BMJ Open

Study protocol for a single-centre randomised controlled trial to investigate the effect of lung recruitment in paediatric patients after cardiac surgery

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ABSTRACT

Introduction A number of published studies have revealed that lung recruitment can improve oxygenation, shorten the duration of mechanical ventilation (MV) and decrease mortality in adults with acute hypoxaemic respiratory failure, especially patients with acute respiratory distress syndrome. However, few articles have assessed lung recruitment in paediatric patients, especially after cardiac surgery. This clinical trial aimed to determine whether lung recruitment can reduce the duration of MV in paediatric patients with hypoxaemic respiratory failure after cardiac surgery.

Method and analysis In this trial, we will randomly assign 234 paediatric patients (aged 28 days to 14 years) within 72 hours after cardiac surgery with an arterial oxygen tension (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (PaO_2/FiO_2) of <300 to either a lung recruitment group or a conventional group. The primary endpoint will be the duration of MV. The secondary endpoints will be ventilator-free days, PaO_2/FiO_2, respiratory system compliance, duration of non-invasive ventilation, reintubation rate, length of intensive care unit stay, length of hospital stay, occurrence of serious adverse events (barotrauma, persistent hypotension and arrhythmia), postoperative pulmonary complications.

Ethics and dissemination The ethics committee of West China Hospital of Sichuan University granted ethics approval for this study (20 August 2019). The results will be published in peer-reviewed journals and presented at conferences.

Trial registration number ChiCTR1900025990.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The protocol will be a randomised controlled trial, so the reliability of the results will be very high.
⇒ The incidence of hypoxaemic respiratory failure in paediatrics with congenital heart disease after surgery is low, and it will take a long time to achieve the expected sample size.
⇒ Because of lack of sufficient research data on lung recruitment in paediatrics, we do not know whether the methods, parameters of recruitment manoeuvre (RM) and the indications of repeat RM are reasonable, which may affect the outcome of patients.

INTRODUCTION

Hypoxaemic respiratory failure, especially acute respiratory distress syndrome (ARDS) after cardiac surgery, is the main cause of prolonged mechanical ventilation (MV). General anaesthesia, extracorporeal circulation, procedure-related lung injury and inappropriate ventilation strategies are risk factors for hypoxaemic respiratory failure in patients after cardiac surgery.[1] A recent prospective multicentre study diagnosed 10% of patients with ARDS after cardiac surgery.[2] Compared with adults, paediatric patients are more likely to suffer from hypoxaemic respiratory failure after cardiac surgery because of their anatomical and physiological characteristics.

Lung recruitment manoeuvres (RM) can prevent alveolar collapse, improve oxygenation and enhance respiratory system compliance by temporarily increasing transpulmonary pressure.[3] Over the past two decades, a number of studies have confirmed the effectiveness of lung recruitment for improving oxygenation, reducing the duration of MV and decreasing mortality in adults with hypoxaemic respiratory failure, especially those diagnosed with ARDS.[4–8] However, studies investigating the clinical use of lung recruitment in paediatric patients are limited. Although several studies have reported that lung RM combined with positive end-expiratory pressure (PEEP) titration can improve oxygenation and decrease the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) in paediatric patients with hypoxaemic respiratory failure, no studies have assessed the effectiveness of lung recruitment in reducing the duration of MV in paediatric patients after cardiac surgery.[9–19]

As a result, this single-centre study was designed to determine whether lung RM combined with PEEP titration can reduce the duration of MV and intensive care unit (ICU) stay, as well as all-cause mortality rate, in paediatric patients after cardiac surgery.

METHODS

Study setting

This study adopted a prospective, single-centre, parallel group, randomised, controlled design and is ongoing at West China Hospital of Sichuan University (January 2020 to December 2022). The ethics committee of West China Hospital of Sichuan University granted ethics approval (20 August 2019).

Eligibility criteria

The inclusion criteria are as follows: (1) paediatric patients after cardiac surgery whose cardiac anatomical deficiency was completely corrected after surgery; (2) paediatric patients aged 28 days to 14 years; (3) partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (PaO_2/FiO_2) of <300 with PEEP ≥5 cm H_2O within 72 hours after surgery.

The exclusion criteria are as follows: (1) paediatric patients deemed unsuitable for lung recruitment by the attending intensivist; (2) presence of an uncuffed endotracheal tube; (3) pneumothorax; (4) severe haemodynamic instability (requiring norepinephrine >0.2 μg/kg/min or epinephrine >0.2 μg/kg/min); (5) lack of consent from the next of kin; (6) diaphragmatic paralysis; (7) central nervous system complications; (8) raised intracranial pressure (>20 mm Hg); (9) bronchopleural fistula; (10) intracardiac shunt.

Participant selection and recruitment

Before identifying and screening patients for eligibility, all patients will be initially ventilated with synchronised intermittent mandatory ventilation-pressure control (SIMV-PC) using a Puritan Bennett 840 Ventilator (Covidien, Medtronic, Minneapolis, Minnesota, USA) for 30 min (figure 1). Then the first arterial blood gas analysis will be obtained. Specific ventilator settings are described in table 1. PetCO2, an index of $PaCO_2$, will be monitored using a carbon dioxide analyser. Informed consent will be obtained by the doctor in charge. All information will be transferred into an electronic database so that the trial office can monitor recruitment and refusal rates.

Intervention

The intervention group comprises patients who have undergone lung recruitment and PEEP titration. The control group comprises patients who have undergone conventional MV. Patients will be prospectively followed from the day of enrolment for at least 28 days or until discharge, whichever comes first.

In both groups, the ventilation and oxygenation goals are as follows: (1) arterial pH, 7.35~7.45; $PaCO_2$, 35–45
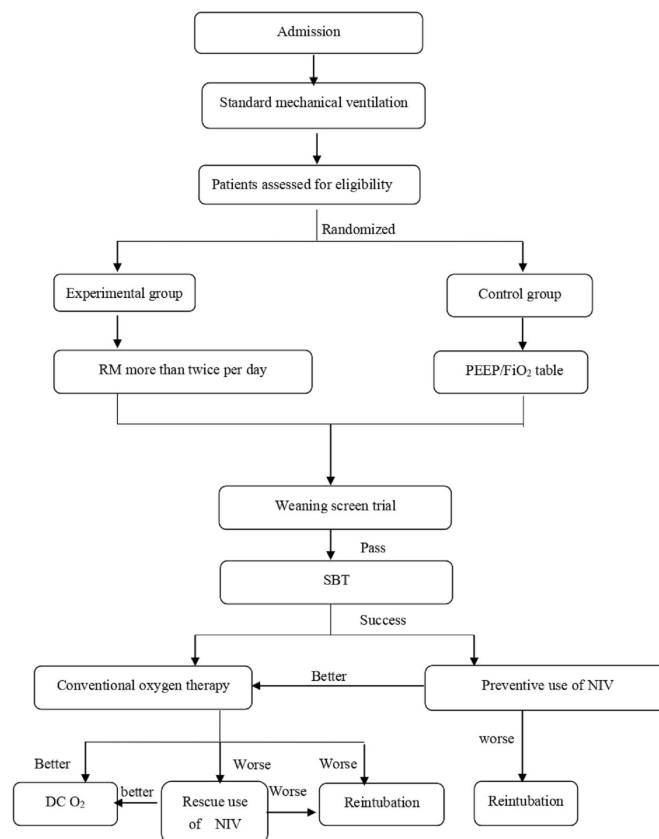

Figure 1 Enrolment and study protocol. FiO2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; RM, recruitment manoeuvre; SBT, Spontaneous Breathing Trials; NIV, non-invasive ventilation.

mm Hg; (2) SpO2, 92%–97% for patients with a PEEP <10 cm H_2O and 88%–92% for patients with a PEEP >10 cm H_2O. To prevent ventilator-induced lung injury, the general principle of ventilator setting includes limiting driving pressure to 15 cm H_2O, plateau pressure to 28 cm H_2O (allowing for slightly higher plateau pressures (29–32 cm H_2O) for patients with increased chest wall elastance), PEEP to 20 cm H_2O. In patients with severe hypoxaemia, FiO2 can be more than 60%.[20] High-frequency oscillatory ventilation (HFOV) should be considered as an alternative ventilatory mode in patients in whom plateau airway pressures exceed 28 cm H_2O in the absence of clinical evidence of reduced chest wall compliance. Extracorporeal Membrane Oxygenation (ECMO) may be considered in patients whose ventilation parameters have been maximised but still cannot achieve adequate gas exchange.[13]

In the conventional group, PEEP and FiO2 will be adjusted according to the PEEP-FiO2 table (table 2) to achieve the target SpO2 described above. In the lung recruitment group, RM and decremental PEEP titration will be performed immediately after enrolment and applied at least twice a day until extubation. RM will also be repeated if patients meet any of the following three conditions: (1) PaO_2 ≤60 mm Hg; (2) SpO2 ≤88%; (3) $PaCO_2$ >45 mm Hg. Additionally, physicians will apply routine care interventions for the general management

Table 1 Ventilator mode and initial settings

Age	Mode	F	Ti	Pi	Ps	FiO$_2$	PEEP	Vsens
4 weeks < age ≤ 1 year	SIMV-PC	30	0.67	12	10	50%	5	1
1 year < age ≤ 3 years	SIMV-PC	25	0.80	12	10	50%	5	1
3 years < age ≤ 12 years	SIMV-PC	20	0.86	12	10	50%	5	1
Age >12 years	SIMV-PC	15	1.0	12	10	50%	5	1

F, frequency; FiO$_2$, fraction of inspired oxygen ; PEEP, positive end-expiratory pressure ; Pi, inspiratory pressure above PEEP; Ps, pressure of support; SIMV-PC, synchronised intermittent mandatory ventilation-pressure control ; Ti, inspiratory time .

of critically ill patients, according to current guideline standards.

RM procedure

Patients will be placed in SIMV-PC mode with a fixed driving pressure of 15 cm H_2O above PEEP. Respiratory rate (RR), inspiratory time and FiO$_2$ will remain unchanged from baseline. Sequential RM will be performed, increasing PEEP by 5 cm H_2O every 2 min until a maximum PEEP of 20 cm H_2O. Then, PEEP will be decreased by 2 cm H_2O every 2 min when PEEP is >10 cm H_2O or by 1 cm H_2O every 2 min when PEEP is <10 cm H_2O. During the decremental phase of the manoeuvre, PEEP will be optimised to achieve better dynamic compliance (Cdyn) (decremental PEEP trial). Then, PEEP will be increased to 20 cm H_2O and maintained for 2 min. After RM, optimal PEEP will be set at the PEEP with the best Cdyn plus 2 cm H_2O, and the other parameters will be returned back to the previous level. Manoeuvres will be manually performed using the Puritan Bennett 840 Ventilator (Covidien, Medtronic, Minneapolis, Minnesota, USA) (figure 2). In our trial, RM will be performed by two respiratory therapists, one performing the procedure and the other monitoring the process.

Weaning from MV

All patients will follow the same analgesia and sedation protocols and treatment principles. Additionally, physicians will apply the same care interventions for general management of patients according to current guideline standards. Physicians will interrupt sedation once daily, and respiratory therapists will manage patients with the Spontaneous Breathing Trials (SBT) safety screen every morning. Patients who pass the SBT safety screen will undergo a 30 min SBT with a pressure support ventilation

of 5–7 cm H_2O, PEEP of 5 cm H_2O and FiO$_2$ of ≤40%. When the SBT safety screen is successful, physicians and respiratory therapists will extubate patients.[21]

Management of nasal continuous positive airway pressure

Patients considered high risk for failed extubation will receive preventative nasal continuous positive airway pressure (NCPAP) in the immediate post-extubation period. Risk factors for extubation failure are as follows: (1) decreased left ventricular systolic function; (2) refractory atelectasis; (3) O-shaped tracheal cartilage and airway stenosis caused by cardiac expansion; (4)>20% decrease in PaO$_2$ after SBT. Patients without these risk factors will receive conventional oxygen therapy, shifting to Noninvasive ventilation (NIV) if any of the following five indications appear: (1) mild-to-moderate dyspnoea, retraction or accessory muscle use, grunting, nasal flaring, head bobbing; (2) abnormal outcomes on arterial blood gas analysis (pH <7.35, PaCO$_2$ >45 mm Hg (1 mm Hg=0.133 kPa), or PaO$_2$/FiO$_2$<250 mm Hg); (3) SpO$_2$ <92% with
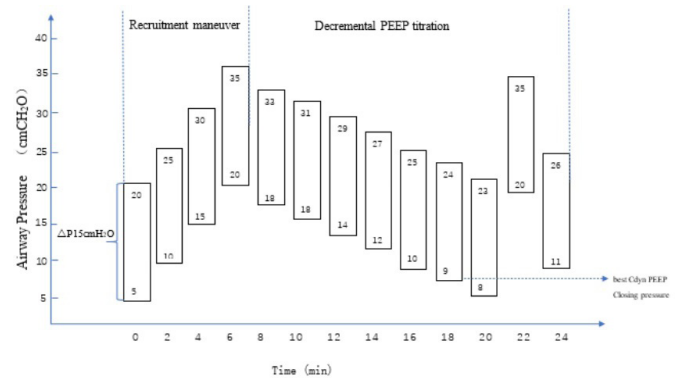
Figure 2 Recruitment manoeuvre (RM) procedure. The RM will be performed in synchronised intermittent mandatory ventilation-pressure control mode with a fixed driving pressure of 15 cm H_2O above positive end-expiratory pressure (PEEP). PEEP will be increased by 5 cm H_2O every 2 min to a maximum of 20 cm H_2O. During the decremental phase of the RM, PEEP will be optimised to achieve better dynamic compliance (Cdyn; decremental PEEP trial). The PEEP with the best Cdyn is called the closing pressure. After the decremental PEEP trial, the RM will be repeated with a PEEP of 20 cm H_2O and a DP of 15 cm H_2O. The optimal PEEP will be the closing pressure plus. 2 cm H_2O. For example, figure 2 shows that the PEEP with the best Cdyn is 9 cm H_2O. Thus, PEEP will be set to 11 cm H_2O.

Table 2 PEEP-FiO$_2$ table

FiO$_2$	PEEP	Adjustment
FiO$_2$ ≤40%	PEEP ≤8 cm H_2O	Increase in PEEP or FiO$_2$
	PEEP >8 cm H_2O	Increase in FiO$_2$
FiO$_2$ >40%	PEEP ≤8 cm H_2O	Increase in PEEP
	PEEP >8 cm H_2O	Increase in FiO$_2$

FiO$_2$, fraction of inspired oxygen ; PEEP, positive end-expiratory pressure .

Table 3	Rapid respiratory rate based on ages
Age (years)	Respiratory rate (breaths per min)
<1	>60
1–2	>45
2–5	>40
>5	>35

supplemental O_2; (4) requiring an oxygen flow of >2 L/min; (5) tachypnoea, RR of >50 breaths per min (<1 year old) or RR >40 breaths per min (1–4 years old).[22–24]

In the initial stage of NCPAP, patients will receive continuous positive airway pressure (CPAP) at 4–6 cm H_2O and a total flow of either 6–12 L/min (infants) or 8–20 L/min (paediatrics) depending on their age. CPAP, FiO_2, and total flow will be adjusted to achieve target oxygenation and ventilation goals, as described above. If SpO_2 is <92%, CPAP will be increased by 1–2 cm H_2O (maximum, 10 cm H_2O) and FiO_2 by 0.05–0.10 per increment. For patients with a SpO_2 of >97%, FiO_2 will be decreased first by 0.05 per decrement until FiO_2 is <0.35. If SpO_2 is still >97%, CPAP will be decreased by 1 cm H_2O per decrement. When a CPAP of 2–3 cm H_2O combined with a FiO_2 <0.35 is sufficient to maintain target oxygenation and ventilation goals, patients will be switched to conventional oxygen therapy.

Indications for reintubation are as follows: (1) respiratory acidosis (pH <7.35 and $PaCO_2$ >45 mm Hg, or an increase in $PaCO_2$ of >15% compared with pre-extubation level); (2) hypoxaemia (FiO_2 >50%, PaO_2 <60 mm Hg or SpO_2 <90%); (3) rapid RR as defined in table 3; (4) respiratory fatigue and severe dyspnoea; (5) inability to maintain the natural airway; (6） persistent respiratory acidosis, hypoxaemia, dyspnoea even on NCPAP/NIV.[25]

Patients with occurrence of the first indication, the second indication or any other two indications will be reintubated.

Patient termination and withdrawal criteria

At any time, the next of kin can retreat patients from the study. Patients may be withdrawn from the study because of: (1) severe adverse events (barotrauma, arrhythmia and cardiac arrest); or (2) violating or deviating from the protocol; or (3） severe hypoxaemia who meet the indication of ECMO or HFOV. If a patient is withdrawn for one of the three reasons mentioned, security analysis will be implemented.

Outcomes

The primary outcome is the duration of MV. The duration of MV refers to the time between admission to the ICU and extubation (hours). The secondary endpoints include PaO_2/FiO_2 (mm Hg), respiratory system compliance, duration of non-invasive ventilation (from the initiation to the weaning, hours), reintubation rate in 48 hours after extubation, length of ICU stay (from the admission the ICU to discharge from ICU, days), length of hospital stay (from the admission the hospital to discharge from hospital, days), occurrence of serious adverse event (barotrauma, arrhythmia and cardiac arrest), postoperative pulmonary complications (respiratory infection, respiratory failure, pleural effusion, pneumothorax, atelectasis, bronchospasm, etc). Before recruiting subjects, ventilator-free days through day 28 was added as a secondary outcome measure based on the lung recruitment studies in adults with ARDS and reviewers' opinions (If the patient dies before 28 days, ventilator-free days equals 0; If the patient is successfully weaned from MV within 28 days, ventilator-free days equals (28 -X); If the patient requires MV for 28 days or more; ventilator-free days equals 0).

Sample size

The duration of MV following cardiac surgery vary substantially across hospitals.[26] At the same time, no previous studies can be used as a reference. According to the information system data of healthcare before and after the implementation of RM in our paediatric intensive care unit (PICU) (2019 vs 2020), the average duration of MV in paediatrics after cardiac surgery was 16 hours and 11 hours, respectively. The study sample size was calculated on the basis of an expected 11 hours of MV in the lung recruitment group and 16 hours in the conventional group. Allowing for a 10% dropout rate, 117 patients are required for each group. After reviewing multiple adult lung recruitment studies, we conclude that the sample size of 234 cases will be sufficient.[5 27 28]

Randomisation

Patients will be randomised in a 1:1 ratio to a conventional group or to a lung recruitment group. The random allocation list was generated by a statistician with no clinical involvement in the trial using a computer-generated random number list. Then the statistician will use sequentially numbered containers to implement the random allocation sequence, and the treatment allocation group will be hidden beyond the coated card in the container. For patients who meet the required criteria, the investigator will open a randomised card that records the treatment allocation group. Hence, treatment allocation will be concealed.

Patient and public involvement

No patient and public involved.

Data collection and inspection

The principal investigators will centralise all data weekly and examine the accuracy of these data to promote data quality. Data collection for each patient will begin on the day that informed consent was received from the patient and will continue until the patient is discharged or transferred to another hospital. Data will be collected using a paper-based case report form (see online supplemental files 1–3) and an electronic database. Investigators will follow a schedule for data collection, including: (1) screening data, informed consent, demographic data,

inclusion and exclusion criteria and enrolment data; (2) baseline information (age, sex, ID, height, weight, diagnosis, type of surgery, pulmonary infection, airway stenosis, pulmonary hypertension, duration of cardio-pulmonary bypass, Paediatric Risk of Mortality score, Risk Adjustment in Congenital Heart Surgery score, Vasoactive-Inotropic Score, antibiotic therapy); (3) daily information on cardiovascular system (heart rate, blood pressure, central venous pressure, urine output, dosage of vasoactive agents), respiratory system (ventilator settings, PaO_2, $PaCO_2$, lung compliance), infection (white blood count, procalcitonin, C-reactive protein, interleukin-6), liver function (bilirubin, alanine aminotransferase, aspartate aminotransferase, albumin), renal function (urea nitrogen, creatinine); (4) prognosis: time of admission to ICU, extubation, initiation of NIV and reintubation, date of transferring out of the ICU and date of discharge/death, whichever comes first.

Adverse events

RM-related adverse events include transient hypotension (4 weeks to 1 year SBP <65 mm Hg, 1 year to 4 years SBP <70 mm Hg, 5 years to 12 years SBP <80 mm Hg, >12 years SBP <90 mm Hg), hypoxaemia (SpO_2 <84%) for more than 1 min, and heart rate decreased or increased by more than 20% of the base value. RM won't be continued in those patients with adverse events and will be started again at another time. Severe adverse events include barotrauma (such as, pneumothorax, subcutaneous emphysema, mediastinal emphysema, interstitial emphysema), arrhythmias and cardiac arrest and so on. If severe adverse events happen, patient will be retreated from RM group. All patients who will receive RM will be monitored for blood pressure, SpO_2 and ECG, and will receive physical examination to assess barotrauma in real time. If necessary, lung ultrasound or chest imaging can be performed during or after the RM. Researchers will record and report adverse events and severe adverse events timely, at the same time, appropriate treatment for those adverse events will be prescribed to patients.

DATA ANALYSIS

Descriptive statistics will be expressed as mean±SD or median and IQR depending on the nature and distribution of the variables. Inferential statistics will use estimates of the mean of the differences and their 95% CIs. Variables normally distributed will be compared with the Student's t-test. For variables without a normal distribution, the Mann-Whitney U rank test will be used for comparison. Categorical variables will be compared using Fisher's exact test. The primary outcome variable (total duration of MV) and ventilator-free days through day 28 will be assessed with the Student's t-test or the Mann-Whitney U rank test dependent on the distribution of the data. The relative risks and their 95% CIs will be estimated. For all these comparisons, we will consider a difference to be statistically significant if p<0.05.

Safety and quality control

Recent studies have demonstrated the efficacy and safety of lung recruitment performed by incremental and decremental PEEP.[8 10 11] The study applicants and other primary investigators performed detailed and rigorous lung recruitment, which was applied to more than 200 patients at our PICU. Each patient demonstrated an increase in PaO_2, improved lung compliance and a decrease in PaO_2, while none of them showed pneumothorax, subcutaneous emphysema or other complications.

ETHICS AND DISSEMINATION

The protocol has been registered at the Chinese Clinical Trial registry. Any revisions to the protocol will be documented in the ClinicalTrials.gov registry. Written informed consent has and will be obtained from all patients. All included patients will be able to access and correct the data. In the event of additional studies from the database, all investigators will keep the results confidential until publicly available, and they will not publish any data related to the database without approval of the principal investigator. We will publish the results of this trial in peer-reviewed clinical journals and present the findings at conferences for widespread dissemination.

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Patient demographics

patient ID _____ age _____ sex   male□ female□

body weight _____ kg height _____ cm ethnic   _____

Preoperative data

diagnosis   _____

pulmonary infec yes□ no□   pulmonary a □yes   (mild /moderate /s□no _____

airway stenosis   yes□ no□

difficulty airway yes□ no□

Operative data

operative route middle incisi lateral incision□

bypass time,mins _____

Circulatory arres yes□   no□

Use of bloodpro yes□( )   ml no□

postoperative P/F(mmHg) _____   _____

ICU Admission

time _____ surgery   _____

diagnosis   _____

PRISM score _____ RACHS score _____

 VIS score in 24 hours _____

  (VIS score= dopamine + dobutamine + 100 × epinephrine + 10 × milrinone + 10 000 ×

 Pituitrin+ 100 × nonepinephrine)

lowest P/F ,mmHg _____

Patient demographics

patient ID _____ age _____ sex male☐ female☐

body weight _____ kg height _____ cm ethnic _____

Preoperative data

diagnosis _____

pulmonary infec yes☐ no☐   pulmonary a☐yes (mild /moderate /s☐no _____

airway stenosis yes☐ no☐

difficulty airway yes☐ no☐

Operative data

operative route middle incisi⟨lateral incision☐

bypass time,mins _____

Circulatory arres yes☐   no☐

Use of bloodpro yes☐( )   ml no☐

postoperative P/F(mmHg) _____   _____

ICU Admission

time _____ surgery _____

diagnosis _____

PRISM score _____ RACHS score _____

 (VIS score in 24 hours)

 (VIS score= dopamine + dobutamine + 100 × epinephrine + 10 × milrinone + 10 000 ×

 Pituitrin+ 100 × nonepinephrine)

lowest P/F ,mmHg _____

	D0	D1	D2	D3	D4
Date					
Circulatory system					
HR（beat/min）					
BP（mmHg）					
mean BP（mmHg）					
CVP（mmHg）					
fluid input（ml）					
fluid output（ml）					
dopamine μg/（kg·min）					
milrinone μg/（kg·min）					
epinephrine μg/（kg·min）					
nonepinephrine μg/（kg·min）					
pituitrinμg/（kg·min）					
Respiratory system					
ventilation mode					
f（/min）					
Pi（cmH$_2$O）					
PEEP（cmH$_2$O）					
FiO$_2$					
PaO$_2$					
PaO$_2$/FiO$_2$					
SaO$_2$					
Laboratory examination					
ABG					
pH					
PaO$_2$（mmHg）					
PaCO$_2$（mmHg）					
BE					
HCO$_3^-$（mmHg）					
Lac（mmol/L）					
Infectious index					
WBC（X10^9）					
PCT					
CRP					
Liver function					
bilirubin					
ALT					
AST					
ALB（g/L）					

Supplemental material

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Renal function
BUN
CREA （umol/L）
Blood routine examination
Plt
Hb （g/L）

	D0	D1	D2	D3	D4
date					
Etiological data					
positive sputum culture	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
pathogen					
Respiratory virus test					
influenza a virus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
adenovirus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
Bocavirus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
rhinovirus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
H1N1	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
Parainfluenza viru	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
chlamydia	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
Human metapneumovirus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
influenza B virus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
Mycoplasma pneumoniae	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
H3N2	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
coronavirus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
respiratory syncytial virus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
TORCH	yes☐ no☐				
tomegalovirus antibody Ig	yes☐ no☐				
Rubella virus antibody IgM	yes☐ no☐				
lex virus antibody type I/II	yes☐ no☐				
oplasma antibody(Tox-Ab)	yes☐ no☐				
Imaging finding					
new or progressive infiltra	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
Body temperature（℃）					
highest body temperature					
lowest body temperature					

	D5	D6	D7	D8	D9
Date					
Circulatory system					
HR （beat/min）					
BP （mmHg）					
mean BP （mmHg）					
CVP （mmHg）					
fluid input （ml）					
fluid output （ml）					
dopamine μg/（kg·min）					
milrinone μg/（kg·min）					
epinephrine μg/（kg·min）					
nonepinephrine μg/（kg·min）					
pituitrin μg/（kg·min）					
Respiratory system					
ventilation mode					
f （/min）					
Pi （cmH$_2$O）					
PEEP （cmH$_2$O）					
FiO$_2$					
PaO$_2$					
PaO$_2$/FiO$_2$					
SaO$_2$					
Laboratory examination					
ABG					
pH					
PaO$_2$ （mmHg）					
PaCO$_2$ （mmHg）					
BE					
HCO$_3^-$ （mmHg）					
Lac （mmol/L）					
Infectious index					
WBC （X10^9）					
PCT					
CRP					
Liver function					
bilirubin					
ALT					
AST					
ALB （g/L）					

Supplemental material

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BMJ Open

Renal function
BUN
CREA（umol/L）
Blood routine examination
Plt
Hb（g/L）

	D5	D6	D7	D8	D9
date					
Etiological data					
positive sputum culture	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
pathogen					
Respiratory virus test					
influenza a virus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
adenovirus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
Bocavirus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
rhinovirus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
H1N1	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
Parainfluenza viru	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
chlamydia	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
Human metapneumovirus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
influenza B virus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
Mycoplasma pneumoniae	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
H3N2	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
coronavirus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
respiratory syncytial virus	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
TORCH		yes☐ no☐			
tomegalovirus antibody Ig					
Rubella virus antibody IgM					
lex virus antibody type I/II					
oplasma antibody(Tox-Ab)					
Imaging finding					
new or progressive infiltra	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐	yes☐ no☐
Body temperature（℃）					
highest body temperature					
lowest body temperature					