, in fact, babies born by Caesarian section in our study were 5 to 22 times more likely to have early onset GBS sepsis compared to those born vaginally. This may be because Caesarian sections were being done for complications due to GBS amnionitis or foetal infection such as foetal distress. Unfortunately, no distinction could be made between Caesarian sections done on mothers whose membranes had ruptured compared to those on whom elective sections were done. Cases of fulminant early onset infection occurring in babies born by Caesarian section with ostensibly intact membranes have been documented.[43]

Just under half of the babies in our study from whom GBS were isolated were ill enough to require nursing in an high care area; in fact, 23% needed ventilatory support. Two thirds of the babies with GBS who required ventilation died, the overall mortality of symptomatic babies being 27% compared to rates quoted in the literature between 27% to 55%. The mortality was significantly higher amongst premature babies (37%) compared to term babies in the study (14%), an observation

already made by other workers who noted a mortality of 77% amongst premature babies and one of 19% amongst neonates born at term with GBS sepsis (the lower mortality seen in our study group probably reflected the advent of improved life-support technology).[74] However, the contribution towards the total mortalities by early onset GBS sepsis was lower at both extremes of birth weight; very LBW babies probably dying by virtue of their prematurity and many of the term babies from complications following birth asphyxia (not related to GBS sepsis but to obstetrical complications), an all too common occurrence at Baragwanath's Maternity Hospital. The fact that three quarters of the babies that died did so during the first day of life gives an indication of how fulminant GBS septicaemia can be. It also means that there usually is not enough time to consider the use of other modalities of treatment such as neutrophil or exchange transfusions, or administrating hyperimmune globulin to improve the outcome as the culture results often are only available after the baby has died.

Less than 10% of the studied babies with early onset GBS infection had an associated meningitis, a much lower proportion than that noted by other researchers who have observed rates as high as 30%.[21] This lower incidence seen amongst the study patients may be due to a reluctance on the part of the doctors to do lumber punctures routinely when suspecting a baby is septic. That, plus the fact that two of the babies with GBS meningitis did not have associated positive blood cultures, emphasizes the importance of obtaining CSF specimens

in cases of suspected sepsis. While evidence of leptomeningeal inflammation has been reported to be absent in up to 77% of cases of early onset GBS meningitis, only two of the study cases did not have an inflammatory response as seen on their CSF.[50] The presence of meningitis did not appear to increase the mortality of GBS septicaemia in our study.

Though some workers [75,76] have reported relative leukopaenia, absolute neutropaenia and leukocytosis to be useful in identifying neonates with GBS infection, only 17% of babies with GBS bacteremia in our study were leukopaenic, 16% had a neutropaenia and none leukocytosis. Only 5% were thrombocytopaenic. Christensen et al also noted that babies with early-onset group B streptococcal infections can die with normal leukocyte counts.[77] Other studies have shown elevated immature neutrophil counts or ratios of immature to total neutrophil counts to be more useful, the latter is said to be elevated in 91% of cases with proven infection and in only 4% of noninfected neonates.[75] These measurements unfortunately are not routinely requested at Baragwanath Hospital and in the absence of other useful haematological markers of infection, should probably be routinely sought. Though the mean WCC of the babies in the study that died was less than that of those who survived, it was not an accurate prognosticating feature as only 41% of those with WCC's less than 5 000/ml died. Other investigations such as countercurrent immunoelectrophoresis, latex particle agglutination, staphylococcal coaggulation and enzyme immunoassay looking for GBS type-specific polysaccharide anti-

gens in body fluids are useful tests to be able to identify rapidly the baby with GBS sepsis even after antimicrobial therapy has begun especially if carried out on concentrated urine when they have an 88% to 96% sensitivity.[78] Once again, these investigations are available, but not done routinely at Baragwanath Hospital.

The significance of the other organisms isolated at the same time as the GBS in five patients is obscure. The most likely explanation is that they are contaminants. Staphylococci are not common pathogens causing congenital infections, and both Klebsiella and Serratia spp are resident GNB in this unit causing nosocomial infections. Interestingly enough, all five babies required admission to the ICU but none of them demised. Despite the theoretical increased risk for developing a nosocomial infection as the already immature immune system is further depressed by GBS sepsis, the neonates with early onset disease did not show an increased incidence of either nosocomial GNB sepsis or systemic fungal infection.

Equally, the large number of S. epidermidis and S. aureus, α haemolytic Streptococci, Corynebacteria spp, Bacillus spp and E. faecalis isolated at birth, though common organisms in the maternal genital tract, are probably contaminants as they rarely cause disease in the neonate. This is supported by the fact that in a proportion of them other organisms were isolated at the same time (12%), that there were apparent outbreaks suggesting that certain doctors at the time did not use a good

technique for taking cultures, and that few of the patients died even though they were not treated with appropriate antimicrobials, just under a half of these organisms being resistant to penicillin with which they would have been treated.

Many of the GNB isolated at birth were probably contaminants as well, but in these cases the organisms isolated were often the GNB responsible at that time for outbreaks of nosocomial infections rather than being present in the genital tract of the mothers. Certainly, the large number of Serratia spp isolated at birth coincided with an outbreak of nosocomial septicaemia due to that organism. Equally, Klebsiella spp were only isolated at birth while these organisms were also an important cause of nosocomial sepsis. Also, the Pseudomonas spp isolated were often multiresistant but the babies did well despite not receiving appropriate antimicrobials. Interestingly enough, unlike the babies from whom GPB were isolated at birth excluding GBS, those from whom GNB were isolated were nearly all admitted to the high care areas. This of course might be due to the fact that these babies were very ill with sepsis due to these organisms but it is extremely unlikely that such large numbers of babies were born already infected with these organisms. However, all attempts at isolating a source for these organisms were fruitless. They were not isolated from mothers' genital tracts, obstetrical instruments, LW personnel or equipment, fluids or drugs administered to the babies. No common factors from the birth history was evident; some babies were delivered at outside clinics and

transferred to Baragwanath Hospital, others delivered by Caesarian section; only few were born to mothers that had spent some time in the hospital during which their genital tract might have become colonized with hospital GNB. The worrying fact was that the same organism was isolated later from some of these babies whose condition had deteriorated. One possibility is that these organisms were contaminants on doctors' hands or in fluids given to the babies; many doctors were taking the initial culture through umbilical lines flushed with heparin and saline. This is probably true for the Klebsiella and Serratia isolates as in only a small proportion of them were other organisms isolated at the same time. Pseudomonas and Enterobacter spp were isolated at one time from the hands of a significant percentage of ICU and TCU staff. The exact number of babies with genuine congenital GNB sepsis in the Unit is thus not known; certainly it plays a lesser role than that due to GBS and GNB are not important pathogens in the low care areas or amongst the well babies with PROM sent to their mothers on antimicrobials; the latter should thus not be empirically commenced on an aminoglycoside. The high degree of resistance shown by these organisms prompted the change to amikacin as sole aminoglycoside used, possibly prematurely if most of these organisms were indeed contaminants, though obviously if these organisms were actually infused into the babies then this decision would have been justified.

Even though coliform organisms are prevalent in the maternal birth canal and most neonates are colonized during delivery, E. coli was only isolated from the blood or CSF in 0,4% of the admissions to the unit. Most cases required nursing in a high care area and carried a 40% mortality, though once again the high proportion from which other organisms were also isolated is suggestive that some of these may have been contaminants.

Anaerobic bacteria were occasionally isolated from babies at birth, the largest single group being the bigger well babies with PROM or offensive liquor sent to their mothers. This is not surprising as it is well known that although anaerobes are responsible for the foul smell of offensive liquor, they seldom cause serious infections in the newborn but correlate well with maternal infections.[11] Even though the mortality of the babies from whom anaerobic bacteria were cultured was highest amongst babies admitted to the ICU and amongst the smaller babies, this was probably only a reflection of the low mortality amongst babies with PROM considered to be well and sent to their mothers.

Due to the uncertainty as to which organisms obtained at birth are contaminants, an exact incidence of culture proven congenital sepsis for Baragwanath's Neonatal Unit cannot be deduced. Altogether, just over 600 babies had positive blood or CSF cultures at birth during the two years studied, 40 with multiple isolates. This means that 10% of those cultured for suspected congenital sepsis or, expressed in another way, 8%

of the admissions had positive cultures, giving an incidence of 8,3 per 1 000 live births for Soweto born babies. However, as many of these cultures are considered to be contaminants, the true incidence of culture proven congenital sepsis must lie closer to that for early onset GBS sepsis, namely 1,9 per 1 000 live births. Likewise, the contribution of congenital infection towards the mortality in the unit lies anywhere between 3% and 12%.

## 2. NOSOCOMIAL INFECTIONS

### 2.1 Gram Negative Infections

Nosocomial septicaemia due to GNB occurred in 3,5% of the study population that survived beyond three days, the highest incidence being amongst the babies admitted to the ICU (10,7%) followed by those admitted to the TCU (3,1%). This is not surprising as these babies have the most invasive procedures done to them such as the insertion of umbilical and other arterial and venous catheters, exposure to respiratory therapy equipment and humidifiers.[25,26] There is also a significantly higher proportion of LBW babies in these wards compared to wards 66/67, where only 0,6% of the babies developed an hospital acquired GNB septicaemia. Thus, the incidence of nosocomial GNB sepsis amongst babies with birth weights <1000g was 15% compared to 1,3% amongst babies with birth weights >2500g; the mean birth weight of babies with nosocomial infections being significantly lower than that of babies with congenital infections. In addition, the prolonged stay of these LBW babies in these areas which are often overcrowded and under-

staffed results in an inevitable breakdown in aseptic techniques and puts them at further risk for acquiring infection. Admission to a high care area also results in rapid colonization of a baby's skin, mucous membranes and gut with the resident organisms which are often multiresistant, the intense antimicrobial pressure in these environments encouraging emergence of resistant mutants.[24] Nearly all babies admitted to the ICU received antimicrobial therapy at some stage and 82% of the admissions to the TCU received first line antimicrobials but many of the remainder received treatment for suspected nosocomial sepsis. This is not an exceptionally high usage of antimicrobials; Bryan et al recorded that 90% of the infants in their neonatal ICU received broad spectrum antimicrobials at some stage during their hospital course.[79] Unlike the experiences of other neonatal units, there was no predominance of acquired GNB sepsis amongst male babies.[36,80] The average age at which these babies developed their infection was two weeks but babies as old as two months were still at risk for acquiring a GNB sepsis.

GNB were thus isolated from less than 10% of all the blood cultures sent on babies suspected of having a nosocomial infection. This is a similar yield to that noted by Hessling et al who recorded a rate of 7,8% while investigating the effects of long-term amikacin usage.[81] The yield was even lower from the CSF's sent on these patients (1,7%) resulting in just under 13% of the babies with acquired GNB septicaemia having an associated meningitis, a much lower incidence than

documented in the literature.[82] Two thirds of the cases of meningitis did not have an associated positive blood culture. This once again emphasizes the importance of doing a lumber puncture in every case of suspected nosocomial infection as otherwise cases of culture proven sepsis would be missed.

Other organisms including another GNB, yeasts and GPB were obtained from the same specimen from which the GNB was isolated in 12% of these patients. Whether this means that one or all were contaminants, or that these were genuine cases of multiple infections is difficult to ascertain. Certainly other investigators have established that sepsis due to more than one organism can occur especially in immune compromised patients.[100]

Babies with nosocomial GNB septicaemia were also at increased risk for developing another septic episode; 27% of these babies had further culture proven septic episodes and an additional 12% had a preceding nosocomial septic episode. They had more than double the risk of developing another GNB infection, and a thirteen fold increased risk of having a yeast infection compared to the rest of the babies that survived beyond three days of age but never had an hospital acquired GNB sepsis. An episode of nosocomial septicaemia would predispose the infant to further episodes by virtue of the fact that supportive care may have to be continued, the stay in an high care area would be prolonged, the immune system further depressed and the baby exposed to another

course of antimicrobials. What is surprising however is that this increased risk for developing a nosocomial infection was not shown for babies with early onset sepsis, for example GBS infection. Morgan et al also reported that 30% of their babies who survived an episode of Klebsiella septicaemia developed another nosocomial infection.[83] Klebsiella spp, the residential GNB responsible for most of the cases of GNB nosocomial sepsis in the Unit for many years, was isolated in just over half of the cases of nosocomial GNB septicaemia during the study period, its importance decreasing during the periods when outbreaks due to other GNB occurred such as Pseudomonas spp (December 1990), Serratia spp (January and February 1990), E. coli (July and August 1990) and Enterobacter spp (December 1989). Klebsiella spp is also responsible for outbreaks of hospital acquired GNB sepsis in many other neonatal units.[84, 85,86,87,88] Morgan et al described an outbreak of Klebsiella septicaemia in their neonatal ICU with a mortality of 70% despite appropriate antimicrobial therapy, half of them dying within 24 hours of the onset of their infection; slightly higher percentages than observed in our study cf. 56% and 38% respectively.[83] Most of their babies acquired their nosocomial Klebsiella septicaemia within one week of birth (66%), again an higher proportion than observed in our study (31%) though they do not indicate the age at which they defined sepsis due to hospital acquired Klebsiella. The mean birth weight of their affected babies was less than ours, 1270g cf. 1590g, and this may explain why their mortality was higher.

They did not comment on any seasonal variation as was noticed amongst the cases of nosocomial Klebsiella septicaemia in our study, though it is difficult to postulate why the incidences should have been higher in the winter months.

Nosocomial septicaemia due to Pseudomonas spp has a low background prevalence in our Unit with only a few cases a month. However, the outbreak observed in December 1990 made it the second most common isolate during the study period. A high proportion of cases came from the ICU where this organism is commonly found in ventilator humidifiers and other solutions. Unfortunately, all attempts at identifying the source of the outbreak failed; specimens of water from the humidifiers and various intravenous fluids sent for culture did not yield Pseudomonas spp, although this organism was subsiquently identified on the hands of personnel. Fortunately, the outbreak abated without any intervention as the mortality proved to be very high (83%).

Unlike sepsis due to the other GNB, that due to E. coli occurred mainly amongst babies admitted to the low care wards, wards 66/67. The babies thus were significantly bigger than those with s psis due to other GNB. This may be because less antimicrobials were used in these wards, which might encourage colonization with more resistant GNB. Both Fryklund et al and Tullus et al observed that faecal colonization with E. coli increased with increasing age and at the expense of other GNB such as Klebsiella spp.[80,89] The monthly incidences of cases

of nosocomial sepsis due to E. coli was very low with a small unexplained outbreak observed during the winter months of 1990.

If hospital acquired septicaemia due to Pseudomonas spp. was uncommon in the Unit, that due to Serratia was virtually unheard of till the end of 1989 following the change in antimicrobial policy to amikacin as sole aminoglycoside used, when an outbreak of amikacin-resistant, gentamicin-susceptible Serratia sepsis occurred. Once again, most of the cases were babies admitted to the high care areas especially those that required ventilation. All efforts at establishing a source failed and the outbreak abated slowly without any intervention. Babies with acquired Serratia sepsis were older than those with sepsis due to other GNB and thus had a lower mortality, though why this age difference should occur was difficult to determine. Though other neonatal units have also reported outbreaks due to Serratia spp, none have associated them with changes in antimicrobial policies.[90,91,92,93,94,95] They all commented on the importance of gut colonization amongst the babies as being the most important reservoir for spread. Fomites such as breast pumps, respirators and mucous extractors may have played major roles in the initiation and maintenance of the spread in some of these outbreaks. The Serratia isolates obtained by Lewis et al had a similar resistance pattern to those observed in our study, showing gentamicin-susceptibility and amikacin-resistance.[96]

Cases of septicaemia due to Enterobacter spp were also uncommon with a small outbreak in December 1989. Outbreaks due to these organisms occurring in neonatal units are not often reported on in the literature.[97]

2.1.1 Antimicrobial Susceptibility Despite using a combination therapy of an aminoglycoside and cephalosporin to treat suspected nosocomial infections in our unit, a regime which has been said to decrease the likelyhood of resistant strains from emerging, resistance amongst GNB occurred first to cefotaxime at the end of 1988, then to ceftazadime within a few months.[98,99,101,102,103] This prompted the withdrawal of their empiric use to treat cases of suspected nosocomial sepsis in April 1989, and vancomycin and amikacin were used instead. This is an accepted form of therapy used in other neonatal units; amikacin is the aminoglycoside least modified by the aminoglycoside-inactivating enzymes frequently elaborated by nosocomial pathogens and vancomycin would be active against resistant Staphylococci and E. faecalis.[104,105,106] Contrary to expectations, withdrawing the use of cephalosporins did not result in an improvement in the resistance to them shown by GNB.[60,79] In fact, despite not using cephalosporins for a year, the incidence of resistance steadily increased especially amongst the Klebsiella, Pseudomonas and Serratia spp. By the end of 1990 nearly a quarter of the GNB were resistant to ceftazadime and 60% to cefotaxime.

Resistant strains often appear shortly after the introduction

of new β-lactam antimicrobials. Bryan et al documented the effects of changing from the empirical use of gentamicin and ampicillin to cefotaxime and ampicillin for treating suspected sepsis because of an outbreak of gentamicin-resistant Klebsiella infections in their neonatal unit.[79] Within 10 weeks of instituting routine cefotaxime therapy infections due to cefotaxime-resistant Enterobacter cloacae appeared; these organisms were gentamicin-susceptible. With the improvement in gentamicin resistance, gentamicin was reinstated as the empirical antimicrobials used. Modi et al noted a similar experience when they substituted gentamicin with cefuroxime.[60] They also observed that a baby did not necessarily have to have received a cephalosporin to be colonized with cefuroxime-resistant Enterobacter. Enzymatic modification is the major method of inactivation, more sophisticated enzymes appearing constantly.[59] This enzymatic resistance may be plasmid or chromosomal mediated. Virtually all GNB have the chromosomal gene for β-lactamase called "ampC" that encodes an enzyme more active in hydrolizing cephalosporins than penicillins. In Serratia spp, indole-positive proteus spp, Citrobacter freundii and Pseudomonas aeruginosa additional genes regulate the production of this β-lactamase. These bacteria can undergo single-step mutations to high-level enzyme producers and, even though the "ampC" enzyme hydrolyses broadspectrum cephalosporins poorly, if enough "amp " β-lactamase is made, resistance results. The amounts of enzyme produced may also be increased by exposure to a β-lactamase inducer. Both

second and third generation cephalosporins are inducers of cephalosporinase activities in the genera Pseudomonas, Serratia and Enterobacter. Multiple drug resistance may arise simultaneously. In most GNB, however, β-lactam resistance results from a plasmid-mediated β-lactamase. More than 30 varieties can be distinguished on the basis of biochemical criteria such as the substrate profile and isoelectric point, but by far the most common plasmid-encoded enzyme is TEM-1; SHV-1 is also frequent in Klebsiella pneumonia and PSE-1 is the most common variety on plasmids in Pseudomonas aeruginosa. Both cefotaxime and ceftazadime show a high degree of stability to plasmid encoded β-lactamase activities and are also relatively resistant to the normal amounts of chromosomally mediated cephalosporinase activities found in most organisms. But, plasmid-mediated β-lactamases with extended spectrums have been reported in a variety of GNB, especially Klebsiella pneumoniae, which provide resistance to oxyimino-β-lactams such as cefotaxime, ceftazadime and ceftriaxone, and aztreonam. Some are related to TEM-1, some to TEM-2 and others to SHV-1. A cefotaximase (CTX-1) elaborated by Klebsiella was identified in 1985 that conferred cross-resistance to a wide variety of β-lactam antimicrobials including other cephalosporins, aztreonam, aminopenicillins, carboxypenicillin and ureidopenicillins. Isolates with this pattern of resistance were found in this study suggesting the presence of the CTX-1 gene in these Klebsiella isolates ought to be sought. All the GNB in our study, except E. coli, were highly resist-

ant to the cephalosporins towards the end of the study period, with 93% of the Pseudomonas isolates being resistant to cefotaxime and 22% to ceftazadime, and half of the Enterobacter spp displaying resistance to both cephalosporins. Klebsiella spp also showed a significant increase in resistance to ceftazadime over the study period, from 5% to 27%. Though reports had indicated that withdrawing the use of cephalosporins during times of increasing resistance would encourage the return to susceptibility, our study certainly did not confirm this.

Amikacin, a semisynthetic derivative of kanamycin, is modified inefficiently or not at all by the majority of aminoglycoside-modifying enzymes and therefore remains active against a number of otherwise aminoglycoside-resistant bacteria.[106,107] It appears from previous studies that the substitution of amikacin for all other aminoglycosides is not necessarily followed by a concomitant increase in resistance to amikacin and that its predominant or exclusive use may, in fact, result in the general reduction of aminoglycoside resistant isolates. Changing to amikacin as sole aminoglycoside used in our Unit in September 1989, however, was associated with the emergence a few months later of amikacin-resistant gentamicin-susceptible Serratia spp, organisms previously seldom observed in the Unit, as the major cause of GNB nosocomial sepsis. The proportion of amikacin resistant GNB prior to the change in policy was already higher (9,5%) than that observed by other investigators, resistance rates ranging from 1,8% to 6%. By the end

of 1990 the resistance had more than doubled. This increasing resistance was not only due to the Serratia spp but amongst the Klebsiella spp amikacin-resistance increased 20 fold, from 1,7% to 34,7%! Van Nhieu et al in Chile[108] noted a similar trend. None of their GNB isolates showed amikacin-resistance prior to changing to amikacin as the only aminoglycoside used in their hospital, following which 42 GNB including E. coli, Klebsiella, Enterobacter and Serratia spp showed amikacin-resistance during a 9 month period. Unfortunately they do not say what proportion of GNB isolates this represented. They observed that this resistance was transferable by conjugation, carried by "IncM" plasmids and mediated by a 6' aminoglycoside acetyl-transferase (AAC(6')), the most frequent cause of amikacin-resistance in GNB isolates, though other enzymes have also been implicated and reduced uptake may also be responsible. These plasmids can be found in the normal faecal flora, providing a potential source for spread to other pathogenic bacteria, and may be extremely stable over long periods and over wide distances. John et al demonstrated the presence of R plasmid-containing multi-resistant Klebsiella pneumoniae that coded for aminoglycoside modifying enzymes (3)-I(ACC(3)-I) and 2"(ANT(2")) in the faeces of 12% of the infants in their neonatal ICU, only a small proportion becoming symptomatic.[109] This R-plasmid was also identified in multiresistant E. coli found in an infant-mother pair months after discharge. The proportion of babies colonized with amikacin-resistant organisms is still smaller than that in whom gentamicin-

resistant organisms are found; Bryan et al recorded that half of the babies in their ICU were colonized with gentamicin-resistant Klebsiella spp, a similar proportion as found by Morgan et al (39%).[79,83] They observed that resistant organisms can be found in the faecal flora without the patient ever having been treated with that antimicrobial. Other investigators (Alan et al) also demonstrated a significant increase in amikacin-resistant GNB following increased amikacin usage, but in their case this coincided with a decrease in the frequency of transmissibility of aminoglycoside resistance among GNB isolates.[110] They thus postulated that the increased resistance observed was due to chromosomal mutation rather than due to R plasmids. Analysis of their results reveals that the organisms that developed amikacin-resistance were Pseudomonas aeruginosa and Proteus mirabilis. Klebsiella pneumoniae did not show an increase in amikacin resistance. Levin et al also observed an increase in amikacin-resistant GNB following increased use of amikacin, from 2% to 7%, with 12% of their Klebsiella isolates being resistant and 23% of their Serratia isolates. They also identified Klebsiella spp that were resistant to amikacin but susceptible to gentamicin. These isolates were shown to produce enzymes AAC-6'-I and APH-3'-IV.[111]

Stanford et al did not find an increase in resistance to amikacin following the use of amikacin as first-line aminoglycoside in their paediatric department, though they only analyzed 3 months prior to the change and compared it to the

next 33 months.[112] Neither did they show any improvement in the resistance patterns to the other aminoglycosides. Interestingly enough, they had changed to exclusive amikacin use when their GNB isolates were only showing 4,8% resistance to gentamicin. It would also have been interesting to know if their observations held true for their intensive care units as it is in these settings that resistant organisms develop. Hessiling et al observed the effect of using amikacin as the sole aminoglycoside in the paediatric department at Tygerberg Hospital over an 18 month period and concluded that the resistance to this drug among GNB did not increase and that resistance to other aminoglycosides, gentamicin, netilmicin and tobramycin, decreased. They, however, analyzed all GNB isolates obtained at that hospital including those obtained from adult patients who continued to be treated with various aminoglycosides. Thus, any effect a change in antimicrobial policy implemented by the paediatric wards on the susceptibility pattern of GNB might have been masked.[81]

Larson et al identified Serratia isolates that were gentamicin-susceptible, tobramycin-resistant that produced AAC(6'). However, the amikacin MIC's were only 16 to 32 µg/ml and the frequency of AAC(6') production was not shown to increase with increased amikacin use.[113] In addition, the production of AAC(6') in these isolates was shown not to be plasmid mediated but rather chromosomal in origin, a finding that had previously also been made by John et al.[109] Gaynes et al demonstrated that their Klebsiella and Serratia isolates that showed amik-

acin and tobramycin resistance but gentamicin susceptibility produced a novel 3'-phosphorylase, APH(3'), encoded on a 6,8-kilobase plasmid (pRPG101).[114] Lambert et al recovered the same enzyme carried by pIPI841, a 63 kilobase plasmid, in Acinetobacter isolates.[115] Numerous other plasmids have since been identified by Jacoby et al carrying genes encoding for amikacin-modifying enzymes.[116] It is an open question whether such factors as the daily dose, frequency of administration, or combination with other drugs play a role in the selection of amikacin resistance plasmids.[117] It will be interesting to see what the effect, if any, once daily dosing with amikacin now employed in the Unit will have on resistance patterns.

Though it appeared that withdrawing the use of gentamicin encouraged the emergence of susceptible strains in our study, this was not so, the improved resistance being due to the appearance of the gentamicin-susceptible Serratia, Klebsiella isolates remaining 80% resistant. Van Landuyt et al demonstrated decreased resistance to gentamicin among Enterobacteriaceae and Pseudomonas aeruginosa following its withdrawal.[118] Young et al also showed decreasing resistance to gentamicin during a 15 month period of amikacin usage which was mainly attributed to falling resistance amongst Pseudomonas aeruginosa isolates.[119] They also demonstrated an increase in amikacin resistance by both Pseudomonas, Serratia and Acinetobacter spp.

Unfortunately, organisms demonstrating amikacin resistance

also are often resistant to third generation cephalosporins; just under half of our amikacin-resistant Klebsiella isolates were resistant to ceftazadime and 70% to cefotaxime. Thus, the emergence of an endemic population of clinical bacterial isolates that are able to evade kill by aminoglycosides may have simultaneously selected for bacteria with an enhanced capacity to resist many antimicrobial agents, even some that have not yet been introduced into standard clinical practice. An interesting phenomenon observed in our study was the isolation of successively more resistant strains of GNB from several babies involving Klebsiella, Serratia, Pseudomonas and Enterobacter isolates. Whether this reflects an increasing ability of the organism to modify more antimicrobials or the selection of strains originally present due to antimicrobial pressure is not clear. Reports on the development of resistance to cephalosporins in originally susceptible organisms while the patient was on therapy have been published, but this has not been documented for other antimicrobials.[60]

Imipenem was the only other antimicrobial that could be used in our Unit in cases of suspected nosocomial sepsis as resistance to the remaining antimicrobials was so high. It has a broad antibacterial spectrum covering both GPB and GNB, and may act synergistically with aminoglycosides. Extended-spectrum β-lactamases are unable to confer resistance to imipenem, but a few organisms produce a specialized imipenem-hydrolyzing β-lactamase, including rare isolates of Serratia spp, Enterobacter cloacae, Bacteroides fragilis and all

strains of Xanthomonas multophilia.[59,120] The responsible genes are chromosomal, which would limit the spread to other bacteria. In a few organisms imipenem resistance has been associated with altered penicillin-binding proteins. Pseudomonas aeruginosa can also readily become resistant to imipenem specifically through the loss of an outer-membrane protein that provides a channel for the entry of imipenem, and a similar mechanism has been proposed for imipenem resistance in Enterobacter aerogenes. 23% of the Pseudomonas isolates in our study showed imipenem resistance.

**2.1.2** Mortality Though the mortality due to nosocomial GNB septicaemia was comparable to that in other units, it remains unacceptibly high and was responsible for a quarter of all the deaths that occurred after three days of age in the Unit, being the most important cause of death amongst babies with birth weights of 1500g to 1999g. Not surprisingly the mortality was highest amongst babies with birth weights <1000g (72%) as they would not have received any ventilatory or inotrope support when their condition deteriorated. The highest mortality was found amongst the babies with Pseudomonas septicaemia (83%) and the lowest amongst those with an acquired Serratia infection (38%). Generally, the mortality due to nosocomial sepsis was higher than that due to congenital infections, 56,5% vs. 23,4% as has been noted by other researchers.[32] Interestingly enough, the presence of meningitis did not result in an increased mortality.

An important finding was that the change in antimicrobial policy for treating suspected cases of hospital acquired sepsis which resulted in only one drug being used that would cover for GNB instead of two did not result in a higher mortality. If anything, the mortality decreased (54% vs. 67%), probably reflecting hightened awareness and improved care of infected babies during the study period. Most authorities would advocate treating GNR sepsis in the neonate with combination therapy.99 The change to first-line amikacin therapy also did not have an adverse effect on the mortality.

2.1.3 Haematology The WCC and platelet count were poor indicators of acquired sepsis and also not useful in prognosticating the outcome, except in the babies with Pseudomonas or Serratia septicaemia when a platelet count below 100 000/ml was associated with a higher mortality. These are surprising findings as one would have thought that babies with neutropaenia would have carried a worse prognosis than those without.

In summary, nosocomial septicaemia was an important cause for increased morbidity and mortality in our Unit. Though hand spread must be an important mechanisms by which GNB were transferred from baby to baby, members of staff were rarely identified as carrying these organisms.[121] Equally, they were seldom isolated from the environment in proximity to affected babies. The most important recevoir of these organisms is amongst the neonates themselves. Morgan et al demonstrated that faecal carriage in these babies is constant; none of

their babies studied ceased rectal carriage whilst in their unit.[83] As these infants are discharged home still colonized with these organisms and can remain so for months, the possibility of disseminating these organisms to the general population is particularly worrying.[122,123]

2.2 Systemic Fungal Infections

Systemic fungal infection occurred in 1,7% of all the admissions to the Unit during the study period; the highest rate being among admissions to ICU (6,2%) and among babies with birth weights <1000g (7,9%), though most of the cases occurred in babies with birth weights between 999g and 1500g. These are similar rates compared to other researchers though some report much lower rates.[124,125,126,127,128,129] Most of the cases were due to Candida spp though the number of cases declined during 1990, the last two months of which saw cases of Torulopsis glabrata appearing. Whether this was related to a concurrent project involving the use of prophylactic oral mycostatin is conjecture. The relationship between hospital acquired GNB septicaemia and fungaemia has already been mentioned, the fungal infection occurring more often after than before the GNB infection. The babies with systemic fungal infections were thus older than those with nosocomial GNB sepsis, mean age of 22 days vs. 14 days. One wonders how many more babies would have developed a fungaemia had they not succumbed to, for example, their Klebsiella septicaemia which often proved to be rapidly fatal.

Candida infections are thought to arise from invasion or disruption of colonized mucosal or epithelial surfaces; certainly a strong correlation between systemic fungaemia and bowel pathology was demonstrated in our study. Infants with mucocutaneous candidiasis are at increased risk of developing invasive candidiasis especially if of LBW.[130] A third of the babies with mucocutaneous candidiasis in the study by Roger et al developed systemic candidiasis.[127] Treatment of the mucocutaneous lesions with nystatin did not preclude subsequent development of invasive candidiasis which occurred as late as two months after the diagnosis of mucocutaneous candidiasis. The incidence of systemic candidiasis in that study amongst babies with birth weights <1500g was 4,5% cf. 5,4% in our study. They also demonstrated that prolonged duration of antimicrobial therapy and duration of endotracheal intubation were associated with invasive candidiasis. The possibility that some antimicrobial agents may directly stimulate the replication of candida remains controversial.[131] It is difficult to know whether the association with prolonged endotracheal intubation is causal by providing a route directly to susceptible lung parenchyma, or merely a marker of the sickest infants. Weese-Mayer et al in addition noted associations with parenteral nutrition including iv fat emulsions, also demonstrated in our study which showed a 13 to 30 increased chance of developing a fungal infection if on parenteral nutrition than if not.132 However, it is not clear if the fungaemia is due to the bowel pathology for which the

baby was parenterally alimented or whether it is due to the intravenous solutions per se. Fungaemia developed in 0,9% of the babies in their intensive care nursery, a much lower proportion than in ours cf. 6,2%. Unfortunately, the use of prophylactic oral nystatin since birth in at risk LBW babies has not been shown to prevent the development of systemic fungal infections later on.[133]

The mortality due to systemic fungal infections in our study was 45%, babies who acquired their infection in the ICU having a mortality of 57%. Unlike deaths due to GNB septicaemia, that due to fungaemia was not higher amongst LBW babies, an unexplained finding. It accounted for 10% of all deaths among babies older than three days of age, though it is often difficult to ascertain whether the baby died from the fungal infection or from septicaemia caused by another organism, 56% of them having at least one other episode of nosocomial septicaemia, a higher proportion than was found amongst babies with nosocomial GNB sepsis (39%). Though there is a general impression that systemic fungal infections are not as fulminant as that due to GNB, 22% of the babies with fungaemia who died did so within 24 hours of being cultured for suspected sepsis and 62% of the deaths occurred within a week. This meant that a large proportion of babies were never treated for their fungal infection.

Once again, haematological parameters were unhelpful in identifying babies with systemic fungal infections or in

prognosticating their outcome.

## 2.3 Gram Positive Isolates

GPB were isolated in a slightly smaller number of babies older than three days than GNB during our study (207 vs. 222), the most common isolate being S. epidermidis (48%), followed by S. aureus and E. faecalis. Whether a large proportion of these isolates were contaminants is difficult to determine. Certainly, S. epidermidis has become an increasingly important cause of nosocomial bacteremia in many neonatal ICU's especially amongst LBW weight infants making up as much as 73% of all nosocomial blood culture isolates.[134,135,136,137,138] The emergence of coagulase-negative Staphylococci as pathogens in neonatal ICU's is thought to be associated with the widespread use of broadspectrum antimicrobials in these units though other factors certainly promote the occurrence of such infections in the premature newborns.[139] As opsonization is a key process in host resistance to Staphylococci, the decreased opsonic activity observed in premature neonates would predispose them to infections due to these normally harmless commensals.[140,141] Moreover, heat-stable opsonins (opsonic antibodies to S. epidermidis) which are restricted to the IgG class in sera from normal adults, are completely lacking in sera from premature neonates.[142] They are even absent in term babies suggesting that either opsonically active IgG antibodies to Staphylococci are inactivated during transplacental transfer or opsonic IgG does not cross the placenta. Coagulase-negative Staphylococci are also capable of adhering to

plastic catheters due to hydrophobic bonding.[143] This may be inhibited by the hydrophilic serum protein albumin, and sub-inhibitory concentrations of cephalothin, vancomycin and, especially clindamycin. However, once established, catheter-related coagulase-negative Staphylococci are difficult to eradicate with antimicrobials. The role of slime production by coagulase-negative Staphylococci in adhesion to plastic materials is less well defined.[144] Christensen et al found that coagulase-negative strains of Staphylococci isolated from patients with catheter-related infection were more often slime-producers than strains not associated with an infection, but this is probably a secondary phenomenon following adhesion by hydrophobicity that protects them from the host's defense system.[145] Fleer et al reported that more than 90% of their cases of coagulase-negative Staphylococci occurred in babies with birth weights <2500g and that all were receiving intravenous therapy and nearly 80% were on parenteral nutrition.[146] This was not observed in our study; only 22% of the babies from whom S. epidermidis was isolated had received parenteral alimentation.

Because coagulase-negative Staphylococci also constitute commensal skin flora, these isolates are considered a common cause of contamination of blood cultures.[147] D'Angio et al showed that the skin of all premature babies admitted to an intensive care nursery were colonized with a predominant biotype of S. epidermidis within a week, 82% of which showed multiple antimicrobial resistance and 95% slime production, a

feature associated with pathogenicity.[148] Infants so colonized may be at greater risk for subsequent infection with these strains of coagulase-negative Staphylococci especially via intravascular catheters. It is difficult to interpret the significance of these organisms when isolated from a blood culture as the babies are usually treated immediately and thus one cannot confirm the isolate with repeat cultures as would be done in older patients. Quantitation by means of lysis-direct plating has been advocated as one method of predicting contamination.[149] Sepsis is deemed not to be present if bacterial counts less than or equal to 5 CFU/ml are obtained. However, Hammerberg et al demonstrated that only 7% of coagulase-negative Staphylococcal blood isolates were associated with identical contaminants obtained from the venipuncture sites and thus did not advocate the routine quantitation of neonatal blood cultures.[150] Evaluating the FBC including the immature to total neutrophil ratio has not been shown to facilitate the interpretation of blood cultures growing coagulase-negative Staphylococci in the neonatal period (Geme et al).[149] Many of the S. epidermidis obtained in our study were probably contaminants, the doctors' techniques for taking cultures falling very short of that recommended by Hammerberg, many of the cultures having been taken through arterial lines that had been placed many days earlier. Even if all the cultures reflected true bacteremia and not contamination, then S. epidermidis only accounted for 17% of all nosocomial isolates in our Unit.

Previous epidemics of S. aureus have been characterized by skin disease with little systemic illness. The increased use of umbilical catheters has resulted in an increase in the number of systemic infections due to S. aureus.[151] Very small numbers of S. aureus are capable of initiating newborn colonization making the identification of any factor in the environment as the source of infection difficult. Attendants' hands are probably the most important source of infant colonization. Wolinsky et al[152] showed that 85% of infants colonized with S. aureus resulted from an attendant's touch. By five days the colonization rate of infants in a neonatal unit may range from 40% to 90%; the sites of colonization including the umbilicus, rectum, nares and skin. The disease rate amongst these infants, however, is low being around 3%, but, in the case of epidemics due to virulent hospital strains may be as high as 70%.[139] Whether these strains will become widespread in nurseries and the extent to which resistant organisms are virulent remains to be seen.

E. faecalis until recently was not considered an important cause of neonatal sepsis.[153] Dobson et al, however, noted an increase in late-onset E. faecalis sepsis in their neonatal unit with an incidence of 0,7 per 1 000 live births, a much higher incidence than noted in our study (0,05 per 1 000 live births).[154] The incidence of early-onset sepsis in their study due to E. faecalis did not show a concommitant increase remaining at 0,1 per 1000 live births. The increase was attributable to the increased survival of very LBW infants due

to improved ICU management. 20% of the late-onset cases were associated with NEC, a similar proportion as observed in our study (23%). The early-onset cases occurred in near term babies who were not particularly ill and did not appear to have any obstetrical risk factors. The late onset occurred amongst LBW babies who were ill and had received several courses of antimicrobials, most of them on ventilation and with umbilical catheters in situ . Meningitis was present only amongst babies with late-onset disease, 15% having meningeal involvement, a lower proportion than found in our study cf. 30%. Polymicrobial sepsis occurred in 12% of the patients, most with NEC, a much lower proportion than observed in our study (33%). Both conditions carried a low mortality of 6-8%. All isolates were susceptible to ampicillin and vancomycin but an aminoglycoside was added to their treatment as both penicillin and vancomycin are only bacteriostatic for E. faecalis. The isolates obtained in our study were much more resistant, only half being susceptible to ampicillin.

## 2.4 Summary

The overall incidence of nosocomial infections in our unit is thus not definite as one cannot be sure which, if any, of the isolates from blood and CSF cultures were contaminants. Assuming that all the cultures were genuine, then the rate would be as high as 7,1 (445/6349). Rates amongst premature babies approaching 20% have been reported by Jarvis et al;[84] making similar assumptions, 8,8% (359/4072) of our LBW babies developed a nosocomial septicaemia, the highest rate being

amongst babies with birth weights <1000g (28,6%) (40/140) and approximately 18% (160/ 899) of babies admitted to the ICU were affected. Nosocomial infections would then have been responsible for 36% (177/489) of all deaths occurring after three days of age. The yield of positive blood cultures was twice as high when taken for suspected nosocomial sepsis compared to congenital infection, 20% (592/3000) vs. 10% (633/ 6000). Only 5% of the CSF's sent for culture yielded a growth.

3. NECROTISING ENTEROCOLITIS

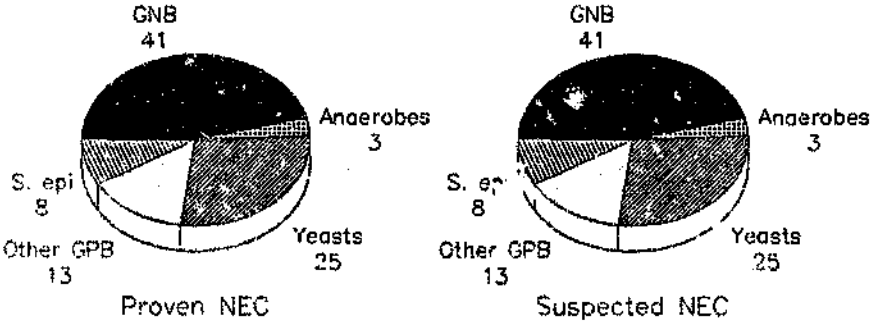
The association between nosocomial GNB sepsis and systemic fungal infections with NEC was most striking. However, this has been observed before by other workers; blood cultures have been shown to be positive in approximately one third of patients with NEC.[28] However, the organisms associated with NEC probably just reflect the colonic flora; they are not necessarily the responsible agents in the pathogenesis of NEC. Healthy babies acquire a complex bacterial flora within days of delivery whereas in those requiring intensive care and those on antimicrobials only one or a few atypical species are present in the faeces, often in much greater number as infants have not received any passive maternal protection against them. With time the diversity of colonizing species increase but the process can be interrupted or reversed by the administration of broad spectrum antimicrobials.[80,84] Faecal carriage rate of Klebsiella or Enterobacter spp in a neonatal unit of 42% and of E. coli of 14% has been reported.[61,83] One

study showed that antimicrobial usage in neonatal units promoted carriage of drug-resistant faecal bacteria among untreated infants more than among the treated neonates.[155] That is, antimicrobial therapy made the infants sources rather than recipients of nosocomial strains. Because the organisms isolated from the blood of babies with NEC reflect the current colonic colonization flora, the common pathogens identified have shifted recently from Gram negative enteric bacilli to S. epidermidis which has become an important cause of nosocomial sepsis in many neonatal ICU's. Uauy et al studied the occurrence of NEC in very LBW babies (<1500g).[156] Proven NEC occurred in 10% of their study infants and suspected NEC in 17%. Positive blood cultures were obtained in 44% of the babies with proven and 34% of suspected NEC compared to 15% amongst babies with neither bowel pathology. Interestingly enough, S. epidermidis and other GPB were the most frequent isolates in all except the babies with NEC who perforated when enteric gram negative organisms were most frequently isolated (49%). Candida spp made up 6% of all isolates, being more important among babies with suspected NEC when it made up 17% of the isolates. The incidence of proven NEC in the equivalent category of babies in our study was similar (7%) (78/1123), but that of suspected NEC lower (9%) (106/1123), probably reflecting a lower index of suspicion amongst our doctors than the real occurrence of less cases. The proportion of these babies with proven NEC or suspected NEC and positive blood cultures in our study was much higher, 60% (47/78) and

44% (47/106) respectively, whereas 15% (137/939) of our babies under <1500g without bowel pathology had positive blood cultures, the same as observed by Uauy et al. The most common organism isolated in our babies with NEC was, however, not S. epidermidis, which only accounted for 6% of positive blood cultures obtained from babies with proven NEC and 9% of those from babies with suspected NEC, but GNB. GNB accounted for 53% of the positive blood cultures obtained from our babies with proven NEC and 45% from those with suspected NEC. Yeasts were isolated much more frequently in our study making up a quarter of the positive blood cultures obtained from the babies with NEC (see Fig. 4.1). Expressed in another way, 40% of the babies from whom a GNB was isolated in our study and 43% from whom a yeast was isolated had either proven or suspected NEC. With the data available to us we were not able to differentiate those babies who had perforated from those who had not as one might have expected to isolate more organisms from cases of perforation.

Circumstantial data had suggested that NEC might be associated with an infectious agent; the disease occurs in epidemics which have been associated with single pathogens such as E. coli, Klebsiella spp, Salmonella spp, S. epidermidis, Clostridium butyricum and various viruses, and personnel have been observed themselves to be ill at the time of outbreaks of NEC.[157,158,159,160] The difficulty in isolating specific microorganisms though, has created the thought that NEC may be due rather to a bacterial toxin. Endotoxins released by enteric

Fig 4.1 Organisms Isolated in Babies with NEC



bacteria have been implicated as has tumour necrosis factor and platelet activating factor.[161] Delta toxin released by coagulase negative Staphylococci found in the faeces of babies has also been associated with the development of NEC.[160]

The mortality observed in our study of babies with NEC is very high, being 74% among babies with proven and 40% among those with suspected NEC. The mortality was not greater if blood cultures were positive in cases of proven NEC, probably reflecting the inherent high mortality of this bowel entity, However, the mortality was much higher in cases of suspected NEC if there was a concomitant positive blood culture. This probablly indicates that, in cases of suspected NEC without a positive blood culture the babies just had feeding difficulties, whereas in the remainder the gastrointestinal signs were a reflection os sepsis which would carry a higher mortality.

## 4. CONCLUSION

One cannot stress enough the important role infections play in the morbidity and mortality among babies admitted to Baragwanath's neonatal unit. Though there were many episodes of culture proven sepsis, when one actually takes into account the large number of patients passing through the Unit, the incidences are comparable to that observed by other investigators, as is the mortality in our Unit. The most important message must be that it is emperative to continue the surveillance that was instituted for this study as the prevalence of the organisms responsible for neonatal sepsis are continuously

changing as are their susceptibility patterns. Due to the suboptimal obstetric care received by pregnant women in Soweto, there probably is not much that can be done to modify the impact of congenital infections on their babies. However, much can be done to decrease the incidence of hospital acquired infections. Beside the basic aseptic techniques familiar to medical personnel, though often not adhered to in our Unit due to overcrowded, understaffed conditions, there are a number of other recommendations to attempt to decrease the number of babies compromised by nosocomial infections. It certainly is tragic to see a critically ill baby survive his original illness only to succumb to an infection courtesy of the hospital.

5.1 Recomendations

5.1.1 Diagnosis Accurate diagnosis of neonatal sepsis is difficult because there is no definitive diagnostic test: even blood cultures have an unacceptibly low sensitivity. In order to treat rapidly all neonates in our Unit with sepsis and minimize therapy for those without, further laboratory investigations such as levels of acute phase reactants should probably be performed. A scoring system using these together with a good clinical evaluation as advocated by St. Geme et al might be used to determine more accurately which baby is indeed septic and needs therapy.[162,163,164]

Nowhere does this hold more true than for the innumerable babies from whom Staphylococci were isolated. In order to

determine if at least the S. epidermidis isolated from the blood are contaminants or not, the lysis direct-plating quantitative technique as mentioned above could be adopted.

5.1.2 Antimicrobials Antimicrobial use should bestrictly controlled; the effect of broad spectrum antimicrobials on the normal gut flora of the neonate and the subsequent predilection to sepsis with multiresistant organisms has already been mentioned. Certainly, the use of intramuscular amikacin in the treatment of well babies with PROM or offensive liquor is not substantiated as only one GNB was isolated from these babies during the two years studied. In order to formulate what antimicrobials should be used in the unit, routine surveillance is neccessary.[165,166] At present only organisms isolated from the blood and CSF of ill patients are being recorded; ideally this should be extended to culture and sensitivity testing of other sites such as tracheal aspirates from intubated babies and rectal swabs from others in order to identify the current organisms in the Unit and their resistance patterns.[167] However, unless one intends to isolate colonized babies from those that aren't, this would be a costly exercise with little additional benefit, the organisms obtained from blood and CSF cultures invariably being those already present in the babies' gastrointestinal tract.[80,84] Routine surveillance permits the introduction of alternative first line treatment regimes on a rotational basis which may help in controlling the emergence of resistant strains let alone ensure that babies are receiving appropriate anti-

microbials. Whichever antimicrobial combination is used, care must be taken to avoid antagonism and to detect the emergence of resistant strains as they occur. This may entail changing the empiric regimen on a cyclical basis in order to minimize the problem and maintain an acceptable level of clinical response.[168] Controlling the development of resistance to an antimicrobial requires attention to the complex relationship between the use of the compound and factors such as how, and to which species, a particular resistance can be selected; why the strains carrying the genetic determination survive and/or multiply in a particular ecological niche; how plasmids and/or transposons carry the resistance gene; and what regulates the transferability of a plasmid.[169,170] The application of newer techniques in molecular epidemiology such as plasmid fingerprinting and gene probes and the identification of enzymes produced by microorganisms which are being used in other parts of the world, could also be used here as an epidemiological tool.[171] This would extend our knowledge of the nature and spread of multiresistant bacteria through our Unit, especially in the specialized ecosystems of the ICU and TCU.

As far as the usefulness of identifying colonized well babies is concerned, some workers managed to control outbreaks in their units by cohorting these babies; Morgan et al controlled their outbreak of gentamicin resistant Klebsiella by cohorting colonized infants and cross-infection control measures. However, it took them seven months to clear their unit by this method.[83] On the other hand, White et al[166] found that

surveillance for resistant organisms was not of value for predicting those infants who become infected. Furthermore, they found that the number of infected infants waxes and wanes independently of cross-infection control measures. Certainly, to be effective, measures designed to control the spread of resistance genes must be anticipatory, since by the time a plasmid epidemic is recognized, a large reservoir of patients have already been colonized ("iceberg effect").

Many of the organisms isolated in our Unit are multiresistant and the remaining number of drugs that could possibly be used is very limited with quinalones being contraindicated at the present time in neonates, imipenem-resistant strains may not be treatable, The determination of antimicrobial synergy using the checkerboard dilution technique might be of great benefit to determine what antimicrobials to use in treating septicaemia due to these organisms.[172] The results obtained in vitro, however, are often not what is observed in vivo; patients often do better with combination antimicrobial therapy despite no advantage having been shown in vitro. The usual method for testing in vitro antimicrobial combinations involves the exposure of a given bacterial inoculum to a constant or static concentration of the antimicrobial agent. However, in vivo, in the treatment of patients with clinical infection, antimicrobial concentrations are changing continuously in serum and in infected tissue or fluid. Thus, bacteria at the site of an infection are exposed in vivo to oscillating concentrations of antimicrobial drugs. Zinner et

al have developed a two-compartment in vitro pharmacokinetic model that allows them to expose bacterial inoculums to changing concentrations of antimicrobials in a manner that mimics their actual concentrations in human subjects.[101] Even organisms resistant to both antimicrobials used in a combination therapy can exhibit synergism. Therapy using both an aminoglycoside and a cephalosporin to treat multiresistant GNB showing in vitro resistance to both these antimicrobials has been shown to have a synergistic effect both in vitro as born out by the checkerboard tube dilution method and in vivo in that the clinical response was favourable. Isolates that show aminoglycoside resistance attributed to a permeability barrier can be synergistically inhibited by a combination containing ureidopenicillins that disrupt the cell wall and facilitate the transport of aminoglycosides to the ribosomes. Amikacin has been shown to be the most reliable synergistic aminoglycoside regardless of the $\beta$-lactam used. Clinically meaningful synergism produced by amikacin occurs in organisms moderately resistant (MIC <64$\mu$g/ml). In addition, combination therapy is thought to prevent the emergence of resistance.[102]

As subinhibitory concentrations of antimicrobials may result in increased numbers of resistant strains and therapeutic failure it is mandatory that drug levels be monitored. This has only been possible in our neonatal ICU, the large numbers of babies otherwise involved making it impossible both practically and financially.

5.1.3 Adjuvent Therapy As it is evident that many babies die from sepsis despite being on appropriate antimicrobial therapy, other adjuvant forms of therapy have been considered. Though it has been advocated that combining immunotherapy with antimicrobials might have a synergistic effect in the treatment of neonates with sepsis, work done by Leonard et al on GBS sepsis demonstrated that high doses of nonspecific immunoglobin may in fact cause blockade of opsonophagocytosis of GBS via Fc receptor blockade especially in the presence of neutropaenia.[173] High doses of GBS type-specific immunoglobin on the other hand appeared to be beneficial, more work in this regard being necessary.[174,175] Even though Haque et al showed significantly fewer deaths among babies given immunoglobin plus antibiotics than among babies not given immunoglobin, this study was not blinded nor placebo controlled.[176] Christensen et al[177] in a double-blinded, placebo-controlled study, though not showing an improvement in the mortality between babies with early-onset sepsis who received immunoglobin and those who did not, demonstrated improvement in a number of immunologic, haematologic and physiologic measurements resulting in a shortened hospital stay. They also demonstrated the safety of immunoglobins given to babies with sepsis; many theoretical complications such as hypotension due to the formation of antigen-antibody complexes with rapid release of potent inflammatory mediators were not observed. The use of immunoglobin therapy to reduce the mortality of congenital infections in the Baragwanath context is not feasible at

present due to the expense and lack of availability of specific immunoglobins. Inability of identifying the infected newborn would result in large numbers of babies being treated on suspicion, many unnecessarily.

5.1.4 Nosocomial Infections Selective decontamination of the gut as has been tried in adult ICU's might be effective in preventing colonization of the high risk neonate's bowel with resistant, pathogenic GNB. Groeninges et al were the first to advocate the use of oral antimicrobials to suppress undesirable organisms from colonizing the gut of patients admitted to intensive care units.[178] Reidy et al compared the colonization rate of their patients treated with oral tobramycin, polymixin E and amphotericin B with a control group. Rectal colonization with hospital acquired GNB fell from 60% to 20% and those present were less resistant whereas fungal colonization was completely eliminated being 20% in the control group. Nosocomial infections due to GNB and fungae were also decreased but there was no effect on GPB infections, these organisms showing an increase in resistance.[179,180] Others have suggested the use of avirulent, susceptible strains to colonize high-risk individuals but these approaches remain experimental. Prevention of colonization of the neonate's gut by Candida spp using antifungal agents would most likely prevent systemic disease as well (Baley et al).[129] To date, effective strategies have not been defined; certainly, a study performed in this unit using oral mycostatin did not effect the rectal carriage rate though the incidence of systemic

fungal infections did decline. The use of fungal agents other than nystatin still needs to be evaluated; the use of short courses of low-dose systemic antifungal agents is speculative.

Immunoglobin infusions have also been used prophylactically in preterm infants in an attempt to decrease the incidence of nosocomial sepsis.[181,182 183] The apparent failure of this therapy in various studies may have been due to the fact that predetermined doses were given at fixed intervals, no effort having been made to adjust the therapy according to a target serum level. Clapp et al[184] gave immunoglobin to preterm infants throughout their hospital stay to achieve a serum IgG level of 700mg/dL and showed a significant decrease in the number of episodes of nosocomial sepsis. However, this form of therapy is cumbersome, let alone expensive, levels of IgG having to be determined routinely and treatment adjusted accordingly in order to ensure that the target level was maintained and thus not really feasible in our Unit. New approaches in adults using monoclonal antibody to the lipid A moeity of endotoxin may have application in neonates. In addition, the use of anti-TNF must be evaluated in paediatric ICU's.

Cost effective strategies that can be implemented are improvement in routine infection control procedures, limiting the number of babies admitted to the wards and increasing the nursing staff. Education of the personnel on the single importance of handwashing, and ensuring its implementation, may illustrate a simple solution to a complex problem.

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