# Effects of Different Topical Umbilical Cord Care Practices on Cord Separation Time among Neonates in Nakuru County Hospital, Kenya

**Journal of Nursing Care & Reports** 

Research Article

# Lucy Kinanu<sup>1\*</sup> Margaret Chege<sup>2</sup> James Mwaura<sup>1</sup> Ann Karani<sup>1</sup>

<sup>1</sup>University of Nairobi, College of Health Sciences, School of Nursing Sciences, Nairobi

<sup>2</sup>Former Senior Lecturer University of Nairobi, College of Health Sciences, School of Nursing Sciences, Nairobi

# \*Correspondence author

# Lucy Kinanu

University of Nairobi College of Health Sciences School of Nursing Sciences Kenya

Submitted: 9 Oct 2020; Published: 27 oct 2020

#### **Abstract**

Umbilical cord separation time is critical in the neonatal care as it disturbs both pediatricians and care takers. Cord detachment delay predisposes the site to higher chances of bacterial colonization and omphalitis, prolonging hospital stay with far reaching negative implications to the entire family. Community based studies have indicated that commonly used topical umbilical cord applications, although preventing omphalitis, may delay stump separation.

Keywords: Chlorhexidine, Alcohol, Dry Care, Cord Separation Time

#### **Objective**

Current study determined umbilical cord separation time among neonates on different topical cord care interventions (Dry, CHX and Alcohol) in Nakuru County Hospital.

#### **Methodology**

Randomized controlled trial. A total of 540 new-borns randomly assigned to receive 1 of 3 cord care regimens; twice cord cleansing with either 4% chlorhexidine (Group 1), or 70% alcohol (Group 2) and dry cord care (Group 3 as control).

#### Results

The mean cord separation time for chlorhexidine was (M=2.21, SE=0.25) which significantly differed from mean time taken for dry care intervention (M=0.35, SE=0.26). Chlorhexidine also prolonged the umbilical cord separation time when compared to alcohol cord care (M=2.21 $\pm$ 0.25 vs. M=1.86  $\pm$ 0.26). Comparing Alcohol and dry care showed alcohol to slightly prolonged the cord separation time more than dry cord care, although this was not statistically significant (M=1.86  $\pm$ 0.26 vs M=0.35  $\pm$ 0.26; p>0.05).

#### Conclusion

In this study, dry cord care had the shortest umbilical cord separation time when compared to both alcohol and chlorhexidine applications, and we recommended it in our set-up.

#### **Background Information**

Cord detachment delays increases bacterial infection risk making its care crucial and of great importance [1]. Even with low incidence of omphalitis, the open wound of the umbilical stump remains an entry point for pathogenic bacteria, and the undetached cord stump often worries mothers [2]. Asserted that rapid healing of the cord is an important aspect of infection prevention though ccommonly used topical applications delay separation for 1 to 5 days [3].assessing topical cord care effect in preventing omphalitis and death, concluded that antiseptic use prolongs the umbilical cord detachment time. Different topical applications on the umbilical cord has yielded controversial outcomes and findings. [4]. studied chlorhexidine use in community settings, and their data on mortality though showing a 3% reduction of random-effects in chlorhexidine group had the cord separation time increased by up to 1.7 times. Separation time of up to 10 days have been reported (WHO 2013). [5]. asserted that topical chlorhexidine use prolonged separation time up to ~50% and indicated that dissatisfaction might be expressed by caretakers.

# Methodology

Setting: The study was conducted in Nakuru County Hospital, a level 5 hospital situated in Nakuru town of Kenya. This is a teaching referral hospital whose labour ward has twelve beds for first stage of labour and eight delivery couches. It averages one thousand spontaneous vertex deliveries (SVD) and three hundred caesarean sections monthly. [7]. indicated it as having highest sepsis-related early neonatal mortality rate (36%) in

the country.

#### Study design and participants

This was a randomized controlled trial involving 540 healthy term SVD new-borns (38-42 weeks gestation). The new-borns were recruited within twelve hours of delivery, were free of congenital anomalies, weighed 2500 to 4000 grams, and had Apgar scores of at least 8 at first minute. Additionally, they had nothing applied to the umbilical cord stump, were roomed-in with their mothers, and had breast fed within one hour. Excluded were neonates requiring immediate transfer to neonatal intensive care unit, those born outside the hospital, and those on any form of medication, born of mothers referred from other hospitals with labour complications or other medical conditions.

# **Randomization and Sampling**

Eligible babies were randomized into one of three groups subjected to either 4.0% chlorhexidine or 70% alcohol for test groups, or into dry cord care group serving as control. Block randomization was used to minimize imbalance in the differences in ward staff shifts and also equalize numbers in the different care groups. All babies born from 6 pm to 6 am were thus entered into one block and vice versa. Their parents gave informed consent for participation. Mothers randomly picked shuffled colour coded cards (NBI (Chlorhexidine), MSA (Alcohol) and KSM (dry care) that allocated neonates into the three study groups.

#### **Randomization and Sampling**

Eligible babies were randomized into one of three groups subjected to either 4.0% chlorhexidine or 70% alcohol for test groups, or into dry cord care group serving as control. Block randomization was used to minimize imbalance in the differences in ward staff shifts and also equalize numbers in the different care groups. All babies born from 6 pm to 6 am were thus entered into one block and vice versa. Their parents gave informed consent for participation. Mothers randomly picked shuffled colour coded cards (NBI (Chlorhexidine), MSA (Alcohol) and KSM (dry care) that allocated neonates into the three study groups.

# Intervention

Chlorhexidine and alcohol solutions were applied to the cord as soon as possible up to within 12 hours of birth and then repeat applications done twice daily for up to 7 days. Thus, groups 1 and 2 were assigned to twelve hourly application of 4% Chlorhexidine and 70% alcohol respectively. For control group, cord was only cleaned and dried as recommended by WHO. In case of soiling, the cord was wiped with sterile cotton wool balls that had been soaked in boiled-cooled water. For test groups, after proper hand washing with soap and water, three sterile cotton balls soaked with either chlorhexidine or alcohol solution were used to gently cleanse the umbilical cord stump from top down and up to 5mm radius of the surrounding skin. The first application was demonstrated by the investigator in the hospital, and was done twice daily by caretakers at home following discharge. This was done for seven days. Sufficient

sterile cotton wool balls and chlorhexidine / alcohol solution were freely supplied. Caregivers in all groups received educational messages as per their cluster and advised on follow-up during the entire neonatal period.

#### **Data Collection Procedure**

Data on demographics, socio-economic factors, obstetric factors and cord care practices were collected from the care-taker using structured questionnaire in Kobo Collect software.

Umbilical cord Swabs were taken by a trained laboratory technologist from the base of the umbilical cord within twelve hours of delivery and on the seventh day after intervention. The specimens were collected by a dry sterile swab soaked in Amies transport medium (Oxiod, England), labelled with baby's code name and delivery date. Swabs were thereafter transported in Stuart's medium (Merck - Germany) and sent to bacteriology laboratory within one hour of collection. All specimens were cultured in the blood agar and MacConkey agar plates (Merck Germany) and incubated for 24-48 hours at 37oC. Baseline swabs, collected from each baby before commencement of interventions, were monitored for bacterial growth in the first 24 hours after collection. Those showing infections were reviewed by a clinician, started on treatment and excluded from the study

New-borns of all 3 groups were followed up at day 3, 14, 21 and 28 for any signs of umbilical cord infection and features of sepsis during the entire neonatal period. On day seven all the neonates were brought back to the facility for a follow-up umbilical cord swab. Mothers were oriented about the signs of umbilical infection during their hospital stay and asked to report to the researcher if any of the signs were noticed. The researcher made follow-up communication with parents / designated family members via phone calls on assigned dates. If any signs of cord infection were reported, parents were requested to return their babies to the hospital immediately for investigations and/or treatment.

# **Outcome Measurement**

In this study, omphalitis was defined as Pathogenic Bacterial culture in the umbilical cord swab within 24 hours and /or on the follow up on the seventh day showing single isolates or predominantly single isolates with or without any physical signs on the skin.

#### **Quality Control**

To ensure data quality, research assistants were all qualified professionals though not working in the facility to prevent bias. The solutions used were all handled privately by the principal investigator and handed over to the research assistants bearing the cluster codes to ensure double blinding of both the clients and the research assistants.

#### **Data Analysis**

Data in Kobo Collect of the 485 participants completing the study were entered into Microsoft Excel and transported into Statistical Package for Social Sciences (SPSS) version

22 for analysis. Descriptive statistics using frequency and proportions were computed to describe the basic attributes of the respondents as well as the occurrence of omphalitis. Chi-square test was used to determine whether there was difference among the different group in relation to the basic characteristics. The effectiveness of the regimens were determined using multiple logistic regression by considering the variables revealing significant difference at p<0.05 during the descriptive comparison analysis.

**Ethical Considerations:** The study was approved by the Institutional Review Board and permission granted by both Nakuru county and the facility administration. Consent was obtained from parents of the neonates and participants who developed omphalitis or needed treatment were all referred to a pediatricians stationed within the facility.

#### **Results**

# Socio-demographic characteristics of the mothers and new-born babies

A total of 485 participants completed the trial thus: chlorhexidine (n=165), alcohol (n=157) and dry cord care (n=163). Most mothers were aged 19-24 years (41.6%), were married (77.9%), had secondary education (55.1%) and were Christians (95.3%). Thirty one percent (30.7%) of households had one child while 6.2% of households had five or more children. The highest proportion of neonates had birth weight ranging between 3.01-3.50 kgs (49.3%), had 9 APGAR score in the first one minute (70.3%), and initiated breast feeding in less than 1 hour (99.4%). Fifty four percent (53.6%) of mothers had no formal education and 91% earned Kshs  $\leq$ 15,000. Distribution of the socio-demographic and socio-economic characteristics is given in Table 1.

Variables	Total, (N=485)		Chlorhexidine group (165)		Alcohol group, (157)		Dry cord care group, (163)	
	N	%	n	%	n	%	n	%
Age in years								
19-24	202	41.6	67	40.6	72	45.9	63	38.7
25-29	141	29.1	59	35.8	41	26.1	41	25.2
30-34	97	20	27	16.4	31	19.7	39	23.9
35 and above	45	9.3	12	7.3	13	8.3	20	12.3
Marital Status								
Married	378	77.9	127	77.0	124	79.0	127	77.9
Single/divorced	107	22.1	38	23.0	33	21.0	36	22.1
Level of Education								
Primary	142	29.3	47	28.5	50	31.8	45	27.6
Secondary	267	55.1	94	57.0	82	52.2	91	55.8
College	76	15.7	24	14.5	25	15.9	27	16.6
Religion								
Christian	462	95.3	156	94.5	151	96.2	155	95.1
Muslim	23	4.7	9	5.5	6	3.8	8	4.9
Number of children								
One	149	30.7	44	26.7	54	34.4	51	31.3
Two	130	26.8	45	27.3	31	19.7	54	33.1
Three	138	28.5	58	35.2	48	30.6	32	19.6
Four	38	7.8	7	4.2	14	8.9	17	10.4
Five and above	30	6.2	11	6.7	10	6.4	9	5.5
Occupation								
Permanent employment	37	7.6	13	7.9	11	7.0	13	8.0
Self/Causal Employment	188	38.8	55	33.3	68	43.3	65	39.9
Not employed	260	53.6	97	58.8	78	49.7	85	52.1
Monthly income in S	hillings		·		•	·		
15,000 and less	439	90.5	152	92.1	144	91.7	143	87.7
20,000	13	2.7	4	2.4	2	1.3	7	4.3
	-	•		-	•		-	

30,000 and above	33	6.8	9	5.5	11	7.0	13	8.0
Birth weight								
2.50-3.00 Kgs	130	26.8	41	24.8	33	21.0	56	34.4
3.01-3.50 Kgs	239	49.3	84	50.9	83	52.9	72	44.2
3.51-4.00 Kgs	116	23.9	40	24.2	41	26.1	35	21.5
APGAR score in the	first one m	inute	•	·				
8	138	28.5	38	20.0	46	29.3	54	33.1
9	341	70.3	125	80.0	109	69.4	107	65.6
10	6	1.2	2	1.2	2	1.2	2	1.2
Initiation of breast fe	eding	·	·		·	·	·	
< 1 hour	482	99.4	163	98.8	156	99.4	163	100
> 1 hour	3	0.6	2	1.2	1	0.6	0	0.0

 Table 1 : Socio-demographic and socioeconomic characteristics of the mother, and neonatal characteristics

# **Obstetric characteristics of the mothers**

Most mothers visited public health facility (86.4%), had  $\geq$  4 ANC visits (56.7%), had 37-38 gestational weeks (43.1%), and laboured for 11–14 hours (35.9%) with 3 hours' duration of membrane rupture (43.5%) and clear liquor (99.6%). Almost all (99.8%) had SVD deliveries. There was no difference in distribution of obstetric factors in various intervention groups as shown in Table 2.

Variables	Total, (N=485)		chlorhex	idine group (165)	Alcohol group,	(157)	Dry cordcare group, (163)		
	n	%	n	%	n	%	n	%	
Place of ANC	attendance	e							
Public facility	419	86.4	144	87.3	134	85.4	141	86.5	
Private facility	66	13.6	21	12.7	23	14.6	22	13.5	
Number of AN	C visits								
Once	15	3.1	3	1.8	5	3.2	7	4.3	
Twice	55	11.3	20	12.1	24	15.3	11	6.7	
Thrice	140	28.9	55	33.3	39	24.8	46	28.2	
Four times and above	275	56.7	87	52.7	89	56.7	99	60.7	
Gestation durin	ng deliver	y		·	•		·		
37 to 38 weeks	209	43.1	66	40.0	67	42.7	76	46.6	
39 to 40 weeks	206	42.5	72	43.6	65	41.4	69	42.3	
41 to 42 weeks	70	14.4	27	16.4	25	15.9	18	11.0	
Duration of lab	or in hou	rs							
< 8	44	9.1	15	9.1	15	9.6	14	8.6	
8-10	117	24.1	36	21.8	42	26.8	39	23.9	
11-14	174	35.9	62	37.6	55	35.0	57	35.0	
15 and above	150	30.9	52	31.5	45	28.7	53	32.5	
Duration of me	embrane r	upture							
One hour	79	16.3	23	13.9	35	22.3	21	12.9	
Two hours	171	35.3	59	35.8	46	29.3	66	40.5	
Three hours	211	43.5	75	45.5	65	41.4	71	43.6	
Four hours	24	4.9	8	4.8	11	7.0	5	3.1	

Nature of liqu	uor							
Clear	483	99.6	164	99.4	157	100.0	162	99.4
Meconium	2	0.4	1	0.6	0	0.0	1	0.6
Mode of deli	very				·			
SVD	484	99.8	164	99.4	157	100.0	163	100.0
Caesarian	1	0.2	1	0.6	0	0.0	0	0.0
Maternal HIV	/ status							
Negative	427	88.0	151	91.5	137	87.3	139	85.3
Positive	58	12.0	14	8.5	20	12.7	14	14.7

Table 2: Obstetric characteristics of the mothers

# **Umbilical cord care practices**

Majority of the mothers washed hands after visiting toilet (89.5%) and changing the baby (96.3%). Mothers who washed hands when eating were 30.9% and 40.6% did when cooking. Eighty eight percent of mothers used basin while washing hands whereas 56.6% cleaned the umbilical cord with antiseptics. Majority (86.6%) applied baby diapers folded backwards and roomed in with the baby (93.2%). This is presented in table 3.

Variables	Total, (N=485)		Chlorhexidine group (165)		Alcohol group, (157)		Dry cord care group, (163)		χ2 value	df	p value*
	n	%	n	%	n	%	n	%			
Washing hands	s after v	isiting to	oilet								
No	51	10.5	17	10.3	20	12.7	14	8.6	1.48	2	0.478
Yes	434	89.5	148	89.7	137	87.3	149	91.4			
Washing hands	s after cl	nanging	the bab	y							
No	18	3.7	6	3.6	9	5.7	3	1.8	3.39	2	0.183
Yes	467	96.3	159	96.4	148	94.3	160	98.2			
Washing hands	s when e	eating					•				
No	335	69.1	115	69.7	107	68.2	113	69.3	0.10	2	0.953
Yes	150	30.9	50	30.3	50	31.8	50	30.7			
Washing hands	s when c	cooking					'			<u>'</u>	
No	288	59.4	102	61.8	88	56.1	98	60.1	1.17	2	0.558
Yes	197	40.6	63	38.2	69	43.9	65	39.9			
Methods/ways	of wash	ning han	ds	•							
On a basin	428	88.2	148	89.7	134	85.4	146	89.6	8.60	4	0.072
On basin and tap	35	7.2	14	8.5	10	6.4	11	6.7			
Тар	22	4.5	3	1.8	13	8.3	6	3.7			
How to clean t	he umb	ilical co	rd				•			<u>'</u>	
Clean with antiseptic	274	56.6	136	82.4	126	80.8	7.4	247.62	6	<0.001	
Clean with boiled water	63	13.0	4	2.4	11	7.1	48	29.4			
Clean with wet/dry cloth	147	30.3	25	15.2	19	12.1	93	57.1			
Application of	diaper	folded b	ackward	ls on the baby	(observ	re)				·	
Yes	420	86.6	143	86.7	143	91.1	134	82.2	5.43	2	0.066

No	65	13.4	22	13.3	14	8.9	29	17.8			
Always staying with the in the same room											
Yes	452	93.2	149	90.3	149	94.9	154	94.5	3.32	2	0.190
No	33	6.8	16	9.7	8	5.1	9	5.5			

<sup>\*</sup> Significant at p<0.05 bolded

Table 3: Umbilical cord care practices

(I) client cluster	(J) Comparison cluster	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval		
					Lower Bound	Upper Bound	
dry care	Alcohol	34695	.25691	.368	9510	.2571	
	Chlohexidine	-2.20870*	.25036	.000	-2.7973	-1.6201	
Alcohol	dry care	.34695	.25691	.368	2571	.9510	
	Chlohexidine	-1.86174*	.25541	.000	-2.4622	-1.2612	
Chlohexidine	dry care	2.20870*	.25036	.000	1.6201	2.7973	
	Alcohol	1.86174*	.25541	.000	1.2612	2.4622	

Dependent Variable: time taken for the cord to drop off Tukey HSD

**Table 4:** Umbilical cord separation time

# Discussion

It is argued that the cord stump that stays longer has a higher risk of being infected. Omphalitis can be extremely serious, causing sepsis, due to increased permeability of the umbilical vessels that persists until approximately 20 days of age of the newborn [7]. Omphalitis also delays detachment and can increase the duration of hospitalization and cost of care unnecessarily [8]. Prevention of this disease and its associated neonatal mortality is of great public health importance [9]. The commonly used topical applications used for prevention of omphalitis usually delay the separation time for 1 to 5 days and may increases the risk of omphalitis and hospitalization [10].

#### **Chlorhexidine and Dry Care**

In this study, the cord separation time was chlorhexidine intervention (M=2.20870, SD=.25036) which significantly differed from mean time taken for dry care intervention (M=.34695, SD=0.256) and alcohol intervention (1.86174, SD = .256). These findings agreed with Rosanna et al (2016) who indicated significant difference in the mean cord separation time between the 2 groups (dry cord care: 10.1 days [standard deviation, SD = 4.0] vs 70% alcohol: 12.0 days [SD = 4.2]; P < 0.001). Similarly [11]. Asserted that more than being protective against omphalitis dry cord care also reduced the umbilical cord separation time in Palestine. These findings agree with several other findings from both community and health facility set-ups [12]. Also confirmed that dry cord care was associated with reduced separation time. Delayed detachment in antiseptic use could be caused by normal flora destruction around the umbilicus. However as indicated by the WHO recommendation of washing the umbilical cord with soap and water when soiled, frequency of cleaning the cord with water keeping it wet can slightly prolong the separation time to a varying duration though no known study has been done to compare the frequency of washing time and separation

among the dry umbilical cord care practices. More so the quality or cleanliness of the water used can also serve as a source of infection.

# **Chlorhexidine and Alcohol**

According to this study, Chlorhexidine prolonged the umbilical cord separation time. Compared to alcohol cord care, chlorhexidine intervention (M=2.20870, SD=.25036) significantly differed from mean time taken for alcohol intervention (M=1.86174, SD=.256). Though not many studies were found comparing CHX to alcohol. Roba et al (2019) in a meta-analysis indicated that chlorhexidine topical application prolonged the cord separation time with almost three days compared to alcohol cord care modalities. [13]. also confirms that Chlorhexidine prolongs separation time compared to alcohol.

#### Alcohol and dry care

In this study, alcohol slightly prolonged the cord separation time than dry cord care though not statistically significant; alcohol intervention (M=1.86174, SD=.256) while dry care intervention (M=0.34695, SD=0.256). These findings agree with Al-Shehri [14]. In a meta-analysis who asserted that alcohol topical application was associated with prolonged umbilical cord separation time compared to dry cord care this further agrees with [15-17]. Conducted a community study comparing use of 70% alcohol to dry cord care on separation time and confirmed that alcohol prolongs cord separation time compared to dry care.

# Conclusion

While Chlorhexidine digluconate would be considered for topical umbilical cord care in prevention of omphalitis, it is least effective than both alcohol and dry care interventions in time taken for umbilical cord to fall off. Further studies should be done to determine the preferable duration of chlorhexidine application that would not prolong cord separation time.

#### References

- Ahmadpour Kacho M, Zahedpasha Y, Hajian K, et al., (2006) The effect of topical application of human milk, ethyl alcohol 96%, and silver sulfadiazine on umbilical cord separation time in newborn infants. *Arch Iran Med* 9: 33–38.
- 2. Liu MF, Lee TY, Kuo YL, Lien MC (2012) Comparative effects of using alcohol, natural drying, and salicylic sugar powder on umbilical stump detachment of neonates. *The Journal of perinatal & neonatal nursing.* 26: 269-74.
- 3. Zupan J, Garner P, et al. (2014) Topical umbilical cord care at birth. *Cochrane Database Syst Rev*
- 4. Imdad A, Bautist RMM, et al., (2013) Umbilical cord antiseptics for preventing sepsis and death among newborns. *Cochrane Database of Systematic Reviews*. JohnWiley & Sons, Ltd
- 5. World Health Organization. (2013). Recommendations on Postnatal care of the mother and new born. World Health Organization; Geneva, Switzerland.
- Mullany LC, Shah R., et al. (2013) Chlorhexidine Cleansing of the Umbilical Cord and Separation Time: A Cluster-Randomized Trial. American Academy of Pediatrics
- 7. Kenya Demographic and Health Survey (KHDS) (2014)
- 8. Lvaro Iglesias E, Ferna ndez Calvo F, Recio Pascual V (2008) Common umbilical pathology. In: Neonatologi a AE de P and SE de, editor. Diagnostic Therapeutic Protocols for AEP: Neonatology. *Madrid* 398-404.
- Allam NA, Megrin WAA, Talla AM (2015) The Effect of Topical Application of Mother Milk on Separation of Umbilical Cord for Newborn Babies, *American Journal* of Nursing Science 4: 288-296.
- Karumbi J, Mulaku M, Aluvaala J, English M, Opiyo N (2013) Topical Umbilical Cord Care for Prevention of Infection and Neonatal Mortality. *The Pediatric Infectious Disease Journal* 32:78-83.
- 11. Pezzati M, Rossi S, Tronchin M, Dani C, Filippi I, Rubaltell FF (2003) Umbilical cord care in premature infants: the effect of two different cord-care regimens (salicylic sugar powder vs chlorhexidine) on cord separation time and other outcomes., *Pediatrics* 112: e275.
- 12. Rosanna Q, Kim L, Tina D et al., (2016) 70% Alcohol versus Dry Cord Care in the Umbilical Cord Care Medicine (Baltimore) 95: e3207.
- 13. Shahrour M, Sawalha NA, Masri M, et al., (2017) Alcohol versus dry umbilical cord care among newborn infants in occupied Palestinian territory: *a controlled trial The Lancet* 390: 2-3
- 14. López Medina MD (2020) Umbilical cord separation time, predictors and healing complications in newborns with dry care 15: e0227209.
- 15. Roba AA, Tefera M, Worku T, et al. (2019) Application of 4% chlorhexidine to the umbilical cord stump of newborn infants in lower income countries: *a systematic review and*

- meta-analysis.
- 16. Al Shehri. (2019) The Use of Alcohol versus Dry Care for the Umbilical Cord in Newborns: A Systematic Review and Meta-analysis of Randomized and Non-randomized Studies Cureus 11: e5103.
- 17. Nourian M, Allaii F, et al. (2009) Comparison of the effect of Alcohol 70% versus dry cord care on cord bacterial colonization and cord separation time among new-borns, *Pakistan journal of medical science 25: 1.*

**Copyright:** ©2020 **Lucy Kinanu**. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.