THE LANCET
Respiratory Medicine

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Kneyber MCJ, Khemani RG, Bhalla A, et al. Understanding clinical and biological heterogeneity to advance precision medicine in paediatric acute respiratory distress syndrome. *Lancet Respir Med* 2022; published online Dec 22. https://doi.org/10.1016/S2213-2600(22)00483-0.

Table: **Ongoing intervention and observational studies in PARDS**

	Study type	Sample size	Eligibility criteria	Intervention or assessment	Key outcomes	Status
Paediatric ARDS Neuromuscular Blockade Study (PAN; NCT02902055)	Multicentre, double-blind, phase 4 RCT	178	Age <5 years; need for mechanical ventilation with tidal volume 5–8 mL/kg ideal bodyweight and PEEP ≥5 cm H_2O; early moderate-to-severe PARDS (OI ≥12 or OSI ≥9·09) originating from any cause; within 48 h of PICU admission	Continuous neuromuscular blockade (rocuronium 1 mg/kg per h) *vs* placebo for 48 h	Cumulative respiratory morbidity score 1 year after PICU discharge	Recruiting (estimated study completion date: May 1, 2024)
Real-Time Effort Driven Ventilator Management (REDvent; NCT03266016)	Single-centre, single-blind, phase 2 RCT	276	Age >1 month to ≤18 years; supported on mechanical ventilation with PARDS (pulmonary parenchymal disease; OI ≥4 or OSI ≥5); within 48 h of initiation of invasive mechanical ventilation	Ventilator management using a CDS tool for lung and diaphragm protection *vs* usual care	Duration of weaning (up to 28 days)	Recruiting (estimated study completion date: June 30, 2023)
Identifying PARDS Endotypes (NCT03539783)	Single-centre case-control study	60 (30 intubated patients with PARDS, 30 patients with non-lung injury-related conditions)	Age 1 month to 18 years; admitted to the PICU with expected duration of ≥7 days; PARDS group intubated with acute changes on chest x-ray, OI ≥4 or OSI ≥5, and known or suspected insult consistent with ARDS within 7 days; control group admitted with non-lung injury-related conditions	Bronchial epithelial cell brushing for gene-expression profiling	Identification of PARDS endotypes using unbiased cluster analysis of gene expression	Recruiting (estimated study completion date: March 31, 2025)
Long Term Follow up of Children Enrolled in the REDvent Study (NCT03709199)	Single-centre, prospective observational follow-up study	240	Enrolled in REDvent	Ventilator management using a CDS tool for lung and diaphragm protection *vs* usual care	Ventilation inhomogeneity using lung clearance index with nitrogen washout 6 months after ICU discharge; neurocognitive function (Batelle-2 or WISC-5 cognitive tests) 3 months after ICU discharge; health-related quality of life (PedsQL) 3 months after ICU discharge; functional status scale 3 months after ICU discharge	Recruiting (estimated study completion date: March 1, 2024)
Prone and Oscillation Pediatric Clinical Trial (PROSpect; NCT03896763)	Multicentre, open-label, 2×2 factorial, response-adaptive RCT	800	Age 2 weeks to 20 years; intubated and mechanically ventilated with moderate-to-severe PARDS* for <48 h	CMV *vs* HFOV; prone *vs* supine positioning	Ventilator-free days at day 28	Enrolling by invitation (estimated study completion date: July 31, 2026)

Clinical Decision Support Tool in PARDS Pilot Study (NCT04068012)	Multicentre observational study	180	Age >1 month to ≤18 years; supported on mechanical ventilation with pulmonary parenchymal disease and OI ≥4 or OSI ≥5; within 72 h of initiation of invasive mechanical ventilation and expected to require >72 h mechanical ventilation	Ventilator management using a CDS tool for lung and diaphragm protection and to guide liberation from the ventilator	Implementation feasibility; protocol adherence	Recruiting (estimated study completion date: June, 2023)
Pediatric Acute Respiratory Distress Syndrome Asia Study (PARDSPROASIA; NCT04068038)	Multicentre, prospective cohort study	800	Age ≤21 years; on ventilatory support for PARDS*	Screening of all PICU admissions and collection of epidemiological and clinical data	Prevalence of PARDS; 60-day mortality; ventilator-free days at day 28;† ICU-free days at day 28;† requirement for ECMO†	Recruiting (estimated study completion date: Aug 1, 2023)
Linking Endotypes and Outcomes in Pediatric Acute Respiratory Distress Syndrome (LEOPARDS; NCT04113434)	Multicentre, prospective cohort study	500	Age 44 weeks to <17·5 years; admitted to PICU for acute (≤7 days of risk factor) respiratory failure requiring invasive mechanical ventilation; bilateral infiltrates on chest x-ray; OI ≥4 or OSI ≥5	Assessment of plasma protein biomarkers and peripheral blood gene expression	28-day mortality; presence of two or more PARDS endotypes using a 100-gene-expression-based classifier; occurrence of de-novo PARDS subphenotypes using 12 protein biomarkers and whole-genome transcriptomics of peripheral blood; ventilator-free days at day 28†	Recruiting (estimated study completion date: December, 2024)
Infants With Severe Acute Respiratory Distress Syndrome: The Prone Trial (NCT05002478)	Single-centre, open-label RCT	14	Age >36 weeks to <24 months; intubated and mechanically ventilated for ≥6 h and expected to require invasive ventilatory support for ≥12 h; severe PARDS (OSI ≥12·3); clinical picture strongly suggestive of acute bronchiolitis or pneumonia	Prone *vs* supine positioning after surfactant administration	Change in OSI at 6 h; change in lung ultrasound at 6 h;† change in distribution of end-expiratory lung volume at 6 h;† change in distribution of tidal volume at 6 h†	Recruiting (estimated study completion date: Dec 31, 2024)
Continuous Infusion Versus Intermittent Boluses of Cisatracurium in the Early Management of Pediatric ARDS (NCT05153525)	Single-centre, open-label, phase 4 RCT	60	Age 1 month to 18 years; within 48 h of PARDS diagnosis*	Intermittent boluses of cisatracurium *vs* intravenous infusion of cisatracurium for 24 h	Duration of mechanical ventilation (up to 10 days)	Recruiting (estimated study completion date: Aug 5, 2022)
ARDS in Children and ECMO Initiation Strategies Impact on Neurodevelopment	Multicentre, prospective cohort study (PROSpect ancillary study)	550 from the ELSO registry; 1000 from PROSpect	ECMO group: moderate-to-severe PARDS;‡ intubated and on ECMO for <7 days; bilateral lung disease on chest x-ray	ECMO *vs* protocolised therapies (CMV *vs* HFOV; prone *vs*	Change in functional status scale 1 year after PICU discharge; change in health-related quality of life (PedsQL) 1 year after PICU discharge; proportion with a new morbidity at	Recruiting (estimated study completion date: June, 2026)

(ASCEND; NCT05388708)			Protocolised therapy group: enrolled in PROSpect	supine positioning)	1 year after PICU discharge; all-cause mortality at hospital discharge or 90 days; change in paediatric overall performance category 1 year after PICU discharge;† change in paediatric cerebral performance category 1 year after PICU discharge†	
Endotypes in Children with Severe Acute Respiratory Distress Syndrome: Impact on Response to Treatment (ENSNARE)	Multicentre observational study (PROSpect ancillary study)	300	Enrolled in PROSpect	Assessment of plasma protein biomarkers and whole-blood genome-wide gene expression; latent class analysis to relate expression profiles to treatment responses	Identification and characterisation of endotypes using latent class analysis and gene-expression profiling; assessment of differences in outcomes and responses to treatment between PARDS endotypes; identification of potential pathways involved in differences between endotype outcomes and response to treatment	Recruiting (estimated study completion date: June, 2026)
Microbiome and Nutrition in Severe PARDS Trial (MANTIS)	Multicentre observational study (PROSpect ancillary study)	800	Enrolled in PROSpect	Stool and endotracheal aspirate sampling for assessment of gut and lung microbiomes	Relationship between early enteral nutrition exposure and butyrate-producing faecal bacteria, faecal butyrate, and patient outcomes; relationship between faecal short-chain fatty acids and lower respiratory tract inflammation, acute lung injury, and innate immune cell gene-expression patterns	Recruiting (estimated study completion date: June, 2026)

ARDS=acute respiratory distress syndrome. CDS=computerised decision support. CMV=conventional mechanical ventilation. ECMO=extracorporeal membrane oxygenation. ELSO=Extracorporeal Life Support Organization. HFOV high-frequency oscillatory ventilation. ICU=intensive care unit. OI=oxygenation index. OSI=oxygen saturation index. PARDS=paediatric acute respiratory distress syndrome. PedsQL=Pediatric Quality of Life Inventory. PEEP=positive end-expiratory pressure. PICU=paediatric ICU. RCT=randomised controlled trial. WISC-5=Wechsler Intelligence Scale for Children—Fifth Edition. *Defined by PALICC criteria. †Secondary outcomes. ‡Defined by OI or OSI criteria in patients with bilateral lung disease on chest x-ray (one OI ≥16 or two OIs ≥12 and ≤16 at least 4 h apart, or two OSIs ≥10 at least 4 h apart, or one OI ≥12 and ≤16 and one OSI ≥10 at least 4 h apart).