Bubble continuous positive airway pressure for children with severe pneumonia and hypoxaemia in Bangladesh: an open, randomised controlled trial

Mohammod J Chisti, Mohammed A Salam, Jonathan H Smith, Tahmeed Ahmed, Mark A C Pietroni, K M Shahunja, Abu S M S B Shahid, Abu S G Faruque, Hasan Ashraf, Pradip K Bardhan, Sharifuzzaman, Stephen M Graham, Trevor Duke

Summary

Background In developing countries, mortality in children with very severe pneumonia is high, even with the provision of appropriate antibiotics, standard oxygen therapy, and other supportive care. We assessed whether oxygen therapy delivered by bubble continuous positive airway pressure (CPAP) improved outcomes compared with standard low-flow and high-flow oxygen therapies.

Methods This open, randomised, controlled trial took place in Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh. We randomly assigned children younger than 5 years with severe pneumonia and hypoxaemia to receive oxygen therapy by either bubble CPAP (5 L/min starting at a CPAP level of 5 cm H_2O), standard low-flow nasal cannula (2 L/min), or high-flow nasal cannula (2 L/kg per min up to the maximum of 12 L/min). Randomisation was done with use of the permuted block methods (block size of 15 patients) and Fisher and Yates tables of random permutations. The primary outcome was treatment failure (ie, clinical failure, intubation and mechanical ventilation, death, or termination of hospital stay against medical advice) after more than 1 h of treatment. Primary and safety analyses were by intention to treat. We did two interim analyses and stopped the trial after the second interim analysis on Aug 3, 2013, as directed by the data safety and monitoring board. This trial is registered at ClinicalTrials.gov, number NCT01396759.

Findings Between Aug 4, 2011, and July 17, 2013, 225 eligible children were recruited. We randomly allocated 79 (35%) children to receive oxygen therapy by bubble CPAP, 67 (30%) to low-flow oxygen therapy, and 79 (35%) to high-flow oxygen therapy. Treatment failed for 31 (14%) children, of whom five (6%) had received bubble CPAP, 16 (24%) had received low-flow oxygen therapy, and ten (13%) had received high-flow oxygen therapy. Significantly fewer children in the bubble CPAP group had treatment failure than in the low-flow oxygen therapy group (relative risk [RR] 0·27, 99·7% CI 0·07–0·99; p=0·0026). No difference in treatment failure was noted between patients in the bubble CPAP and those in the high-flow oxygen therapy group (RR 0·50, 99·7% 0·11–2·29; p=0·175). 23 (10%) children died. Three (4%) children died in the bubble CPAP group, ten (15%) children died in the low-flow oxygen therapy group, and ten (13%) children died in the high-flow oxygen therapy group. Children who received oxygen by bubble CPAP had significantly lower rates of death than the children who received oxygen by low-flow oxygen therapy (RR 0·25, 95% CI 0·07–0·89; p=0·022).

Interpretation Oxygen therapy delivered by bubble CPAP improved outcomes in Bangladeshi children with very severe pneumonia and hypoxaemia compared with standard low-flow oxygen therapy. Use of bubble CPAP oxygen therapy could have a large effect in hospitals in developing countries where the only respiratory support for severe childhood pneumonia and hypoxaemia is low-flow oxygen therapy. The trial was stopped early because of higher mortality in the low-flow oxygen group than in the bubble CPAP group, and we acknowledge that the early cessation of the trial reduces the certainty of the findings. Further research is needed to test the feasibility of scaling up bubble CPAP in district hospitals and to improve bubble CPAP delivery technology.

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International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh (M J Chisti PhD, M A Salam MBBS, Prof T Ahmed PhD, K M Shahunja MBBS, A S M S B Shahid MBBS, A S G Faruque MPH, H Ashraf MD, P K Bardhan MD, Sharifuzzaman MBBS)**; Centre for International Child Health, The University of Melbourne Department of Paediatrics, Murdoch Children's Research Institute and Intensive Care Unit, Royal Children's Hospital, Melbourne, VIC, Australia** (M J Chisti, Prof S M Graham PhD, Prof T Duke FRACP)**; Portex Unit of Paediatric Anaesthesia, UCL Institute of Child Health, London, UK** (J H Smith FRCA)**; Public Health for South Gloucestershire, South Gloucestershire, UK** (Prof M A C Pietroni FRCP)**; and International Union Against Tuberculosis and Lung Disease, Paris, France** (Prof S M Graham)

Correspondence to:
Prof Trevor Duke, Centre for International Child Health, The University of Melbourne Department of Paediatrics, Murdoch Children's Research Institute and Intensive Care Unit, Royal Children's Hospital, Melbourne, 3052 VIC, Australia
trevor.duke@rch.org.au

Introduction

In 2010, an estimated 120 million episodes of pneumonia in children younger than 5 years old, and 14 million cases progressed to severe pneumonia, as defined by WHO.[1] In 2011, an estimated 1·3 million children died from pneumonia.[1] Hypoxaemia is a major risk factor for death in children with pneumonia,[2,3] and effective management of severe pneumonia and hypoxaemia is a major challenge for clinicians in developing countries.[4] In addition to antibiotics and supportive care, WHO recommends oxygen supplementation if the arterial oxygen saturation measured by pulse oximetry (SpO_2) is less than 90%, or if a child has cyanosis, is unable to feed, or shows other danger signs.[5] WHO recommends giving oxygen by nasal cannula at the following flow rates: 0·5–1 L/min for neonates, 1–2 L/min for infants and children younger than 2 years, and 2–4 L/min for children 2 years and older,[5] and improving oxygen therapy has been shown to reduce mortality from severe pneumonia in developing countries.[6] However, despite the provision of oxygen, antibiotics, and supportive care, case-fatality rates for severe pneumonia and hypoxaemia are high in many hospitals in developing countries (5–15% in observational studies).[7–14] We aimed to assess the role of other respiratory support, which could be given to the most severely ill children with pneumonia in resource-limited settings.

For the **trial protocol** see http://dspace.icddrb.org/dspace/bitstream/123456789/5348/1/icddrbrbprotocol-2011-PR10088.pdf

Continuous positive airway pressure (CPAP) is widely used for children with moderate or severe respiratory distress in intensive care units (ICU) in developed countries. The most common method to deliver CPAP is via a mechanical ventilator, which is not available in most health facilities in developing countries. However, bubble CPAP is possible using simple, low-cost material.[15] This method generates positive-end-expiratory pressure by connecting the expiratory limb of a breathing circuit to a tube, which is submerged in water. The distance that the distal end of the expiratory tube is under water is equivalent to the pressure (in cm H_2O) that will be generated in the upper airway if an adequate seal has been made in the patient interface and bubbles appear in the water bottle.[15] Modified nasal oxygen prongs can be used, making it minimally invasive and almost as easy for nurses to apply as standard flow oxygen therapy. Bubble CPAP has been used successfully in neonatal care in developed countries since the 1970s, and is promoted for its simplicity, low cost, and potential applicability for neonatal care in low-resource settings.[16,17] However, the efficacy of bubble CPAP has not been assessed for children with pneumonia in developing countries.[18]

Another popularised method of respiratory support beyond standard flow oxygen supplementation uses a humidified high-flow mixture of air and oxygen via a nasal oxygen cannula. This method has also been used effectively for neonatal respiratory distress, acute viral bronchiolitis, and other disorders in developed countries.[19–23] High-flow oxygen therapy has been shown to reduce the need for mechanical ventilation in ICUs, but as for bubble CPAP, has not been assessed in developing countries.

We aimed to assess whether respiratory support using bubble CPAP is more effective than standard low-flow oxygen therapy or high-flow oxygen therapy to reduce treatment failure or death in children with severe pneumonia.

Methods

Study design and patients

We did an open, randomised controlled trial of three methods of oxygen therapy for children with severe pneumonia and hypoxaemia in Bangladesh. Patients were treated with bubble CPAP, low-flow nasal cannula, or high-flow nasal cannula oxygen therapies in addition to WHO standard management of very severe pneumonia.

The study was undertaken at the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh. The ICU of this hospital manages about 600 children with severe pneumonia each year. The study was approved by the Research Review Committee and the Ethical Review Committee of the International Centre for Diarrhoeal Disease Research, Bangladesh (approval ID: PR 10088) and the Human Research Ethics Committee of the University of Melbourne (approval ID: 1135724). The trial protocol is available online.

Children were eligible for study enrolment if they were younger than 5 years, met clinical criteria for a diagnosis of severe pneumonia defined by WHO on the basis of cough, difficult breathing, and tachypnoea (central cyanosis, inability to breastfeed or drink, severe chest indrawing, tracheal tug, head nodding, grunting, and general danger signs [lethargy, reduced level of consciousness, and convulsions]),[5] and had hypoxaemia in room air, measured using a pulse oximeter (OxiMax N-600, Nellcor, Boulder, CO, USA). Children with severe respiratory distress or hypoxaemia (SpO_2 <90% in room air) were referred to the ICU.[5] We excluded children with known congenital heart disease, asthma, or upper-airway obstruction, and premature infants (unless their corrected age was 0 months or older). We also did not recruit children who already fulfilled the definition of treatment failure at presentation because they might have needed a higher level of respiratory support than those who did not have treatment failure. Written informed consent was obtained from a parent of the participating children before enrolling them in to the study.

Randomisation and masking

Patients were randomly assigned (1:1:1) to one of three groups: bubble CPAP, standard low-flow oxygen therapy, or high-flow oxygen therapy. The randomisation sequence was prepared before study commencement by an independent statistician at the International Centre for Diarrhoeal Disease Research, Bangladesh, who had no other involvement in the trial. Randomisation was done with use of the permuted block methods, using Fisher and Yates tables of random permutations.[24,25] A block size of 15 patients was constructed to reduce predictability and the probability of serious mid-block inequality in the planned interim analyses. The randomisation numbers were provided to the study investigators in sequentially numbered, sealed, opaque envelopes containing the name of the treatment on a card inside the envelope. The study physician opened the next numbered envelope when a patient had formally entered in to the trial after informed consent from parents or caregivers. After treatment allocation, the child was given their allocated therapy by the study physicians or study nurses; no-one who was involved in the care of the patient or the conduct of the study was masked to treatment assignment.

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Procedures

At enrolment, we recorded weight, presence of severe wasting (weight-for-length/height *Z* score of less than –3 of the WHO Child Growth Standards median) or nutritional oedema, severe anaemia (haemoglobin <50 g/L), severe sepsis, or convulsion. Venous blood was collected for bacterial culture and to measure serum glucose, sodium, and creatinine concentrations. Sepsis was defined as the presence or presumed presence of infection with hyperthermia or hypothermia (rectal temperature >38·5°C or <35·0°C, respectively) and tachycardia.[26] Severe sepsis was defined in the absence of dehydration or after correction of dehydration as sepsis plus the presence of poor peripheral perfusion (weak or absent peripheral pulses), and capillary refill time greater than 3 s or hypotension. Urine or stool culture was done as clinically indicated.

The bubble CPAP system was constructed locally using standard nasal oxygen prongs (Ventlab, Mocksville, NC, USA), tubing used for administration of intravenous fluids (Opso Saline, Dhaka, Bangladesh), and a water-filled, transparent shampoo bottle. Gas flow was provided by oxygen concentrators (Airsep Intensity, Buffalo, NY, USA) in most cases. The technique has been described in detail elsewhere.[15] The positive end-expiratory pressure provided by CPAP was started at 5 cm H_2O and increased up to 10 cm H_2O if the child was not responding.

Low-flow oxygen therapy was delivered directly from oxygen cylinders via nasal cannula. Flow rates of oxygen were 0·5–2 L/min for children younger than 2 years and 2–4 L/min for children 2 years of age and older, according to WHO recommendations.[5]

To deliver high-flow oxygen therapy, we used an oxygen concentrator (Airsep Intensity; modified by Diamedica, Bratton Fleming, UK) to provide a mixture of air and oxygen of 2 L per kg of bodyweight per min up to a maximum of 12 L/min. The high-flow oxygen was passed through a room-temperature water humidifier to prevent drying of nasal mucosa and delivered via nasal oxygen prongs, as previously described.[15]

In view of the high mortality associated with mechanical ventilation at Dhaka Hospital (protocol), we planned for children who had treatment failure on low-flow oxygen therapy to be given bubble CPAP or high-flow oxygen therapy as a second-line therapy after re-randomisation. If children fulfilled the criteria for clinical failure on bubble CPAP or high-flow oxygen therapies, they were put on mechanical ventilation.

All children received WHO standard management for very severe pneumonia, including parental ampicillin and gentamicin, nasogastric feeding or intravenous fluids if the child had very severe respiratory distress, and hourly monitoring of clinical signs of respiratory distress and SpO_2. The children also received treatment for comorbidities, including malnutrition, according to WHO guidelines.[5,27] Children who did not improve within 48–72 h of commencing first-line antibiotics were switched to second-line agents (a combination of ceftriaxone and levofloxacin, according to Dhaka Hospital protocol). All children were followed-up until 1 month after discharge or until death.

We recorded all adverse events, including signs of heart failure, convulsions, and nosocomial infection during treatment and follow-up. A data and safety monitoring board assembled before the study reviewed adverse events. All deaths and serious adverse events were notified to the data and safety monitoring board within 24 h. This included a detailed report provided by the study investigators containing clinical information, the timeline of illness and deterioration, and the treatments received. The data and safety monitoring board reviewed each death to identify any avoidable factors. As the trial participants could not be masked, the data and safety monitoring board was indirectly aware of the number of deaths in each treatment group. Safety outcomes were analysed by intention to treat.

Outcomes

The primary outcome was treatment failure, defined as two or more of the following criteria: severe hypoxaemia (SpO_2 <85%) after at least 30 min of study intervention; signs of severe respiratory distress, including moderate to severe chest wall in-drawing, tracheal tug, nasal flaring, or grunting respirations; and partial pressure of carbon dioxide greater than 60 mm Hg and pH less than 7·2 in capillary blood gas. Treatment failure was also declared if the child needed mechanical ventilation, died at any time during hospital stay or within 30 days of discharge, or left the hospital against medical advice. Secondary outcomes included length of hospital stay, nosocomial infections, rates of isolation of *Mycobacterium tuberculosis*, bacterial aetiology, and multiorgan failure at 7 days. A full list of secondary outcomes is presented in the protocol. Posthoc analyses included time to resolution of hypoxaemia, time to normalisation of age-specific respiratory rate, and time to normalisation of lower chest wall in-drawing. Time to resolution of hypoxaemia was defined as the number of hours from enrolment during which the child had SpO_2 of 90% or more while not receiving supplemental oxygen and was stable in room air for 24 h.

Statistical analyses

We based initial sample size calculations on data gathered at the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh, between January and October, 2010. 86 children with severe pneumonia and hypoxaemia were treated with low-flow oxygen therapy, and 26 (30%) fulfilled the study criteria for treatment failure (protocol). We based the sample size on a 40% relative reduction in treatment failure (from 30% to 18%) with bubble CPAP or high-flow oxygen therapy compared with low-flow oxygen therapy, with 90% power and an α error of 0·05 (two-sided test of

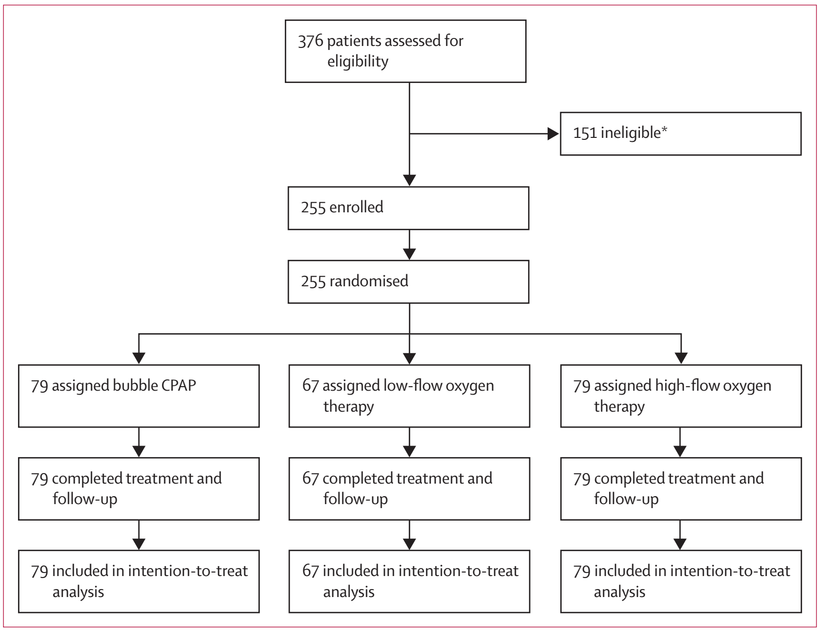

Figure 1: **Trial profile**
*Reasons for ineligibility are listed in the appendix.

	Total (n=225)	Bubble CPAP therapy (n=79)	Low-flow oxygen therapy (n=67)	High-flow oxygen therapy (n=79)
Age, months	7·0 (3·8–13·0)	9·0 (3·0–14·0)	7·5 (4·0–11·0)	6·5 (4·0–13·0)
Not breastfed (from birth or since neonatal period)	41 (18%)	10 (13%)	15 (22%)	16 (20%)
Severe wasting (<–3 *Z* score against weight for length)	49 (22%)	19 (24%)	12 (19%)	18 (23%)
Nutritional oedema	19 (8%)	6 (8%)	6 (9%)	7 (9%)
Diarrhoea	112 (50%)	40 (51%)	36 (54%)	36 (46%)
Some dehydration	24 (11%)	11 (14%)	4 (6%)	9 (11%)
Severe dehydration	13 (6%)	5 (6%)	4 (6%)	4 (5%)
Crackles on chest auscultation	211 (94%)	74 (94%)	63 (94%)	74 (94%)
Wheeze on chest auscultation	21 (9%)	8 (10%)	7 (10%)	6 (8%)
SpO_2 on enrolment, %	86% (82–88)	85% (81–88)	86% (82–88)	86% (82–88)
Convulsions	16 (7%)	8 (10%)	3 (5%)	5 (6%)
Severe sepsis or septic shock	17 (8%)	6 (8%)	5 (8%)	6 (8%)
Bacteraemia	27 (12%)	6 (8%)	10 (15%)	11 (14%)
Severe anaemia (haemoglobin <50 g/L)	3 (1%)	0	2 (3%)	1 (1%)
Pathogenic bacteria in stool culture	9/92 (10%)	4/32 (13%)	1/27 (4%)	4/33 (12%)
Bacterial growth in urine culture	10/68 (15%)	5/27 (19%)	4/23 (15%)	1/18 (4%)
Raised serum creatinine*	92 (41%)	33 (42%)	28 (42%)	31 (39%)
Hypoglycaemia (blood glucose <3 mmol/L)	3 (1%)	2 (3%)	0	1 (1%)
Hyponatraemia (serum sodium <130 mmol/L)	25 (11%)	8 (10%)	3 (5%)	14 (18%)
Hypernatraemia (serum sodium >150 mmol/L)	32 (14%)	13 (17%)	8 (12%)	11 (14%)

Data are n (%), n/N (%), or median (IQR). CPAP=continuous positive airway pressure. SpO_2=arterial oxygen saturation by pulse oximetry. *>36 μmol/L for infants aged <1 year; >66 μmol/L for children aged 1–5 years.

Table 1: **Baseline characteristics**

proportions), allowing for a 10% dropout rate. On this basis, 325 children were required in each group.

We analysed data with Epi Info (version 6) and Stata (version 12). We analysed treatment failure and death using χ^2 and Fisher's exact tests when the number in any cell of a 2×2 table was less than five. We calculated relative risks (RRs) and 99·7% CIs for the primary outcome and RRs and 95% CIs for secondary outcomes. We analysed continuous variables using the Mann-Whitney test. We calculated RRs and 95% CIs and used log-linear binomial regression to identify the predictors of treatment failure and death and to adjust the primary outcome and the secondary outcome of mortality, for the significant predictors of these adverse outcomes. Analysis was by intention to treat, and we made no post-hoc exclusions.

Interim analyses were planned after every 12 months. The threshold for discontinuing the trial in the interim analyses was a significant difference in the primary outcome (treatment failure) between the three treatment groups. Between August, 2011, and August, 2013, two interim analyses were reviewed by the data and safety monitoring board (appendix). In the first analysis (February, 2012), the board noted a higher proportion of patients with clinical failure in the low-flow oxygen therapy group than in the bubble CPAP and high-flow oxygen therapy groups combined. The board recommended that recruitment be temporarily stopped on Feb 15, 2012, in the low-flow oxygen therapy group pending external statistical advice, but that recruitment to the other groups should continue. Independent opinion was provided by a statistician from the University of Melbourne, Australia, who advised that it was not valid to stop the low-flow oxygen therapy group because the interim analyses required a lower p value than the final analysis. After the first interim analysis, the board recommended that the threshold to stop the trial at a second interim analysis should be $p<0·003$ for the primary outcome. Thus, the low-flow oxygen therapy group was reinstituted on May 16, 2012, by which time an additional 14 children had been enrolled in the bubble CPAP group and 13 in the high-flow oxygen therapy group. In July, 2013, after the board had reviewed a number of deaths, a second interim analysis was deemed necessary. The board asked the study investigators to present the interim analysis including the primary outcome and deaths at its meeting on Aug 3, 2013, by which time data were available for 225 trial participants. The board and investigators decided to stop the study because of the significantly higher number of deaths in the low-flow oxygen therapy group. We therefore present the 2 year study data involving all 225 participants. We present 99·7% CI for the unadjusted intention-to-treat primary outcome because the p value deemed to be significant at the second interim analysis was 0·003. The data and safety monitoring board recommended that we consider p value of less than 0·05 as significant for the

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secondary outcome of death, thus we present the 95% CI for secondary analyses.

The data and safety monitoring board oversaw the interim analyses. This study is registered with ClinicalTrials.gov, number NCT01396759.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 4, 2011, and July 17, 2013, 376 children younger than 5 years were admitted with severe pneumonia and hypoxaemia and assessed for eligibility. 151 (40%) children did not meet the study inclusion criteria (appendix). Of the 225 (60%) children who met the inclusion criteria and provided informed consent, 79 (35%) children were randomly allocated to receive bubble CPAP for provision of oxygen therapy, 67 (30%) to low-flow oxygen therapy, and 79 (35%) to high-flow oxygen therapy. All 225 children completed the allocated interventions and were included in analyses (figure 1).

Baseline characteristics of the patients, were generally similar between treatment groups, although hyponatraemia seemed more frequent in the high-flow oxygen therapy group than in the low-flow oxygen therapy group (table 1; appendix).

The median duration of respiratory support was 36 h (IQR 24–93) for bubble CPAP, 36 h (24–84) for high-flow oxygen therapy, and 42 h (24–96) for low-flow oxygen therapy. 120 (53%) children were switched from first-line to second-line antibiotics (appendix). 18 (8%) children received intravenous dextrose to correct hypoglycaemia, 49 (22%) received micronutrient supplementation for severe malnutrition, 21 (9%) received a blood transfusion, and 13 (6%) were treated for tuberculosis (appendix).

Across all treatment groups, 31 (14%) children had treatment failure and 23 (10%) children died (table 2, figure 2). Children who received bubble CPAP had a significantly lower risk of treatment failure than did those who received low-flow oxygen therapy (table 2). However, no difference in risk was noted between patients who received oxygen by bubble CPAP and high-flow nasal cannula (table 2). 26 (84%) of the 31 children who fulfilled the criteria for clinical failure were mechanically ventilated as rescue therapy, and 23 (88%) children died. Of the 16 children for whom low-flow oxygen therapy failed, eight were shifted to bubble CPAP for second-line treatment and eight were shifted to high-flow oxygen therapy (figure 2). Three (38%) of the eight children who received second-line bubble CPAP (and an additional child who failed bubble CPAP and was mechanically ventilated) survived, and two (25%) of eight children who received second-line high-flow oxygen therapy survived (figure 2). The proportion of children who died was significantly lower in the bubble CPAP group than in the low-flow oxygen therapy group (p=0·022). The proportion of children who died were similar in groups of patients receiving low-flow and high-flow oxygen therapy (table 2). No significant difference was noted in the number of deaths between patients in the bubble CPAP therapy group and the high-flow oxygen therapy group.

See Online for appendix

We noted no difference in time to resolution of hypoxaemia between the three treatment groups (table 3). Median time to normalisation of age-specific respiratory rates was shorter in children receiving oxygen through bubble CPAP than in those receiving low-flow oxygen (table 3).

Log-linear binomial regression analyses identified several independent risk factors for treatment failure and

	Total (n=225)	Bubble CPAP therapy (n=79)	Low-flow oxygen therapy (n=67)	High-flow oxygen therapy (n=79)	Bubble CPAP *vs* low-flow oxygen therapy		Bubble CPAP *vs* high-flow oxygen therapy	
					RR (99·7% CI)	p value	RR (99·7% CI)	p value
Total treatment failure*	31 (14%)	5 (6%)	16 (24%)	10 (13%)	0·27 (0·07–0·99)	0·0026	0·50 (0·11–2·29)	0·175
Clinical failure†	31 (14%)	5 (6%)	16 (24%)	10 (13%)	0·27 (0·07–0·99)	0·0026	0·50 (0·11–2·29)	0·175
Severe hypoxaemia (SpO_2 <85%)	31 (14%)	5 (6%)	16 (24%)	10 (13%)	..	..	..	..
Clinical signs of severe respiratory distress	35 (16%)	7 (9%)	16 (24%)	12 (15%)	..	..	..	..
PCO_2 >60 mm Hg and pH <7·2	1 (0·5%)	0	1 (2%)	0	..	..	..	..
Intubation or mechanical ventilation	26 (12%)	5 (6%)	11 (16%)	10 (13%)	0·39 (0·08–1·77)	0·052	0·50 (0·11–2·29)	0.175
Deaths	23 (10%)	3 (4%)	10 (15%)	10 (13%)	0·25 (0·07–0·89)	0·022‡	0·30 (0·09–1·05)	0·082
Left hospital against medical advice	0	0	0	0	..	..	..	..

Data are n (%). CPAP=continuous positive airway pressure. RR=relative risk. SpO_2=arterial oxygen saturation by pulse oximetry. PCO_2=partial pressure of carbon dioxide. *At least one of: clinical failure, intubation/mechanical ventilation, died, or left hospital against medical advice. †At least two of: severe hypoxaemia, severe respiratory distress, or PCO_2 >60 mm Hg and pH <7·2. ‡For deaths we calculated 95% CI.

Table 2: **Reasons for treatment failure, by treatment group**

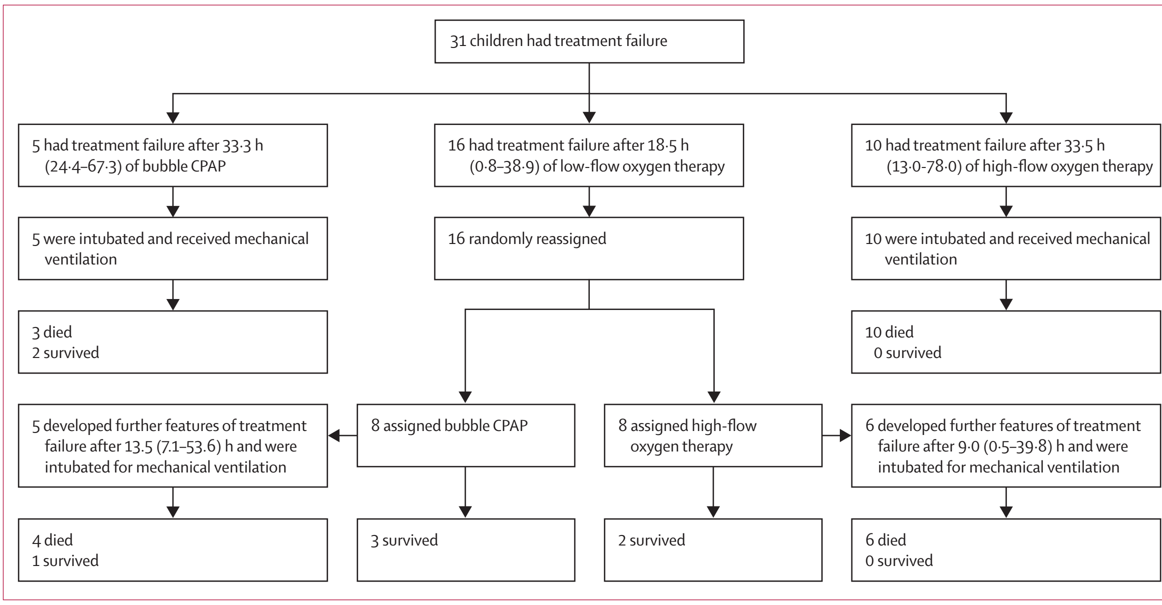

Figure 2: **Flow diagram of second-line treatment and survival in children who had treatment failure**
Data are median (IQR). CPAP=continuous positive airway pressure.

	Bubble CPAP therapy (n=79)	Low-flow therapy (n=67)	High-flow therapy (n=79)	Bubble CPAP *vs* low-flow oxygen therapy (p value)	Bubble CPAP *vs* high-flow oxygen therapy (p value)
Length of hospital stay, days	5 (3–7)	4 (3–7)	5 (3–7)	0·277	0·493
Duration of remission of hypoxaemia, h	36 (24–96)	42 (24–96)	36 (24–85)	0·773	0·479
Duration of normalisation of respiratory rate, h*	36 (24–96)	60 (36–96)	48 (24–72)	0·045	0·349
Duration of normalisation of lower chest wall in-drawing, h	60 (48–96)	72 (36–111)	72 (48–96)	0·838	0·743

Data are median (IQR). CPAP=continuous positive airway pressure. *Age-specific normal respiratory rates: children aged <2 months: <60 breaths per min; children aged 2–11 months: <50 breaths per min; children aged 12–59 months: <40 breaths per min.

Table 3: **Comparison of the secondary outcomes and post-hoc analyses, by treatment group**

death, including severe malnutrition, severe sepsis, convulsion, hypernatraemia, and bacteraemia. Despite adjusting for these potential confounders, children who received bubble CPAP had a significantly lower risk of treatment failure than did the other treatment groups (adjusted RR 0·29, 95% CI 0·12–0·70; p=0·005; appendix). In a similar analysis to explore potential confounding in the observed differences in death, the lower risk of death among children who received bubble CPAP remained (RR 0·22, 95% CI 0·07–0·68; p=0·008 after adjusting for other risk factors for death or treatment failure; appendix).

34 (15%) children developed clinical signs of heart failure, nine (4%) developed generalised convulsions, 17 (8%) developed hyponatraemia, and 28 (12%) developed hypernatraemia (appendix). Nine (4%) children developed abdominal distension, and 13 (6%) developed nosocomial infection. The rates of isolation of *M tuberculosis* and bacterial aetiology are reported in the appendix.

Discussion

Results of our randomised controlled trial in children with severe pneumonia in Bangladesh showed that fewer children who received bubble CPAP had treatment failure and death than did those who received standard low-flow nasal cannula oxygen therapy.

The recognition that hypoxaemia is the primary risk for mortality in children with pneumonia and the poor access to oxygen therapy in many settings has prompted calls for oxygen to be more widely available in developing countries. WHO has included oxygen on its list of essential medicines and provides guidelines for the use of oxygen therapy in pneumonia. However, even with the provision of oxygen, appropriate antibiotics, and other supportive care, mortality for severe pneumonia exceeds 10% in some hospitals. Mechanical ventilation is the cornerstone of intensive respiratory care in industrialised countries; however, in many developing countries, mechanical ventilation is not feasible, safe, or affordable. CPAP is in widespread use for the management of respiratory disease in neonates and children in industrialised countries. The methods of delivery can be expensive mechanical ventilators, almost all of which have a CPAP mode, or the much cheaper CPAP drivers. Bubble CPAP is an alternative method, which this and other studies have shown to be feasible in developing countries (panel).[29,30] CPAP has several mechanisms of action. In pneumonia, CPAP can reduce hypoxaemia by increasing functional residual lung capacity above alveolar closing capacity, thereby recruiting collapsed

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alveoli and reducing ventilation-perfusion mismatch. In bronchiolitis, CPAP reduces the work of breathing.[31,32] Positive end-expiratory pressure is not generated when standard low-flow oxygen therapy through nasal prongs is used, but can occur when a nasopharyngeal catheter is used to deliver oxygen.[33] A nasopharyngeal catheter can be an efficient way of delivering oxygen, but because the oxygen delivered bypasses the nasal turbinates, it must be humidified. Oxygen delivery through a nasopharyngeal catheter is associated with risks of gastric distension and cannula blockage and, in our experience, many nurses are reluctant to pass a nasopharyngeal catheter.

We stopped the trial before the projected sample size (n=325 in each treatment group) mainly because of a difference in number of deaths between treatment groups. Children receiving bubble CPAP oxygen therapy had a 75% (95% CI 11–93) lower probability of death and a 73% (99·7% CI 1–93) lower probability of treatment failure than children receiving standard low-flow oxygen therapy. We considered whether clinical differences between groups might have affected the differences in deaths and the primary outcome. However, after adjusting for all identifiable risk factors as potential confounders, the benefits of bubble CPAP remained significant. Case-fatality data from 2007 (case-fatality rate 21%)[27] and 2010 (27%; protocol) also suggest that the effect of bubble CPAP on mortality was substantial. The proportion of children who died (15%) in the low-flow oxygen therapy group of this trial was lower than mortality data previously reported at Dhaka Hospital,[28] possibly as a result of the benefit of being in a trial, overall improvements in quality of care over time, or differences in disease severity, but the proportion of children who received bubble CPAP who died (4%, 95% CI 2–12) was substantially lower than in the low-flow oxygen therapy group, despite a similar degree of severity at admission.

We acknowledge that to end a trial early might yield overestimates of the effect, especially if the trial is relatively small. Moreover, because the trial was done in a single centre, we do not claim that these results are definitive and applicable to all settings. However, in view of the much higher mortality in the low-flow oxygen therapy group than in the bubble CPAP group, we felt that it was unethical to continue recruiting patients to the low-flow oxygen therapy group in our centre. We felt that future patients at the International Centre for Diarrhoeal Disease Research, Bangladesh, should have the benefit of bubble CPAP as a standard rather than experimental therapy, and this is now implemented. We also acknowledge that two interim analyses of the primary outcome reduce the precision of the results, but we adjusted the p value on the primary outcome for this ($p<0·003$) and felt that doing annual interim analyses and having close oversight by the data and safety monitoring board were the best ways to undertake the trial, having the safety of patients and the ethical conduct of the study as major overriding principles.

Panel: Research in context

Systematic review

We searched Medline for reports published until March 31, 2014, in all languages, with the search terms "bubble cpap" OR "bubble continuous positive airway pressure" AND "child*" OR "paediatric" OR "Pediatric" OR "infant*" OR "neonate*". We also searched Medline with the search terms "high flow nasal cannula" OR "humidified high flow nasal cannula" AND "neonate" OR "Child*". For the treatment of severe pneumonia in developing countries, WHO recommends standard flow oxygen therapy using a nasal cannula, but in many hospitals, the mortality from severe pneumonia exceeds 10%. Results of a study[28] of 198 children with severe pneumonia admitted to the Dhaka Hospital ICU in 2007, showed that 108 (55%) children had hypoxaemia and that the case-fatality rate was high (21%) among the 108 children with severe pneumonia and hypoxaemia, despite the availability of appropriate antibiotics, oxygen therapy, and good nursing care. The authors of a systematic review of the use of bubble continuous positive airway pressure (CPAP) in neonates[16] in developing countries concluded, on the basis of a small number of studies, that bubble CPAP was safe and reduces the need for mechanical ventilation. Although the use of bubble CPAP for pneumonia in developing countries has been described,[28,29] no controlled trials of bubble CPAP have addressed clinical outcome such as treatment failure or mortality.

Interpretation

In our study involving Bangladeshi children with severe pneumonia and hypoxaemia, oxygen therapy delivered by bubble CPAP via oxygen concentrators was associated with a reduced risk of treatment failure and mortality compared with standard flow oxygen therapy. Further research is needed to improve the robustness of the concentrator technology in delivering CPAP and to assess effectiveness in different contexts and on a larger scale.

The trial did not conclusively show that bubble CPAP was better than high-flow oxygen therapy in terms of treatment failure because it was stopped early, before the required number of patients could be recruited. To continue the trial without the low-flow oxygen therapy group was considered by the investigators and the data and safety monitoring board, but would have required a sample size recalculation, and would thus be largely a new study. High-flow oxygen therapy is not easier to administer than bubble CPAP by the methods we used. So even if equivalence is ultimately shown in a much larger trial, the International Centre for Diarrhoeal Disease Research, Bangladesh, would probably not adopt high-flow oxygen therapy instead of bubble CPAP. However, we acknowledge that in other settings and with other delivery devices, preferences might differ and any differences in efficacy between the two therapies will remain uncertain until further research is done.

The initial sample size calculation was based on data from patients in the ICU of the Dhaka Hospital, International Centre for Diarrhoeal Disease Research, Bangladesh, in 2007 and 2010. At the time, standard oxygen therapy and, although not frequently used, a mechanical ventilator were the available types of respiratory support. The mortality for children needing mechanical ventilation at Dhaka Hospital in 2010 was high (21 [81%] of 26 children who received mechanical ventilation for severe pneumonia died). For this reason, the protocol recommended that children for whom low-flow oxygen therapy failed should have a trial of bubble CPAP or high-flow oxygen therapy before intubation and mechanical ventilation. We felt that to subject all children who reached clinical failure on low-flow oxygen therapy to mechanical ventilation would not give them the potential benefit of less invasive but higher level respiratory support. This decision was predicated on some of the reasons for the high mortality associated with mechanical ventilation, such as complications from mechanical ventilation in a resource-limited setting (low staff–patient ratio, unfamiliarity with the use of mechanical ventilation, nosocomial infection, endotracheal tube dislodgement, difficulties with sedation, and other supportive skills required for safe mechanical ventilation). The counter-argument that high mortality in the pre-study era was merely because of late initiation of mechanical ventilation, was also considered, but was not thought to be a probable major factor.

The bubble CPAP equipment used in our study was cheap and easy to use by nurses and doctors. The circuit was made locally using an oxygen cannula, intravenous tubing, and a shampoo bottle. Oxygen flow in the CPAP circuit and for high-flow oxygen therapy was provided with an oxygen concentrator. This delivered effective flows to generate CPAP and was sufficient for high-flow oxygen therapy for the entire duration of therapy in 97 (79%) patients. In 26 (21%) patients, the concentrator worked initially, but later failed to deliver sufficient gas flow to achieve bubbling and therefore failed to generate CPAP, or, in the case of high-flow oxygen therapy, caused a drop in flow to less than 2 L/kg per min. The median time to failure of the concentrator in 26 patients (13 patients in the bubble CPAP group and 13 in the high-flow oxygen group) was 22 h (12–79) for bubble CPAP and 24 h (19–108) for high-flow oxygen therapy. In these cases, we changed to oxygen provided from a central pipeline. All concentrators were checked by technicians, and none were found to have mechanical faults. After resting the concentrator for 6–12 h, it was again effective in generating flows sufficient for CPAP or high-flow oxygen therapy. We concluded that these failures were the result of machine fatigue. These apparent limits of oxygen concentrator technology mean that a back-up source of oxygen or gas flow is needed for safe and effective bubble CPAP or high-flow oxygen therapy. These limits also point to the need for improved oxygen concentrator technology if concentrators are to be more widely used for bubble CPAP.

CPAP drivers (ie, air flow pumps) can be used to deliver CPAP. CPAP drivers are effective for patients who only need additional airway pressure, such as patients with muscle weakness, hypoventilation, or upper airway obstruction. However, children with severe pneumonia have hypoxaemia because of ventilation-perfusion mismatching in the lungs. Opening of collapsed alveoli with air-driven CPAP might be effective, but patients with severe pneumonia often need to increase the fraction of inspired oxygen to avoid dangerous hypoxaemia. Most CPAP drivers do not come with an in-built oxygen source, so the model becomes complicated when treating both ventilation failure and severe hypoxaemia. We wanted to assess a method of bubble CPAP that could potentially be used to treat severe hypoxaemic pneumonia in district-level hospitals where oxygen cylinders or piped oxygen are often unavailable. Using oxygen concentrators and a bubble CPAP circuit provides stand-alone respiratory support, but in view of the limitations of current technology, a back-up oxygen source is needed.

The proportion of patients with severe malnutrition (22%), severe sepsis (8%), and other comorbidities in our study population means that the trial could be relevant to other developing countries with high child mortality and where children with severe pneumonia and hypoxaemia might present with such comorbidities.

Bubble CPAP therapy could be beneficial in hospitals in developing countries where the only respiratory support for treating childhood severe pneumonia and hypoxaemia is standard flow oxygen. The feasibility of scaling up bubble CPAP in district hospitals and improving simple technology to deliver bubble CPAP and oxygen awaits further research.

Contributors
TD, MJC, JHS, and MACP conceived the study and developed its design. Patient recruitment was done by MJC, JHS, TA, MACP, ASGF, PKB, S, KMS, ASMSBS, and MAS. MJC, TD, and MAS analysed the data. TD and MJC wrote the first draft of the report. TD, MAS, SG, MACP, and HA supervised the PhD research of MJC, on which this study was based. All authors contributed to the writing of the final version.

Declaration of interests
We declare no competing interests.

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