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## Case Report

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## BCG-Associated Osteomyelitis: A Case Report

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**KEYWORDS:** BCG (*Mycobacterium bovis* BCG); Osteomyelitis; PCR (Polymerase Chain Reaction).

### INTRODUCTION

BCG (*Mycobacterium bovis* BCG) is a vaccine for preventing childhood tuberculosis (TB). The World Health Organization registered freeze-dried Tokyo-172 seed lot as an international reference vaccine strain in 1965, and ever since, the Tokyo-172 BCG has been used, not only in Japan, but also all over the world. However, there are some severe adverse reactions that developed beyond vaccination site and regional ipsilateral axillary lymph-nodes. Osteomyelitis is a very rare but serious late complication of BCG-immunization and results from generalized dissemination of BCG.<sup>1</sup> We present a case of a 23-month-old boy with a mass lesion in the right shoulder.

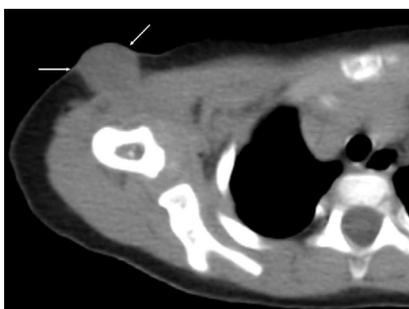
### CASE REPORT

A 23-month-old Japanese boy with a mass lesion in the right shoulder was referred to our hospital. His parents noticed it and took him to hospital to consult. He was born by a normal vaginal delivery with a normal Apgar score, and was 82 cm tall, and weighs 9.8 kg now. He had no history of any diseases. On physical examination, the mass lesion was soft and slightly moved by touch. He could freely move his shoulder without pain or discomfort by it. His blood test and laboratory data showed elevated WBC (9600/ $\mu$ L (normal 3500-9000/ $\mu$ L) and LDH (318 IU/L (normal 106-211 IU/L), and showed decreased IgG 476 mg/dL (normal 800-1600 mg/dL), and IgA (44 mg/dL (normal 100-350mg/dL). CRP, IgM and others were normal. From these results, a chronic infectious disease due to weakened immune systems was suspected. On X-ray, questionable rounded radiolucent area with clear osteosclerotic margin was visualized in the proximal metaphysis to diaphysis of the right humerus (Figure 1). The right shoulder CT showed low density mass lesion in the subcutaneous fat tissue (Figure 2). The right humerus showed rounded radiolucent lesion with osteosclerotic margin (Figure 3). In order to check both the bone lesion and the subcutaneous soft tissue mass, we took right shoulder MRI. The subcutaneous mass lesion showed slightly high signal intensity on T2 weighted axial image (Figure 4a, arrow) and low signal intensity on T1 weighted axial image (Figure 4b, arrow). On contrast study, it showed ring enhancement (Figure 4c, arrow) suggestive of abscess formation. The proximal humerus showed low signal intensity on T1 weighted image (Figure 4b, arrowhead) and well enhancement on gadolinium-enhanced fat suppression T1 weighted axial image (Figure 4c, arrowhead). In addition, that enhanced area was connected with the proximal humeral lesion on gadolinium-enhanced fat suppression T1 weighted sagittal and coronal images (Figure 5a and 5b arrows). These findings suggested that both were the same lesion. We suspected chronic osteomyelitis with abscess formation of the right humerus from MRI finding and his symptoms. However, technetium-99 m MDP (250.0 MBq) bone scintigraphy showed no increased radioactive tracer in the right shoulder (Figure 6), suggestive of a cold abscess formation like tuberculosis. We asked his mother when and where on his body he was injected with the BCG vaccine. He had the Tokyo-172 BCG vaccine administered to his right shoulder when he was 2 weeks old. The abscess formation was present in the injection site of the vaccination of BCG. We diagnosed BCG-associated osteomyelitis and performed

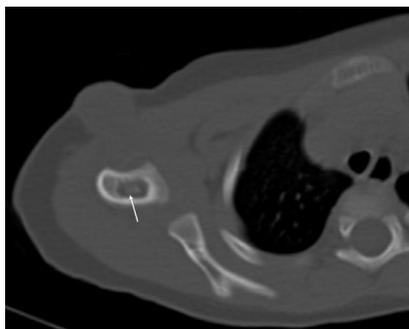
the subcutaneous abscess drainage and the curettage of the proximal humerus. Tuberculosis-polymerase chain reaction (Tb-PCR) was also performed from the subcutaneous abscess and it was positive. He received isoniazid (INH) and rifampins (RFP) therapy for one year. His right humerus was fully recovered. His immune systems became normal.



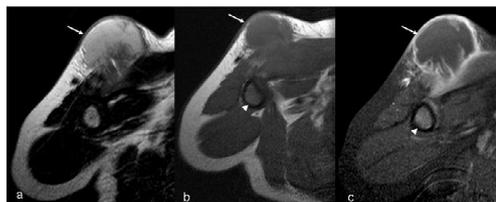
**Figure 1.** X ray of right humerus. A rounded radiolucent area with clear osteosclerotic margin is visualized in the proximal metaphysis to diaphysis of the right humerus (arrow). We cannot detect soft tissue mass in this radiograph.



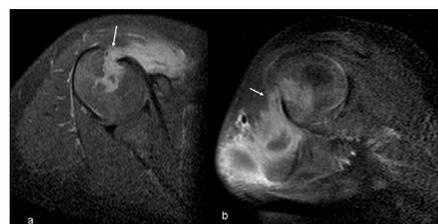
**Figure 2.** Right shoulder CT (soft tissue density window) Low density mass lesion is visualized in the subcutaneous fat tissue of the right shoulder joint (arrow).



**Figure 3.** Right shoulder CT (bone density window) Low density area with osteosclerotic margin is present within the right humerus (arrow).



**Figure 4.** Right shoulder MRI: a. T2 weighted axial image, b. T1 weighted axial image, c. gadolinium-enhanced fat suppression T1 weighted axial image. Subcutaneous soft tissue mass shows slightly high signal intensity on T2WI (a, arrow), and low signal intensity on T1WI (b, arrow). The bone lesion shows low signal intensity on T1WI (b, arrowhead). On contrast study, the subcutaneous soft tissue mass is ring-enhanced, suggestive of abscess formation (c, arrow). The bone lesion also shows enhancement (c, arrowhead).



**Figure 5.** Right shoulder MRI: Gadolinium-enhanced fat suppression T1 weighted axial image. a. sagittal image, b. coronal image. Both the soft tissue mass and the bone lesion are connected with each other (a, b arrows). Both are compatible with osteomyelitis with subcutaneous abscess formation.



**Figure 6.** Technetium-99 m MDP (250.0 MBq) bone scintigraphy. Whole bone scintigraphy shows no abnormal increased radioactive tracer. The right shoulder lesion is suspicious for cold abscess formation due to tuberculosis osteomyelitis.

**DISCUSSION**

Outbreak of the BCG-associated osteomyelitis is influenced by a Japanese vaccination. In Japan, children were vaccinated with BCG until they reached the age of 4. Tuberculosis Control Law, which provides a legal basis for national tuberculosis control, was amended in 2004 and entered into force on April 1, 2005.<sup>2</sup> After that, infants could have a BCG vaccination within 6 months after birth for 2005 to March 2013 to prevent tuberculosis. Therefore, a lot of infants had it at the same time when they received a medical check at 3 to 4 months after birth. Ever since, the rate of

patients with BCG-associated osteomyelitis and osteitis increased by approximately 4 times in Japan (1.25 patients/year (2001-2004) vs. 4.14 patients/year (2005-2011)).<sup>3</sup> In addition, patients who were vaccinated the BCG within 4 months after birth were prone to be infected with the BCG-associated osteomyelitis and osteitis.

This might be because the immune system, especially cell-mediated immunity of the infants at 3 to 4 months after birth is immature yet.

Today, the amendment of the Preventive Vaccination has changed since April, 2013, and children must receive the BCG vaccine between ages of 5 months and 1 year. We have to know whether patients with the BCG-associated osteomyelitis will decrease or not.

Several authors reported that some children have primary immunodeficiency diseases and there are a number of primary immune deficiency diseases prone to BCG complications.<sup>4,5</sup> Hoshina et al<sup>5</sup> reported that patients who had multiple osteomyelitis diagnosed with interferon- $\gamma$  receptor 1 deficiency from their genetic analysis. Development of osteomyelitis of patients with no gene abnormality was 10 months (1-46 months). It was late as compared to the patients with gene abnormalities (9.5 months) (7-15 months).<sup>6</sup>

In our case, the patient had the BCG vaccination at age of 5 months in 2012 and found the BCG-associated osteomyelitis as a non-painful mass 18 months later. From his laboratory data, he might be a temporary immunodeficiency state because he was too young when he was vaccinated. However, he didn't have any primary immunodeficiency diseases or gene abnormalities. He has been growing up without any problems after his treatment.

The BCG-associated osteomyelitis occurs in long bones such as femur, humerus, and tibia. It does not necessarily occur in a bone which is close to the injected site of the BCG vaccination. X-rays of the BCG osteomyelitis show a lucent lesion with modelling deformity and a periosteal reaction. This fills in slowly with time and ongoing treatment. MRI is useful to detect BCG osteomyelitis with abscess formation. Bone scintigraphy is characteristic to the BCG osteomyelitis. We cannot detect any accumulation of radioactive tracer in the lesion. However, all image findings of the BCG osteomyelitis are extremely similar to ones of tuberculosis osteomyelitis.<sup>7</sup> Therefore, we need to consider the possibility of tuberculosis osteomyelitis as well.

## CONCLUSION

BCG-associated osteomyelitis is a rare complication after BCG vaccination. Infants who were vaccinated the BCG within 5 months after birth are prone to be infected with the BCG-associated osteomyelitis because their immune system is immature. We need to check their primary immunodeficiency diseases or gene abnormalities when we suspect the BCG-

associated osteomyelitis.

**CONFLICTS OF INTEREST:** None.

## CONSENT

Authors obtained written informed consent from the patient for publication of this manuscript.

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## Research

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# Umbilical Cord Care After the First Day From Birth: A Case Control Study in a Northeastern Italian Hospital

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## ABSTRACT

**Background:** Recently the use of antibacterial agents to clean and dry the stump of the newborns' umbilical cord (UC) after birth has been abandoned by many neonatal units. Aim of this study was to compare the occurrence of adverse events (AEs), time to UC separation and caregivers' satisfaction among newborns treated with *dry cord care* versus 70% alcohol after one day from birth in an Italian Hospital.

**Methods:** From June 2014 to September 2014, 100 infants were enrolled for the study. Soon after birth, all the newborns were treated in the same way: their UC was cleansed with 70% alcohol, using a sterile gauze. One day after the birth, in the control group the UC was regularly cleansed with 70% alcohol twice a day, while in the case group, from the first nappy change, *dry cord care* was performed cleansing the UC with sterile saline solution (NaCl 90%), using a sterile gauze twice a day. In all cases UC was left without any dressing upon it as well. The time to UC separation and any AEs (local and systemic infections, haemorrhage, granuloma formation) were reported by mothers. Carers' perception regarding the two procedures were collected by a questionnaire between 6 and 24 hours after birth, and 1 month later.

**Results:** We found a significant difference in the mean cord separation time between the two groups [*dry cord care*: 9.1 days (standard deviation (SD)=3.1] versus 70% alcohol: 11.3 days (SD=4.6);  $p<0.01$ ], while no significant AEs and carers' satisfaction on the procedures resulted. Instead, change of treatment at home was more frequent in *dry cord care* group (23.9% versus 6.1%;  $p<0.01$ ).

**Conclusions:** This study confirms that *dry cord care* is an easy, accepted and safe method of handling the UC in healthy newborn infants born in a high-income hospital setting.

**KEYWORDS:** Umbilical cord care; Dry cord care; 70% alcohol; Cord separation time; Caregivers' satisfaction.

## INTRODUCTION

The umbilical cord (UC) which connects the baby and placenta in uterus (the womb) is made of blood vessels and connective tissue. It is covered by a membrane that is normally bathed in amniotic fluid. After birth, cutting the cord physically and symbolically separates the mother and her baby. The cord stump (CS) dries, falls off and the wound heals.<sup>1</sup>

The cord usually separates between 5 and 15 days after birth. Before the separation, the remaining stump can be considered to be a healing wound and thus a possible route for infection through the vessels into the baby's blood stream.<sup>1</sup>

Soon after a normal delivery, the skin of the newborn baby including the CS is colonised mainly by non-pathogenic bacteria such as coagulase negative *Staphylococci* and *Diphtheroid* bacilli. Pathogenic bacteria such as *Coliforms* and *Streptococci* may also be present on the skin<sup>2</sup> and can track up the CS causing infection.

In the developing countries, one third of the deaths are caused by infections, mostly because of the delivery environment (generally the community and the houses). Cord infection may be localised to the UC (omphalitis) or, after its entry into the blood stream, it becomes systemic (e.g., neonatal sepsis).<sup>2</sup> The most observed infections upon the CS and the abdominal surface are due to bacterial omphalitis with polymicrobial aetiology,<sup>3</sup> but also to *Clostridium tetani*.<sup>4</sup> The onset of the symptoms is usually observed between the 5<sup>th</sup> and the 9<sup>th</sup> day of life.

While there is a general agreement about the clean technique for cutting the cord using a sterile cutting instrument (blade or scissors) and regards to clean hands to avoid infection, there is less accord on what is the best care of the CS.<sup>1</sup>

Internationally, the World Health Organisation (WHO) has advocated since 1998 for the use of dry UC care (keeping the cord clean without application of anything - where anything stands for a dye, an antiseptic, or an antibiotic - and leaving it exposed to air or loosely covered by a clean cloth, in case it becomes soiled it is only cleaned with water).<sup>5</sup> Also the American Academy of Paediatrics considers no antiseptic treatment to be superior to any other<sup>6</sup> and the guidelines from the German Association for Neonatology and Paediatric Intensive care recommend clean care and keeping the UC dry.<sup>7</sup>

On the basis of a Cochrane review<sup>1</sup> and other several studies,<sup>8-12</sup> WHO recommends daily chlorhexidine (7.1% chlorhexidine digluconate aqueous solution or gel, delivering 4% chlorhexidine) application to the UC stump during the first week of life for newborns who are born at home in settings with high neonatal mortality (30 or more neonatal deaths per 1000 live births), while *dry cord care* for newborns born in health facilities and at home in low neonatal mortality settings.

According to the literature, *dry cord care* can be performed in several different ways, even though it is called with the same name. In some studies<sup>13</sup> it was defined as the act of cleansing the UC and the surrounding area with water ad soap, whereas in others it was described as the act of letting the UC dry without the application of any solution whatsoever.<sup>13</sup>

Aim of this study was to compare the occurrence of all adverse events (AEs) and the cord separation time among newborns treated with *dry cord care* versus 70% alcohol in an Italian Hospital to give a valid recommendation to clinicians. Further endpoints were caregivers' acceptance of treatment and satisfaction with it.

## MATERIALS AND METHODS

Study subjects were recruited from June 2014 to September 2014 at a Northeastern Italian Hospital, where about 500 deliveries take place annually. The minimum sample size (N=100) was calculated using the formula of estimating a single population (N=500) portion, taking 15% proportion of 6% margin of error and 95% confidence level.

Infants were considered eligible according to the inclusion criteria reported in Table 1 which are in line with inclusion criteria in other similar studies.<sup>11,14</sup> After obtaining written consent by parents, during the considered period the first 50 subjects were assigned to control group and the last 50 infants to case group (*dry cord care*).

NEWBORNS' INCLUSION CRITERIA TO THE RESEARCH
Birth between the 37 <sup>th</sup> and the 42 <sup>nd</sup> week of pregnancy
Vaginal and caesarean section
Apgar score of $\geq 7$ at 5 minutes after birth
Birth weight $\geq 10^{\text{th}}$ percentile
Without inborn or genetic disorder
No maternal complication during pregnancy or delivery
Parental consent
Italian speaking parents

Table 1: Criteria to including newborns in the experimental study.

Soon after birth, the newborns of both groups were treated in the same way following the hospital procedure: their UC was cleansed with 70% alcohol using a sterile gauze. A dry gauze was wrapped around the stump and fixed with a net. This dressing was usually supposed to stay in place for at least 24 hours, if not contaminated. Then the treatment was changed after the first 24 hours: in the control group the UC was regularly cleansed twice a day with 70% alcohol with a sterile gauze and left without any dressing upon it, while in the case group *dry cord care* was performed from the first nappy change cleansing the UC with sterile saline solution (NaCl 90%), using a sterile gauze twice a day, and left without any dressing upon it as well. In case of urine or meconium/faeces contamination, these procedures had to be performed more often in order to reduce the consequent risk of infection.

A researcher collected new born's and mother's data: delivery (natural, caesarean section, vacuum extractor), birth weight, parenthood order, sex, type of breast feeding at discharge, mother's age and education.

A questionnaire (available on request), organised in different pathways for primipare and pluripare, was administered to mothers in two moments: at first soon after birth, between the 6<sup>th</sup> and the 24<sup>th</sup> hour after delivery, in hospital and one month after child birth at home by phone. Variable investigated were: mother's knowledge about the UC care, anxiety level in hospital and at home regards the treatment, type of breastfeeding at home,

occurrence of AEs and their treatments, cord separation time, changes in cord care procedures at home, alternative products, access to outpatient care, carers' opinion about the treatment in terms of satisfaction, anxiety and compliance to the instructions given by hospital personnel.

Parents were asked to record signs of UC local or systemic infections categorised into four gradations (none, mild, moderate, or severe) according Mullany.<sup>10</sup> Mild was defined as redness or swelling limited to the CS only; moderate was defined as less than 2 cm extension onto the abdominal skin at the base of the CS; and severe was defined as spreading noticeably ( $\geq 2$  cm) outward from the base of the stump. In case of systemic infection (also known as neonatal sepsis), the describing criteria were the admission diagnosis of the newborn in the Paediatric Unit, the contingent analysis and the cultural exams. The study also detected the umbilical granuloma that is the most common umbilical abnormality in the neonate.<sup>11</sup>

Criterion to define CS fall was the complete detachment of the stump from the newborn's abdominal surface.

Ethical approval for this study was not needed, because *dry cord care* was already approved by the scientific community.

Data collected were entered in an Excel spreadsheet and were analysed using the statistical software SPSS, version 20. Pearson Chi-square test and Mann – Whitney test, for mean comparison, were used. Statistical significance was defined as  $p \leq 0.05$ .

**RESULTS**

One hundred inborn healthy term infants were recruited from June 2014 to September 2014 distributed equally in experimental

group (*dry cord care*) and control group (70% alcohol). It was possible to collect a full data set from 95 of them, whereas 5 of mothers did not attend the follow up.

Table 2 shows the newborns' and mothers' characteristics in the two groups under study.

Table 3 reports questions administered to mothers at home one month after childbirth: type of breastfeeding at home, occurrence of AEs, changes in cord care procedures at home, use of alternative products and cord separation time. The incidence percentage of granuloma was 2.2% in *dry cord care* group. 11.0% (5/46) of *dry cord care* group mothers went to paediatrician and 4.1% (2/49) of control group ones.

Table 4 describes mothers' knowledge, satisfaction and anxiety regards to UC treatment. Regards to previous knowledge about UC care, primipare reported health professionals (paediatric nurses, midwives) as principal sources of information, while magazines, internet, opinions of relatives and friends as alternative sources, while pluripare acquired knowledge during previous pregnancies. Only *dry cord care* obtained a score  $\leq 4$  in 3 cases in question on satisfaction with treatment management and results. This satisfaction was related to the doubts about the practice and not regards to the occurrence of AEs.

Pluripare that experienced both treatments were asked to give a preference on them: 40.9% (9/22) chose *dry cord care*, 31.8% (7/22) referred 70% alcohol and 27.3 (6/22) did not express their opinion.

**DISCUSSION**

Even if in 2013 WHO recommended clean *dry cord care* for infants born in health facilities and at home in low neonatal mor-

INFANTS		dry cord care group N(%) Total=46	70% alcohol group N(%) Total=49	p value
Type of delivery	Natural	27(58.7%)	37(75.5%)	0.15
	Caesarean section	14(30.4%)	7(14.3%)	
	Vacuum extractor	5(10.9%)	5(10.2%)	
Birth weight (g)	Mean (SD)*	3410.91(368.02)	3298.27(402.73)	0.18
Parenthood order	First-born	22(47.8%)	27(55.1%)	0.31
	Second-born	22(47.8%)	17(34.7%)	
	Third-born	2(4.3%)	5(10.2%)	
Sex	Female	23(50.0%)	20(40.8%)	0.37
	Male	23(50.0%)	29(59.2%)	
Breastfeeding at discharge	Breast	45(97.8%)	46(93.9%)	0.34
	Formula	1(2.2%)	3(6.1%)	
	Combination	/	/	
MOTHERS		dry cord care group n=46	70% alcohol group n=49	p value
Age(years)	Mean (SD)*	32.0(5.3)	32.7(5.0)	0.4
Education	Primary school	1(2.2%)	/	0.18
	Secondary school	3(6.5%)	14(28.6%)	
	High school	28(60.9%)	20(40.8%)	
	University	14(30.4%)	15(30.6%)	

\*standard deviation

Table 2: Baseline characteristics of subjects (infants and mothers) in the two groups under study.

Questions		dry cord care group N(%) Total=46	70% alcohol group N(%) Total=49	p value
Method of infant feeding at home	Breast	33(71.7%)	32(65.3%)	0.79
	Formula	5(10.9%)	7(14.3%)	
	Combination	8(17.4%)	10(20.4%)	
Adverse Events	No	36(78.3%)	40(81.6%)	0.78
	Yes	10(21.7%)	9(18.4%)	
Type of Adverse Event	Mild infection	2(20%)	2(22.2%)	0.62
	Moderate infection	/	/	
	Severe infection	/	/	
	Redness, bleeding	7(70%)	7(77.8%)	
	Granuloma	1(10%)	/	
	Systemic disease	/	/	
Procedure change at home	No	35(76.1%)	46(93.9%)	<0.01
	Yes	11(23.9%)	3(6.1%)	
Alternative products	Silver nitrate	1 <sup>§</sup> (9.1%)	1 <sup>§</sup> (33.3%)	/
	Peroxide	1 <sup>^</sup> (9.1%)	1 <sup>^</sup> (33.3%)	
	70% Alcohol	8 [4] <sup>^</sup> [4] <sup>§</sup> (72.7%)	/	
	Pomade	/	1 <sup>§</sup> (33.3%)	
	Eosine	1(9.1%)	/	
Cord separation time (days)	Mean (SD) <sup>*</sup>	9.1 (3.1)	11.3 (4.6)	<0.01
	Range	3-16	3-23	/
	Median	10	12	/

\*standard deviation

§medical decision

<sup>^</sup>autonomous caregivers' decision

Table 3: Questions administered to mothers at home one month after childbirth, distributed in the two groups under study.

Questions		dry cord care group N(%) Total=46	70% alcohol group N(%) Total=49	P value
Background knowledge	Yes	35(76.1%)	39(79.6%)	0.76
	No	11(23.9%)	10(20.4%)	
	Yes among pluripare	24/46(52.2%)	24/49(49.0%)	0.76
Satisfaction (score:0-10) <sup>*</sup>	Mean (SD) <sup>§</sup>	8.8(2.0)	9.4(1.1)	0.21
	Range	1-10	5-10	/
Anxiety in hospital	Yes	5(10.9%)	7(14.3%)	0.61
	No	41(89.1%)	42(85.7%)	
Anxiety at home	Yes	1(2.2%)	2(4.1%)	0.59
	No	45(97.8%)	47(95.9%)	

\* score 0-10: 0 corresponds=no satisfaction and 10=maximum level of satisfaction

§ standard deviation

Table 4: Questions administered to mothers regards to knowledge, satisfaction and anxiety about the umbilical cord treatment. distributed in the two groups under study.

tality settings, healthcare working in neonatal unit and caregivers use different procedures to care the UC according their experiences and their preferences. Also in high-income countries, where mortality is very low, important outcomes in the first month<sup>1</sup> of life regards to UC care must include more frequently AEs such as irritation, redness of the navel wall, weeping and bleeding of the navel, rarely infections like omphalitis, sepsis, and umbilical granuloma and the time to separation of the UC stump.<sup>11</sup>

This case-control study compared two UC care procedures: *dry cord care* and 70% alcohol. *Dry cord care* is the procedure in which the umbilical stump is kept “clean and dry without applying anything” where anything stands for a dye, an antiseptic, or an antibiotic.<sup>5</sup> In this study *dry cord care* was performed from the first nappy change cleansing the UC with sterile saline solution (NaCl 90%), using a sterile gauze twice a day, and left without any dressing upon it as well. The research, confirming data shown in other trials conducted in healthy term infants born in high-income or middle-income hospital set-

ting,<sup>2,15-17</sup> found no difference in occurrence of UC AEs between the two groups, that also did not have statistically significant differences in percentages distribution of baseline characteristics of newborns (type of delivery, birth weight, parenthood order, sex, breastfeeding at discharge and at home) and of mothers (age, education).

In literature the mean UC separation time ranged from 4 to 16 days depending on the intervention and study setting.<sup>2,10,17</sup> Studies which applied nothing to the cord had mean separation times of about nine/ten days.<sup>14-17</sup> Meta-analysis of four studies with alcohol as the comparator showed a trend towards cord separation being significantly prolonged in the alcohol group but there was no significant difference in cord separation,<sup>1</sup> while the present study showed a statistical difference between the two groups: in *dry cord care* the mean UC separation time was about 2 days before of control group one (9 days versus 11 days). In literature the clinical impact of delays of cord separation is unknown, but it has social and cost implications: delay makes mothers anxious, and it increases the number of domiciliary

midwife visits to home.<sup>18</sup> It follows that health workers and families prefer more rapid cord separation.<sup>2</sup> The present research confirms that the mothers in the *dry cord care* group have less anxiety even if the absolute number is very low.

This study detected also the occurrence of granuloma. It is an over growing tissue during the healing process of the belly button, usually occurs in reaction to a mild infection. It is not a congenital abnormality but represents continuing inflammation of granulation tissue, that has not yet epithelialized.<sup>19</sup> In the present study the incidence percentage of granuloma was equal to 2.2% in *dry cord care* group much lower than the finding of Kapellen et al<sup>11</sup> of 11.7%.

About mothers' compliance to the technique, the study showed that caregivers used different products more often in *dry cord care* group than in the 70% alcohol group. In some cases, this was a personal decision based on knowledge and beliefs, in others the reason of the change was a medical prescription due the onset of a complication. There was a variety of alternative products that caregivers used from pomade to peroxide and of course the shift to 70% alcohol. An interesting finding was the utilization of silver nitrate in two cases because there were opposing opinions about the application of this product upon the UC. In fact a prolonged use of silver nitrate can cause the onset of chemical burns to the newborns' skin. For this reason, literature advises a more conservative approach to the infective complications of the umbilical area (granuloma) such as a 70% alcohol treatment.<sup>20,21</sup>

Regards to caregivers' perception about the UC care, the research highlighted no differences between the experimental and control group us in satisfaction with management and results of the treatment and in anxiety reported by mothers at home. The few cases that expressed a scarce satisfaction with *dry cord care* were not connected to the onset of complications, but only to scepticism among an experimental treatment. The literature offers other examples of studies that considered the carer's opinion about *dry cord care* compared with other techniques. For instance between chlorhexidine powder and *dry cord care*, chlorexidine seems to be the favourite one, therefore the carers would administer this treatment to their next child.<sup>11</sup> In the present study the researcher asked pluripare, experimented both the treatments in different pregnancies, which they preferred and why. About 40% of them would administer *dry cord care* to their next child appearing to more gentle and comfortable for the newborn.

Taking into account the costs of the two treatments, *dry cord care* resulted less expensive than 70% alcohol: a 250 ml bottle of 70% alcohol costs 5.10 €, where the same amount of sterile saline solution costs 1.20 €.

The study had three limitations. First, it was conducted on babies and their mothers who were only eligible for selection criteria, and it may not be generalised to other cultures or countries. The second limitation is related to difficulties of

standardised procedures in collecting the culture samples from UC in home setting. Therefore it was not possible to provide the determination of microorganisms responsible of detected complication. Third, data on UC complications and treatments was obtained by telephone interview of mothers and not through direct observation by healthcare professionals. Of course before hospital discharge, parents were instructed to look for the warnings signs of UC complications and to contact their healthcare provider if in doubt.

## CONCLUSION

This case-control study compared two different procedures for the UC care in infants born in a high-come hospital: *dry cord care versus 70% alcohol*. No statistically significant differences between the two UC care practices resulted regards to the occurrence of UC AEs (local infection, systemic disease, granuloma, bleeding, etc.) and to the caregivers' satisfaction, while time of UC separation was significant shorter in *dry cord care* group and more frequently mothers' *dry cord care* group changed the treatment at home.

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## CONFLICTS OF INTEREST

The authors have no competing interests.

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# Assessing the Evidence: Student Response System Versus Computer Based Testing for Undertaking Multiple Choice Question Assessment in Undergraduate Nursing Education

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## ABSTRACT

There is a dearth of evidence focusing on student preferences for computer-based testing *versus* testing *via* student response systems for summative assessment in undergraduate education. This quantitative study compared the preference and acceptability of computer-based testing and a student response system for completing multiple choice questions in undergraduate nursing education. After using both computer-based testing and a student response system to complete multiple choice questions, 192 first year undergraduate nursing students rated their preferences and attitudes towards using computer-based testing and a student response system. Results indicated that seventy four percent felt the student response system was easy to use. Fifty six percent felt the student response system took more time than the computer-based testing to become familiar with. Sixty Percent felt computer-based testing was more users friendly. Seventy Percent of students would prefer to take a multiple choice question summative exam *via* computer-based testing, although Fifty percent would be happy to take using student response system. Results are useful for undergraduate educators in relation to student's preference for using computer-based testing or student response system to undertake a summative multiple choice question exam.

**KEYWORDS:** Computer-based testing; Student response system; Summative assessment; Undergraduate nursing education.

## INTRODUCTION

Student response systems, sometime known as 'class response systems' or 'clickers' have been used in education for over 35 years.<sup>1</sup> Indeed in terms of health care education authors have reported their usefulness in nursing<sup>2</sup> dentistry<sup>3</sup> radiology<sup>4</sup> and medicine.<sup>5</sup> In a University setting, they have been used with a variety of learners, from undergraduate to postgraduate students. Nonetheless, it has been noted that the majority of the existing literature in relation to their utility is anecdotal and there remains a clear need for rigorous exploration on the use of this technology.<sup>6</sup> This is particularly true for the role of student response systems in summative assessments.

From the literature the advantages of using student response systems in teaching have been delineated.<sup>7</sup> It has received a positive review from students and enhanced their learner engagement and participation.<sup>8</sup> Within nursing education, student response systems have been shown to: increase classroom engagement<sup>1</sup>; provide more effective and efficient nurse education<sup>8</sup>; and students themselves have highlighting that they help to improve acquisition and

retention of knowledge.<sup>9</sup> However, while positives have been described, there are limitations to using a student response system which have also been noted. These include the fact that the corresponding receiver must be connected to and recognised by the computer prior to the software being started, otherwise responses will not be collected. Additionally, there must be technical familiarisation with the system to ensure there is minimal distraction from the course of study.<sup>10</sup>

## BACKGROUND

This is the first year that a novel module on Evidence Based Nursing (EBN1) has run in the current undergraduate nursing education curriculum within the recruiting University. What brought the authors to this topic was the need to select a useful format to conduct summative assessment. In this instance this refers to the summative year 1 EBN1 computer-based testing of a multiple choice question exam for undergraduate nurses (approximately 450 per year). The students are divided over two intakes per year, approximately 350 in October (including adult, children, mental health and learning disability specialism) and approximately 100 in February (adult specialism only). In some cases, due to the lack of a computer suite to accommodate the larger student numbers, all students cannot take a multiple choice question exam at one time and half must wait in a holding room until a computer is available, meaning the time is doubled for the exam. Module coordinators (JR and CL) sought an alternative, but prior to uptake recognised the importance of testing such a system as student response system. To this end they conducted two formative assessments (one using computer-based testing and one using a student response systems) and evaluated preferences for both from the students. The role of using student response systems to improve active teaching and learning and for formative assessments is well documented.<sup>1,8-12</sup> However, using student response systems for summative assessment is sparsely reported within the literature<sup>13</sup> and there is a dearth of evidence on student preferences for computer-based testing *versus* student response systems for summative assessment.

### Student Response Systems

Student response systems are small hand-held devices that can be used either anonymously or a student can authenticate themselves by entering usually their student/exam number, to collect individual responses for exam purposes. They allow students to answer questions in real time.<sup>14</sup> A Universal Serial Bus (USB) radio based receiver attached to a classroom computer collects all data including the responses provided. The benefit of engaging students with student response systems in teaching has previously been discussed.<sup>1,8-12</sup> However this paper will focus on student's preferences for using student response systems, compared to computer-based testing, in summative examinations.

### Computer-based Testing

Computer-based Testing is conducted within the recruitment site through a University student homepage. The assessment is ac-

cessed through the module homepage from within the University virtual learning environment. This multiple choice question assessment is scheduled for each individual student and is only available for completion during a predefined time period. Students are required to attend a University computer suite, log into their student account and complete the multiple choice questions assessment in an exam invigilated environment.

## METHODOLOGY

This study is based on quantitative data collection and analysis.

### Participants

During the academic year of 2014-2015, the EBN1 module was conducted in year 1 of the undergraduate nursing degree programme at a School of Nursing and Midwifery, taught in a large University within the United Kingdom. Data for this study was gathered from the October 2014 intake of students (n=324). This intake comprises adult, children, learning disability and mental health nursing students. The module comprised lectures, an online e-resource and small group tutorials. The module coordinators (JR and CL) standardised all teaching material for the small group tutorials to ensure all groups covered the same material in an identical fashion. At the end of phase 1 (November 2014) we asked students to complete a set of formative multiple choice questions *via* computer-based testing. At the end of Phase 2 (February 2015) we asked students to complete a set of formative multiple choice questions *via* a student response systems. Following the formative assessment completed by the student response system at the end of Phase 2, we asked students their opinion and preferences of computer-based testing and the student response systems (Table 1 presents the statements asked). All data was analysed using descriptive statistics. Prior to conducting this study, ethical permission to conduct this work was gained from The School Research Ethics Committee of the School of Nursing and Midwifery, within the recruiting University.

### Computer-based Testing

Students accessed the multiple choice questions *via* Question Mark software on their chosen computer (home or university) at a time convenient to them. Immediate feedback was given to all students on completion of the formative assessment.

### Student Response System

Students were located in a lecture theatre and given a student response systems (Turning Point NXT) handset and paper copy of the multiple choice questions which they worked through individually using self-paced polling.

### Evaluation

In planning the evaluation the aim was to explore the more convenient and user friendly option for students when undertaking

a multiple choice question exam. We asked 6 questions based on this to all students in the October 2014 intake. The questions were on: ease of use; format of delivery of question; preference for use in a multiple choice question exam; user friendliness; and time to become familiar with technology.

**RESULTS**

Of the October 2014 intake of undergraduate nursing students (n=328), 210 students signed into actively participate in the evaluation. Participants who answered the questions asked ranged from 192- 157. Table 1 below details the questions asked, answer choices provided and the number of participates who responded.

In assessing the ease of use of the student response system handset (Question 1, respondents=187) 74% of respondents either strongly agreed (37%) or agreed (37%) that the handset was easy to use (12% undecided) with only a minority disagreeing (8%) and strongly disagreeing (5%). The format of the question when using the student response system is that the questions are provided on written sheet and the students’ works thought the questions at their own pace (self-paced polling). On asking if this format enabled students to engage with the multiple choice questions (question 2, respondents=182) the majority of respondents felt it did, with 27% strongly agreeing and 32% agreeing. 21% of respondents were undecided with 20% disagreed that the format enabled them to engage with the questions (9% disagreeing and 11% strongly disagreeing). On asking the students which mode takes more time to become familiar with (question 3, respondents=157) the majority of students who answered

(56%) felt the student response system took more time or both the student response system and computer-based testing system took the same time to become familiar with (33%), with only 11% answering that the computer-based testing system took more time for them to become familiar with. On asking if the student response system or computer-based testing system was more user friendly (question 4, respondents=190) 60% of those who responded felt the computer-based testing system was more user friendly. 27% preferred the student response system with 13% having no preference for either system. In relation to this study, we were particularly interested in the possibility of using the student response system for future summative multiple choice question examinations. We therefore asked students if they would prefer to take a multiple choice question exam using computer-based testing or student response system (question 5, respondents=174). 70% of those who responded stipulated they would prefer to take *via* computer-based testing, with 30% preferring to take *via* student response system. Nonetheless, 50% of students would have been happy to take a multiple choice question exam using the student response system (question 6, respondents=192) with 28% strongly agreeing, 22% agreeing. 30% of those who responded disagreed (14% disagree, 16% strongly disagreeing) and would not have been happy to use the student response system to complete a multiple choice questions, with 20% of respondents undecided.

**DISCUSSION**

In this article, the authors examine the preferences of year 1 undergraduate student nurses in using computer-based testing and a student response system for multiple choice question ex-

Question	Answers	Number of Responses
1. The SRS was easy to use	Strongly agree – 37% Agree – 38% Undecided – 12% Disagree – 8% Strongly disagree – 5%	187
2. The format of the questions in the SRS assessment enabled me to engage with the questions	Strongly agree – 26% Agree – 32% Undecided – 22% Disagree – 9% Strongly disagree – 11%	182
3. Which takes more time to become familiar with?	Student response system – 56% Computer based testing – 11% Both take the same time to become familiar with – 33%	157
4. Which is more user friendly?	Student response system – 27% Computer based testing – 60% No preference – 13%	190
5. If you were to take an MCQ summative exam, which mode would you prefer to use?	Student response system – 30% Computer based testing – 70%	174
6. I would be happy to use the SRS in an exam setting	Strongly agree – 28% Agree – 22% Undecided – 20% Disagree – 14% Strongly disagree – 16%	192

Table 1: CBT/SRS Evaluation questions and responses.

aminations. This study has limitations and it is important that the findings are viewed in light of these. The study is limited to only one group of students. Furthermore, while there were over 300 students within this group, those who responded to questions for this evaluation ranged from 157-192. Thus, findings may not be representative of the whole cohort. Nonetheless, this study is novel as it has exposed the same groups of students to multiple choice question formative examinations *via* both computer-based testing and a student response system and explored preferences for mode of examination. The role of using student response system in formative assessments is well documented<sup>1,8-12</sup> but there is a paucity of literature currently available examining student preferences for computer-based testing *versus* student response systems for summative assessment.

The student response system is a relatively new system within the University and was never used within EBN1 prior to asking students to undertake the formative multiple choice questions. Thus, student's familiarisation with this system, as opposed to computer-based testing which is used regularly throughout the module, is expected to be much lower. It would therefore be worthwhile integrating the student response system into lectures and tutorials to engage the students with the system and increase familiarisation with it and repeat the evaluation. Indeed the value of integrating such methods of active learning into education has been previously documented.<sup>1,11,15</sup> The authors intend to do this with the future intakes of students.

The availability of a single computer suite, which is sufficiently large to house over 300 students who need computer access for a multiple choice question examination, is a major factor in choosing a student response system or computer-based testing for a summative assessment. In an already busy University examination fortnight at the end of each year, the availability of such a room is not always met. Indeed, for previous multiple choice question exams half of the intake of students have sat an multiple choice question exam with the other half in a 'holding room' so that they cannot discuss the test with those who have taken it, until the first half have completed. For the second half of students this means the exam period takes twice as long and they must wait in exam conditions for half to complete the exam prior to them sitting the exam. Considering a multiple choice question exam can be conducted with a student response system in any classroom which can invigilate 300 students, is a major advantage to both students and invigilating staff's time and could make optimal use of University resources. In relation to using computer-based testing or a student response system as opposed to paper testing for multiple choice questions there are two main advantages. Firstly, the tests are marked automatically with both computer-based testing and student response systems as opposed to being marked by hand by academic staff or hand fed into a machine readable answer sheet. Secondly within a University setting, old tests cannot simply be thrown away, if the multiple choice question exams was paper based this would mean the storage and then disposal of copious answer sheets. By delivering a multiple choice question test either by computer-based testing or a student response system, it eliminates this ex-

pense.

## CONCLUSIONS

This study has used quantitative methods to compare the preference and acceptability of computer-based testing and a student response system for completing multiple choice questions in undergraduate nursing education. Study findings indicated that the student response system was easy to use but took more time than the computer-based testing to become familiar with. The majority of students indicated they would prefer to take a multiple choice question summative exam *via* computer-based testing, although half of those surveyed would be happy to take using a student response system.

Technology is a fast and evolving medium in higher education and educators must investigate the pedagogical value of new development to establish their usefulness for undergraduate education. The integration of regular student response systems usage into lectures alongside current computer-based learning activities is needed to ensure students are familiar with both forms of equipment. After this, further research is needed to ascertain which mode is more acceptable to students for a multiple choice question examination. The accessibility, convenience and implication for University resources, particularly examination timetabling, that could come from using the student response system for examination purposes underscores the importance of such work. Nevertheless research must demonstrate students' receptiveness and acceptability of using a student response system prior to it being implemented.

**CONFLICTS OF INTEREST:** None to declare.

## CONSENT STATEMENT

The authors obtain written informed consent from the participants for submission of this manuscript for publication

## ETHICAL APPROVAL STATEMENT

Prior to conducting this study, ethical permission to conduct this work was gained from The School Research Ethics Committee of the School of Nursing and Midwifery, within the recruiting University.

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## Research

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# Stress beyond the Neonatal Intensive Care Unit (NICU) Discharge: Implications to Outcome

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## ABSTRACT

**Purpose:** The high-risk parental experience in the neonatal intensive care environment is a major stress event that is not necessarily resolved with discharge. Many parents report “walking on eggshells” with worry and stress for up to a year beyond the birth of their infant. Because stressors can induce behavioral, physiological, and biochemical changes to such a degree that family adaptation is challenged, attempting to resolve stressors before the discharge should be a goal. The ethical concept of beneficence (doing good) provides the Neonatal Intensive Care Unit (NICU) nurse with a framework for wanting to lower stressors as much as possible prior to discharge. The purpose of this study was to examine the relationship between high-risk experiences including high-risk pregnancies, deliveries, and NICU admissions and unresolved parental stress up to a year after delivery.

**Method:** Women in a day care center with infants under a year old were tested for their emotional status and pregnancy related demographics.

**Principal Results:** Findings show a positive correlation between two factors, both NICU admission of a newborn and parental stress ( $r=.88$ ) and a high risk primiparous births without NICU admissions and parental stress ( $r=.72$ ).

**Major Conclusion:** While this is a pilot study, the findings illustrate unresolved parental stress well beyond the birth of the baby, providing ethical support for early identification of stressed parents and interventions to normalize that stress before discharge. When parents report significant stress after their deliveries or infants' NICU admissions, and there is no specific intervention to identify and reduce this stress, high levels of stress may last and be measurable even a year later.

**KEYWORDS:** Parental emotion; Stress; Neonatal intensive care unit (NICU); High-risk pregnancy; High-risk birth.

**ABBREVIATIONS:** NICU: Neonatal Intensive Care Unit; FEE: Family Emotional Expressiveness; IRB: Institutional Review Board.

## INTRODUCTION

Parental stress experiences related to pregnancy, childbirth, and upto a year beyond the postpartum period are examined across disciplines in research of term, preterm, and high-risk deliveries to identify causative factors for early intervention. In a large study of women (N=783) and 671 of their male partners, the prenatal attitudes and feelings of these subjects provided some explanation for the differences in parental stress in the first year.<sup>1</sup> Although women in this study reported higher levels of parental stress than men, negative feelings or attitudes by either parent towards the pregnancy, birth, and first weeks at home with the infant were strongly correlated with high parental stress for both parents. This suggests that all parents are at risk for a significant stress experience following the birth of a baby, yet the incidence and intensity of the stress experience for parents of extreme premature infants and high-risk deliveries may have lasting effects as well as long-term consequences.

There is a growing body of research evidence that examines the postpartum stress experience of mothers of the extremely premature infants. According to findings, mothers of premature infants are at increased risk for postpartum depression and post-traumatic stress, yet screening factors for early identification are not standardized practice. In a recent study of mothers of premature infants (N=135), investigators found that maternal sociodemographic factors as well as the infant's physiologic stability did not contribute to early identification of postpartum traumatic stress in the Neonatal Intensive Care Unit (NICU).<sup>2</sup> These findings differ slightly from another study of parental stress (N=100) in the NICU, in that older parents and interruption of breast feeding plans were associated with higher stress levels but not necessarily postpartum traumatic stress.<sup>3</sup> Studies agree that the postpartum transition to parenthood is a major life stress, yet the incidence of postpartum traumatic stress in full-term births is 6%.<sup>4</sup> This is a much different statistic in the premature population. In a study of mothers of extremely premature infants (N=78), 25.6% showed symptoms of postpartum traumatic stress related to their perceived severity of the infants' developmental outcome later in life.<sup>5</sup> These findings provide the ethical foundation to question the current practices to mitigate stress experiences.

Any parental stress experience arising from NICU admissions is not a surprise. The hectic, technological intensive care environment of the NICU presents a challenge for nurses to integrate care that supports the development of premature infants while facilitating mother-infant attachment and supporting parents as collaborators in the care of their infant. Parents face barriers imposed by the challenging environment of the NICU that shift the parents' focus from their baby and the "normal" attachment process to equipment and technology that supports their infant's life.

Interventions have been tried to relieve the stress of parents during the NICU experience. A study of high-risk pregnant women (N=42) tested a nurse-led educational intervention on maternal stress prior to delivery and 48 to 72 hours after admission to the NICU.<sup>6</sup> Although the intervention significantly decreased maternal stress related to the NICU environment ( $p=.01$ ), it did not influence the stress related to later attachment. What this suggests is that ongoing education is important for adaptation to the environment, but other interventions are needed to facilitate attachment and support parents beyond discharge. In a review of literature, the facilitator role of the NICU nurse to promote parental attachment by encouraging active participation in care, skin-to-skin holding, breastfeeding, and communication while assessing parental stress and offering mitigating interventions across the NICU experience is key.<sup>7</sup> While this may not alter the stress experience beyond discharge, it offers interventions to improve attachment in the NICU that could have a lasting effect as the parent's transition home.

### Stress Beyond Discharge

If the goals of neonatal nursing care are to support physiologic

and developmental growth of the infant while managing family and infant stressors, then assessing stressors and intervening to minimize stressors should become essential components of neonatal nursing practice. A study examining the relationship between postnatal depression and first year parenting stress of mothers of premature infants born at <32 weeks gestation (N=123) found that women with postnatal depression at 6 weeks after birth had a higher incidence and intensity of parenting stress the first postpartum year.<sup>8</sup> This relationship of postnatal depression to prolonged parenting stress experiences lasting up to a year gives insight to the needs of screening and intervention for all new parents. A second study examining postpartum stress and depression of Taiwanese mothers of premature infants born at 32+ weeks gestation (N=203) had similar findings with an important addition to the understanding of predictors of long-term parenting stress.<sup>9</sup> Taiwanese mothers with general health issues such as sleep disturbances, anxiety, and interpersonal difficulties experienced higher levels of stress beyond discharge ( $p<.001$ ). These findings give practitioners insight on factors that contribute to the stress experiences of all new parents.

In order to build an educational and counseling program, researchers studies mothers of young infants who were free of all signs of depression (N=322). They attempted to identify factors that caused parental stress and to identify mitigating coping styles.<sup>10</sup> Identified sources of highest stress for mothers were sleep problems (81.4%), body image problems (93.9%), and breast problems (94.9%). Highest baby related stressors were feeding problems (93.5%), dressing and baby care (98.6%), and recognizing health issues (95.5%). Although 84.2% reported stress related to returning to work, only 10.6% of the women had returned to work at the time of the study. The "Ways of Coping with Stress" inventory used in this study measured two main coping styles: a problem-oriented active problem solving approach or an emotional, passive approach that has dimensions of helpless and submissive coping. The findings are concerning as these were married mothers of term infants free of birth experiences that are perceived traumatic and without postpartum depression. Many of these women reported stressors and reported being unable to cope, using emotional-passive coping styles on the helpless approach dimension ( $p<.05$ ). These findings demonstrate that prolonged stress following the birth is not discerning of family demographics.

### Problems with Unresolved Stress can also Impact Relationships with the Infant

What is known is that unresolved stressors can induce behavioral, physiological, and biochemical changes in all people, regardless of age and circumstances; the resulting problems are not limited to immune system compromise, cardiovascular changes, depression, and negatively impact long-term health outcome.<sup>3,8,9</sup> New parents experience extra stressors of adaptation to caring for an infant, family responsibilities, self care issues, and lack of regular sleep. In a large study examining attachment-sleep relationships and attachment security and emotionality of mother-infant dyads (N=776), negative emotionality significantly influ-

enced attachment security and later behavior problems ( $p < .05$ ) as the infant becomes a toddler.<sup>11</sup> Because these parental relationships are integral for attachment security and are associated with self-regulation behaviors of toddlers and children, research correlates high quality early social and emotional experience of infants to improved cognitive development. That is not to say that parental stress experiences should be non-existent in the infant's environment, but, instead, should be one of a wide range of emotions the infant experiences since they are sensitive to their parent's moods and emotions.<sup>12</sup> This range of emotions helps infants develop self-regulation and self-soothing behaviors that are later correlated better to cognitive development. The problems that arise with unresolved stress are associated with highly emotional environment, which becomes a part of the psychological development of the infant very early in life.<sup>12</sup> Findings suggest that infants nurtured in highly emotional environments may lack emotional nurturance themselves, becoming toddlers with delayed language acquisition and cognitive development.

In reviewing the literature, it is clear that the high-risk parental experience in the neonatal intensive care environment is a major stress event that is not necessarily resolved with discharge. Many parents report "walking on eggshells" with worry and stress for up to a year beyond the birth of their infant. Because stressors can induce behavioral, physiological, and biochemical changes to such a degree that family adaptation is challenged, resolving stress before the discharge should be a goal. The purpose of this study was to examine the relationship between high-risk experiences including high-risk pregnancies, deliveries, and NICU admissions and maternal emotions that could lead to unresolved parental stressors.

**MATERIALS AND METHODS**

This study was a cross-sectional, correlational design to examine the relationship of high emotionality to stress and pregnancy and birth risk factors. After obtaining University Institutional Review Board (IRB) approval to conduct the study, data was collected over a 3-month period at a single child care center located in a South Atlantic State of the Mid-Atlantic region. The center provides infant, toddler, pre-school and kindergarten care to a diverse population of approximately 180 children, specifically targeting children with risk factors including poverty (40%), foster care (10%) and disabilities (20%).

A convenience sample of 54 mothers of infants 6-months of age or older enrolled at the center participated in this study after signing an informed consent. The mothers completed the self-reporting demographic data and the Family Emotional Expressiveness (FEE) tool at home and returned it to the

center for analysis. Of the 54 women, 77.7% were employed 20 hours or more per week, 92.5% were married, 81.5% of the women were first-time mothers, and more than 70% of the women had attended some college.

**Instrument**

The family emotional expressiveness (FEE) is a 12 item self-report scale that measures a family's range of positive and negative emotions and the frequency of them. Answers range from 0 (Never) to 4 (Always). Cronbach's Alpha of the instrument was =.77.<sup>13</sup> Validity of the instrument was not reported in recent literature however, this scale it is consistently used to predict child behavior patterns in a larger body of research. According to the literature, it is considered a good fit to measure emotional climates of family and information on corresponding infant behaviors.<sup>14</sup>

**Data Analysis**

Data analysis was conducted to describe the sample and to determine the relationship between stress measured as emotionality and high-risk family experiences including high-risk pregnancies, deliveries, and NICU admissions. The level of significance was set at  $\alpha = .05$ .

**RESULTS**

The sample of mothers (N=54) each completed the family emotional expressiveness (FEE), a 12 item self-report scale that measures a family's range of positive and negative emotions, In addition, the mothers completed a 10-question demographic tool on the pregnancy and birth of the infant. Data was coded and Pearson correlation coefficients were used to determine relationships related to stress, family emotions, and demographics.

The demographic data was examined for the stressors identified in the review of literature such as returning to work or first baby. The majority of the mothers were working at least 20 hours per week (77.7%) and were married (92.5%). Many had problems during pregnancy, such as health issues of hypertension (N=6), gestational diabetes (N=17), asthma (N=4), preeclampsia (N=2), and thyroid problems (N=2). The high-risk pregnancy and birth without a NICU admission was significantly correlated to the lasting family stress experience ( $r = .72$ ). In most instances, the infant at the child care center was the first baby (81.5%). The infant sample has a mean gestational age at birth of 39.3 weeks. At the time of the study, infant ages ranged from six to eleven months with a mean of 8 months, 7 days. Table 1 summarizes the key stressor results from the demographic data.

	1 <sup>st</sup> Baby	High-risk pregnancy	NICU Admission	NICU 7 days or longer
<b>Number</b>	44	31	13	3
<b>Percentage</b>	81.5%	57.4%	24.1%	5.5%

Table 1: Demographic summary of stressors.

The family emotional expressiveness (FEE) results described family emotions to twelve situations that would induce responses for most people. The mothers rated how they would express themselves in situations that may evoke a positive or negative emotional response. Negative situations such as showing unhappiness, going to pieces when pressure builds up, and arguing with a family member were countered by positive situations such as expressing excitement, spontaneously hugging a family member, and expressing happiness. The questionnaires were scored for each mother, yielding a FEE score described as high or low emotions. The total scores ranged from 1.34 to 3.64 where 0-1 is low emotions and 3-4 are high emotions. Although the mean score of 2.79 further describes a higher emotional expressiveness score, the breakdown of these scores gives insight to the maternal experience.

Of the 54 mothers participating, 36(66.7%) reported often feeling negative emotions by expressing disappointments, arguing with family members, blaming others for problems, and falling apart under pressure. Less than 19% of the mothers rarely experienced negative emotions. More than half of the mothers (53.7%) reported rarely expressed their happiness to family members or expressed excitement over future plans. Only 13 of the mothers (24.1%) reported experiencing positive emotions with most scoring high on expressing deep love to their partner. Although the expressiveness items can be difficult to interpret as an absolute, the scores yield trends of emotional expressiveness. The statistical analysis was completed using Pearson correlation coefficients to examine the relationship of the reported family emotionality scales of the FEE to the stressors. Results revealed a significant relationship for all NICU admissions, regardless of severity of condition or length of stay, to family stress ( $r=.88$ ). These mothers reported much higher family stress than all other mothers of this sample. The relationship of family stress to high-risk primiparous pregnancies without NICU admissions was the second significant finding. Family stress increased significantly when it was the first pregnancy and that pregnancy was considered high-risk due to maternal complications and/or illness ( $r=.72$ ). First pregnancies and first infants in general were not significantly correlated to higher family stress.

## DISCUSSION

The infants of this sample of mothers were all term or near-term births with a mean gestational age of 39.3 weeks. The fact that 24.1% of the infants were admitted to the NICU with only three NICU stays 7 days or longer suggests that this sample does not represent the very low birth weight infants described in research that associates post-traumatic stress experiences with families that take up to a year to mend.<sup>2,5</sup> Because the results of this study illustrate a lasting, unresolved stress for all families with infants admitted to the NICU ( $r=.88$ ), one must question how even the short stays in the NICU result in similar emotions. The longitudinal Swedish study of Hildingsson and Thomas may offer some answers; these researchers found that even if a woman *perceived* her pregnancy, birth or transition home as stressful, regardless of actual circumstances, which this stress lasted up to one year.

The mothers who identified their experience as a high-risk pregnancy reported many health issues. These high risk health issues, even without the infant admission to the NICU, was significantly correlated to the lasting family stress experience ( $r=.72$ ). These findings are consistent with the NICU admission experiences and supported by the findings of other researchers.<sup>1</sup>

## LIMITATIONS

The primary limitation of this study is the sample size. This sample is representative of the child care center and geographic location and, although these findings may not be generalizable to other child care populations without additional research, the data adds to the literature on the long-term family stress experience after high-risk births.

## IMPLICATIONS FOR NICU AND MATERNAL CHILD NURSES

Implications for NICU and maternal-child nurses as well as childbirth educators focus on education, communication, and early intervention to support families before, during, and after the birth of their infants. If how parents perceive their birth experiences clearly contribute to the family emotions over the first year, then early intervention to decrease stress should be offered. Mindfulness-based interventions with parents have been shown to help reduce stress and anxiety associated with birth experiences while giving parents tools for coping beyond discharge.<sup>15</sup> This technique helps individuals alter their perspective of events to reduce the stress response, which, over time, will make that person more cognizant of emotions. Moreover, at-risk families should have focused discharge education and information of stress and coping as well as follow-up care for the first year after the birth of their baby.

## IMPLICATIONS TO FURTHER RESEARCH

Because this study illustrates the unresolved family stress from high risk pregnancies and deliveries to admissions to the NICU, identification of at-risk families early in pregnancy and research with interventions is necessary. Studies that include a counseling component to resolve family stress across the pregnancy and first year following birth, as well as research examining the family stress response over time would open doors to better early family interventions. Suggestions for specific research study should be included here. Counseling has a two-fold benefit of (1) intervention during stress crisis and (2) educational interventions that promote family coping across the lifespan.

## CONCLUSION

NICU nurses support families while in the NICU. This study shows the importance of doing so, and the ethical need for referral and intervention to lower stress levels. The findings illustrate unresolved family stress can last well beyond the birth of the baby, and provides support for early identification of stressed families and interventions to normalize that stress before discharge. Although that source of stress differs for each family,

understanding the relationship of high emotions to cognitive and psychological development of the infant is a considerable basis for screening and intervention.

#### CONFLICTS OF INTEREST

There are no declared conflicts of interest in the manuscript including financial, consultant, institutional, and other relationships that might lead to bias.

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## Review

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# Oxygen and Resuscitation: Saturations, Oxidative Stress and Outcomes in Premature Infants

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## ABSTRACT

Fetus develops in a relatively hypoxemic environment *in utero*, however they need supplemental oxygen at birth when born prematurely  $\leq 32$  weeks' gestation. Reduced antioxidant defenses from lack of induction of antioxidant enzymes at birth, predispose premature infant susceptible to toxic effects of oxygen such as bronchopulmonary dysplasia and brain injury. Studies have demonstrated that even short exposures to 100% oxygen at birth could have long term implications. Guidelines and nomograms were published in 2010 regarding oxygen concentrations to be administered along with the oxygen saturations (SpO<sub>2</sub>) to be targeted in the first ten minutes after birth in both term and premature infants. We review the impact of differing oxygen concentrations in the first 10 minutes soon after birth on oxygen saturations, the biochemical effects of oxidative stress and on clinical outcomes in premature infants. Initiating resuscitation with an oxygen concentration of 21% O<sub>2</sub> to 30% O<sub>2</sub> as recommended by resuscitation guidelines is a good starting point, despite the lack of evidence of well-defined SpO<sub>2</sub> targets in premature neonates, which necessitate large clinical trials. Starting low oxygen concentration at resuscitation, facilitates lower oxidative stress which is desirable in premature infants with immature anti-oxidant defenses at birth. However, there is insufficient evidence to indicate that resuscitation with lower oxygen concentration ( $\leq 30\%$  O<sub>2</sub>) at birth will decrease BPD or other clinical outcomes in premature neonates.

**KEYWORDS:** Resuscitation; Oxygen; SpO<sub>2</sub>; Premature infants; Bronchopulmonary dysplasia; Oxidative Stress.

## INTRODUCTION

Fetus develops in a hypoxemic environment *in utero* and an abrupt transition to a normoxic extra-uterine environment can generate a physiologic oxidative stress even in term infants.<sup>1,2</sup> Premature infants <32 weeks' gestation, with functional and structural immaturity of the cardio-pulmonary system often require resuscitation at birth, which includes administration of supplemental oxygen. Hyperoxia is one of the important generators of reactive oxygen species (ROS) and excess ROS is kept in check by antioxidant enzyme systems (AOEs). Reduced antioxidant defenses in premature infants at birth, from lack of induction of AOE systems,<sup>3,4</sup> make them particularly susceptible to the toxic effects of oxygen.<sup>5</sup> Supplemental oxygen in premature infants contributes to development of bronchopulmonary dysplasia (BPD),<sup>6</sup> retinopathy of prematurity<sup>7</sup> and brain injury.<sup>8</sup> Optimal management of oxygen during neonatal resuscitation becomes particularly important because of the evidence that insufficient or excessive oxygenation can be harmful to the newborn infant.<sup>9</sup>

It was common to use pure oxygen at resuscitation of premature infants until as recently as 2010, when Neonatal Resuscitation Program (NRP) issued guidelines for oxygen concentrations to be administered at birth and nomograms were made available for oxygen saturation targets in term and premature infants.<sup>9</sup> Studies have defined the percentiles of oxygen saturation (SpO<sub>2</sub>) as a function of time from birth in uncompromised babies born at term.<sup>10,11</sup>

Resuscitation guidelines recommended in 2010 that the goal in babies resuscitated at birth, whether born at term or preterm, should be an oxygen saturation value in the interquartile range of preductal saturations measured in healthy term babies following vaginal birth at sea level.<sup>9</sup>

The guidelines recommend preductal SpO<sub>2</sub> of 60%-65% at 1 min; 65%-70% at 2<sup>nd</sup> min; 70%-75% at 3<sup>rd</sup> min; 75%-80% at 4<sup>th</sup> min and 80%-85% at the end of 5 minutes. The SpO<sub>2</sub> values between 5 and 10 minutes after birth to be 85%-95%.<sup>9</sup> The SpO<sub>2</sub> guidelines were applicable for both term and premature infants, to be achieved by initiating resuscitation with air or blended oxygen and titrating the oxygen concentration to achieve a SpO<sub>2</sub> in the target range using pulse oximetry.<sup>9</sup> Recently, the guidelines were updated to achieve saturation target range by initiating resuscitation with a low oxygen concentration (21% O<sub>2</sub> to 30% O<sub>2</sub>) and recommended against initiating resuscitation with high supplementary oxygen concentration (65% O<sub>2</sub> to 100% O<sub>2</sub>)<sup>12</sup> in premature infants. However, oxygen concentration can be increased to 100% O<sub>2</sub> in a bradycardic infant (heart rate <60/min) after 90 seconds of resuscitation with a lower concentration of oxygen, until the heart rate recovers to normal.

There is a large body of evidence that blood oxygen levels in uncompromised babies generally do not reach extra

uterine levels until about approximately 10 minutes after birth. We review the evidence in premature infants by focusing into three main areas related to oxygen resuscitation at birth: (A) The effects of oxygen concentration administered at resuscitation on SpO<sub>2</sub> in the first 10 minutes after birth; (B) The biochemical effects of oxygen resuscitation on parameters of oxidative stress; (C) The long-term clinical outcomes of oxygen administered at resuscitation in these infants.

**Oxygen Resuscitation and Oxygen Saturations (SpO<sub>2</sub>)**

As the 2015 resuscitation guidelines recommend to initiate resuscitation in premature infants with a low oxygen concentration (21% to 30% O<sub>2</sub>), all these studies are reviewed. The studies that administered 21% O<sub>2</sub> or 30% O<sub>2</sub> as one of the oxygen resuscitation groups are summarized in Table 1. In the three studies wherein the infants were resuscitated in 21% O<sub>2</sub>,<sup>13-15</sup> room air failed to maintain the targeted SpO<sub>2</sub> and almost all infants required supplemental oxygen. However, resuscitation in 100% O<sub>2</sub> resulted in hyperoxic infants with SpO<sub>2</sub>>95%.<sup>14</sup> Oxygen titration strategy after initial resuscitation with 100% O<sub>2</sub> resulted in higher number of infants achieving targeted saturations.<sup>14</sup> The studies imply that if premature infants were initially resuscitated with 21% O<sub>2</sub>, then careful attention should be placed to heart rate and SpO<sub>2</sub>, so that the oxygen can be titrated upwards to achieve saturations as per neonatal resuscitation guidelines. In a

Study	Methods	Conclusions
<b>21% O<sub>2</sub> Resuscitation</b>		
Wang et al <sup>15</sup> (23-32 weeks GA)	21% O <sub>2</sub> (n=18) vs. 100% O <sub>2</sub> (n=23) Targeted SpO <sub>2</sub> – 100% O <sub>2</sub> grp: FiO <sub>2</sub> ↓ for SpO <sub>2</sub> >95% at 5 min. 21% grp – ↑ FiO <sub>2</sub> for SpO <sub>2</sub> <70% at 3 min or for SpO <sub>2</sub> <85% at 5 min (↑ to 50% × 30 secs; no response ↑ to 75% × 30 secs; no response – ↑100% O <sub>2</sub> )	All infants resuscitated in the RA received O <sub>2</sub> ≤3 min; Resuscitation with RA failed to achieve targeted SpO <sub>2</sub> by 3 min; recommend not to use RA for resuscitation of premature neonates.
Dawson et al <sup>13</sup> (<30 weeks GA)	21% O <sub>2</sub> (n=105) vs. 100% O <sub>2</sub> (n=20) Targeted SpO <sub>2</sub> – 80 to 90%; FiO <sub>2</sub> ↓ by 10% if SpO <sub>2</sub> >90; FiO <sub>2</sub> ↑ for SpO <sub>2</sub> <70% at 5 min or SpO <sub>2</sub> <90% at 5 min + HR<100	97/105(92%) in the 21% O <sub>2</sub> group were subsequently treated with supplemental O <sub>2</sub> at 5.05(4-5.5) min.
Rabi et al <sup>14</sup> (<32 weeks GA)	21% O <sub>2</sub> (Low O <sub>2</sub> strategy; titrate up; n=34); 100% O <sub>2</sub> and then wean (mod. O <sub>2</sub> strategy) (n=34); 100% O <sub>2</sub> (high O <sub>2</sub> strategy; n=37); Targeted SpO <sub>2</sub> – 20% O <sub>2</sub> q 15 secs to achieve SpO <sub>2</sub> of 85-92%	Titration down from 100% O <sub>2</sub> was more effective at maintaining SpO <sub>2</sub> in the range of 85-92 and these infants spent nearly twice as long in the target range as infants resuscitated in 21% O <sub>2</sub> .
Kapadia et al <sup>16</sup> (24-34 weeks GA)	21% O <sub>2</sub> (n=44; lox grp) vs. 100% O <sub>2</sub> (n=44; hox grp) Targeted SpO <sub>2</sub> -21% O <sub>2</sub> grp: NRP guidelines; 100% O <sub>2</sub> grp: FiO <sub>2</sub> adjusted by 10% to target SpO <sub>2</sub> of 85-94	Lox decreased oxygen load by half; had less oxidative stress at one hour of age and reduced incidence of BPD
Kumar et al <sup>25</sup> (24-32 weeks GA)	21% O <sub>2</sub> (n=6) vs. 40% O <sub>2</sub> (n=7) vs. 100% O <sub>2</sub> (n=5) Targeted SpO <sub>2</sub> – First 10 min of birth no change in FiO <sub>2</sub> and SpO <sub>2</sub> were blinded; 10-30 min: SpO <sub>2</sub> <85% ↑FiO <sub>2</sub> and SpO <sub>2</sub> >95% ↓ FiO <sub>2</sub> 10% q 60 secs	Defined the natural evolution of SpO <sub>2</sub> in 21%, 40% & 100% O <sub>2</sub> in the first 10 min; 21% O <sub>2</sub> had SpO <sub>2</sub> mostly within the NRP limits; 40% O <sub>2</sub> had SpO <sub>2</sub> below the NRP-LL in the first 5 min; 100% O <sub>2</sub> above NRP-UL
<b>30% O<sub>2</sub> Resuscitation</b>		
Escrig et al <sup>17</sup> (≤28 weeks GA)	30% O <sub>2</sub> (n=19; lox grp) vs. 90% O <sub>2</sub> (n=29; hox grp) Targeted SpO <sub>2</sub> – FiO <sub>2</sub> adjustment based on HR; SpO <sub>2</sub> between 85-90	FiO <sub>2</sub> ↑ stepwise to ~45% in LOX; ↓ to 45% O <sub>2</sub> in HOX for a SpO <sub>2</sub> of around 85% at 5-7 min in both groups. No difference in morbidity including BPD and ROP. No deaths <28 days in both groups.
Vento et al <sup>18</sup> (24-28 weeks GA)	30% O <sub>2</sub> (n=37; lox grp) vs. 90% O <sub>2</sub> (n=41; hox grp) Targeted SpO <sub>2</sub> – preductal SpO <sub>2</sub> of 75% at 5 min and 85% at 10 min	FiO <sub>2</sub> ↑ stepwise to ~55% at 5 min; lower incidence of BPD & less markers of oxidative stress (urine/GSSG/GSH) in the LOX group.
Rook et al <sup>19</sup> (<32 weeks GA)	30% O <sub>2</sub> (n=99; lox grp) vs. 65% O <sub>2</sub> (n=94; hox grp) Targeted SpO <sub>2</sub> – FiO <sub>2</sub> ↓ for SpO <sub>2</sub> >94%; FiO <sub>2</sub> ↑ for HR<100/min before 10 min	FiO <sub>2</sub> ↑ stepwise to ~40% by 7 min in LOX; FiO <sub>2</sub> ↓ to ~40% by 11 min in HOX group; No difference in oxidative stress markers or BPD between groups

**Table 1:** Studies that administered 21% O<sub>2</sub> to 30% O<sub>2</sub> as the initial gas at resuscitation in premature infants. Saturation targets specific for individual studies are mentioned.

recent study, starting with 21% O<sub>2</sub> at resuscitation and adjusting FiO<sub>2</sub> to achieve preductal SpO<sub>2</sub> set by NRP was not only feasible but also decreased oxygen load and lowered oxidative stress in premature infants.<sup>16</sup>

Escrig et al noted that 30% O<sub>2</sub> can safely be used to resuscitate premature neonates, which can then be adjusted to infant's needs, reducing the oxygen load on the infant.<sup>17</sup> Vento et al later validated that 30% O<sub>2</sub> for resuscitation, may have additional benefits of lowering oxidative stress, and decreasing the risk of BPD.<sup>18</sup> However, a recent study comparing 30% O<sub>2</sub> or 65% O<sub>2</sub> at resuscitation, did not find differences in oxidative stress markers or BPD among the two groups<sup>19</sup> (Table 2). Resuscitation with lower oxygen concentration led to earlier lower FiO<sub>2</sub> mean and hence oxygen load at resuscitation (40% O<sub>2</sub> by 7 min in 30% O<sub>2</sub> group versus 40% O<sub>2</sub> at 11 min in 65% O<sub>2</sub> group).<sup>19</sup> Despite using diverse target saturations in the first 10 minutes, all the three studies demonstrate the feasibility of administering 30% O<sub>2</sub> at resuscitation in premature infants. The oxygen concentration was titrated upwards to meet SpO<sub>2</sub> targets in all studies: To 40%,<sup>19</sup> 45%<sup>17</sup> or 55% O<sub>2</sub><sup>18</sup> by 5 minutes of birth. The studies indicate that 30% O<sub>2</sub> can be used as a starting point to resuscitate a premature infant.

As short-term exposures to high concentration to oxygen can be associated with adverse long-term effects, low oxygen strategy at resuscitation is well-intended and appropriate, however the evidence is not full-proof. Firstly, no two resuscitation studies conducted so far (including 21% O<sub>2</sub> and 30% O<sub>2</sub> resuscitation studies; Table 1) had similar saturation targets in the first 10 minutes after birth, making comparisons among studies difficult. Second, the 2010 NRP guidelines states that the saturation data are extrapolations from term infants.<sup>9</sup> The lack of induction of anti-oxidant enzyme systems soon after birth<sup>20</sup> along with generation of ROS by hyperoxia, makes it highly likely that the suggested SpO<sub>2</sub> targets in the first 10 minutes after birth are 'relatively hyperoxic' for premature infants. The physiology of oxyhemoglobin curves is different in term and premature infants.<sup>21-23</sup> Maintaining similar saturations in both term and pre-

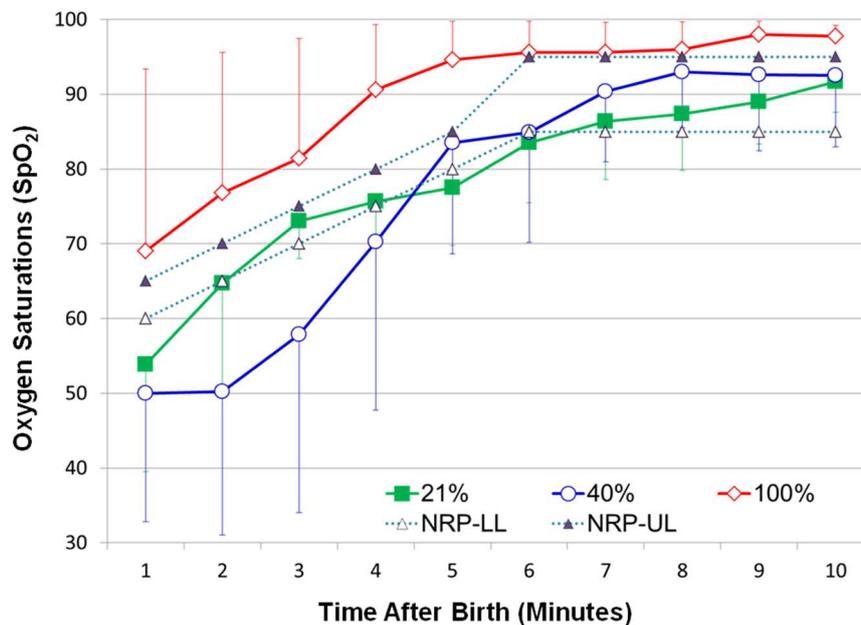
term infants may lead to higher oxygen delivery, higher oxidant load and down regulation of hypoxia inducible factor (HIF-1) and vascular endothelial growth factor (VEGF) expression in premature infants. HIF-1 expression is tightly linked to O<sub>2</sub> concentration *in vivo* and hyperoxia or even normoxia in the developing lung rapidly induce HIF degradation and hence VEGF expression.<sup>24</sup> Predicating SpO<sub>2</sub> in premature infants based on term saturations is difficult, as molecular signaling, growth and its interaction with the developing fetus at transition are different in an extremely preterm infant compared to an infant at term. Studies should address appropriate SpO<sub>2</sub> targets in premature infants, particularly in the first 10 minutes after birth.

The natural evolution of SpO<sub>2</sub> in infants resuscitated in room air may provide some insight into SpO<sub>2</sub> targets in the first ten minutes in premature infants. In a small pilot study infants <32 weeks GA were randomized to 21%, 40% or 100% O<sub>2</sub> and resuscitated as per 2005 NRP guidelines.<sup>25</sup> Oxygen groups and SpO<sub>2</sub> were unmasked at 10 minutes of age and FiO<sub>2</sub> was adjusted to maintain SpO<sub>2</sub> of 85%-95% for the next 20 minutes. The study was stopped at 30% enrollment following publication of the 2010 NRP guidelines, which is a limitation. The mean SpO<sub>2</sub> values were 50%, 53% and 69% at 1 min; 77%, 83% and 95% at 5 min and 92%, 92% and 98% at 10 min in 21% O<sub>2</sub>, 40% O<sub>2</sub> & 100% O<sub>2</sub> groups respectively (Figure 1).<sup>25</sup> Resuscitation of premature infants with 100% O<sub>2</sub> resulted in SpO<sub>2</sub> values above the upper limit of the 2010 NRP guidelines (Figure 1: Red line, Open diamonds); 40% O<sub>2</sub> resuscitated group had mean SpO<sub>2</sub> values below the NRP lower limit in the first five minutes and within the NRP defined SpO<sub>2</sub> target range from 6 to 10 minutes (Figure 1: Blue line, Open circles); 21% O<sub>2</sub> resuscitated group had mean SpO<sub>2</sub> values bordering the NRP lower limit in the first five minutes and within the NRP defined SpO<sub>2</sub> target range from 6 to 10 minutes (Figure 1: Green line, Closed squares). Similarly, there were no differences in SpO<sub>2</sub> at 10 and 30 minutes after birth among the groups.<sup>25</sup> Infants in 21% O<sub>2</sub>, 40% O<sub>2</sub> and 100% O<sub>2</sub> groups were weaned to 24.8% (±5), 27.9% (±6) and 38% (±20) O<sub>2</sub> respectively at 30 minutes of age.<sup>25</sup> Despite aggressive weaning, FiO<sub>2</sub> administered was significantly higher in

Study	Methods	Conclusions
Vento et al <sup>18</sup> (24-28 weeks GA)	30% O <sub>2</sub> (n=37; lox grp) vs. 90% O <sub>2</sub> (n=41; hox grp) OS Markers – Blood (D0, D1, D3) - GSSG/GSH Urine (D1, D7) – o-tyrosine/ phenylalanine; 8OHdG/2dG; 8-iso-prostaness; isofurans	GSSG/GSH: ↑ D1 & D3 in HOX grp o-tyrosine/phenylalanine ↑ on D1, D7; 8OHdG/2dG ↑ on D1, D7; Isofurans ↑ on D1 in HOX grp
Ezaki et al <sup>26</sup> (<35 weeks GA) Mild-Mod Asphyxia	Reduced O <sub>2</sub> grp (to maintain SpO <sub>2</sub> of 90-95; n=23); 100% O <sub>2</sub> grp(n=21); OS Markers - Blood (60 min) - TH; RP	TH ↑ in 100% O <sub>2</sub> grp; RP-NS; RP/TH ↓ in 100% O <sub>2</sub> grp
Kapadia et al <sup>16</sup> (24-34 weeks GA)	21% O <sub>2</sub> (n=44; lox grp) vs. 100% O <sub>2</sub> (n=44; hox grp) OS Markers – Blood (Cord, 1 <sup>st</sup> hour) - TH; BAP	Cord - NS; 1 <sup>st</sup> hour - TH ↓; BAP ↑ in LOX grp
Rook et al <sup>19</sup> (<32 weeks GA)	30% O <sub>2</sub> (n=99; lox grp) vs. 65% O <sub>2</sub> (n=94; hox grp) OS Markers – Blood(D2) – GSH synthesis & concentration Urine (D0, D6) - o-tyrosine/ phenylalanine; 8OHdG/2dG; 3-NT	GSH synthesis & concentration - NS Urine (D0, D6) - o-tyrosine/ phenylalanine; 8OHdG/2dG; 3-NT - NS between groups
Kumar et al <sup>25</sup> (24-32 weeks GA)	21% O <sub>2</sub> (n=6) vs 40% O <sub>2</sub> (n=7) vs. 100% O <sub>2</sub> (n=5) OS Markers – Blood (24 h, 1 wk, 4 wk) – GSH/GSSG Urine (24 h, 1 wk, 4 wk) – 8OHdG; 3-NT	GSH/GSSH ↓ 100% O <sub>2</sub> at 24 h; 3-NT ↑ in 40% O <sub>2</sub> and 100% O <sub>2</sub> over time; 8OHdG ↑ at 4 wks in all groups

GSH: Reduced glutathione; GSSG: oxidized glutathione; 8OHdG: 8-hydroxy-2'-deoxyguanosine; 2-dG: 2'-deoxyguanosine; TH: Total hydro peroxide; RP: Redox potential; BAP: Biologic antioxidant potential; 3-NT: 3-nitro tyrosine; NS: No significance between groups.

Table 2: Studies that measured oxidative stress markers as part of oxygen resuscitation in premature infants.



**Figure 1:** Oxygen saturations (SpO<sub>2</sub>) in premature infants <32 weeks GA during the first 10 minutes after birth in the three resuscitated groups. The concentration of oxygen was constant for the first 10 minutes at 21% O<sub>2</sub> [■-; green]; 40% O<sub>2</sub> [○-; blue] and 100% O<sub>2</sub> [◇-; red] in the three groups. Each time point represents mean±SD. SpO<sub>2</sub> significantly increased over time in the first 10 minutes after birth in all infants ( $P<0.0001$  mixed model ANOVA). Upper (---▲---) and lower (---△---) SpO<sub>2</sub> limits (NRP 2010 guidelines) are superimposed on the SpO<sub>2</sub> curves of the three O<sub>2</sub> resuscitated groups. SpO<sub>2</sub> in the 100% O<sub>2</sub> group was above NRP-upper limit; resuscitation with 21% or 40% O<sub>2</sub> maintained SpO<sub>2</sub> within the NRP range from 5 to 10 minutes of life (with permission from the authors.<sup>25</sup>)

the 100% O<sub>2</sub> group to maintain the target SpO<sub>2</sub> until 30 minutes of age; however, there was no significant difference in FiO<sub>2</sub> between 40% O<sub>2</sub> and 21% O<sub>2</sub> groups during the weaning process. The novelty of this study was in administering a fixed concentration of oxygen and blinding the study gas for the first 10 minutes irrespective of the SpO<sub>2</sub>. Larger studies are needed to address SpO<sub>2</sub> targets in premature infants to help define the oxygen concentration at resuscitation, however starting at 21% O<sub>2</sub> to 30% O<sub>2</sub> as recommended by NRP is a good starting point.

#### Oxygen Resuscitation and Oxidative Stress in Premature Neonates

Several studies have addressed the role of oxidative stress markers in relation to oxygen resuscitation (Table 2). The studies have used common markers of oxidative stress such as GSH/GSSG ratio, total hydroperoxide and 8-hydroxy-2'-deoxyguanosine (8-OHdG). Most of the studies measured oxidative stress markers within the first week of birth<sup>16,18,19,25,26</sup> and occasionally up to 4 weeks of age.<sup>25</sup> The studies validated that resuscitation with higher oxygen concentration leads to oxidative stress, particularly in the first week after birth. This may be related to production of reactive oxygen species from higher oxygen load at birth in the face of inadequate antioxidant defense mechanisms. Both, GSH/GSSG ratio<sup>25</sup> and oxidative balance ratio,<sup>16</sup> were lower within 24 hours of birth following resuscitation with high oxygen concentration. Both these markers are useful measures of oxidative stress in tissues. Two other studies had bronchopulmonary dysplasia (BPD) as the primary outcome with measurements of oxidative stress markers<sup>18,19</sup> within the first 4 weeks of age. In the study by Vento et al, o-tyrosine to phenylalanine ratio, a marker of protein oxidation and 8-OHdG/2-dG ratio, a

marker of oxidative DNA damage were increased in the high oxygen group compared to low oxygen group on day 7; and this may be related to the oxygen load and generation of ROS from oxygen administered at resuscitation.<sup>18</sup> These markers of protein and DNA oxidation were also correlated with later development of BPD.<sup>18</sup> However, the same oxidative markers were not significantly different among the two oxygen groups in the study by Rook et al<sup>19</sup> (Table 3). Almost contrasting results between the two studies may be related to differences in target saturations in the first 10 minutes; changes in oxygen load from differences in the high oxygen resuscitated group (90% O<sub>2</sub><sup>18</sup> versus 65% O<sub>2</sub><sup>19</sup>) and finally from varying definitions of BPD at 36 weeks (physiologic or clinical) among the resuscitated groups.<sup>18,19</sup> Also oxidative stress could result from factors other than oxygen administered, such as mechanical ventilation in immature newborns. Nonetheless, the studies demonstrate that lower oxygen concentration may help in facilitating lower oxidative stress which is desirable in premature infants with immature anti-oxidant defenses at birth.

#### Oxygen Resuscitation and Clinical Outcomes in Premature Neonates

Immature lungs can be acutely injured by either oxygen or mechanical ventilation resulting in altered alveolar or vascular development of the lung leading to development of bronchopulmonary dysplasia (BPD).<sup>27</sup> Even though, antenatal steroids, gentle ventilation techniques and surfactant administration have decreased the incidence and severity of BPD in more mature infants, it is still a major problem in extremely low birth weight infants. Free radicals are elevated in plasma within 24 to 48 hours after birth,<sup>28</sup> and in bronchoalveolar lavage (BAL) within

Study	Methods	Conclusions
Vento et al <sup>18</sup> (24-28 weeks GA)	30% O <sub>2</sub> (n=37; lox grp) vs. 90% O <sub>2</sub> (n=41; hox grp) Outcome – death <28 days + incidence of BPD (O <sub>2</sub> at 36 wks PMA)	Infants in LOX group received fewer days of O <sub>2</sub> , MV, CPAP and developed less BPD
Kapadia et al <sup>16</sup> (24-34 weeks GA)	21% O <sub>2</sub> (n=44; lox grp) vs. 100% O <sub>2</sub> (n=44; hox grp) Primary outcome – Oxidative balance ratio; Secondary – incidence of BPD (O <sub>2</sub> at 36 wks PMA)	Infants in LOX group received fewer days of O <sub>2</sub> , MV & developed less BPD
Rook et al <sup>19</sup> (<32 weeks GA)	30% O <sub>2</sub> (n=99; lox grp) vs. 65% O <sub>2</sub> (n=94; hox grp) Outcome – BPD at 36 wks PMA (Walsh et all criteria)	BPD - not significantly different between the high & low O <sub>2</sub> groups
Oei et al <sup>30</sup> (<28+6 weeks GA) Meta-analysis of 8 studies	Low O <sub>2</sub> : ≤30% O <sub>2</sub> grp(n=251); high O <sub>2</sub> : ≥60% O <sub>2</sub> grp (n=253) Outcome – short-term morbidities and mortality	Mortality – ns [34/251-low O <sub>2</sub> vs. 32/258-high O <sub>2</sub> ]; BPD – ns [81/217-low O <sub>2</sub> vs. 93/226-high O <sub>2</sub> ]; IVH Gr3/4 – ns; ROP≥St3 – ns; NEC – ns; PDA – ns

LOX: Low oxygen group; HOX: High oxygen group; BPD: Bronchopulmonary dysplasia; PMA: Post menstrual age; MV: Mechanical ventilation; CPAP: Continuous positive airway pressure; IVH: Intraventricular hemorrhage; ROP: Retinopathy of prematurity; NEC: Necrotizing enterocolitis; PDA: Patent ductus arteriosus; ns: not significant between groups.

**Table 3:** Oxygen resuscitation studies and clinical outcomes in premature infants.

a week,<sup>29</sup> in premature infants who subsequently develop BPD. Whether the oxygen load as determined by the concentration of oxygen delivered at resuscitation predisposes to BPD is not clear. Resuscitation studies have addressed this issue with BPD as the primary outcome measure (Table 3). There are conflicting results on the effects of oxygen concentration at resuscitation and BPD. Two studies have reported beneficial effects of resuscitation with low oxygen concentration (21% O<sub>2</sub> - 30% O<sub>2</sub>) on decreasing the incidence of BPD.<sup>16,18</sup> However, oxygen concentration at resuscitation (30% O<sub>2</sub> vs. 65% O<sub>2</sub>) had no effect on the incidence of BPD in a relatively larger study.<sup>19</sup> Interestingly, the same study did not find significant difference in oxidative stress markers among the groups. More recently, a meta-analysis of eight randomized studies of low (≤30% O<sub>2</sub>) vs. high oxygen (≥65% O<sub>2</sub>) resuscitation, found no difference in major clinical outcomes including death or BPD in infants ≤28 weeks gestation.<sup>30</sup> The results of all these studies come with limitations. Meta-analysis included studies done over a relatively long period of time, during which time the clinical practices have evolved regarding management of BPD. Secondly, individual studies had relatively different SpO<sub>2</sub> targets in the first 10 minutes of birth; leading to an inhomogeneous starting point and a variation in FiO<sub>2</sub> adjustment to suit SpO<sub>2</sub> targets specific for each study. This could result in changes in oxygen load in the first 10 minutes impacting markers of oxidative stress and BPD. In a Canadian retrospective cohort study of 17 NICUs, a higher risk of severe neurologic injury or death among preterm infants of ≤27 weeks' gestation was observed following a change in practice to initiate resuscitation with room air or an intermediate oxygen concentration (21% O<sub>2</sub> - 40% O<sub>2</sub>)<sup>31</sup> in these infants. At this time, there is insufficient evidence to indicate that resuscitation with lower oxygen concentration (≤30% O<sub>2</sub>) at birth will decrease BPD or other clinical outcomes such as severe intraventricular hemorrhage, retinopathy of prematurity (Stage ≥3), necrotizing enterocolitis or patent ductus arteriosus.

## CONCLUSIONS

Optimal management of oxygen resuscitation is important as suboptimal or excessive oxygenation can be harmful to the newborn infant. Aggressive use of pulse oximetry in the delivery room to measure SpO<sub>2</sub> and titrating the fraction of inspired oxygen to desired SpO<sub>2</sub> target range is feasible and practical.

Current SpO<sub>2</sub> guidelines in premature infants are based mostly on studies from term infants. However, the current recommendations of administering lower O<sub>2</sub> concentration of 21% O<sub>2</sub> - 30% O<sub>2</sub> to initiate resuscitation and against using high oxygen concentrations (65% O<sub>2</sub> to 100% O<sub>2</sub>) are based on resuscitation studies in premature infants. Administering low oxygen concentrations at resuscitation has not been conclusively proven to improve outcomes. Nonetheless, it decreases the oxygen load in the first 30 minutes after birth contributing to improvement in oxidative stress markers in these infants.<sup>18,25</sup> The effects of oxidative stress in early life and its effects later in adults on cellular function is still not known. It has been noted that resuscitation with 100% O<sub>2</sub> immediately after birth has been associated with an increased risk of childhood cancer<sup>32,33</sup> and the risk was more pronounced when the resuscitation lasted for 3 minutes or longer.<sup>33</sup> Although this association was independent of asphyxial injury,<sup>32</sup> oxygen exposure may be a proxy for a poor transition to extra uterine environment. Oxygen is a drug and has to be used judiciously. Studies have to be done to define SpO<sub>2</sub> targets in premature infants and to determine the impact of low versus high oxygen resuscitation on clinical outcomes with long-term follow-up of these infants. It is important to adhere to the SpO<sub>2</sub> nomogram and oxygen concentration to be administered at birth, as per resuscitation guidelines until new information becomes available. Titrating the oxygen concentration to defined saturation targets with pulse oximetry is the best course at this time. Research into the critical role of heart rate and the myocardial oxygen dynamics at resuscitation, its responses to oxygenation and ultimately on long-term neurodevelopmental outcomes may help to clarify the oxygen concentration during resuscitation in premature infants.

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