

# Clinical Research Informing Neonatal Care at the University Hospital of the West Indies: 50 Years Experience

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## ABSTRACT

*Neonatology has rapidly grown over the past few years to its present status of a highly technologically driven specialty. Centres in resource restricted countries tend to adopt management guidelines from the developed world and integrate them into local practice. Although international neonatal practices have influenced neonatal care at the University Hospital of the West Indies (UHWI), over the past fifty years there has been local clinical research done at the hospital that has informed local practice. Causes of neonatal mortality have been documented and this has informed neonatal resuscitation practices, infection control policies and ventilatory support of premature infants. Changes in the incidence of various aetiologies of jaundice over the years have altered how jaundiced neonates are investigated and managed. Research on neonatal sepsis has informed antibiotic choices and treatment regimes. Studies on preterm infants have informed management policies on ensuring optimal thermal environment, on the timing of discharge and on neurodevelopmental follow-up. It is clear that clinical research at the UHWI has informed neonatal care at the institution over the past 50 years and it is hoped that it will continue to do so for the next 50 years and beyond.*

**Keywords:** clinical research, neonatal care

# La Investigación Clínica al Servicio de la Información para el Cuidado Neonatal en la Universidad de West Indies: 50 Años de Experiencias

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## RESUMEN

*La neonatología se ha desarrollado rápidamente en los últimos años hasta alcanzar su presente estado como especialidad altamente informada por la tecnología. Los centros en países con recursos limitados tienden a adoptar lineamientos para el tratamiento tomados del mundo desarrollado e integrarlos a la práctica local. Aunque las prácticas neonatales a nivel internacional han influido en el cuidado neonatal en el Hospital Universitario de West Indies (HUWI), durante los últimos cincuenta años se han realizado investigaciones clínicas locales en el hospital, que han informado la práctica local. Las causas de la mortalidad neonatal han sido documentadas, y la información obtenida ha venido a formar parte de las prácticas de resucitación neonatal, las políticas de control de las infecciones, y el soporte ventilatorio de los infantes prematuros. Los cambios en la incidencia de varias etiologías de ictericia a lo largo de los años, han alterado la forma en que se investigan y tratan los neonatos con ictericia. La investigación sobre la sepsis neonatal ha informado las opciones sobre los antibióticos así como los regímenes de tratamiento. Los estudios sobre los infantes pretérmino (bebés prematuros) han pasado a informar las conductas de tratamiento con respecto a asegurar un ambiente térmico, en relación con el tiempo del alta, así como con respecto al seguimiento del neurodesarrollo. Está claro que la información proveniente de la investigación clínica en HUWI ha pasado a ser parte del cuidado neonatal en la institución en los últimos 50 años, y se espera que continúe siéndolo más allá de los próximos 50 años.*

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**Palabras claves:** investigación clínica, cuidado neonatal

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## INTRODUCTION

The field of neonatology has grown exponentially from its inauspicious beginnings, where premature infants were shown being cared for in incubators as a side-show at fairs and exhibitions, to a highly technologically driven speciality. So too has the Newborn Special Care Nursery at the University Hospital of the West Indies (UHWI) grown from a side-room on the postnatal ward to a 30-bed unit with a six bed neonatal intensive care unit. While neonatal care at the UHWI has been influenced by international neonatal practices, it has also been quietly shaped by local clinical research. The aim of this paper is to describe how local clinical research at the UHWI has informed neonatal care at the institution over the past 50 years.

In 1963, Miller *et al* reported that ABO incompatibility, maternal diabetes and Rh incompatibility were the only significant causes of jaundice found in 400 neonates born at the University College Hospital (UCH) between January 4 and March 6, 1963. Glucose-6-dehydrogenase deficiency (G6PD) was not found to be a significant cause (1). In 1969, Macnamara made the observation that in a six-year period at the UCH between nine and 20 exchanges for ABO incompatibility were carried out each year, whereas Rhesus sensitization accounted for an average of three exchanges per year (2). He attributed the low incidence of Rh sensitization to the low occurrence of the Rh negative factor in the general Jamaican population (3%) as documented by Gibbs (3).

Massive pulmonary haemorrhage as a cause of neonatal death was reviewed by Thorburn in 1963. Examinations were carried out on 27 newborn infants dying with massive pulmonary haemorrhage. Pulmonary haemorrhage occurred in 8% of neonatal deaths; 52% of cases died early in the neonatal period. Anoxia was considered to be the main causal agent in the majority of early cases (4).

In 1966, Thorburn and Curzen published results of a perinatal mortality review undertaken between July 1, 1963 and June 30, 1965 at the UCH. They noted that there were 80 neonatal deaths during the study period with only seven of them occurring after the first week of life, giving a neonatal mortality rate (NMR) of 15.6/1000 live births. The most common causes of mortality were intrapartum anoxia (30.3%), congenital malformations (17.1%) and hyaline membrane disease [23.7%] (5).

Lowry *et al*, a decade later, reported on perinatal mortality for the period July 1, 1973 to June 30, 1975. They had a total of 71 neonatal deaths, eight occurring after seven days of life, giving a NMR of 16.74/1000 live births. They noted that 58% of neonates die within the first 24 hours and 89% by the end of the first week of birth. The most common causes of mortality were respiratory distress syndrome

[RDS] (19.7%), infection (18.3%), intrapartum anoxia (11.7%) and congenital malformations (11.3%). Compared to the previous study, fatal neonatal infection appeared to be more common and there was a greater frequency of immature neonates: 25% compared to 20% (6).

It is clear that knowing the causes of neonatal mortality at UHWI would have influenced management strategies that would have been implemented to decrease NMR. The high rate of intrapartum anoxia would have been the genesis for present policies that dictate a member of the paediatric staff attend all preterm deliveries, all deliveries complicated by meconium stained liquor, all Caesarean sections and any delivery where fetal jeopardy is detected or anticipated.

In 1975, Moore and Lowry documented the prognosis for extremely low birthweight babies. The status of 35 children who weighed < 1500 g born at the UHWI between 1969 and 1973 was compared with 37 matched normal birthweight controls at age 2 to 6 years. The low birthweight infants were physically smaller when compared to controls and this persisted even after correction for gestational age. No significant physical handicaps were identified but more of the low birthweight children failed to pass a developmental screening test as "normal" (8/35) than controls (2/37)  $p < 0.04$ . The authors suggested that a more complete follow-up of these low birthweight infants was needed (7). The findings from this study more than likely resulted in the expansion of the mandate of the Premature clinic to ensure the surveillance of growth and development of all premature infants at UHWI.

Kahn and Lowry conducted a prospective study between August 1973 and March 1975 to document the degree of cold stress occurring in immature newborns (< 37 weeks gestation) in a tropical environment. The mean admission temperature of 175 immature neonates was  $35.4 \pm 0.8^\circ\text{C}$  ( $95.4 \pm 1.5^\circ\text{F}$ ) with a range of  $33.0\text{--}37.44^\circ\text{C}$  ( $91.4\text{--}99.4^\circ\text{F}$ ). It appeared that the low admission temperatures were secondary to exposure to unfavourable ambient temperatures on the Labour ward ranging from  $22.2\text{--}26.6^\circ\text{C}$  [ $72\text{--}80^\circ\text{F}$ ] (8). Following this, there was the introduction of the use of heat lamps in the management of these infants at the UHWI followed by the use of radiant warmers and finally the use of a transport incubator to help limit cold stress to these infants.

In 1978, Lowry and Bailey published growth curves (weight, length, head circumference) for neonates 27–42 weeks gestation. Birthweight, vertex-heel length and head circumference were measured in 1230 newborn infants delivered at the UHWI and admitted to the Newborn Special Care Nursery between January 1974 and December 1976. Twins, babies with congenital malformations and those of mothers with haemoglobinopathies or diabetes mellitus were excluded. The patterns of birthweight at gestational ages

based on menstrual history indicated that the menstrual history, when used alone, was not a reliable indicator of gestational age (9). These growth curves were incorporated into the charts of all babies admitted to the nursery and is still utilized today.

Sparke and Lowry analysed neonatal deaths at the UHWI over the four-year period 1974–1977, the NMR was 16.87/1000 live births. Babies < 1500 g accounted for 52.6% of all deaths although they represented only 1.68% of total live births. The authors developed a graph of percentage mortality by gestational age for use in predicting survival of infants which would be useful for those in prenatal care. The majority of deaths were due to one of five conditions: RDS, intrapartum hypoxia, congenital malformations, infection and hypoxia in very immature babies. Findings from this study also suggested that there was a high incidence of infection and this was a priority area that needed to be addressed (10). This helped inform infection control policies where hand-washing, use of gowns and proper cleansing of equipment were emphasized.

Lowry *et al* reported on early discharge of low birthweight babies in 1980. Between July 1, 1975 and June 30, 1976, seventy-three babies (30 M, 43 F) weighing between 1206–1810 g were selected to be allowed home once they had normal clinical signs apart from small size, could maintain a stable temperature in an unheated room, had established adequate feeding and mother was able to cope with the baby at home. Fifty-seven babies did well at home, one baby died of pertussis and nine were readmitted within three months of discharge. Analysis did not suggest that a longer period of hospitalization would have reduced the number of admissions. Babies gained weight faster at home than in hospital (11). This still holds in 2012 where there is no absolute weight that a premature infant has to attain before discharge from the unit, once the above parameters have been attained.

A total of 434 babies of 28–36 weeks gestation admitted to the Newborn Special Care Nursery at the UHWI between 1974–1976 were studied by Lowry to determine the frequency and mortality of RDS. Thirty-two per cent of these infants were found to have RDS and 21.6% of them died, a mortality rate of almost two times that of developed countries (12). This highlighted the need to offer these infants ventilatory support beyond just administering oxygen *via* headbox and no doubt played a role in initiating the use of bubble continuous positive airway pressure (CPAP) in the nursery and later on mechanical ventilation in the main intensive care unit (ICU).

Gibbs *et al* found an incidence of 20.5% for G6PD deficiency in a group of infants with neonatal jaundice at the UHWI in 1978. In that study, G6PD deficiency was detected in 16 (69.6%) of a group of 23 neonates who had unexplained moderate to severe jaundice. The findings suggested that G6PD might be an important cause of neonatal jaundice in our setting (13, 14). These findings showed that between

1963 and 1978, G6PD had now assumed more importance in the aetiology of jaundice at the UHWI and should be included in the investigation of jaundiced infants.

In 1987, McFarlane reported on group B streptococcal (GBS) septicaemia at the UHWI. During a three-year study at the Newborn Special Care Nursery, the incidence of GBS septicaemia was 1.4/1000 live births. Group B streptococcal accounted for 35% of blood culture isolates and was the most frequent cause of septicaemia. There was an overall mortality rate of 36% (15). Trotman and Bell in a 10-year retrospective review of all inborn neonates admitted to the Newborn Special Care Nursery of the UHWI with GBS infection between January 1, 1991 and December 31, 2000 documented an incidence of 0.91/1000 live births. The most common clinical diagnosis was bacteraemia without an identified focus of infection (17, 61%), followed by pneumonia (8, 28%) and meningitis (3, 11%). One neonate died, giving a case fatality rate of 3.6% (16). The difference in mortality between the two studies may be related to the fact that in the early part of the 1987 study, babies with GBS septicaemia were treated with 50 000 u/kg/d IV penicillin 12 hourly. This was subsequently changed because of the high mortality rate in infants on this regimen. In the latter study, babies were initially started and maintained on doses 6–8 times that dose, illustrating how findings in the earlier study influenced management of GBS at the UHWI.

Bell *et al* conducted a retrospective review of all neonates with culture proven sepsis admitted to the UHWI between 1 January 1995 and 31 December 2000. There were 135 cases of culture-proven sepsis, 115 were inborn, giving an incidence of 6.7/1000 live births. Nine neonates (7%) died. The single most common organism isolated was *Klebsiella sp* (28%). Gentamicin resistance rate for *Klebsiella sp* was 46%; seven (18%) *Klebsiella sp* isolates showed a multiple antibiotic resistant pattern. *Klebsiella sp* accounted for four (44.4%) of the deaths (17). In another study looking at predictors of poor outcome in these neonates, prematurity, very low birthweight and female gender were found to be predictors of poor outcome in those with bacterial sepsis (18).

The results of these two studies offer important insights into the epidemiology of neonatal sepsis at the UHWI. They provide evidence on which to base selection of appropriate antibiotic regimes in the treatment of neonates with sepsis, as well as for the implementation of strategies for prevention of neonatal sepsis. Physicians involved in newborn care need to recognize the important role that *Klebsiella sp* plays in neonatal sepsis and its contribution to neonatal mortality. Empiric antibiotic regimes for gram-negative sepsis must take into consideration the high rates of gentamicin resistance that are now prevalent.

Barton *et al* reviewed the admission records of all neonates admitted for sepsis evaluation to the Newborn Special Care Nursery of the UHWI between January 1995 and December 2000. They found that urinary tract infection

(UTI) was an important cause of serious bacterial infection in neonates, affecting one in three babies with proven bacterial infection and it may be the first indicator of underlying structural abnormalities (19). The findings of a high incidence of UTIs in neonates in the first 24 hours of life with concomitant negative blood cultures underscored the need to maintain a urine culture as part of a sepsis work-up in neonates in the first 24 hours of life at the UHWI despite the recommendations in the international literature.

In a retrospective review between January 1, 1990 and December 31, 2001, Trotman *et al* described the maternal and neonatal characteristics of breastfed infants with hypernatraemic dehydration admitted to the UHWI over a twelve-year period. A total of 24 babies fulfilled the criteria for hypernatraemic dehydration; eighty-three per cent of babies were exclusively breastfed. Mean ( $\pm$  SD) age at presentation was 7.4 ( $\pm$  3.8) days. Identified factors contributing to insufficient intake in the neonates included difficulty latching on (61%), anatomical breast abnormalities (43%) and lack of social support (54%). Babies who had a home visit by nurses had a lower mean serum sodium, were less dehydrated and were significantly less acidotic than those who had not been visited [ $p < 0.05$ ] (20).

Findings from this study suggest that in addition to educating healthcare workers and mothers of the advantages of breastfeeding, knowledge of the risk factors and symptoms of this unwanted complication must also be stressed. It is important that a system for early review of at-risk-mothers who are not visited by the domiciliary service of the UHWI be initiated ideally three days post discharge to detect and/or prevent the morbidity and mortality associated with hypernatraemic dehydration.

Olugbuyi *et al* conducted a retrospective descriptive study looking at the outcome of all neonates weighing less than 1500 g admitted to the Newborn Special Care Nursery at the UHWI between March 1987 and February 1997. Four hundred and thirty-two infants were included in the study, 54% survived. There was a significant difference in survival between infants weighing greater than 1000 g, 74% survived, and infants weighing less than 1000 g, 20% survived ( $p < 0.001$ ). As birthweight and gestational age decreased, the risk of dying increased. When gestational age and time period of birth were controlled for, birthweight remained a significant predictor of mortality (21).

Trotman and Lord examined outcome of all live, inborn, very low birthweight infants admitted to the Newborn Special Care Nursery of the UHWI between January 1, 2002 and December 31, 2003 in a two-year retrospective review. Multiple regression analyses showed birthweight  $\geq 1000$  g, female gender and use of prenatal steroids to be independent predictors of survival (22). These two authors also looked at the outcome of babies weighing  $< 1000$  g during the same time period. They found gestational age  $\geq 27$  weeks and weight  $\geq 750$  g to be associated with increased survival  $p < 0.001$  (23).

These three studies clearly demonstrate that birthweight and gestational age are important predictors of mortality in our setting and improving the survival of low birthweight infants is a key factor in decreasing NMR.

Trotman and Garbutt conducted a retrospective review to determine predictors of outcome in term infants with hypoxic ischaemic encephalopathy (HIE) at the UHWI during the six-year period 1998–2003. The stage of encephalopathy, seizures on admission, the need for more than one antiepileptic for seizure control and an abnormal neurological examination at hospital discharge were found to be associated with poor outcome. An abnormal neurological examination at discharge had a positive predictive value of 88% and a negative predictive value of 84% for poor outcome, with a sensitivity and specificity of 60% and 96%, respectively (24). Findings from this study dictates that if post HIE an infant has an abnormal neurological examination at the time of discharge from hospital, that infant should be followed-up and monitored in a specialist neurology clinic and parents counselled about the guarded prognosis for normal neurodevelopmental outcome.

Prior to 2001, neonates requiring mechanical ventilation at the UHWI were accommodated depending on the availability of space in the main ICU, a then eight-bed unit. Review of the outcome of these babies by Trotman *et al* over a 15-year period revealed that RDS was the most common reason for admission (67%); there was a 50% decrease in the number of neonates gaining access to the ICU in the 1990s and there was no significant change in mortality over the 15-year period (47%). Only 10% of babies requiring ventilatory support gained access to mechanical ventilation (25). From these findings, it was concluded that to achieve further decline in the NMR, a greater proportion of neonates requiring ventilatory support should have access to mechanical ventilation. In addition, there should be a decrease in the lag time between onset of respiratory failure and commencement of mechanical ventilation. The need for the establishment of a NICU was therefore justified.

In 2001, a newly refurbished Newborn Special Care Unit with a six-bed NICU was opened at the UHWI. Analysis of patterns of utilization of the NICU by Trotman in 2006 showed that the number of babies and the number of premature babies ventilated had increased yearly. The number of babies accepted from other hospitals was also steadily increasing. Additionally, it was seen that the premature infant with RDS placed the greatest demand on the resources of the NICU. They had the greatest utilization of ventilation, they were more likely to die, they required more prolonged periods of ventilation and they had a higher incidence of complications (26).

Trotman and Barton showed that the establishment of a neonatal intensive care unit resulted in improved survival of very low birthweight infants. A retrospective analysis of the outcome of inborn very low birthweight infants admitted to the Newborn Special Care Nursery of the UHWI pre (period

1) and post (period 2) establishment of a neonatal intensive unit was conducted. There was improved survival during period 2 when 69% of infants survived compared to period 1 when 55% survived ( $p = 0.02$ ). This increased survival was due to an increase in survival of infants weighing 750–999 g in period 2 when 65% of infants survived compared to 29% in period 1 ( $p < 0.05$ ). The establishment of a neonatal intensive care unit has resulted in improved survival of very low birthweight infants; further improvement in survival of these infants will be dependent on increased accessibility to surfactant therapy, initiation of total parenteral nutrition and availability of trained personnel (27).

Finally, Trotman and Henny-Harry carried out a retrospective review of all neonates with hyperbilirubinaemia requiring medical intervention at the University Hospital of the West Indies between January 1, 2006 and June 30, 2007. Predictors of severe hyperbilirubinaemia (total serum bilirubin level  $\geq 400 \mu\text{mol/l}$ ) were determined. Exclusive breastfeeding, oxytocin use in the mother during labour and G6PD deficiency in the infant were found to be independent predictors of severe hyperbilirubinaemia (28).

Based on the findings in this study, it was recommended that all neonates requiring phototherapy for hyperbilirubinaemia be routinely tested for G6PD deficiency especially if they were male. Neonates whose mothers receive oxytocin during labour should be closely monitored and followed-up post discharge for the development of hyperbilirubinaemia. Additionally, mothers should not be discharged from the postnatal ward until breastfeeding is adequately established; women with difficulties breastfeeding should be identified on the postnatal ward and continued support for breastfeeding should be offered post discharge from hospital. It is clear that clinical research at the UHWI has informed neonatal care at the institution over the past 50 years and it is hoped that it will continue to do so for the next 50 years and beyond.

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