Echography-Guided Surfactant Therapy to Improve Timeliness of Surfactant Replacement: A Quality Improvement Project

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Objective To improve time of surfactant administration with a surfactant replacement protocol based on semi-quantitative lung ultrasound score (LUS) thresholds.

Study design Quality improvement (QI), prospective, before-after, pilot study. In a 6-month period surfactant replacement was based only on inspired oxygen fraction (FiO_2) thresholds. In the second 6-month period, surfactant was given when either the FiO_2 or LUS exceeded the limits. The main QI measures were the proportion of neonates receiving surfactant within the first 3 hours of life and maximal FiO_2 reached before surfactant replacement. Secondary QI measures were the duration of respiratory support and ventilator-free days. Data were also collected for 1 year after the study to verify sustainability.

Results Echography-guided Surfactant THERapy (ESTHER) increased the proportion of neonates receiving surfactant within the first 3 hours of life (71.4%-90%; $P < .0001$) and reduced the maximal FiO_2 reached before surfactant replacement (0.33 [0.26-0.5]) vs 0.4 [0.4-0.55]; $P = .005$). The global need for surfactant did not significantly change. ESTHER also resulted in a significant decrease in duration of invasive ventilation and ventilator-free days.

Conclusions ESTHER improved the timeliness of surfactant administration and secondary QI indicators related to surfactant replacement. *(J Pediatr 2019;212:137-43)*.

See editorial, p 8

Continuous positive airway pressure (CPAP) has become the first-line therapy for respiratory distress syndrome (RDS).[1,2] Surfactant replacement therapy is recommended when continuous positive airway pressure (CPAP) fails[1,2] and is more effective to decrease mortality and/or bronchopulmonary dysplasia (BPD) when used within the first 2-3 hours of life.[3] However, identifying patients in need of surfactant replacement within this narrow interval of time remains a challenge. Surfactant administration is currently based on the inspired oxygen fraction (FiO_2).[1] Yet, the suggested FiO_2 cut-off values are arbitrary, do not accurately describe oxygenation, are not strictly based on underlying pathophysiology and, finally, may be attained after the optimal time-window for treatment.

Hence, it would be useful to have an early predictive tool for surfactant need to ensure timely surfactant administration. Lung ultrasound was first used in neonatal intensive care units (NICUs) approximately 10 years ago and has rapidly showed its usefulness in the diagnosis of RDS and other neonatal lung diseases.[4,5] Our group started using lung ultrasound in 2013 when we began a lung ultrasound-based program with training sessions that were first offered for team physicians, then later made available for visiting colleagues. In 2014, we gradually adopted lung ultrasound as the first-line imaging technique for patients with signs of respiratory distress. With our growing experience, we wished to explore further applications of this technique through several lung ultrasound-based clinical research projects. Between the end of 2014 and the first half of 2016, we developed and evaluated a semiquantitative lung ultrasound score (LUS) that showed high accuracy in evaluating lung aeration and predicting surfactant need in CPAP-treated preterm neonates.[6,7] These results demonstrated the usefulness of LUS in identifying potential candidates for surfactant replacement at an early stage. We, therefore, decided to integrate LUS into our surfactant administration protocol. Thus, we modified our surfactant administration criteria from FiO_2 thresholds based on the

BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
ESTHER	Echography-guided Surfactant THERapy
FiO_2	Inspired oxygen fraction
LUS	Lung ultrasound score
NICU	Neonatal intensive care unit
QI	Quality improvement
RDS	Respiratory distress syndrome

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European guidelines[1] to a combination of FiO_2 and LUS thresholds, basing surfactant administration on the criterion that reaches cut-off values first. We called the new protocol ESTHER (Echography-guided Surfactant THERapy). Our aim was to improve the timeliness of surfactant administration in preterm neonates.

We followed the Plan-Do-Study-Act cycle to develop and test the quality improvement (QI) intervention of the integration of LUS into surfactant administration protocol (**Figure 1**; available at www.jpeds.com).[8]

Methods

The project was implemented in an academic, tertiary, 28-bed NICU with ~4000 deliveries/year and with a particular interest in respiratory care and research. Nursing assignment is typically 2 patients for every nurse, varying with the patients' clinical severity. Neonates received full prenatal care, including antenatal steroids, delayed cord clamping, and magnesium sulphate, when appropriate, following current guidelines.[1,9-11] Respiratory care is provided according to a formal NICU protocol based on physiology-driven gentle ventilation, early use of rescue high frequency oscillatory ventilation, and aggressive use of noninvasive respiratory support techniques.[12,13]

Intervention

The intervention was the change of surfactant administration protocol for neonates ≤32 weeks of gestation with RDS. In the first 6 months of 2016 (standard period), surfactant was administered in the first 72 hours of life, if the FiO_2 increased above 0.3 or 0.4 for infants $\leq 28^{6/7}$ and $\geq 29^{0/7}$ weeks of gestation, respectively. From the second half of 2016 (ESTHER period) and onward, surfactant was administered for RDS when either the FiO_2 exceeded the above-described limits or LUS was higher than 8, whichever occurred first. This LUS threshold was chosen because it has the best diagnostic accuracy.[7] All permanent NICU physicians had been fully trained in the use of lung ultrasound since the end of 2014, and therefore, the intervention did not coincide with the introduction of lung ultrasound in the NICU. There were no problems in the practical implementation of the change.[14] New residents and fellows receive training in lung ultrasound when they begin work in our NICU. They first perform lung ultrasound under the supervision of a senior physician, until they achieve sufficient competency. Lung ultrasound has a short learning curve,[15] and high interobserver agreements for basic lung ultrasound signs and for LUS calculation.[6,16] Transversal and/or longitudinal scans of the anterior and lateral chest walls are performed with a high-resolution, micro-linear, 15 MHz "hockey stick" probe (CX50; Philips Healthcare, Eindhoven, The Netherlands). LUS calculation is described elsewhere.[6,7] During the standard period, LUS was calculated for research purposes for one of our diagnostic accuracy studies and was not used to guide surfactant administration.[7] During the ESTHER period, LUS was integrated into the clinical protocol.

Surfactant was always administered as 200 mg/kg poractant-α (Curosurf; Chiesi Farmaceutici, Parma, Italy) through the intubation-surfactant-extubation technique. A second 100 mg/kg dose was given, if FiO_2 remained above 0.3, after at least 10 hours from the first treatment. Surfactant redosing was not performed before 10 hours from the first administration because this is the median half-life of dipalmitoylphosphatidylcholine in preterm neonates requiring multiple surfactant doses.[17] No other NICU clinical protocol was changed during 2016, and the number of deliveries and the local epidemiology did not change during this period.

Study of the Intervention

Our primary objective was to increase the number of babies receiving surfactant in the first 3 hours of life. We used the model for improvement as a framework to implement and test the effect of the ESTHER protocol on this purpose over a period of 6 months.[18] A before-after approach was chosen to evaluate the effect of ESTHER introduction in particular NICU characterized by significant expertise in lung ultrasound and respiratory care.[19] Although this design does not account for potential secular trends, this bias seems negligible given the short period evaluated and the absence of other changes in clinical protocols and local epidemiology.

All inborn neonates ≤32 weeks of gestation, admitted to the NICU with RDS during 2016, were subdivided into those born in the first 6 months (standard period) and in the second half of 2016 (ESTHER period). RDS was defined with the typical lung ultrasound appearance and clinical criteria described earlier.[20]

Exclusion criteria were (1) chromosomal abnormalities or complex congenital malformations; (2) congenital lung diseases; (3) early onset severe sepsis and/or septic shock, as defined elsewhere[21]; (4) congenital pneumonia diagnosed according to previously detailed criteria[12]; (5) meconium or blood aspiration syndrome, defined as meconium or blood-stained amniotic fluid and airway secretions, onset of respiratory failure early from birth, and typical lung imaging[22,23]; (6) bile acid pneumonia, as previously described[24,25]; and (7) need for surgery in the first week of life.

Measures

For neonates treated with surfactant, the following outcomes were chosen as primary QI measures: the proportion of surfactant-treated neonates who received the drug within the first 3 hours of life; and the maximal FiO_2 reached before surfactant replacement. To verify that the protocol was sustainable over time, we also analyzed these data for infants fulfilling the same inclusion criteria and admitted to the NICU during the year after the end of this study (sustainability period). Secondary QI measures were the duration of invasive ventilation and CPAP or noninvasive ventilation, the duration of O_2 therapy and ventilator-free days, defined as the number of days spent in the NICU without invasive ventilation within the first 28 days of life, and considered

zero for patients who died in the NICU.[26] These QI measures were chosen because early surfactant replacement within 2-3 hours of life is known to be associated with a significant reduction in mortality and the composite mortality/BPD when compared with later administration.[3] We hypothesized that reduced oxygen exposure early in life, and shorter length of invasive respiratory support, might be the causative mechanisms for these reductions.[27] We did not focus directly on mortality and BPD as these are complex and multifactorial endpoints influenced by several variables. However, mortality and BPD (defined according to the National Institute of Child Health and Human Development criteria[28]) were reported to describe the population subjected to the intervention.

Basic clinical data were extracted and the Critical Risk Index for Babies-II score[29] was analyzed to confirm that clinical severity at the NICU admission did not change overtime. Small for gestational age babies were identified according to Fenton curves.[30] We also recorded the total surfactant treatment and re-treatments in the 2 periods. All data were taken in real-time from the electronic patients' file or the NICU monitoring system and anonymously recorded in a secured spreadsheet. Although ethical approval is not needed for this type of study according to current local regulations, the protocol was approved by the local ethical committee (SRLF/CE n.17/33). Parents received a written information about the project upon NICU admission. The revised Standards for Quality Improvement Reporting Excellence (SQUIRE2) guidelines were followed through the project.[31]

Statistical Analyses

A formal sample size calculation was not feasible. Nevertheless, taking into account the number of admissions to our NICU, it seemed reasonable to recruit about 100 neonates/cohort and we considered this as a "convenience sample size." Data were tested for normality with the Kolmogorov–Smirnov test and expressed as a mean (SD) or median (IQR) as appropriate. Basic population data were compared between the 2 groups by using Student, Mann–Whitney, χ^2, or Fisher exact test, as appropriate. Main outcome data were analyzed by McNemar (proportions of babies receiving surfactant within the first 3 hours of life) or Mann-Whitney test (maximal FiO_2 reached before surfactant administration). Need for surfactant treatments and re-treatments were also contrasted with the McNemar test. Comparisons between ESTHER and sustainability period were also performed with the same tests. Secondary outcomes data were analyzed with Mann-Whitney test. Analyses were performed with SPSS v 15.0 (SPSS Inc, Chicago, Illinois) or MedCalc 13.3.3 (MEDCALC Corp, Ostend, Belgium) and $P < .05$ were considered to be statistically significant.

Results

Standard and ESTHER periods were similar, confirming the lack of change in local epidemiology (Table I). The lung ultrasound procedure lasted on average 5 minutes, and no desaturations or other problem related to the intervention were reported. Another 95 patients fulfilling inclusion criteria were observed during the 1-year sustainability period, and their baseline data were similar to those of the standard and ESTHER periods (data not shown).

Table I. Baseline data of the population divided into the 2 study periods

Variables	Whole population (217)	Standard period (113)	ESTHER period (104)	*P*
Gestational age (wk)	28.8 (2)	29 (2)	29 (2.1)	.402
Birth weight (g)	1183 (350)	1177 (361)	1193 (342)	.791
SGA neonates	12 (5.5%)	7 (6%)	5 (5%)	.643
Prenatal steroids	200 (92.2%)	108 (96%)	91 (87%)	.130
Cesarean delivery	137 (63.1%)	65 (58%)	72 (68%)	.122
5' Apgar score	9 [8-10]	9 [8-10]	9 [7-10]	.07
CRIB-II score	7.2 (3.6)	8 (3)	7 (4)	.09
Silverman score	3 [1-4]	3 [1-4]	2 [1-4]	.161
NICU stay (d)	34 [15-52.2]	34 [16-57]	34 [15-51]	.441
BPD	57 (26.2%)	34 (30%)	23 (22.1%)	.203
Mortality	20 (9.2%)	13 (11%)	7 (7%)	.317

CRIB-II, Critical Risk Index for Babies-II; *SGA*: small for gestational age.
Data are expressed as mean (SD), median [IQR], or number (%). Prenatal steroids are expressed as any dose of betamethasone; Silverman score is reported as the max value obtained before surfactant replacement (if any) and anyway during the first 24 hours of life. All scores are given in dimensionless numbers. Data are compared with Student, Mann-Whitney, χ^2, or Fisher exact test, as appropriate.

Need for surfactant did not change significantly, as it was administered to 63 (55%) and 40 (39%; $P = .999$) neonates in the standard and the ESTHER period, respectively. Surfactant re-treatment was given to 25 (40%) and 8 (20%; $P = .504$) babies in the standard and ESTHER period, respectively. During the ESTHER period, only 3 neonates received surfactant because they had FiO_2 above the protocol threshold. All the other patients received surfactant because they had a LUS higher than the cut-off value.

The proportions of neonates receiving surfactant within the first 3 hours of life significantly increased from 71% to 90%; $P < .0001$; Figure 2). The maximal FiO_2 reached before surfactant administration was significantly lower in the ESTHER (0.33 [0.26-0.5]), than in the standard period (0.4 [0.4-0.55]; $P = .005$).

These figures did not change for 1 year after the study. In fact, 42 out of 95 babies (44%) needed surfactant and 34 (81%) of them received it within 3 hours of life ($P = .999$ vs the ESTHER period), and the maximal FiO_2 reached was (0.34 [0.3-0.45]); $P = .787$ vs the ESTHER period). During this sustainability period all surfactant treatments were indicated by LUS, ie, no neonate received surfactant because of FiO_2 above the protocol threshold.

During the ESTHER period, only 5 patients received surfactant beyond the optimal time-window, and several patients had a late surfactant administration during the standard period (Figure 3).

Secondary QI measures during the ESTHER period were a significantly reduced for invasive ventilation and ventilator-free days (Table II). BPD incidence did not

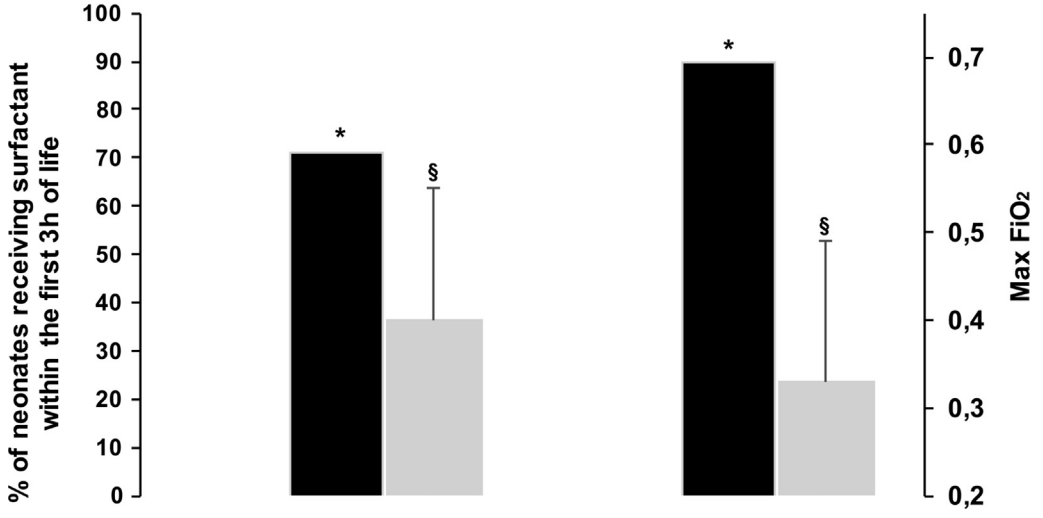

Figure 2. Primary quality improvement measures. *Black and gray columns* represent the proportions (% on the *left axis*) of surfactant-treated neonates receiving surfactant within the first 3 hours of life, and the maximal FiO_2 (median on the *right axis*) reached before surfactant replacement, respectively. *T-bars* represent interquartile range of FiO_2. *$P < .0001$; §$P = .005$.

change during the study period or in the following years (data not shown).

Discussion

The use of LUS can improve timeliness of surfactant administration, thereby increasing the quality of respiratory care under the conditions typical of our NICU. No problems were encountered changing from the FiO_2-based approach to the LUS-based protocol. LUS seemed to help in optimizing timing of surfactant therapy. In addition, we were able to demonstrate an improvement in some secondary QI measures, such as the duration of invasive ventilation and ventilator-free days. Since the end of this study, ESTHER represents our routine protocol for surfactant replacement.

Our results are fully consistent with the reduction in mortality and BPD obtained by an early surfactant replacement,[3] as these results might be explained by the decreased ventilation-induced inflammation and the related alveolarization derangement.[32] We observed a reduction in maximal FiO_2 reached before surfactant administration, and we hypothesize that administering less oxygen early in life might also reduce oxidative lung injury that contributes to BPD development.[33] Conversely, the duration of noninvasive respiratory support did not change, as preterm neonates may remain dependent on these support techniques for reasons other than RDS. We cannot exclude that further improvements may be possible through the Plan-Do-Study-Act cycle. For instance, we are currently integrating lung ultrasound into specific algorithms,[8] similar to those implemented in adult critical care.[34] **Figure 1** depicts possible future developments: adapted algorithms coupled with simulation training might also be helpful to optimize the NICU workflow.

Surfactant replacement therapy is a cornerstone of neonatal critical care, albeit it is still essentially unguided by any biological or clinical tool, and might, thus, be performed in a suboptimal way, thereby reducing efficacy and usefulness.[3] This stands in contrast to how other NICU interventions, such as antibiotics, temperature-control, or parenteral nutrition, are well guided. LUS has previously proven its reliability in predicting surfactant replacement in neonates with RDS,[6,7] and its introduction within the ESTHER protocol demonstrates that it may actually guide surfactant therapy. Crude value of FiO_2 reached in the first hours of life have been proposed as predictor for CPAP failure, however, different FiO_2 thresholds have been suggested and these are highly influenced by the type of CPAP, interfaces, nursing, and respiratory care policies applied in different NICUs.[35,36] Moreover, FiO_2 showed a diagnostic accuracy lower than LUS to predict need for surfactant administration.[6,7,35] Only one other QI study about the timeliness of surfactant administration has been published. However, this was performed in a North American unit and aimed to improve surfactant prophylaxis given in the delivery room by respiratory therapists.[37] Moreover, the before-mentioned QI study is no longer useful, as trials have since demonstrated the superiority of early CPAP and surfactant therapy over prophylaxis.[1,2]

A particular strength of our project is the context in which it was developed, and this also represents its main limitation. ESTHER was introduced into a NICU with a particular interest in respiratory care and research. In addition, the whole medical and nursing team was already proficient in the use of lung ultrasound,[14] and the implementation of ESTHER did not require any particular effort or change for the team. Therefore, our results cannot be directly applied to any other NICU, if the local setting does not present similar characteristics in terms of respiratory and ultrasound

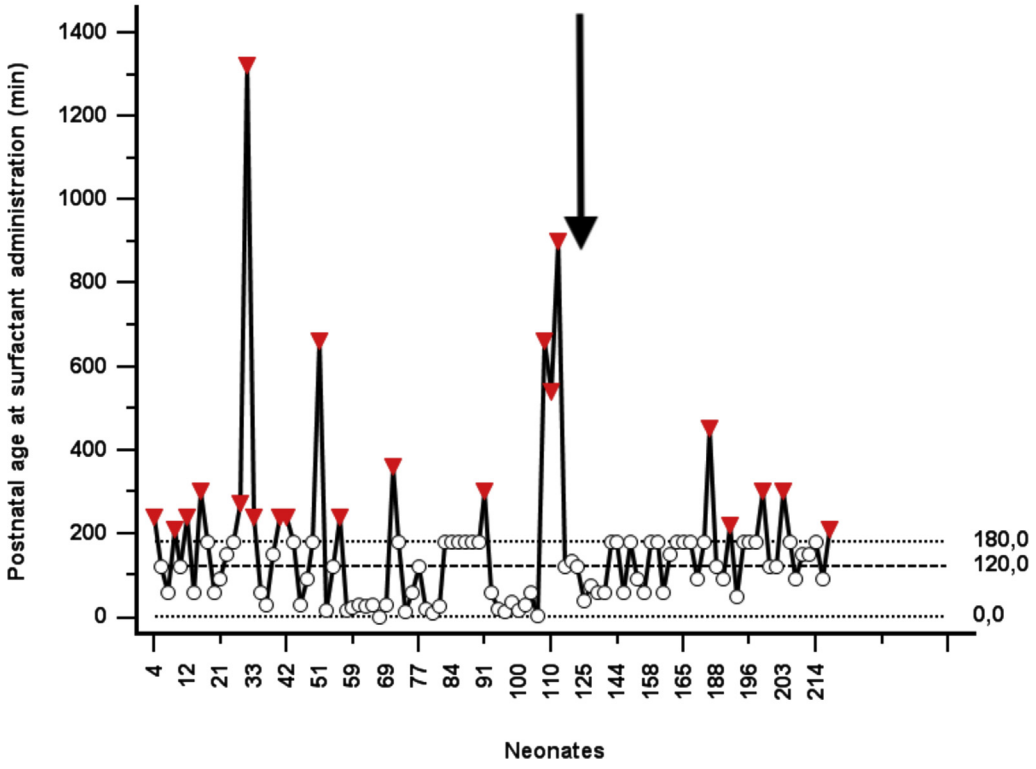

Figure 3. Process control chart. Postnatal age at surfactant administration is depicted for surfactant-treated neonates. *Hatched lines* represent the optimal time-window for surfactant replacement (between the first 180 minutes of life). The *arrow* represents the implementation of ESTHER protocol. *Open circles* and *full triangles* represent neonates receiving a timely or a late surfactant administration, respectively. Only 5 neonates had a late surfactant replacement after the introduction of ESTHER.

expertise. However, this "know-how" is easily transferable, as can be seen by the quick spread of the use of lung ultrasound in neonatology and the number of course attendees, congresses, social media initiatives, and publications on the subject.[8] Our results should encourage similar projects in other units and hopefully help to verify if ESTHER may impact on major clinical outcomes. The ESTHER implementation seems sustainable as our results were confirmed by assessment of babies hospitalized over 1 year after the protocol change. Moreover, ESTHER protocol introduction did not have any direct cost. This is likely to be the same in any other NICU because an ultrasound machine is almost invariably available. Other experiences using simple qualitative lung ultrasound have also been suggested to predict the need for respiratory interventions[37] and may be even easier to implement, although semiquantitative lung ultrasound using dedicated scores provide more refined information.[8] Finally, ESTHER introduction did not significantly change the frequency of surfactant administration, ie, ESTHER did not lead us to intubate more patients, but rather allowed a more patient-tailored administration giving surfactant earlier to patients who actually needed it.

Table II. Secondary quality improvement measures

Secondary measures	Standard period	ESTHER period	*P*
Duration of invasive ventilation (h)	48 [1-192]	11 [0-72]	**.001**
Duration of noninvasive ventilation/continuous positive airway pressure (d)	38 [8-56]	34 [16-52]	.830
Duration of O_2 therapy (d)	15 [1-47]	16 [1-39]	.468
Ventilator-free days (d)	22 [12-27]	27 [19-28]	**.012**

Data are expressed as median [IQR].
Values in bold are statistically significant.

Our work has some limitations. Results could depend on lung ultrasound reliability, however a higher interobserver agreement for RDS diagnosis and LUS calculation has been already demonstrated irrespective of the operator experience.[6,14] Although ESTHER improves timeliness of surfactant replacement, we cannot say anything about its actual impact, if any, on major NICU clinical outcome. Such an evaluation would demand a larger randomized multicenter study. However, it is well known that earlier surfactant administration improves clinical outcomes[3] and ESTHER is noninvasive, inexpensive, and feasible. In the absence of other candidate measures to improve timeliness of surfactant administration, embarking in such a complex multicenter trial could be considered unethical, especially in NICUs where lung ultrasound is already the first line imaging technique or where early surfactant replacement is already satisfactorily achieved. We acknowledge to have enrolled a relatively small population. However, ours was a homogeneous population of preterm neonates with RDS, excluding other types of respiratory failure and represented a whole

year of NICU activity. Finally, the before-after design may be intrinsically biased by the presence of inherent variations (known as "common-cause variations"), related to other clinical improvements, experience gain, epidemiologic changes, or secular trends during the study.[19] This cannot be completely excluded, although we believe the bias to be minimal because no other protocol or policy was changed during the study; the study lasted a relatively short period of time; the whole team was already proficient in the use of lung ultrasound at the time of ESTHER introduction, and, thus, no significant experience gain occurred during the study.

ESTHER is sustainable and may improve timeliness of surfactant replacement for preterm infants with RDS in a NICU with proficiency in lung ultrasound and respiratory care. ESTHER may be introduced in other settings with similar conditions and expertise. ■

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Field Anthropometry Independent of Precise Age

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Mid-upper arm circumference (MUAC) is considered to be a surrogate measure of fat-free mass. Measurement of MUAC for assessing nutritional status in undernourished children was first reported by Derrick B. Jelliffe and his wife Patrice Jelliffe (popularly known as Dick and Pat) in field surveys in Haiti.[1] This method gained popularity because it was easy to measure and required only a simple nonstretchable measuring tape. Over next few years, the relative age-independence of MUAC in first few years of life was demonstrated, making it a useful anthropometric measure in populations in which the precise age of children was not well known. In this editorial published 50 years ago in *The Journal*, Jelliffe commented on various anthropometric measures and ratios—arm circumference, weight-for-length, weight-for-head circumference, chest:head circumference—which have the potential to be used independent of precise age.

Over next 2 decades, MUAC was frequently but intermittently used in the field settings, but in absence of any acceptable cut-off, its utility was limited. The interest in MUAC resurfaced in the last decade when it was realized that in addition to being a simple and relatively age-independent measure between the ages of 6 months and 5 years, it has an important role in identifying malnourished children at high risk of mortality. In 2009, the World Health Organization and United Nations International Children's Emergency Fund adopted MUAC <115 mm as a criterion for defining severe acute malnutrition.[2] Over next few years, more studies demonstrated that MUAC <115 mm predicts mortality equally or even better[3] than weight-for-height Z score < -3; and that it identifies a different subset of severely malnourished children than weight-for-height Z score < -3. So, now even when the precise age of child is known, MUAC is an important tool in assessing nutritional status of under-5 children. Applications of MUAC are further increasing with its potential role in identification of obesity; and malnutrition in children aged <6 months.

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Appendix

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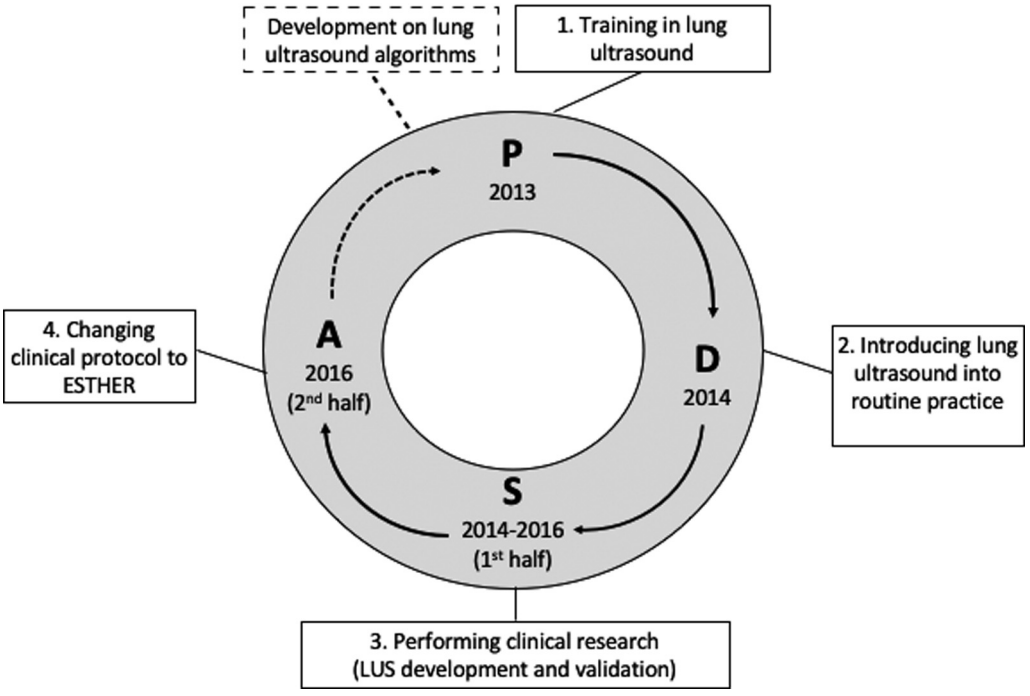

Figure 1. Pathway of the quality improvement project according to the Plan-Do-Study-Act cycle. *Black border boxes* represent main achievements of the process. The process was started in 2013 when we began to introduce lung ultrasound in our NICU. In 2014, we gradually adopted lung ultrasound as the first-line imaging technique for patients with signs of respiratory distress. Between the end of 2014 and the first half of 2016, we performed 2 diagnostic accuracy studies on semiquantitative lung ultrasound score.[6,7] Starting from July 2016, we changed our surfactant administration protocol, following results of these studies and the accumulated experience in lung ultrasound. The *last arrow* and *box* are hatched as they represent future possible improvements.