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An audit of neonates admitted to the general ward at Charlotte Maxeke Johannesburg academic hospital

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University of the Witwatersrand
Research Report
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An Audit of Neonates Admitted To the General Ward at Charlotte Maxeke Johannesburg Academic Hospital

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August 2013

DECLARATION

I, Tanusha Ramdin, declare that this thesis is my own work. It is being submitted for the degree of Masters in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or any other University.

24th day of August 2013

Johannesburg

A scientific paper, based on my research report has been submitted to African Journal of Emergency Medicine to be considered for publication.

DEDICATION

To my parents

Abstract

South Africa is one of the countries in which neonatal mortality has either remained the same or decreased marginally over the past 20 years (1). Resource constraints result in early discharge of well newborns and curtailment of follow up home visits by nurses. This potentially high-risk group of infants may contribute to these neonatal deaths post hospital discharge. In addition, once a neonate has been home, they are no longer admitted to the neonatal unit but to the general paediatric wards that may lack specialized neonatal care.

Numerous programs, algorithms, education drives and protocols have been devised in an attempt to improve the quality of healthcare offered to the newborn. These have led to a perceptible decline in the neonatal mortality and morbidity rates respectively. The neonatal mortality and morbidity rates remain unacceptably high however, particularly in resource poor settings.

Aim: The aim was to determine the profile and outcome of neonates admitted to the general paediatric wards at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Methodology: Audit of all newborns (<28days) admitted to the general wards from 1 January 2011 to 30 April 2011. Patients transferred from other tertiary hospitals were excluded.

Patients with incomplete records were also excluded

Results: There were a total of 73 neonates admitted with a mean weight of 3.2kg (SD 0.65). The median age for 0-7 days was 4 days and for 8-28 days was 17 days. The majority of neonates 41/73 (56.2%) were male and 21/73 (28.8%) were HIV exposed. In the HIV exposed group only 16/21 (76%) were on HIV prophylaxis. Although antenatal care (ANC) was received by 76.7% of mothers, this is lower than ANC received by the general population. Lack of ANC could possibly be a risk factor for admission of neonates. Possible risk factors for serious illness included 8 (11%) were ex premature infants and 11 (15.1%) had a low birth weight (<2.5 kg). Individual indicators for severity of illness by World Health Organization (WHO) Integrated Management of Childhood and Neonate Illness (IMCNI) were used. The most frequent indicators were tachypnoea (RR>60) 34 (46.6%), jaundice 30 (41.1%) and only 1 (1%) presented with convulsions. Respiratory distress was very sensitive (100%) and relatively specific (76%) for detecting bronchopneumonia (BRPN) with a LR of 3.98. The other clinical indicators were neither specific nor sensitive in detecting serious illness.

Most 45 (61%) were referred from the local clinic. The commonest diagnoses were bronchopneumonia (BRPN) 20 (27.4%), neonatal sepsis (NNS) 22 (30.1%) and jaundice 22 (30.1%). Two patients died (2.7%). Their diagnoses were NNS and BRPN

Conclusions: There are a significant number of newborns admitted to the general paediatric wards, although the mortality rate in this group was low. IMCNI guidelines remain the most sensitive indicator of the need for admission, and “routine” blood investigations are often non-contributory Community based care and education programmes as well as targeted neonatal care in hospitals for this group is warranted.

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Abbreviations

BC	:	Blood Culture
BRPN	:	Bronchopneumonia
CMJAH	:	Charlotte Maxeke Johannesburg Academic Hospital
CoNS	:	Coagulase Negative Staphylococcus
CRP	:	C - Reactive Protein
CSF	:	Cerebrospinal Fluid
CXR		Chest X-Ray
DOA	:	Dead On Arrival
E.coli	:	Escherichia coli
E.faecalis	:	Enterococcus faecalis
ED		Emergency Department
FBC	:	Full Blood Count
GA		Gestational Age
GP	:	General Practitioner
GROUP B STREP		Group B Streptococcus
HB		Haemoglobin
HGT	:	Human Glucose Test
HIV	:	Human Immunodeficiency Virus
ICU	:	Intensive Care Unit
IHMR	:	In Hospital Mortality Rate
IMCI	:	Integrated Management Of Childhood Illness
IMNCI	:	Integrated Management Of Neonatal And Childhood Illness
KMC	:	Kangaroo Mother Care
LBW		Low Birth Weight
LP		Lumbar Puncture
LR	:	Likelihood Ratio
LRT	:	Lower Respiratory Tract
MC & S	:	Microscopy, Culture And Sensitivity
MDG	:	Millennium Developmental Goal
MTCT	:	Mother To Child Transmission
NNJ	:	Neonatal Jaundice
NNS	:	Neonatal Sepsis
NPV	:	Negative predictive value
Percentage	:	Percentage
PMN	:	Polymorphoneucleocytes
PMTCT	:	Prevention Mother To Child Transmission
PPV	:	Positive predictive value
PUV	:	Posterior Urethral Valves
RTHC	:	Road To Health Card
RVD	:	Retroviral Disease
SBI	:	Serious Bacterial Infection
SD		Standard Deviation
URT	:	Upper Respiratory Tract

UTI	:	Urinary Tract Infection
VLBW	:	Very Low Birth Weight
WCC	:	White Cell Count

Introduction

In 2008 an estimated 1.2 million neonatal deaths occurred in Sub-Saharan Africa (2). This accounts for a third of the world's annual neonatal death toll. The most important causes were infection (29%), prematurity and complications thereof (29%) and birth asphyxia (23%) (1, 2).

The Millennium Development Goal 4 (MDG4) aims to reduce the mortality rate for children below 5 years of age by 66 % before 2015 compared to rates in 1990. Childhood mortality in South Africa is however increasing (3). Globally neonatal mortality comprised at least 41% of the mortality rate for children below 5 years of age (4). To reduce neonatal mortality the burden and spectrum of disease needs to be analyzed. The current management practices in our Emergency Departments (EDs) needs to be scrutinized, in order to be improved upon.

Numerous programs, algorithms, education drives and protocols have been devised in an attempt to improve the quality of healthcare offered to the newborn. These have led to a perceptible decline in the neonatal mortality and morbidity rates respectively, which remain unacceptably high, however, particularly in resource poor settings.

Most neonates in South African EDs are routinely subjected to a complete septic workup irrespective of the presenting complaint, an exceedingly high percentage of neonatal presentations are unnecessarily hospitalized. This stems from poor insight, inadequate resources, poor patient follow-up and a lack of education amongst ED staff and parents.

Neonates are highly susceptible to infectious diseases because of their immature immune systems and poorly developed skin barrier. In addition, newborns in developing countries are exposed to environmental risk factors placing them at an even higher risk. According to the World Health Organization (WHO), only 68% of women in developing countries receive some form of antenatal care and only 35% of mothers in the least developed countries had access to skilled health personnel at delivery (4). At the same time, beneficial practices, such as the use of colostrum and exclusive breastfeeding are often ignored or discouraged.

Unfortunately, infants born in hospitals are also at significantly increased risk of neonatal infections compared with industrialized countries because of a lack of adequate infection control (5).

Population-based studies from developing countries have reported clinical sepsis rates from 49 to 170 per 1000 live births (5). Knowledge about the organisms responsible for sepsis in developing countries is essential for targeted empiric therapy when cultures are awaited or not available. A comprehensive review conducted by Ganatra et al showed that Gram-negative organisms were the main pathogens and *Staphylococcus aureus, Escherichia coli* and *Klebsiella spp* caused 44% of all sepsis worldwide(6). However, in Africa there was an overall dominance of Gram-positive organisms especially Group B streptococci. The review went on to highlight that blood cultures remained the gold standard for the diagnosis of neonatal sepsis. However, most district and community hospitals do not possess the necessary infrastructure and the diagnosis of neonatal sepsis is determined clinically.

Simple symptoms and signs that reliably indicate the presence of severe illness that would indicate the need for urgent hospital admission are therefore of major importance. If these reliable indicators were used correctly, they would enable Emergency Department staff to identify the neonates requiring admission and further investigation.

Jeena et al looked at the clinical profile and predictors of severe illness in young South African infants (<60 days of age) at King Edward Hospital in Durban (7). They commented that it is important to have a simple algorithm that could predict the severity of illness to refer these children promptly. They found that the simple features of feeding difficulties, pyrexia, tachypnoea and lower chest in-drawings are useful predictors of severity of illness as well as effective and safe tools for triaging of young infants for urgent hospital management at primary care centres. They also found that neonatal hyper-bilirubinaemia, pneumonia and sepsis are the common conditions for which young infant's required urgent admission. Importantly, they also found that the addition of laboratory testing only marginally improved the prediction of serious bacterial infection (SBI), hence rendering it non-feasible in a resource-poor setting, although basic principles recommend cultures to guide appropriate antibiotic treatment.

Weber et al as part of the Young Infant Clinical Signs Study Group conducted a multi-centre study of clinical signs in an attempt to identify infants with serious illness(8). Clinical signs were recorded using existing WHO Integrated Management of Childhood Illnesses (IMCI) Guidelines. In the group from birth to 6 days of age, the commonest diagnoses were severe infection, pre-maturity and birth asphyxia.

The following 12 symptoms and signs were most predictive of severe illness in the first week of life (8):

1. Temperature > 37.4
2. Temperature < 35.5
3. Respiratory Rate > 60/min
4. Presence of severe chest in-drawing
5. Presence of Cyanosis
6. Presence of Lethargy
7. History of Feeding Difficulty
8. History of Convulsions
9. Movement only when stimulated
10. Grunting
11. Presence of stiff limbs
12. Prolonged capillary refill

The presence of any of these had a high sensitivity (87%) and specificity (74%) for predicting severe illness. They also had good sensitivity (78%) and specificity (74%) in the 7 to 59 day old age group (8).

Simplifying the algorithm to the following seven signs gave a similar sensitivity (85%) and specificity (75%)(8).

1. Temperature > 37.4 or <35.5
2. Respiratory Rate > 60/min

3. Presence of severe chest in drawing
4. Presence of Lethargy
5. History of Feeding Difficulty
6. History of Convulsions
7. Movement only when stimulated

When applied to the 7 to 59 day old group it had a sensitivity of 74% and a specificity of 79%.

Goswami et al evaluated simple clinical signs of illness in young infants (0-2 months of age) and its correlation with the WHO IMCI guidelines (9). They concluded that the IMCI algorithm appeared to be a "promising, feasible and useful intervention strategy to triage and treat young infants in the 7 day to 2 months age group". The tool remained effective when extended to the 0-7 day age group. They also found the addition of the presence of jaundice could increase the tool's sensitivity.

The aforementioned and subsequent studies show the evolution of the new WHO Integrated Management of Neonatal and Childhood Illnesses (IMNCI) guidelines.

Many studies investigated clinical signs, which would predict severe illness or mortality as an outcome in children less than 2 months of age (7, 8, 9, 10). However, it was not possible to combine the data from these articles due to the different study designs, data collection methods and outcomes used. However studies from Ghana, South Africa, Chandigarh and Delhi all contributed to the Young Infant Clinical Signs meta-analysis.

Age had an important impact on the pattern of clinical signs. In infants 7-59 days of age, infection is the dominant clinical diagnosis and respiratory infections and diarrheal illness the most common (10). Interestingly, in the 0 to 6 day old group, the commonest significant predictor across the studies was poor feeding. In the 7 to 59 day old group, poor feeding was again the commonest significant independent predictor. Respiratory signs (tachypnea and chest in drawing) and fever were also reliable indicators. When this review was conducted, jaundice had not been included in the IMCI guidelines. The review provided evidence that jaundice needed to be included in any referral checklist for infants in the 0 to 6 day old age group (7, 8, 9, 10).

Thus far it is evident that training and knowledge of recognition of clinical signs is important. The training and supervision of health workers to identify severely ill children should continue to be given the highest priority. Parents and guardians should also be correctly educated as they play a key role in improving the health status of their children.

In addition to prompt diagnosis and treatment, preventive strategies are essential to reduce the burden of neonatal sepsis. There is a need to provide universal antenatal care for women in developing countries. During the postnatal period, early and exclusive breast-feeding is perhaps the most important intervention to prevent neonatal sepsis. Kangaroo mother care (KMC) has also been proven to be an effective intervention to prevent neonatal sepsis (6) in premature babies.

Lawn JE, et al (11) further emphasized the aforementioned points. The authors re-emphasized that an increasing proportion of deaths in the under 5 years of age group, were neonatal deaths (11). They did provide evidence, however, that effective action was possible even in low resource settings.

Despite increasing attention to neonatal data, child survival programs and funding continue to focus primarily on important causes of death after 4 weeks of life, particularly on malaria and vaccine-preventable conditions. Maternal health programs have focused primarily on the mother. Neonatal deaths can be reduced. Strengthening care within existing maternal and child health programs, and including interventions to target the main causes of neonatal death, will help achieve this target. This study aims towards that specific goal.

Aim

The primary aim was to determine the profile and outcome of neonates admitted to the general paediatric wards. A secondary aim of this research project was to look at effectiveness of the new IMCNI guidelines. The data extracted may provide a foundation upon which neonatal care can be improved.

This study may also contribute towards building a solid foundation based on the above principles. From this foundation a structured and concerted effort can be put into place with a view toward improving the quality of care offered to neonates admitted to the general ward.

Methods

Location

The ED selected is the Paediatric ED at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The department that is linked with the subsequent care of the admitted neonates is the Paediatric department at the CMJAH. Patient records garnered from these departments were used in this study.

Inclusion Criteria

All neonates (less than 28 days) admitted to the general paediatric wards at CMJAH from the 1st January 2011 to the 30th April 2011 were included. Patients transferred from Primary Health Care Facilities and Secondary Level Hospitals are included.

Exclusion Criteria

Patients transferred from other tertiary hospitals were excluded.

Patients with incomplete records were also excluded.

Ethics

All patient records were treated confidentially and data was stored on a password-protected computer to which only the researcher had access. No patient names, patient numbers or health care provider names were entered into the database, hence ensuring anonymity. Only the researcher had access to the patient records. Considering the type of study, there was no requirement for signed parental/guardian consent. The University of Witwatersrand granted ethical clearance (Appendix A). The management staff at CMJAH granted permission to access patient records.

Data Collection and Analysis

Data was captured on a password protected Microsoft Excel Database and thereafter analyzed. Neonatal demographics and growth parameters were noted. The clinical profile was based on the new IMCI guidelines.

Data was tabulated under the following categories: The neonatal profile, the clinical profile, the presentation profile, the risk factor profile, the laboratory profile and lastly the maternal profile.

Data collection sheet- Appendix B

Sensitivity, specificity and likelihood ratio were calculated manually using a calculator and the following formulas.

The tables below show estimates of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false positive probability, and false negative probability (12)

The statistics are defined as follows:

- **Sensitivity** is defined as the proportion of true positive responders (Diagnosis=Positive) that have a positive test result (Marker=Positive).
- **Specificity** is the proportion of true negative responders (Diagnosis=Negative) that have a negative test result (Marker=Negative).
- **PPV** is the proportion of positive test results that are true positive responders.
- **NPV** is the proportion of negative test results that are true negative responders.
- The definition of the **false positive probability** is not universal. We define it as the proportion of true negative responders that have a positive test result.
- Similarly, the definition of the **false negative probability** is defined as the proportion of true positive responders that have a negative test result.
- The **likelihood ratio** of a positive test result (denoted LR^+) is sensitivity divided by 1–specificity.

In evidence-based medicine, **likelihood ratios** are used for assessing the value of performing a diagnostic test. They use the sensitivity and specificity of the test to determine whether a test result usefully changes the probability that a condition (such as a disease state) exists.

Calculation

Two versions of the likelihood ratio exist, one for positive and one for negative test results. Respectively, they are known as the likelihood ratio positive (LR+) and likelihood ratio negative (LR–).
The likelihood ratio positive is calculated as (12)

$$LR+ = \frac{\text{sensitivity}}{1 - \text{specificity}}$$

which is equivalent to

$$LR+ = \frac{\Pr(T+|D+)}{\Pr(T+|D-)}$$

or "the probability of a person who has the disease testing positive divided by the probability of a person who does not have the disease testing positive." Here "T+" or "T−" denote that the result of the test is positive or negative, respectively. Likewise, "D+" or "D−" denote that the disease is present or absent, respectively. So "true positives" are those that test positive (T+) and have the disease (D+), and "false positives" are those that test positive (T+) but do not have the disease (D−).
The likelihood ratio negative is calculated as[12]

$$LR- = \frac{1 - \text{sensitivity}}{\text{specificity}}$$

which is equivalent to[1]

$$LR- = \frac{\Pr(T-|D+)}{\Pr(T-|D-)}$$

or "the probability of a person who has the disease testing negative divided by the probability of a person who does not have the disease testing negative."
The pre-test odds of a particular diagnosis, multiplied by the likelihood ratio, determines the post-test odds. This calculation is based on Bayes' theorem. (Note that odds can be calculated from, and then converted to, probability.)

Application to medicine

A likelihood ratio of greater than 1 indicates the test result is associated with the disease. A likelihood ratio less than 1 indicates that the result is associated with absence of the disease. Tests where the likelihood ratios lie close to 1 have little practical significance as the post-test probability (odds) is little different from the pre-test probability, and as such is used primarily for diagnostic purposes, and not screening purposes. When the positive likelihood ratio is greater than 5 or the negative likelihood ratio is less than 0.2 (i.e. 1/5) then they can be applied to the pre-test probability of a patient having the disease tested for to estimate a post-test probability of the disease state existing. A positive result for a test with an LR of 8 adds approximately 40% to the pre-test probability that a patient has a specific diagnosis. In summary, the pre-test probability refers to the chance that an individual has a disorder or condition prior to the use of a diagnostic test. It allows the clinician to better interpret the results of the diagnostic test and helps to predict the likelihood of a true positive (T+) result (13).

Sensitivity, specificity, positive predictive value, negative predictive value, **false positive probability**, and **false negative probability** are indicated by matching colours in the example table below.

BRPN

Table of Temp > 37.4 by BRPN

Temp > 37.4		***BRPN***		
Frequency *Percent* *Row Pct* *Col Pct*		*NEGATIVE*	*POSITIVE*	*Total*
Temp > 37.4	*N*	41	14	55
		56.16	19.18	75.34
		74.55	**25.45**	
		77.36	**70.00**	
	Y	12	6	18
		16.44	8.22	24.66
		66.67	**33.33**	
		22.64	**30.00**	
	Total	53	20	73
		72.60%	27.40%	100%

The **likelihood ratio** of a positive test result is 30/(1-77.36) = 30/2.64 = 1.33. The likelihood ratio of a negative test result is 77.36/(1-30) = 77.36/60 = 1.29. Both are very close to one, which suggests that the marker has little practical significance.
Calculation of other results is shown appendix C.

Results

Seventy -three neonates fulfilled the criteria for study. Only one neonate was excluded from the study because he was referred from a secondary hospital with a congenital cardiac disease. Thirty -two were females and 41 were males. The mean weight was 3.28kg (SD 0.65). The median age for 0 to 7 days was 4 days and for 8 to 28 days was 17 days. Characteristics of the sample are shown in Table 1

Table 1: Characteristics of study group

Baseline characteristics of study group	
Number of Neonates	73
Female Gender	32 (43.8%)
Male Gender	41 (56.2%)
Exclusive Breastfeeding	43 (58.9%)
RVD Exposed	21 (28.8%)
PMTCT (in RVD exposed group)	16 (76.2%)
Antenatal Care	56 (76.7%)
Anthropomorphic Measurements	
Weight (kg)	3.2 (SD 0.65)

The frequency of the different signs associated with serious illness is shown in Table 2. None of the infants presented with hypothermia. The most common clinical sign was tachypnea (46.6%) followed by jaundice (41.1%).

Table 2: Individual signs

Individual signs for prediction of 'serious illness' for neonates	
Pyrexia (temp>37.5 C)	18 (24.7%)
Hypothermia (temp<35.5 C)	0
Respiratory Rate > 60	34 (46.6%)
Jaundice	30 (41.1%)
Lethargy	19 (26%)
Poor Feeding	2 (2.7%)
Seizures	1 (1.4%)
Movement only when stimulated	3 (4.1%)

Table 3 Risk Factors

Risk Factors	
Prematurity (<37 weeks)	8 (11 %)
Low Birth Weight (<2.5 kg)	11 (15.1%)
Previous ICU admission	0
Perinatal asphyxia	4 (5.5%)

Risk factors for serious illness are shown in Table 3. Most neonates had no risk factors. The most common being low birth weight 11 (15.1%). No babies had been admitted to ICU.

Individual indicators for severity of illness by World Health Organization (WHO) Integrated Management of Childhood and Neonate Illness (IMCNI) are shown in Figure 1. The most frequent indicators were tachypnoea 46.6%, jaundice 41.1% and poor feeding 42.5% and only 1% presented with convulsions.

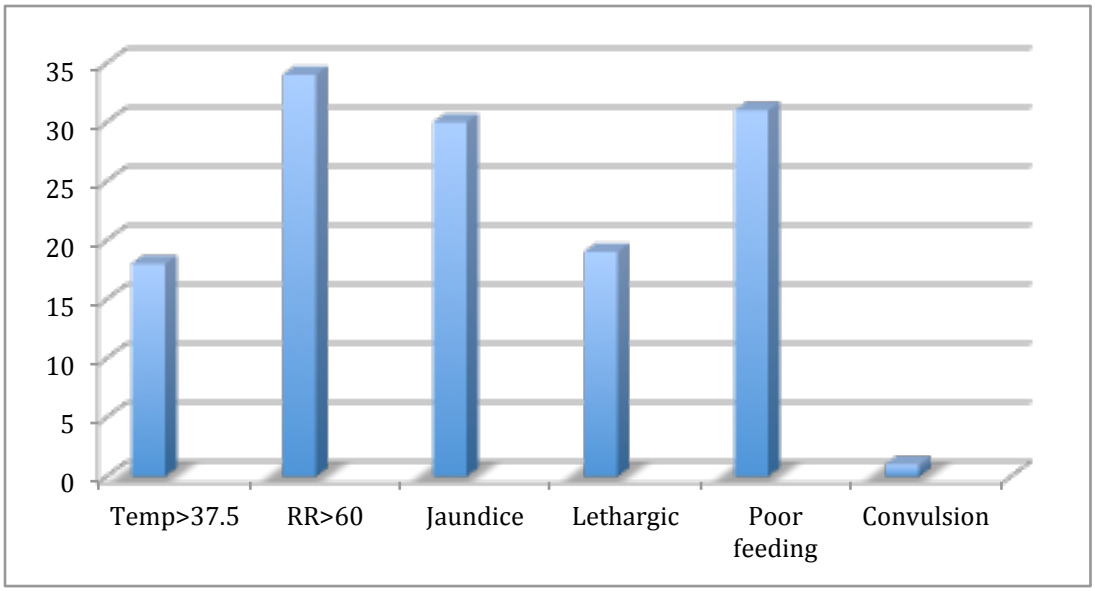

Figure 1: Individual Indicators for severity of Illness

Most neonates admitted were referred from the local clinic 45 (61.1%), 21 (28.8%) were self-referred, 4 (5.5%) were from General Practitioners (GP), 2 (2.7%) from secondary hospital and 1 (1.4%) from private ED are shown in Figure 2.

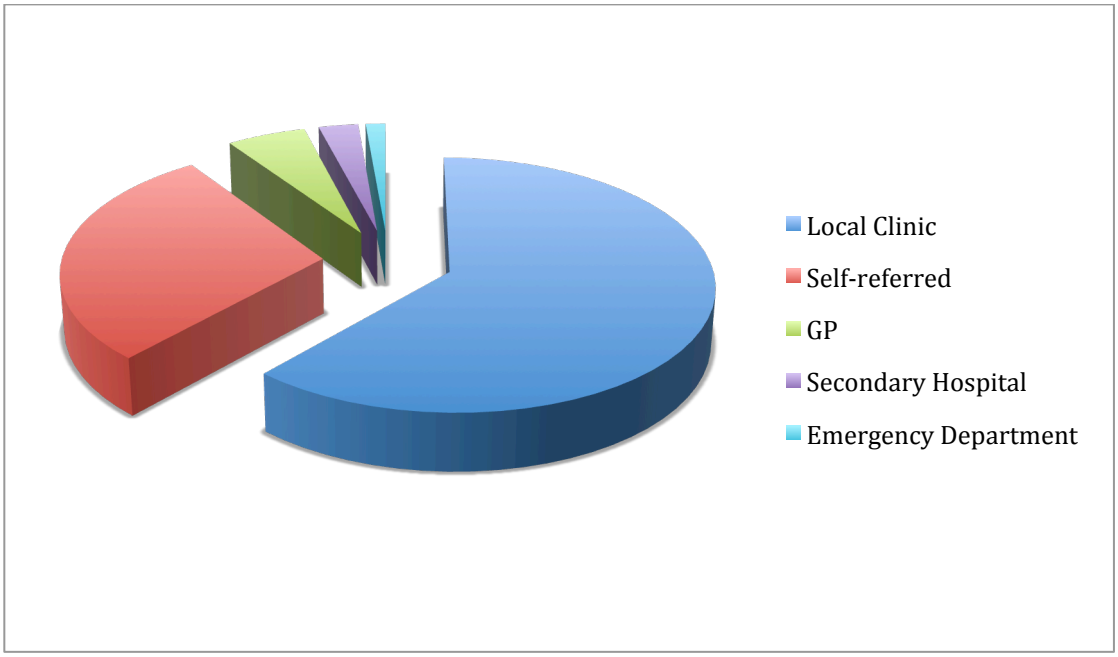

Figure 2: Referral Patterns

The commonest initial presentation is shown in Figure 3 was jaundice 26 (35.6%) and lower respiratory tract (LRT) symptoms 20 (27.4%). Seven had various different presentations including 1 with rat bites.

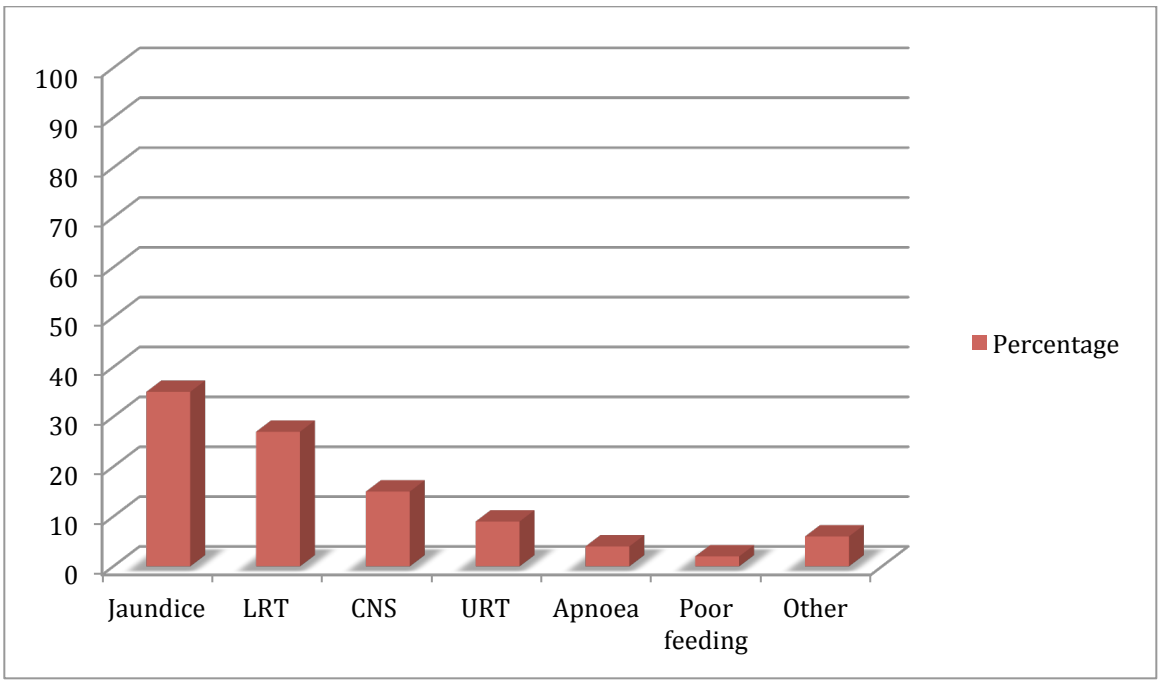

Figure 3: Commonest initial symptoms

Only 9 (12.3%) of the neonates had been previously admitted to hospital. The initial investigation in the ED included a routine glucose (HGT) check 73 (100 %), Chest X-Ray (CXR) 41(56.2 %), urine dipstick 27 (37 %), lumbar puncture (LP) 33 (45.2 %), full blood count (FBC) 64 (87.7 %), C reactive protein (CRP) 64 (87.7 %) and blood culture (BC) 64 (87.7 %). All babies had their glucose assessed whilst only 27 (37%) had a urine analysis done.

The most common initial diagnoses as shown in Figure 4 were bronchopneumonia (BRPN) 20 (27.4%), neonatal sepsis (NNS) 22 (30.1%) and neonatal jaundice (NNJ) 22 (30.1%).

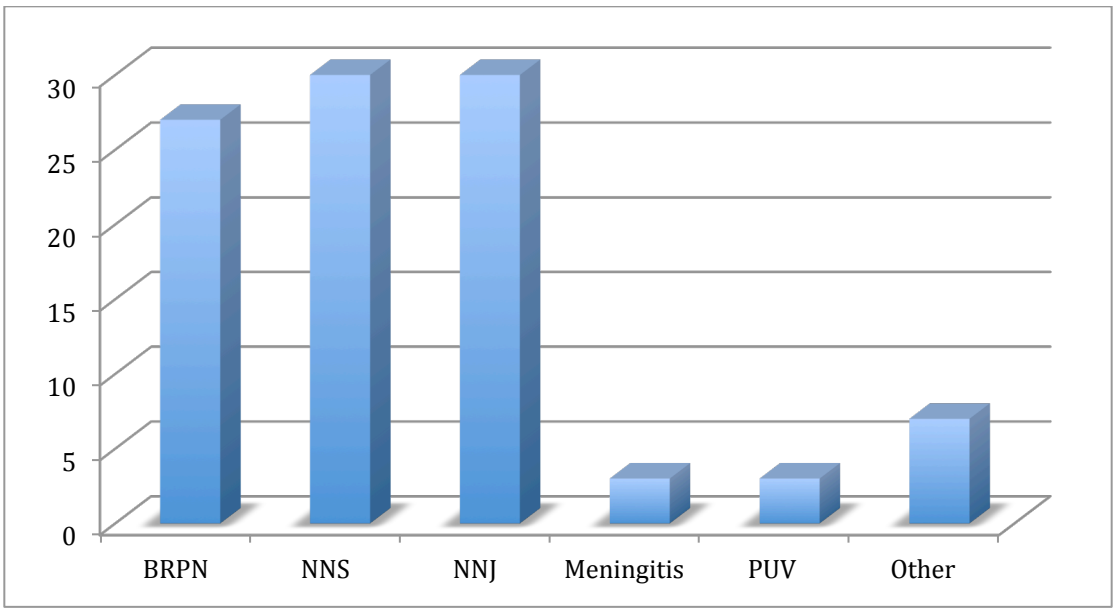

Figure 4: Initial Diagnoses

The final discharge diagnosis as shown in Figure 6 were similar to initial diagnosis include bronchopneumonia (BRPN) 20 (27.4 %), neonatal jaundice (NNJ) 20 (27.4 %), neonatal sepsis (NNS) 23 (31.5 %), meningitis 4 (5.5 %), neonatal hepatitis 2 (2.7 %), posterior urethral valves (PUV) 2 (2.4 %), imperforate anus 1 (1.4 %) and urinary tract infection (UTI) 1 (1.4 %).

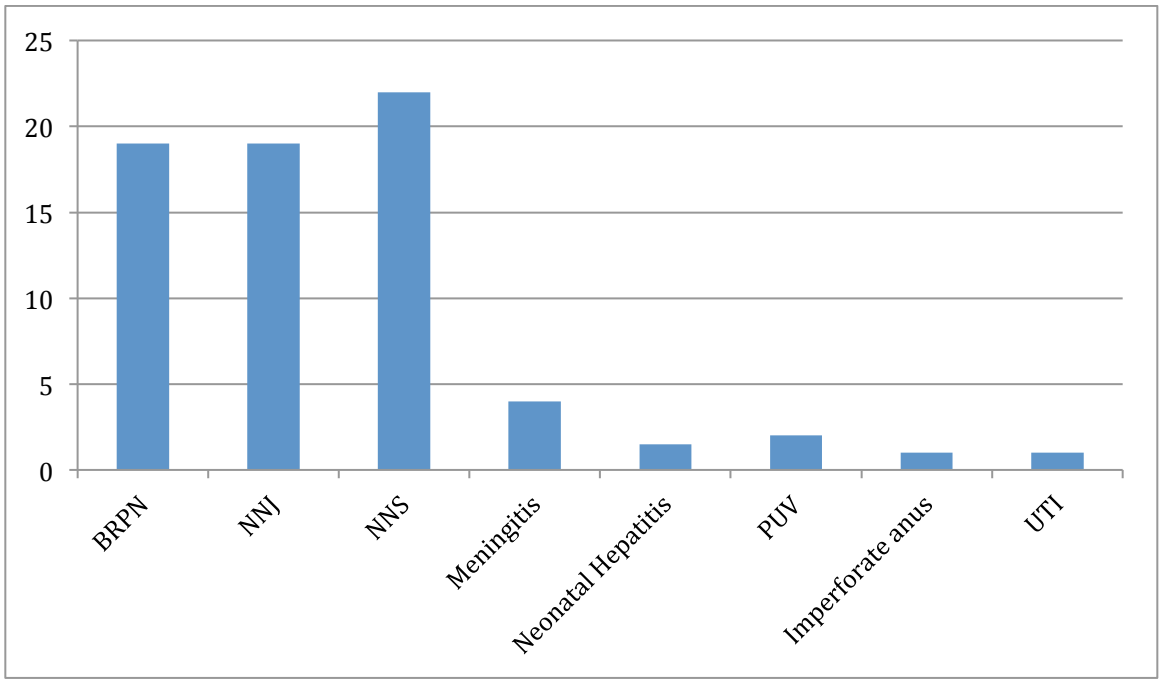

Figure 5: Final Diagnoses

Excusive breast feeding rates were 58.9%. 21 (28.8%) of babies were RVD exposed and 16 (76.2%) of the RVD exposed babies were on prevention mother to child transmission (PMTCT) program (Table 1). Most mothers received antenatal care 56 (76.7 %).

Blood culture results were positive for 9 neonates. The commonest organisms were 4 coagulase negative staphylococcus (CoNS), 2 group B streptococcus (group B strep) and 2 klebsiella.

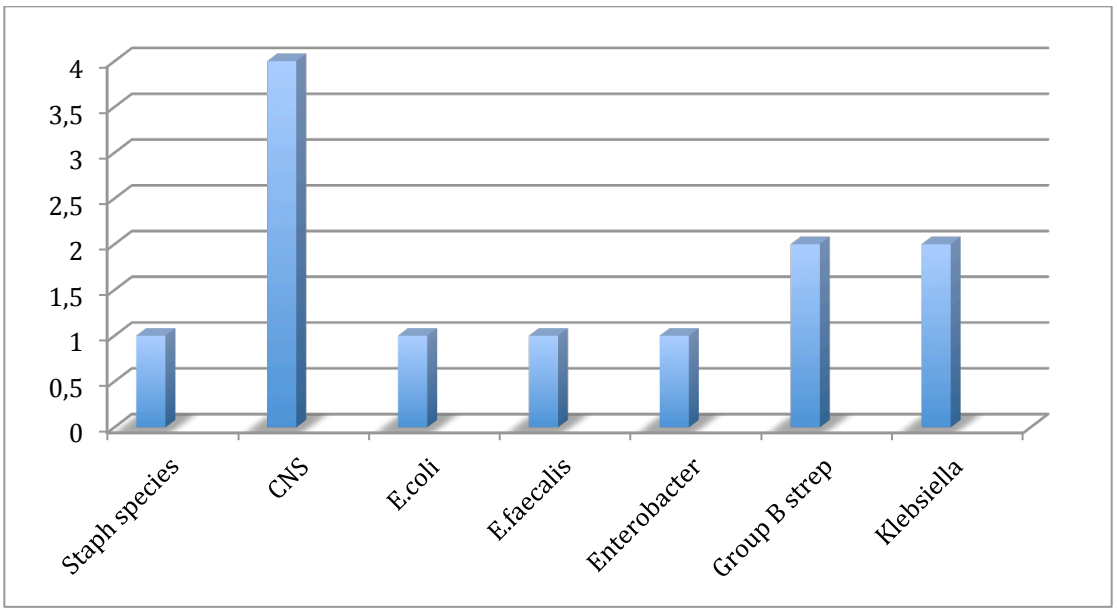

Figure 6: Blood Culture Results

Thirty-nine (53.4%) urine samples were sent for microscopy, culture and sensitivity (mc & s). Three yielded a positive result. Results showed one Escherichia coli (E.coli), one Enterococcus faecalis (E faecalis) and one showed unidentified yeast.

Forty-one (56.2%) CSF cultures were done. Five yielded a positive result. Results showed 2 CoNS, 2-group B streptococcus and one showed unidentified yeast. The unidentified yeast was present in both blood and urine cultures. Thirty-three chest x-rays were done. 28.8% (21) showed evidence of pneumonia. The mean duration of hospital admission was 7 days (SD 5.17). Two neonates died within 24 hours of admission. Their diagnoses were NNS and BRPN

Table 4: Investigations

Investigations	
Blood Cultures	
Negative	45 (74%)
CoNS	4 (5.5%)
E.coli	1 (1.4%)
E. faecalis	1 (1.4%)
Group B Streptococcus	2 (2.7%)
Klebsiella	2 (2.7%)
CSF Culture	
Negative	27 (37%)
CoNS	2 (2.7%)
Group B streptococcus	2 (2.7%)
Yeast	1 (1.4%)
Urine MC&S	
Negative	28 (38.4%)
E.coli	1 (1.4%)
E.faecalis	1 (1.4%)
Yeast	1 (1.4%)

Table 5: Sensitivity and Specificity for BRPN

	BPRN			
	Sensitivity	**Specificity**	**LR+**	**LR-**
Temp > 37	0,30	0,77	1,33	1,11
RR>60	1,00	0,74	3,79	0,00
Jaundice	0,00	0,43	0,00	0,43
Lethargy	0,15	0,70	0,50	0,82
Feeding Difficulty	0,55	0,62	1,46	1,38
Convulsions	0,00	0,98	0,00	0,98
Movement	0,00	0,94	0,00	0,94

Table 6: Sensitivity and specificity for NNS

	NNS			
	Sensitivity	**Specificity**	**LR+**	**LR-**
Temp > 37	0,25	0,75	1,02	1,01
RR>60	0,56	0,56	1,28	1,28
Jaundice	0,31	0,56	0,71	0,82
Lethargy	0,31	0,75	1,27	1,10
Feeding Difficulty	0,44	0,58	1,04	1,03
Convulsions	0,06	1,00	0,00	1,07
Movement	0,06	0,96	1,78	1,03

The above tables show the sensitivity and specificity of clinical indicators predicating severity of illness for the two most important cause of disease in neonates admitted to general ward. Tachypnoea was very sensitive (100%) and relatively specific (76%) for detecting BRPN with a LR of 3.98. The other clinical indicators were neither specific nor sensitive in detecting serious illness.

Discussion

This study provides an audit of neonates admitted to the general ward. It provides insight to the spectrum of disease, risk factors and outcome. It also looks at the validity of the new IMCNI guidelines by WHO in the developing world.

Most neonates are discharged early from the neonatal unit because of major resource limitations. Stable premature infants weighing 1600g are discharged, babies with birth weights more than 1750g are not admitted and well term babies are discharged after 6 hours. Currently there are no routine home visits by nurses and it depends entirely on the parents to seek medical assistance if their babies are sick. Neonates discharged early are potentially a high-risk group because adequate breastfeeding is not established, mothers are often teenagers and there is no screening for jaundice. If requiring readmission, these babies are not admitted to the neonatal wards but to the general paediatric wards. Premature discharge of this vulnerable group might be hazardous and potentially increase hospital admission and mortality rates. However, a study by Mokhachane et al (14) showed if home circumstances are adequate, it is safe to discharge well ex premature infants at a weight of greater than 1650g as compared to greater than 1800g. Earlier discharge of this group of very low birth weight (VLBW) infants might help combat overcrowded and understaffed hospitals with their attendant complications. A longer stay in hospital would also expose these infants to nosocomial infections that increase morbidity and mortality. Oddie et al (15) similarly showed that babies discharged on or before the first postnatal day were not more likely to be readmitted. In this study unlike the South Africa setting, midwives in the UK have a statutory obligation to visit and assess newborns at home after initial discharge regardless of timing of discharge. A study of VLBW infants by Ballot at el (16)

showed a post discharge mortality rate of 5.9% of premature infants weighing initially less than 1500g discharged from neonatal unit

Diagnoses

The most common diagnoses for neonates admitted to the ward were infections, including bronchopneumonia and sepsis. Similar results were found in the seventh report on perinatal care in South Africa. (17).

The age of an infant is a very important consideration to predict the pattern of clinical diagnoses (10). In the current study, for infants less than six days of age, jaundice and infection (including sepsis, pneumonia and meningitis) were the commonest presentations. This was in agreement with previous studies in neonates presenting to the ED (10, 18, 19). It is very important to detect jaundice early to prevent the devastating outcome of kernicterus. In infants 7-28 days the most common clinical diagnoses were respiratory tract infection and sepsis. This is similar to the findings illustrated by Jeena et al (7) whereby in the age group 7-27 days pneumonia, sepsis and hyperbilirubinaemia were the most common diagnosis. Given the syndromic overlap between the clinical presentation of neonatal sepsis and bronchopneumonia they are often grouped together. This poses difficulties in determining the incidence of neonatal pneumonia. In a study by English et al (18) presumed serious infection was also the commonest cause of admission among infants < 2 months of age.

Referrals

The majority of the neonates in this study was referred from local clinics or was self-referred. Clinics and primary health care centres are usually the first port of call for the sick neonate. It is therefore imperative that primary health care nurses and junior doctors are adequately trained in neonatal care.

It is also important that parents are able to identify danger signs, which may suggest when the neonate requires immediate intervention and when the neonate should be taken to the hospital as opposed to a primary health care centre. Most outreach programmes in the community should teach parents how to identify danger signs and when to seek early medical assistance and at the appropriate level of health care facility. The implementation of the new Road to health cards (RTHC) has included more information of the management of common newborn problems.

Clinical predictors of severity of illness

In less developed countries, 'disease specific' algorithms may assist unskilled junior doctors and nurses to identify sick neonates and help them refer the patient early for necessary intervention (10).

Temperature, respiratory distress, poor feeding, chest in drawing, movement when stimulated and convulsions used in the new IMCNI guidelines for infants less than 6 days has a sensitivity of 85% and a specificity of 75% and for infants 7-59 days a sensitivity of 74% and specificity of 79% (8).

The present study looked at clinical predictors of severity of illness in neonates less than 28 days. In those infants admitted to the ward, the likelihood of each clinical sign was determined. The most relevant presenting signs in the current study were tachypnoea and jaundice. Respiratory distress showed a likelihood ratio (LR) of 3 compared to other studies where poor feeding was the most important clinical predictor of severity of illness. In another study the clinical sign of significance were cyanosis (an odds ratio range of 1.5-13.7) (20), which are strongly associated with mortality as a result of hypoxemia, this could be more economically and reliably diagnosed using a pulse oximeter.

Although various studies have shown an overlap between signs and symptoms in several major childhood illnesses (10), the implementation of a simple algorithm, with easily recognizable signs and without need for laboratory testing will assist the recognition and urgent intervention and referral by junior doctors and nurses in all ED in developing countries.

The presence of any of danger signs should prompt healthcare works with basic training to commence further investigation and empiric treatment until reviewed by someone with a higher level of training (11). Such an approach prioritizes sensitivity (not missing a true illness) at the expense of specificity (restricting treatment of that illness without serious illness) in a population of vulnerable patients (20).

Such an approach would be justified due to the high mortality in the neonatal period and limited training and skills of health care workers at hospitals. It is imperative that the IMCNI should be

taught to all health care workers dealing with newborns at all levels of care. Parents should also be made aware of danger signs.

Investigations

Clinical signs and symptoms in neonates are often subtle and non -specific. They routinely undergo a full "septic work up" including FBC, CRP, blood culture, lumber puncture (LP) and urine dipstix.

As shown in this study 67 of 73 (87.7%) patients admitted received a FBC, CRP, B/C and LP. A urine dipstix was done only if indicated. The results suggested a FBC and CRP were not helpful in diagnoses of illness because most FBC and CRP were normal despite infants being clinically ill. The CRP is more useful when done after 24hours post-presentation (21). However, although most blood cultures were negative, a positive result and organism identification assisted with choice of antibiotic and duration of antibiotic used.

In this study the bacterial pathogens cultured in infants admitted to the ward were CoNS, group B streptococcus and Klebsiella pneumonia. This was similar to organisms identified in other developing countries by Ganatra et al (6). Currently all neonates admitted are commenced empirically on ampicillin and gentamicin. Emergence of resistance and virulent strains render common antibiotic regimes ineffective against Klebsiella and CoNS. Ongoing surveillance of positive cultures and antimicrobial sensitivity patterns will guide empiric therapy in this setting.

Mortality

The mortality rate was surprising low. There were 2 deaths (0.3%)comparable to the Seventh Report on Perinatal Care in South Africa (17) which showed an in hospital mortality rate (IHMR) rising from 5.6 /100 to admissions in 2005 to 7/100 admissions in 2009. The mortality rate maybe low as a result of easier access to clinics and hospitals by patients and this is a tertiary institute with well-trained staff in the wards. Another possible reason for the low mortality rate is over-admission because of inappropriate decision by causality officers or registrars for need to admit.

Both infants who died in the study, died within 24 hours of admission due to sepsis and pneumonia respectively. This confirms similar issues pointed out by the above mentioned report that reflects a range of quality of care issues such as late presentation as a result of poor parent education or lack of transport or inappropriate first line assessment and management on admission to hospital. Is it possible that this study is missing a group of neonates that don't present at all to hospital and die at home? According to data in Saving Babies Report (17) almost twice as many neonates than children present as dead on arrival (DOA).

Predictors of admission and the admission rate

Prematurity (<37 weeks), low birth weight (<2.5 kg) and perinatal asphyxia are possible predictors of admission. Black et all showed prematurity and asphyxia was leading causes for

mortality (2). In the current study, 15.1% of babies were LBW. Globally an average of 14% of babies is born with LBW. LBW may be caused by preterm birth or growth restriction of full term babies or a combination of two. Preterm infants have a 15 times greater risk of neonatal death than full term infants. Babies who are both preterm and growth restricted have even a greater risk of death (11). Similarly showed in this study prematurity, LBW and asphyxia are associated with increased morbidity. A study by Oddie et al also showed that babies born at 35-37 weeks gestation and babies less than 2500g at birth were more likely to be readmitted than term babies (15).

Exclusive breastfeeding rates were 58.9% in this study but still low. This shows there still need to be a greater emphasis on promotion of breastfeeding. During the postnatal period, early and exclusive breastfeeding are perhaps the most important intervention to prevent sepsis. Breast milk is known to contain lysosomes, lactoferrin and secretory immunoglobulins IgA, which inhibit E.coli and other pathogens responsible for neonatal sepsis (6). Unfortunately only 37% of neonates in the developing world are exclusively breastfed.

HIV exposed neonates

This study showed 28.8% of babies admitted are RVD exposed. Most RVD exposed 16 of 21 (76.2%) received PMTCT prophylaxis.

Although antenatal care was provided to 76.7% of mothers, this is lower than ANC received by the general population. Lack of ANC could possibly be a risk factor for admission of these neonates. There is definitely a gap in care where many pregnant women are not tested for HIV. HIV care in South Africa is seriously suboptimal and needs drastic and urgent attention. In this

study a third of infants admitted to the general ward are HIV exposed but only 76% has received PMTCT. A quarter of these HIV exposed infants eligible for perinatal anti-retroviral did not receive them. Hopefully this gap in care for pregnant women and HIV exposed infants can be bridged by implementation of new PMTCT guidelines. The scaling up of new guidelines has been targeted to reduce MTCT by 2 % (22) by lowering threshold of commencing ARV in pregnant women and emphasizing exclusive breastfeeding for six months together with infant prophylaxis. Importantly breastfeeding reduces malnutrition and child death. The additional risk of not breastfeeding is further increased by poverty, poor hygiene, unsafe water and poor sanitation. The new guidelines adopt an approach to infant feeding that maximizes infant survival, not only the avoidance of HIV transmission.

There is definitely room for scaling up PMTCT programs and improving rates of antenatal care and maternal education.

Initial vs. Final Diagnosis

Most initial diagnoses made by doctors in the ED correlated well with the final diagnoses made by the paediatrician in the general wards. This shows junior doctors in the ED have adequate training.

Conclusion

In conclusion, a significant number of neonates are admitted to the general paediatric wards. Contrary to most reports, where neonatal deaths account for more than 50% of all infant deaths,

this study demonstrated a much lower mortality rate. The most common diagnoses documented were infections, bronchopneumonia and jaundice.

Neonates may manifest with only subtle signs with significant underlying infection. Clinically distinguishing these with a serious illness from those who are mildly ill may be difficult. This has led to an aggressive approach to illnesses in this age group, usually including diagnostic tests, empiric antibiotics and often hospital admission. However, signs and symptoms of several of the major childhood illnesses contributing to under five mortality have a substantial overlap. Thus, a single diagnosis for a sick infant is often inappropriate because it identifies only the most apparent problem and can lead to an associated and potentially life threatening problem being overlooked.

This study recommends that the revised IMCI strategy should be implemented as a basic algorithm for initiating referral and empiric treatment especially in facilities staffed by healthcare workers with only basic training. Furthermore to promote adherence and improve the diagnostic value of the algorithm, the scaling up of community intervention strategies aimed at educating families on recognition of early danger signs and early seeking help. Together with more training of health workers on recognition and interpretation of suggested danger signs. Such measures should ideally be linked to improved empiric treatment, supportive care and access to healthcare providers with higher levels of training.

As shown by this study a significant number of neonates who have been discharged home are readmitted to paediatric wards. Many of these wards are not designed for providing newborn

care and healthcare worker are not trained in neonatal care. The neonatal care and monitoring is these wards are suboptimal in many hospitals. A decline in neonatal mortality in hospital setting with limited resources can be achieved by simple, low-cost, low technology intervention.

Recommendations

Many perceive the need to improve quality and scaling up of clinical care as a challenge, costly and time consuming.

Simple and cost effective interventions include:

- Implementation of new IMCI guidelines in ED
- Protocol-based management
- Rational admission policies
- Omitting unnecessary investigations
- Rational antibiotics administration
- Educating of mothers with regard to early danger signs,
- Early help-seeking and access to health-care facilities,
- Training and empowerment of junior doctors and nurses,
- Adoption of new PMTCT guidelines
- Improved resource allocation to neonatal services
- Increased number of posts for 'Neonatologist'.

Limitations

This is a single center study. This is a retrospective analysis. The timeframe has been limited to a 4- month period; hence seasonal pathology and seasonal fluctuation in patient numbers will not be accounted for this.

Appendix B - Patient Number: 1

NEONATAL PROFILE	
1. Age of neonate at presentation in days	
2. Gender of Neonate (Male or Female)	
3. Weight in KG	
4. Length in cm	
5. Head circumference in cm	
CLINICAL PROFILE	
1. Temperature > 37.4 (Yes or No)	
2. Temperature < 35.5 (Yes or No)	
3. Respiratory Rate > 60/min (Yes or No)	
4. Jaundice? (Yes or No)	
5. Lethargy? (Yes or No)	
6. History of Feeding Difficulty? (Yes or No)	
7. History of Convulsions? (Yes or No)	
8. Movement only when stimulated? (Yes or No)	
PRESENTATION PROFILE	
1. Date (dd/mm/yy) of presentation	
2. Time (hh:mm) of presentation	
3. Referral mode : Self/Clinic/Hospital	
4. Presenting complaint:	
5. Previous admissions to hospital? (Yes or No)	
6. Chest X-ray done in the ED? (Yes or No)	
7. Bed side glucose done in ED? (Yes or No)	
8. Urine dipstix done in ED? (Yes or No)	
9. Lumbar puncture done in ED? (Yes or No)	
10. FBC done in ED? (Yes or No)	
11. CRP done in ED? (Yes or No)	
12. Blood Culture done in ED? (Yes or No)	
13. Patient admitted? (Yes or No)	
14. Admission Diagnosis:	
15. Duration of in-hospital stay in days.	
16. Discharge date (dd/mm/yy)	
17. Discharge Diagnosis:	

Appendix B Page 2 - Patient Number: 1

RISK FACTOR PROFILE	
1. RVD Exposed? (Yes or No)	
2. Exclusively breastfed? (Yes or No)	
3. Enrolled in PMTCT program? (Yes or No)	
4. History of Pre-maturity? (<37 weeks) (Y or N)	
5. History of Low Birth Weight? (Yes or No)	
6. Previous ICU admissions? (Yes or No)	
7. History of birth asphyxia? (Yes or No)	
INITIAL LABORATORY PROFILE	
1. White Cell Count	
2. Hemoglobin level	
3. Platelet count	
4. CRP level	
5. Blood culture result if done:	
6. Date blood culture done (dd/mm/yy):	
7. Date blood culture result available (dd/mm/yy):	
8. Bed side glucose result:	
9. Urine dipstix result: Leucocytes present? (Y or N)	
10. CSF Polymorph Cell Count:	
11. CSF Lymphocyte Cell Count:	
12. CSF culture result:	
13. Evidence of Pneumonia on CXR? (Yes or No)	
MATERNAL PROFILE	
1. Was the mother registered for ANC? (Yes or No)	
2. Maternal history of UTI? (Yes or No)	
3. Maternal history of Fever? (Yes or No)	
4. Recent antibiotic use? (Yes or No)	

Appendix C

Table of Temp < 35.5 by BRPN

Temp > 35.5	Frequency / Percent / Row Pct / Col Pct	BRPN: NEGATIVE	BRPN: POSITIVE	Total
Temp < 35.5	N	53	20	73
		72.60	27.40	100.00
		72.60	27.40	
		100.00	100.00	
	Total	53	20	73
		72.60	27.40	100.00

Table of RR>60 by BRPN

		BRPN: NEGATIVE	BRPN: POSITIVE	Total
RR>60	N	39	0	39
		53.42	0.00	53.42
		100.00	0.00	
		73.58	0.00	
	Y	14	20	34
		19.18	27.40	46.58
		41.18	58.82	
		26.42	100.00	
	Total	53	20	73
		72.60	27.40	100.00

Table of Jaundice by BRPN

Jaundice		BRPN		
Frequency Percent Row Pct Col Pct		NEGATIVE	POSITIVE	Total
Jaundice	N	23	20	43
		31.51	27.40	58.90
		53.49	46.51	
		43.40	100.00	
	Y	30	0	30
		41.10	0.00	41.10
		100.00	0.00	
		56.60	0.00	
	Total	53	20	73
		72.60	27.40	100.00

Table of Lethargy by BRPN

Lethargy		BRPN		
Frequency Percent Row Pct Col Pct		NEGATIVE	POSITIVE	Total
Lethargy	N	37	17	54
		50.68	23.29	73.97
		68.52	31.48	
		69.81	85.00	
	Y	16	3	19
		21.92	4.11	26.03
		84.21	15.79	
		30.19	15.00	
	Total	53	20	73
		72.60	27.40	100.00

Table of Feeding Difficulty by BRPN

Feeding Difficulty		BRPN		
Frequency Percent Row Pct Col Pct		NEGATIVE	POSITIVE	Total
Feeding Difficulty	N	33	9	42
		45.21	12.33	57.53
		78.57	21.43	
		62.26	45.00	
	Y	20	11	31
		27.40	15.07	42.47
		64.52	35.48	
		37.74	55.00	
Total		53	20	73
		72.60	27.40	100.00

Table of Convulsions by BRPN

Convulsions		BRPN		
Frequency Percent Row Pct Col Pct		NEGATIVE	POSITIVE	Total
Convulsion	N	52	20	72
		71.23	27.40	98.63
		72.22	27.78	
		98.11	100.00	
	Y	1	0	1
		1.37	0.00	1.37
		100.00	0.00	
		1.89	0.00	
Total		53	20	73
		72.60	27.40	100.00

Table of Movement by BRPN

Movement		***BRPN***		
Frequency *Percent* *Row Pct* *Col Pct*		*NEGATIVE*	*POSITIVE*	*Total*
	N	50	20	70
		68.49	27.40	95.89
		71.43	28.57	
		94.34	100.00	
Movement				
	Y	3	0	3
		4.11	0.00	4.11
		100.00	0.00	
		5.66	0.00	
	Total	53	20	73
		72.60	27.40	100.00

NNS

Table of Temp>37.4 by NNS

Temp_37_4		***NNS***		
Frequency *Percent* *Row Pct* *Col Pct*		*NEGATIVE*	*POSITIVE*	*Total*
Temp>37.4	*N*	43	12	55
		58.90	16.44	75.34
		78.18	21.82	
		75.44	75.00	
	Y	14	4	18
		19.18	5.48	24.66
		77.78	22.22	
		24.56	25.00	
	Total	57	16	73
		78.08	21.92	100.00

Table of Temp<35.5 by NNS

Temp_35_5		***NNS***		
Frequency *Percent* *Row Pct* *Col Pct*		*NEGATIVE*	*POSITIVE*	*Total*
Temp<35.5	*N*	57	16	73
		78.08	21.92	100.00
		78.08	21.92	
		100.00	100.00	
	Total	57	16	73
		78.08	21.92	100.00

Table of RR>60 by NNS

RR_60		NNS		
Frequency Percent Row Pct Col Pct		NEGATIVE	POSITIVE	Total
RR>60	N	32	7	39
		43.84	9.59	53.42
		82.05	17.95	
		56.14	43.75	
	Y	25	9	34
		34.25	12.33	46.58
		73.53	26.47	
		43.86	56.25	
	Total	57	16	73
		78.08	21.92	100.00

Table of Jaundice by NNS

Jaundice		NNS		
Frequency Percent Row Pct Col Pct		NEGATIVE	POSITIVE	Total
Jaundice	N	32	11	43
		43.84	15.07	58.90
		74.42	25.58	
		56.14	68.75	
	Y	25	5	30
		34.25	6.85	41.10
		83.33	16.67	
		43.86	31.25	
	Total	57	16	73
		78.08	21.92	100.00

Table of Feeding Difficulty by NNS

			NNS		
	Frequency Percent Row Pct Col Pct		NEGATIVE	POSITIVE	Total
Feeding Difficulty		N	33	9	42
			45.21	12.33	57.53
			78.57	21.43	
			57.89	56.25	
		Y	24	7	31
			32.88	9.59	42.47
			77.42	22.58	
			42.11	43.75	
	Total		57	16	73
			78.08	21.92	100.00

Table of Convulsions by NNS

		NNS		
	Frequency Percent Row Pct Col Pct	NEGATIVE	POSITIVE	Total
Convulsions	N	57	15	72
		78.08	20.55	98.63
		79.17	20.83	
		100.00	93.75	
	Y	0	1	1
		0.00	1.37	1.37
		0.00	100.00	
		0.00	6.25	
	Total	57	16	73
		78.08	21.92	100.00

Table of Movement by NNS

Movement		***NNS***		
Frequency *Percent* *Row Pct* *Col Pct*		*NEGATIVE*	*POSITIVE*	*Total*
Movement	*N*	55	15	70
		75.34	20.55	95.89
		78.57	21.43	
		96.49	93.75	
	Y	2	1	3
		2.74	1.37	4.11
		66.67	33.33	
		3.51	6.25	
	Total	57	16	73
		78.08	21.92	100.00

References

(1.) Velaphi S, Rhoda N. Reducing neonatal deaths in South Africa - are we there yet, and what can be done? SAJCH 2012;6(3):67-71.

(2.) Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet 2010 Jun 5;375(9730):1969-1987.

(3.) South Africa Every Death Counts Writing Group, Bradshaw D, Chopra M, Kerber K, Lawn JE, Bamford L, et al. Every death counts: use of mortality audit data for decision making to save the lives of mothers, babies, and children in South Africa. Lancet 2008 Apr 12;371(9620):1294-1304

(4.) Rajaratnam JK, Marcus JR, Flaxman AD, Wang H, Levin-Rector A, Dwyer L, et al. Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970-2010: a systematic analysis of progress towards Millennium Development Goal 4. Lancet 2010 Jun 5;375(9730):1988-2008.

(5.) Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. Lancet 2005 Mar 26-Apr 1;365(9465):1175-1188

(6.) Ganatra HA, Zaidi AK. Neonatal infections in the developing world. Semin Perinatol 2010 Dec;34(6):416-425.

(7.) Jeena PM, Adhikari M, Carlin JB, Qazi S, Weber MW, Hamer DH. Clinical profile and predictors of severe illness in young South African infants (<60 days). S Afr Med J 2008 Nov;98(11):883-888

(8.) Young Infants Clinical Signs Study Group. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. Lancet 2008 Jan 12;371(9607):135-142

(9.) Goswami V, Dutta AK, Singh V, Chandra J. Evaluation of simple clinical signs of illness in young infants (0-2 months) and its correlation with WHO IMCI algorithm (7 days to 2 months). Indian Pediatr 2006 Dec;43(12):1042-1049.

(10.) Coghill JE, Simkiss DE. Which clinical signs predict severe illness in children less than 2 months of age in resource poor countries? J Trop Pediatr 2011 Feb;57(1):3-8.

(11.) Lawn JE, Kerber K, Enweronu-Laryea C, Cousens S. 3.6 Million Neonatal Deaths--what is Progressing and what is Not? Semin Perinatol 2010 Dec;34(6):371-386.

(12.) Gardner, M.; Altman, Douglas G. (2000). *Statistics with confidence: confidence intervals and statistical guidelines*. London: BMJ Books. ISBN 0-7279-1375-1.

(13.) Harrell F, Califf R, Pryor D, Lee K, Rosati R (1982). "Evaluating the Yield of Medical Tests". *JAMA* **247** (18): 2543–2546. doi:10.1001/jama.247.18.2543. PMID 7069920.

(14.) Mokhachane M, Saloojee H, Cooper PA. Earlier discharge of very low birthweight infants from an under-resourced African hospital: a randomised trial. Ann Trop Paediatr 2006 Mar;26(1):43-51

(15.) Oddie SJ, Hammal D, Richmond S, Parker L. Early discharge and readmission to hospital in the first month of life in the Northern Region of the UK during 1998: a case cohort study. Arch Dis Child 2005 Feb;90(2):119-124

(16.) Ballot DE, Potterton J, Chirwa T, Hilburn N, Cooper PA. Developmental outcome of very low birth weight infants in a developing country. BMC Pediatr 2012 Feb 1;12:11-2431-12-11

(17.) Pattinson R. Overview. Neonatal deaths. In: Pattinson RC, ed. Saving Babies 2008-2009. Seventh Report on Perinatal Care in South Africa Pretoria: Tshepesa Press 2011:33-34, 35.

(18.) English M, Ngama M, Musumba C, Wamola B, Bwika J, Mohammed S, et al. Causes and outcome of young infant admissions to a Kenyan district hospital. Arch Dis Child 2003 May;88(5):438-443.

(19.) Mazhar A, Rehman A, Sheikh MA, Naeem MM, Qaisar I, Mazhar M. Neonates--a neglected paediatric age group. J Pak Med Assoc 2011 Jul;61(7):625-628.

(20.) Opiyo N, English M. What clinical signs best identify severe illness in young infants aged 0-59 days in developing countries? A systematic review. Arch Dis Child 2011 Nov;96(11):1052-1059.

(21.) Diar HA, Nakwa FL, Thomas R, Libhaber EN. Evaluating the QuikRead(R) C-reactive protein test as a point-of-care test. 2012 Feb;32(1):35-42

(22.) WHO PMTCT Strategic Vision 2010. http://www.who.int/hiv/pub/mtct/strategic_vision.pdf.

(23.) Chacko B, Sohi I. Early onset neonatal sepsis. Indian J Pediatr 2005 Jan;72(1):23-26.

(24.) Chirico G, Loda C. Laboratory aid to the diagnosis and therapy of infection in the neonate. Pediatr Rep 2011 Feb 24;3(1):e1.

(25.) Darmstadt GL, Bhutta ZA, Cousens S, Adam T, Walker N, de Bernis L, et al. Evidence-based, cost-effective interventions: how many newborn babies can we save? Lancet 2005 Mar 12-18;365(9463):977-988.
(26.) Malik A, Hui CP, Pennie RA, Kirpalani H. Beyond the complete blood cell count and C-reactive protein: a systematic review of modern diagnostic tests for neonatal sepsis. Arch Pediatr Adolesc Med 2003 Jun;157(6):511-516.
(27.) Perez Solis D, Pardo de la Vega R, Fernandez Gonzalez N, Ibanez Fernandez A, Prieto Espunes S, Fanjul Fernandez JL. Neonatal visits to a pediatric emergency service. An Pediatr (Barc) 2003 Jul;59(1):54-58.
(28.) Schwartz S, Raveh D, Toker O, Segal G, Godovitch N, Schlesinger Y. A week-by-week analysis of the low-risk criteria for serious bacterial infection in febrile neonates. Arch Dis Child 2009 Apr;94(4):287-292.
(29.) West BA, Peterside O, Ugwu RO, Eneh AU. Prospective evaluation of the usefulness of C-reactive protein in the diagnosis of neonatal sepsis in a sub-Saharan African region. Antimicrob Resist Infect Control 2012 Jun 1;1(1):22.