Crystallise

Information Innovation

Rapid Review

Acute Respiratory Distress Syndrome in adults

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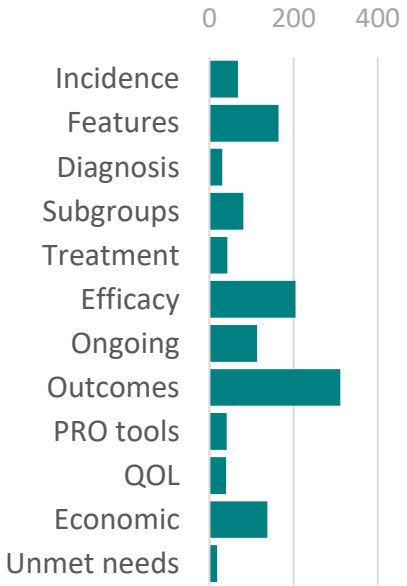
Research Questions

1. How much research has been published on ARDS?
2. What is the incidence/prevalence of ARDS in adults in Europe, North America and other countries?
3. What are the main symptoms, co-morbidities and natural history in patients with ARDS?
4. How is ARDS diagnosed/classified?
5. Are there clear subpopulations that are treated differently, or have differential severity?
6. What are the existing treatment options for ARDS?
7. What is the effectiveness of existing treatment options for ARDS?
8. What interventions are currently being investigated for ARDS and when are these studies due to complete?
9. What are the most common outcome measures reported, in RCTs and non-RCTs of ARDS?
10. What instruments have been used to measure quality of life, in patients with ARDS and their caregivers?
11. What is the impact of ARDS on quality of life in patients or caregivers?
12. What are the costs associated with ARDS?
13. What are the unmet needs of people with ARDS and their caregivers?

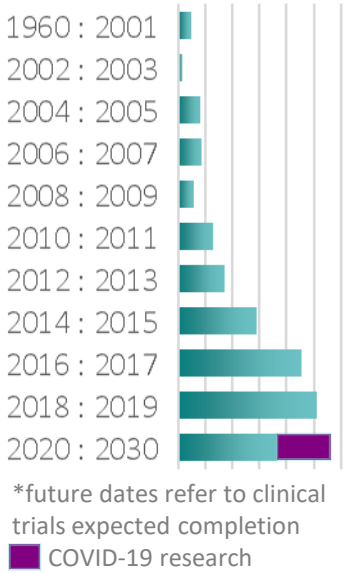
1. How much research has been published?

485 records were prioritised for inclusion in the Evidence Map

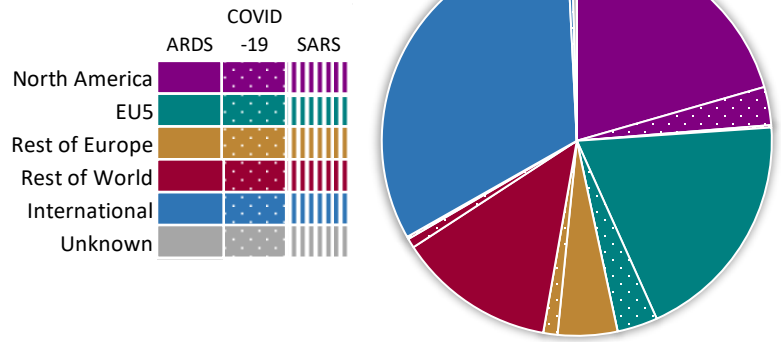
Records identified by topic:



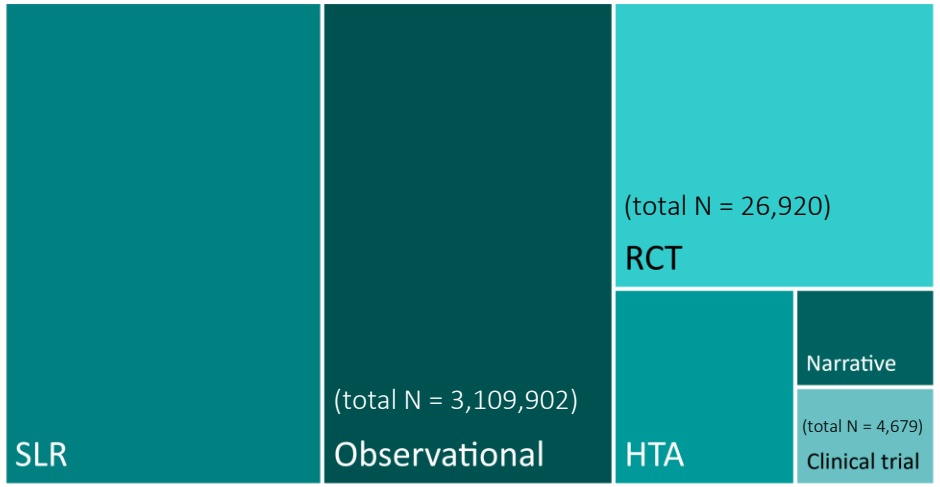
Records identified by publication date:



General study location:



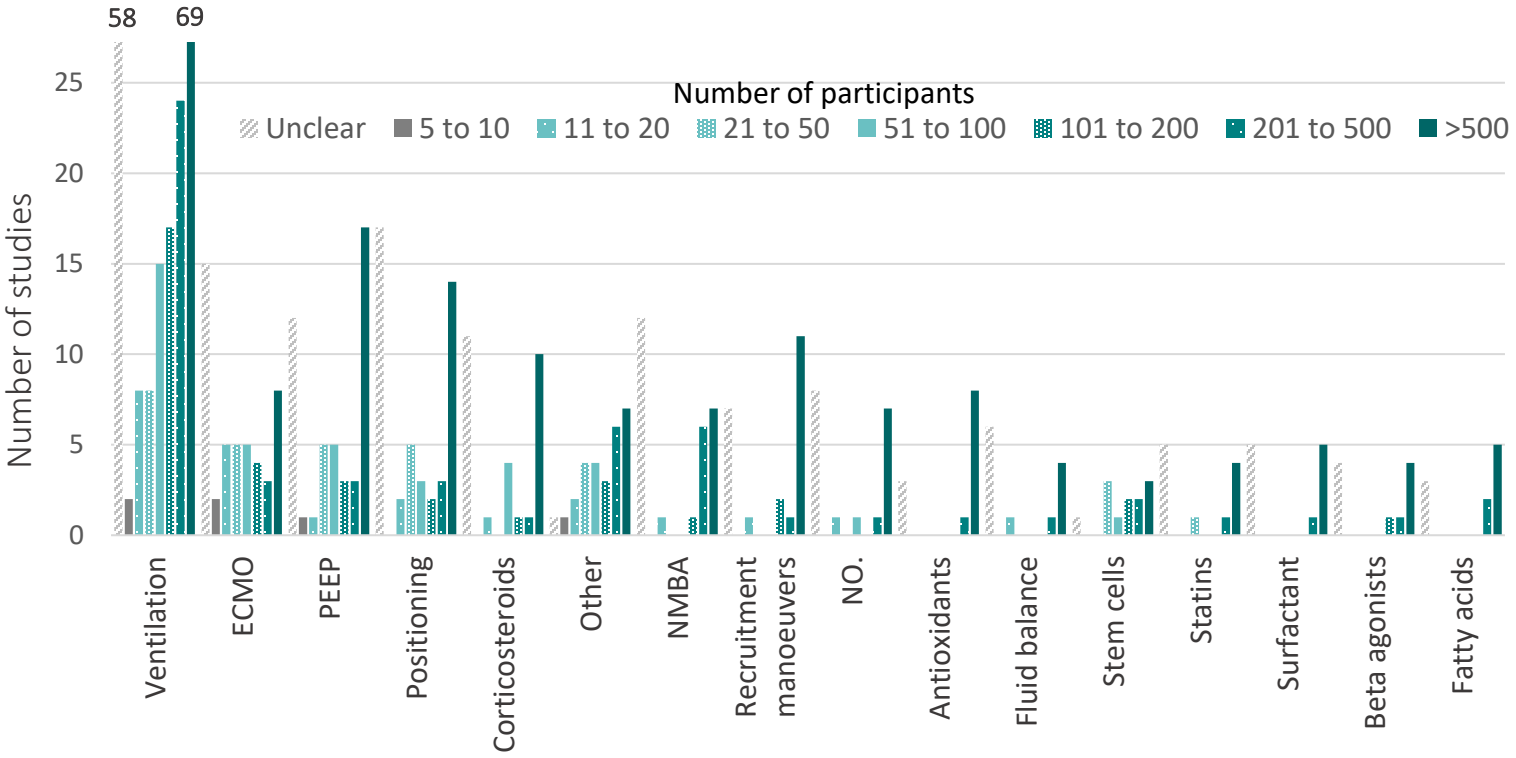
Study types:



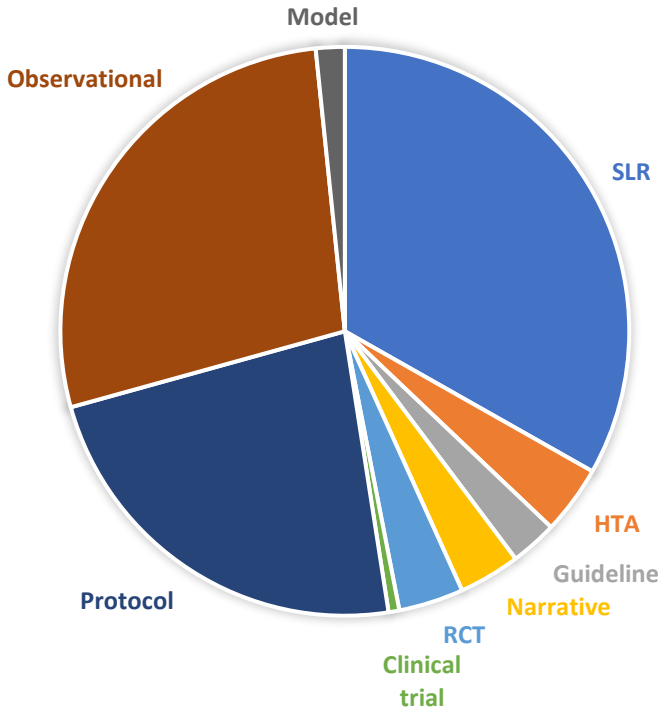
SLRs are indexed as International; Clinical trial = non-randomised intervention study; HTA = health technology assessment or guideline; Narrative = non-systematic review; QOL = quality of life studies; RCT = randomised controlled trial; SLR = systematic literature review

1. How much research is published?

Number of studies discussing each intervention for the treatment for ARDS:
(only the most common interventions are included in the graph)



Types of publications included:

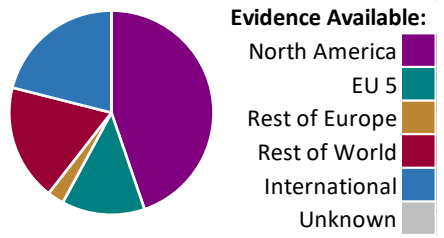


Other interventions evaluated but not included in the graph: angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, albumin, anakinra, anticoagulants, antifungals, antiplatelets, aviptadil, bimosiamose, BIO-11006, carbon monoxide, colony-stimulating factors, continuous positive airway pressure, continuous veno-venous haemofiltration, dornase alpha, Drotrecogin alfa, Extracorporeal carbon dioxide removal, gimsilumab, growth factors, haemofiltration, hydroxychloroquine, imatinib, immunoglobulin, interferon beta, janus kinase inhibitors, levosimendan, lisofylline, palifermin, prostaglandins, remdesivir, sarilumab, siltuximab, sivelestat, tocilizumab, ulinastatin.
ECMO = extracorporeal membrane oxygenation; NMBA = neuromuscular blocking agents; NO = nitric oxide; PEEP = positive end-expiratory pressure

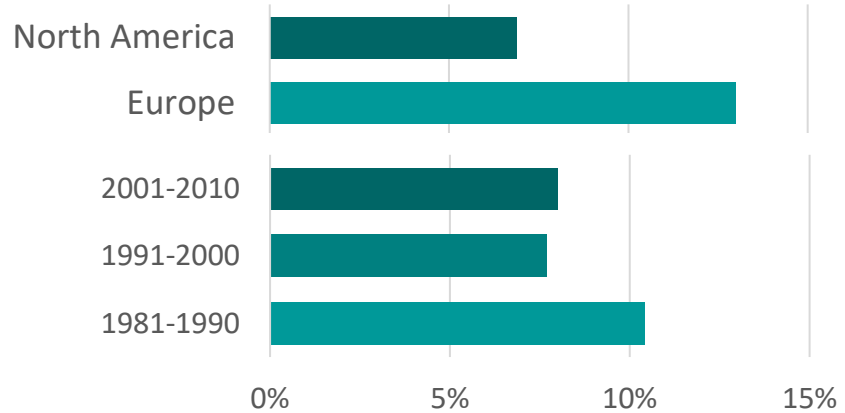
2. What is the incidence/prevalence of ARDS in adults?

Typically occurs in 1% to 10% of patients in ICU

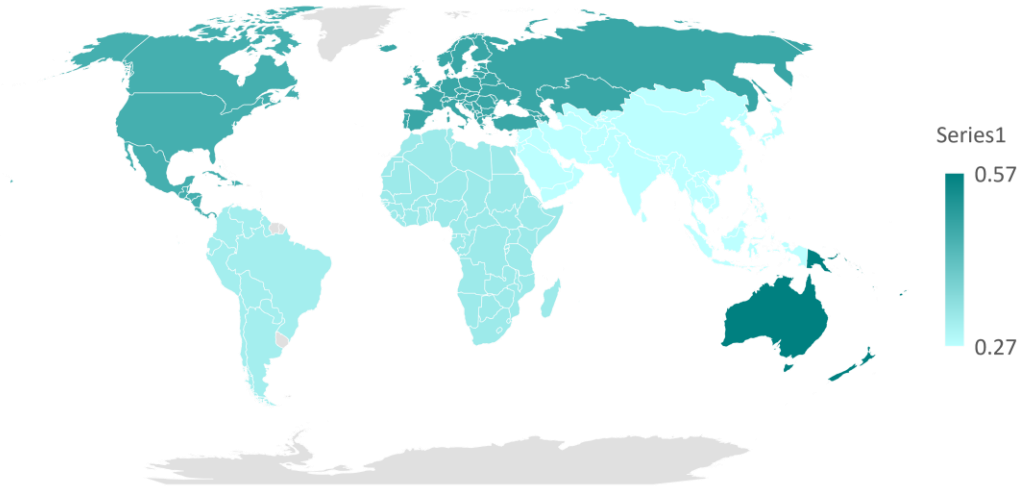
- **1/3 patients with COVID-19** [1]
- Varies substantially according to the diagnostic criteria used [2]
  - One-day observational study in Brazil found prevalence to be:
    - 6.2% according to physician's opinion;
    - 9.7% according to American-Consensus;
    - 24% according to new Berlin definition.



SLR of the median incidence of ARDS in trauma patients [4]



Prevalence of ARDS per ICU admission, by continent [3]



2. What is the incidence/prevalence of ARDS in adults?

- Age-adjusted incidence in Taiwan was 15.19 per 100,000 person-years.[1]
- Invasive and non-invasive ventilator use in ICUs in 50 countries:[2]
  - 30% developed mild ARDS;
  - 47% developed moderate ARDS;
  - 23% developed severe ARDS.
- Predictors of moderate-to-severe ARDS according to one US observational study:[3]
  - Inhalation injury (OR = 1.90; 95% CI 1.01 to 3.54; p = 0.046);
  - Injury Severity Score (OR = 1.04; 95% CI 1.01 to 1.07; p = 0.0021);
  - Pneumonia (OR = 1.98; 95% CI 1.07 to 3.66; p = 0.03);
  - Transfusion of fresh frozen plasma (OR = 1.32; 95% CI 1.01 to 1.72; p = 0.04).
- Incidence of ARDS in critically ill patients is lower with antiplatelet therapy:[4]
  - Odds Ratio = 0.67 (95% CI 0.57 to 0.78).

3. What are the symptoms, co-morbidities and natural history?

Definition according to NICE:

- A particularly severe type of acute respiratory failure. A life-threatening condition that results in abnormally low oxygen levels (hypoxia) or abnormally high carbon dioxide (CO_2) levels (hypercapnia) in the blood.

American-European Consensus Conference (AECC) [1]

- ARDS: An acute inflammatory syndrome manifesting as diffuse pulmonary oedema and respiratory failure that cannot be explained by, but may co-exist with, left-sided heart failure.
- Published 1994, accepted globally but has since been replaced.

Berlin Definition [1]

- Published 2013, widely used.
- Proposes 3 categories of ARDS based on the severity of hypoxemia: mild (200 mm Hg<PaO_2/FiO_2≤300 mm Hg), moderate (100 mm Hg< PaO_2/FiO_2≤200 mm Hg), and severe (PaO_2/FiO_2 ≤100 mm Hg), along with explicit criteria related to timing of the syndrome's onset, origin of oedema, and the chest radiograph findings.

3. What are the symptoms, co-morbidities and natural history?

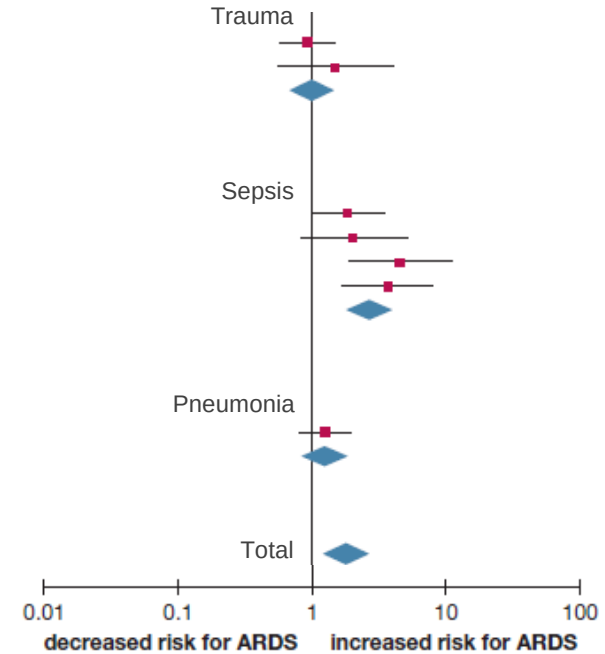
- **Typical features** of ARDS according to a US population-based study from 2009 to 2014: [1]
  - 58% male;
  - Median age 63 years (IQR 51 to 74);
  - ICU mortality 18% to 24%;
  - Hospital mortality 17% to 28%;
  - Risk factors:
    - Shock (23% to 31%);
    - Pneumonia (14 % to 27%);
    - Sepsis (2% to 16%);
    - Trauma (2% to 12%);
    - Multiple transfusions (2% to 12%);
    - Aspiration (3.5% to 14.5%);
    - Pancreatitis (0% to 2.4%);
    - Drug overdose (0% to 7%).

3. What are the symptoms, co-morbidities and natural history?

- Most common **risk factors** mentioned in all included studies:
  - Trauma
  - Sepsis
  - Pneumonia
- Significant risk factors according to one 2009 SLR [1]
  - Injury severity — OR = 1.02 (95% CI 1.01 to 1.04)
  - Thoracic injury — OR = 1.57 (95% CI 1.07 to 2.31)
  - Polytrauma — OR = 2.77 (95% CI 1.62 to 4.74)
  - Pneumonia — OR = 7.52 (95% CI 4.48 to 12.60)
  - >5 units fresh frozen plasma — OR = 2.55 (95% CI 1.17 to 5.55)
  - 6 to 10 units packed red blood cells — OR = 2.24 (95% CI 1.06 to 4.73)

A SLR of inhaled nitric oxide interventions found an increased risk of acute kidney injury in ARDS (RR=1.55, 95%CI 1.15 to 2.09, p = 0.005) but not in patients without ARDS (RR=0.90, 95%CI 0.49 to 1.67, p = 0.75) [2]

Odds ratio for ARDS associated with alcohol consumption, by comorbidity [3]

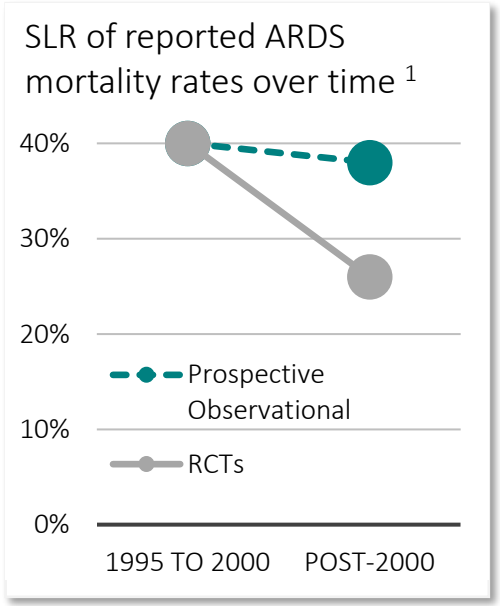


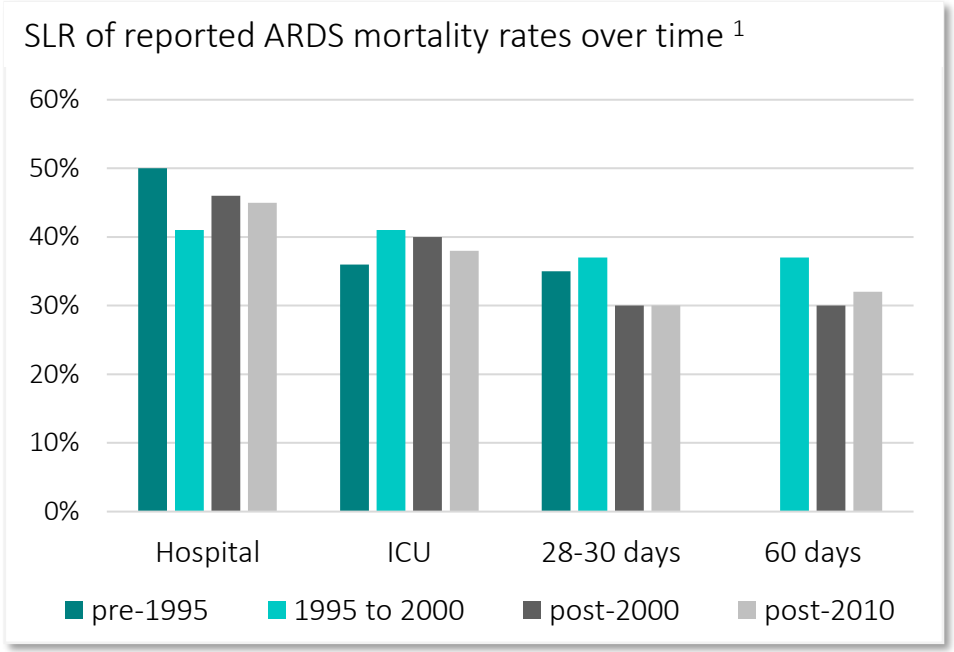
3. What are the symptoms, co-morbidities and natural history?

- **Mortality** typically around 30%.
- Approx. 3% develop gastrointestinal bleeds
  - Subsequent mortality rate increased by 16%.

Some improvements have been seen in mortality rates over time, but this may be confounded by much lower rates reported in RCTs.[1]

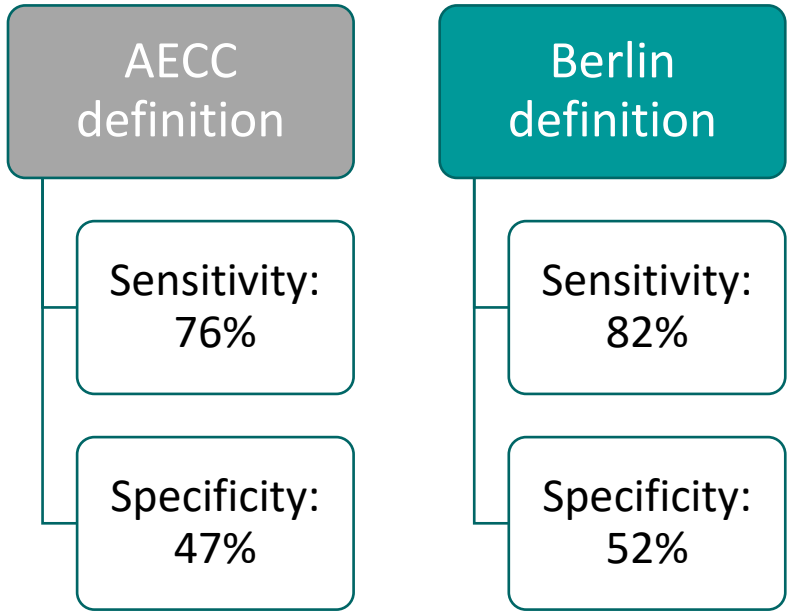
- **Survivors**:
  - Commonly suffer from muscle weakness.[1]
  - Commonly suffer from neuropsychiatric problems.[1]
  - Fewer than 50% have returned to work 12 months after leaving ICU.[1]
  - 26 to 33% have depression.[2]
  - 38 to 44% have anxiety.[2]
  - 22 to 24% have PTSD.[2]





4. How is ARDS diagnosed/classified?

- Different diagnostic criteria have been used, such as the AECC definition and Berlin definition.[3]



- As a syndrome rather than a disease, there is no 'gold standard' diagnostic tool.
- Median time to diagnosis = 2 days (IQR 0 to 3 days).[1]
- Can be divided into different severities by PaO_2/FiO_2 ratio:[2]
  - Mild: 201 to 300;
  - Moderate: 101 to 200;
  - Severe: ≤100.
- Electronic tools such as ASSIST can be used to diagnose ARDS from patients' medical records, with sensitivities of 43 to 98% and positive predictive values of 26 to 90%.[4]
- A four-point lung injury scoring system (Murray Score or LIS) is the most widely used means of quantifying ARDS severity.[5]

5. Are there clear subpopulations?

- Most reported differences in prognosis relate to intervention, time-to-treatment, severity of ARDS, risk factors/comorbidities.
- International prevalence of ARDS by severity: mild = 30.0%; moderate = 46.6%; severe = 23.4%. [1]
- One RCT of PEEP volume found that patients with mild ARDS do not benefit from higher PEEP and might even be harmed. [2]
- Gastrointestinal bleeding in ARDS was associated with a significantly longer length of stay (7.3 vs 11.9, $p<0.001$) and higher mortality (11% vs 27%, $p<0.001$). [3]
- Day-28 mortality was higher in patients with major comorbidities: [4]
  - 27.2% in patients without major comorbidities;
  - 31.1% in patients with COPD;
  - 56% in patients with hematological malignancy.

Reported risk factors for ARDS-related mortality:

Subgroup	Increased risk of mortality
Increases in BMI	OR = 0.89 (95% CI 0.71 to 1.12) [1]
Severe hypoxaemia	OR = 0.51 (95% CI 0.36 to 1.25) [5]
Influenza-related ARDS	RR = 2.45 (95% CI 1.40 to 4.27) [6]

6. What are the existing treatment options?

BMJ Guidelines on the management of acute respiratory distress syndrome [3]

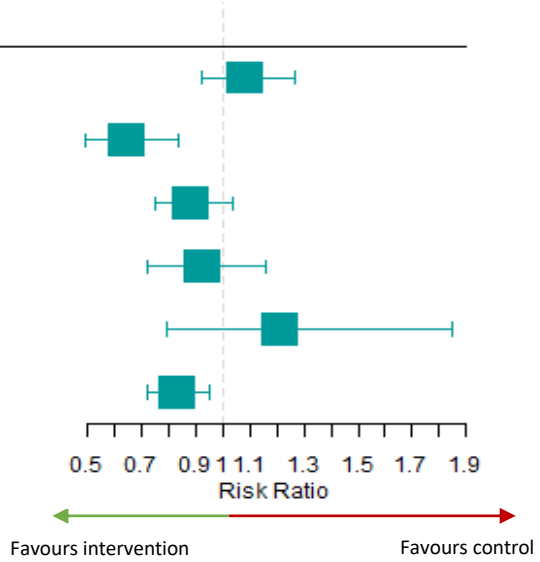
Topic	GRADE recommendation	Conditions
Tidal volume	Strongly in favour	Tidal volume ≤6 mL/kg ideal body weight; Plateau pressure < 30 cmH_2O
Prone positioning	Strongly in favour	Proning for ≥12 hours per day Patients with moderate/severe ARDS (P:F ratio ≤ 20 kPa)
HFOV	Strongly against	
Conservative fluid management	Weakly in favour	
Higher PEEP	Weakly in favour	Patients with moderate or severe ARDS (PF ratio ≤27 kPa)
NMBA	Weakly in favour	Evidence only for cisatracurium besylate Continuous 48 hours infusion Patients with moderate/severe ARDS (≤20 kPa)
ECMO	Weakly in favour	With lung-protective mechanical ventilation Patients with severe ARDS, lung injury score ≥3 or pH <7.20 due to uncompensated hypercapnoea
Inhaled vasodilators	Weakly against	Evidence only for inhaled nitric oxide
Corticosteroids	Research recommendation	
$ECCO_2R$	Research recommendation	

ARDS, acute respiratory distress syndrome; ECCO2R, extracorporeal carbon dioxide removal; ECMO, extracorporeal membrane oxygenation; FICM, Faculty of Intensive Care Medicine; HFOV, high frequency oscillation; ICS, Intensive Care Society; NMBA, neuromuscular blocking agents; PEEP, peek end-expiratory pressure.

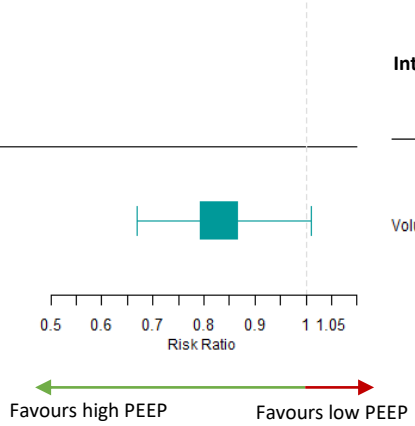
7. What is the effectiveness of existing treatments?

28-day mortality:

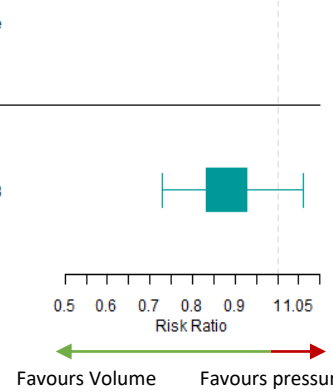
Intervention	Deaths n/N	Measure	Value
Nitric Oxide (1)	Intervention = 202/587 Control = 166/518	RR	1.08
Omega-3 and Antioxidants (Plus Ventilation) (2)	Intervention = 56/231 Control = 87/235	RR	0.64
Recruitment Maneouvers (Plus Ventilation) (3)	Intervention = 183/654 Control = 217/686	RR	0.88
High-freqeuncy Oscillatory Ventilation (4)	Intervention = 409/896 Control = 398/883	RR	0.92
Partial Liquid Ventilation (5)	Intervention = 47/170 Control = 25/132	RR	1.21
Protective Ventilation (6)	Intervention = 233/655 Control = 274/642	RR	0.83



Intervention	Deaths n/N	Measure	Value
High vs. Low PEEP Ventilation (7)	High PEEP = 270/949 Low PEEP = 321/972	RR	0.83



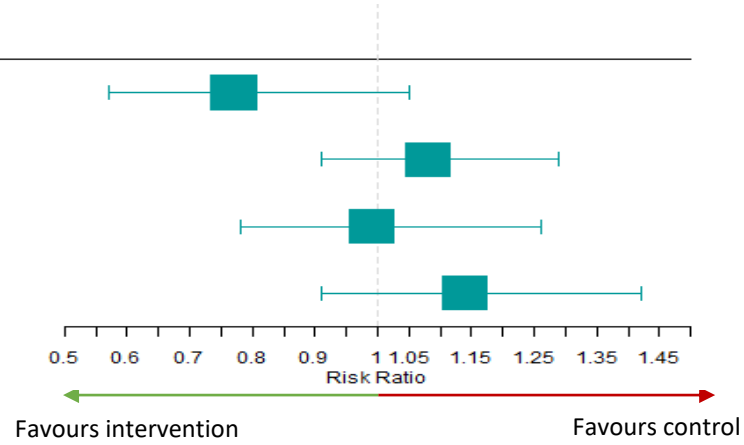
Intervention	Deaths n/N	Measure	Value
Volume vs. Pressure Controlled Ventilation (8)	Volume = 323/1000 Pressure = 284/1000	RR	0.88



7. What is the effectiveness of existing treatments?

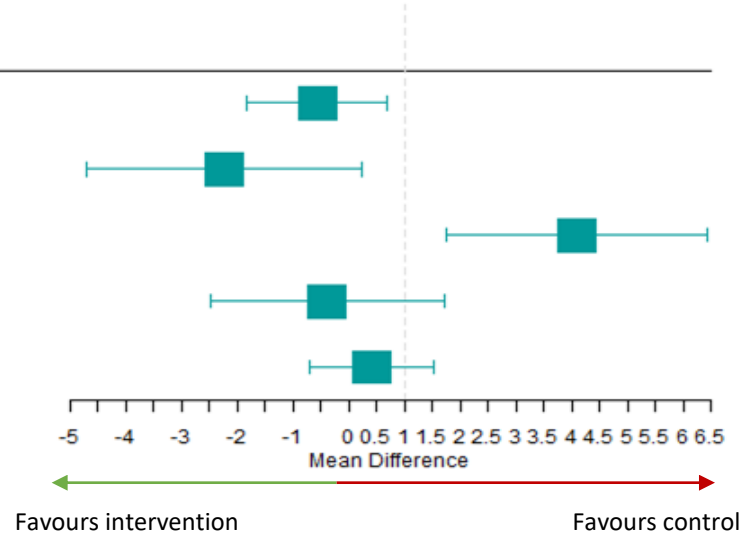
≤3-Month Mortality

Intervention	Deaths n/N	Measure	Value
Corticosteroids (1)	Intervention = 86/304 Control = 101/270	RR	0.77
Surfactants (1)	Intervention = 208/677 Control = 188/661	RR	1.08
Statins (1)	Intervention = 176/668 Control = 177/676	RR	0.99
Beta-agonist (1)	Intervention = 107/332 Control = 89/314	RR	1.14



Ventilator-free days

Intervention	n	Measure	Value
Nitric Oxide (2)	Intervention = 428 Control = 376	MD	-0.57
Partial Liquid Ventilation (3)	Intervention = 170 Control = 132	MD	-2.24
Corticosteroids (1)	Intervention = 262 Control = 232	MD	4.09
Surfactants (1)	Intervention = 173 Control = 172	MD	-0.39
Statins (1)	Intervention = 667 Control = 675	MD	0.4



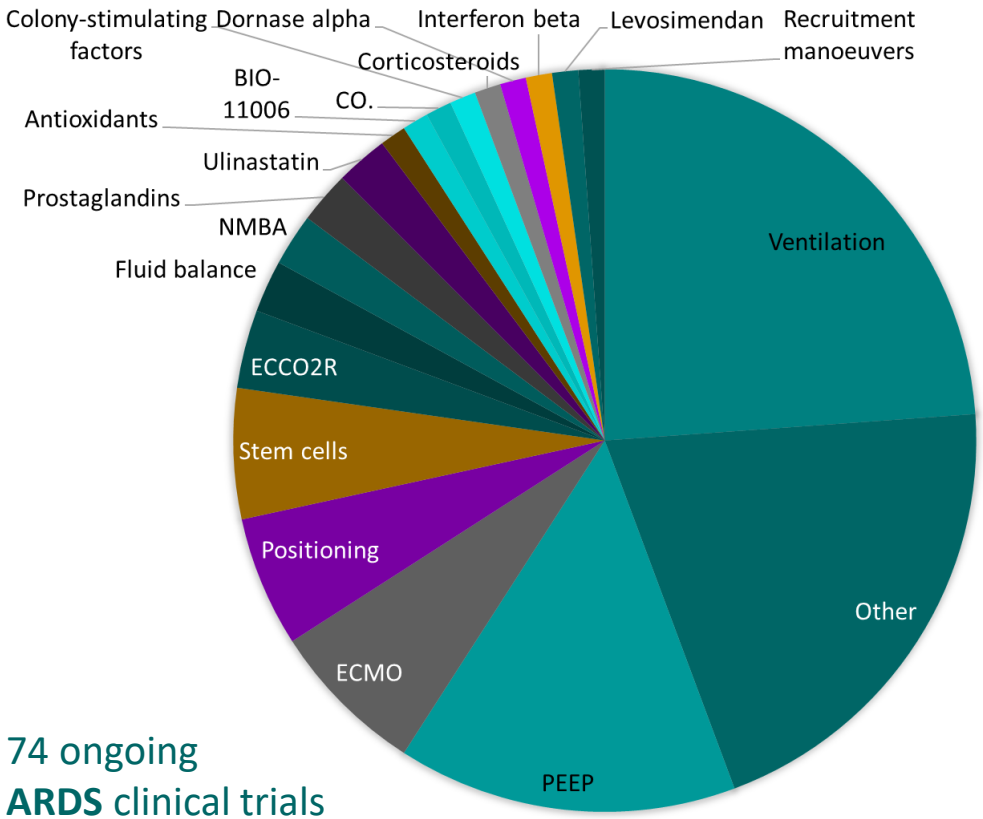
Many SLRs concluded:

- Interventions are effective at improving biochemical measures.
- Improvement in overall rates of mechanical ventilation and mortality were minimal.

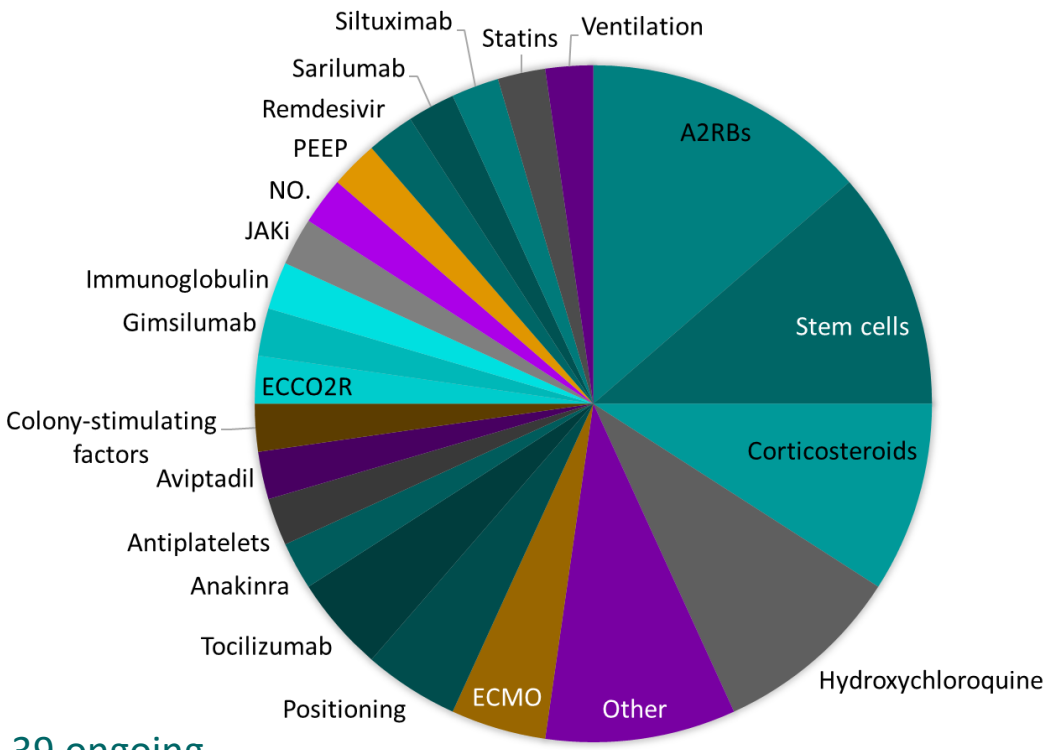
8. What interventions are currently being investigated?

111 records identified on clinicaltrials.gov + 2 published protocols (74 = ARDS; 39 = COVID-19)

Figures below show the number of ongoing trials by disease area and intervention:



74 ongoing
ARDS clinical trials



39 ongoing
COVID-19 clinical trials

More information about interventions on slide 4.

9. What are the most common outcome measures?

All-cause mortality, **28-day mortality**, and **hospital/ICU mortality** were the most common primary endpoints in the clinical trials reviewed and were the most common outcomes of interest in SLRs.

- The most common secondary outcomes were adverse events, hospital length of stay (LOS), ICU LOS, ventilator free-days, and ventilator duration.

Other primary or secondary endpoints reported in several studies include:

- Oxygenation measures:
  - PaO_2/FiO_2 ratio;
  - PaO_2;
  - FiO_2.
- Pulmonary artery pressure;
- Ventilator-induced lung injury;
- SOFA (Sequential Organ Failure Assessments) score.

9. What are the most common outcome measures?

RCTs

- Clinical outcomes:
  - Mortality;
  - Hospital and ICU LOS;
  - Ventilator use and duration.
- Adverse events
- Quality of life:
  - Mental and Physical performance.
- ARDS aetiology:
  - Oxygenation;
  - Lung pressure;
  - Haemodynamics.

Observational studies

- Clinical outcomes:
  - Mortality;
  - Hospital and ICU LOS;
  - Ventilator use and duration.
- ARDS aetiology:
  - Oxygenation;
  - Oxygen saturation;
  - Lung pressure;
  - Arterial pressure;
  - APACHE I/II score;
  - Heart rate;
  - Respiratory rate.

10. What instruments have been used to measure QoL?

The most common instruments reported were:

- Short Form – 36;
- EQ-5D Quality of Life Index;
- Saint George's Respiratory Questionnaire.

Most instruments cited in the abstracts were reported to be responsive to treatment or sensitive to differences between populations.

10. What instruments have been used to measure QoL?

Number of studies mentioning PRO tools, by study type:

PRO tool	Observational studies
SF-36	12
EQ-5D	5
SGRQ	4
SF-12	1
ADL	1
QWB	1
BDI-II	1
CES-D	1
CRQ	1
FPI	1
F-Sozu	1
MAC-S	1
PAS	1
PCL-C	1
PTSS-10	1
SC-90	1
SQOLI	1
SSQ	1

PRO tool	RCTs
SF-36	2
EQ-5D	2
SGRQ	2
Utilities	2
SF-12	2
ADL	1
QWB	1
SF-6D	1

PRO tool	Ongoing clinical trials
SF-36	5
EQ-5D	2
ADL	1
GAD-7	1
HADS	1
IES-R	1
PHQ-9	1
PROMIS	1
PTSS-14	1
RBANS	1
SPPB	1
T-MoCA	1

PRO tools responsive to time/treatment:

Observational studies	RCTs
SF-36*	SF-36*
EQ-5D	ADL
SGRQ	EQ-5D
ADL	QWB
BDI-II	SF-12
CES-D	SF-6D
F-SozU	SGRQ
FPI	Utilities*
PAS	
PCL-C	
PTSS-10	
SC-90	
SF-12	

PRO tools not responsive:

Observational studies	RCTs
CRQ	
MAC-S	
SQOLI	

*some studies found no significant response

The data on this slide was extracted from abstracts and is only illustrative of the instruments used

ADL: Activities of Daily Living, CRQ: Chronic Respiratory Questionnaire, FOSQ: Functional Outcomes of Sleep Questionnaire, PCL-C: PTSD Checklist-Civilian Version, QWB: Quality of Well-Being scale, SGRQ: Saint George's Respiratory Questionnaire, SSQ: Sydney Swallowing Questionnaire, AQoL: Health-related Quality of Life questionnaire, ESS: Epworth Sleepiness Scale, PSQI: Pittsburgh Sleep Quality Index, MAC-S: Manual Ability Classification System, BDI-II: Beck Depression Inventory-II, PTSS-10: Post traumatic stress syndrome 10, PTSS-14: Post traumatic stress syndrome 14, F-Sozu: Social Support Questionnaire, PROMIS: Patient Reported Outcome Measurement Information System, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status, SQOLI: Spitzer's Quality of Life index; SPPB: Short Physical Performance Battery, PHQ-9: Patient Health Questionnaire, GAD-7: General Anxiety Disorder-7, T-MoCA: Telephone version of Montreal Cognitive Assessment test for dementia, IES-R: Impact of Event Scale – Revised.

11. What is the impact on QoL in patients and caregivers?

Patients

- ARDS survivors experience low QoL that rarely improves significantly after 6 months post-hospital discharge. [1]
- QoL is comparable to other patients with critical illness. [2]
- Sepsis [3] and secondary lung injury [4] as the cause of ARDS is associated with a lower QoL.
- 74% of patients suffer from PTSD, fear of suffocation and nightmares.
- Patients treated with ECMO experience less psychological morbidity compared to those treated with conventional mechanical ventilation. [6]

Caregivers

- 31% of patients' family experience PTSD: [7]
  - more common in females;
  - more common with pre-existing mental health problems;
  - more common in those with recent serious physical illness.
- Lower caregiver QoL is associated with more lifestyle interference, and caring for patients with more depressive symptoms. [8]

11. What is the impact on QoL in patients?

Determinants of HRQoL (International SLR, 2017) [1]

Data in the SLR was collected from literature published between 1994 to 2013.
Effect size represents the range reported in the SLR, from one or more studies.

	Determinant	Scale	Effect size
Psychosocial	Depression	SF-36 SF-36 PCS SF-36 MCS	-0.29 to -0.76 -0.17 -0.68 to -0.94
	PTSD	SF-36 PCS SF-36 MCS	0.64 0.76
	Anxiety	SF-36 SF-36 PCS SF-36 MCS EQ-5D	-0.30 to -0.59 -0.18 -0.73 -0.34
	Cognition	SF-36	<0.01 to 0.45
Sociodemographic	Age	SF-36 PCS SF-36 MCS	-0.52 0.07

	Determinant	Scale	Effect size
Disease-related	General morbidity	SF-36 SF-36 PCS SF-36 MCS QWB	-0.52 to -0.75 -0.75 -0.61 -0.27
	ARDS aetiology	SF-36	0.27 to 0.65
	Extent of lung damage	SF-36 PCS SF-36 MCS	-0.10 -0.31
	Lung function testing	SF-36 SF-36 PCS SQLI NHP	-0.04 to -0.59 -0.14 to -0.36 -0.004 to -0.44 -0.36
Care-related	Duration of intubation/ventilation	SF-36 PCS SF-36 MCS SQLI	-0.30 to -0.44 -0.41 to 0.13 0.01
	Duration of hospitalisation	SF-36 PF SF-36 PRF	-0.35 to -0.71 -0.45
	Duration of ICU treatment	SF-36 PF SF-36 PRF SQLI	-0.34 -0.43 -0.03
	ECMO	SF-36 PCS SF-36 MCS	0.25 0.06

12. What are the costs associated with ARDS?

ARDS patients represent:

- 0.28% of US hospital admissions;[2]
- 10.4% of ICU admissions;[1]
- 23.4% of all patients requiring mechanical ventilation.[1]

ARDS has a significant impact on employment:

- 49% to 56% return to work after 1 year (USA);[3,4]
- 65% return to work after 2 years (USA);[3]
- 69% to 77% return to work after 5 years (USA);[5,3]
- Mean loss of earnings per patient per year is $26,949 (USA).[4]

- Disease factors driving up costs: illness severity, mechanical ventilation, number of comorbidities.[3]
- More than 80% of direct costs are hospital-related.[3]
- More than 50% of post-discharge costs occur in year 1.[3]

12. What are the costs associated with ARDS?

Direct Costs		Resource use	
Total hospital costs	**$47,800** (USA)[3] to **~$81,000** (converted from 2002 CAD)[2]	Duration of ventilation	**8 days** (Italy)[1] to **20.9 days** (Int.)[5]
Total ICU costs	**~$61,000** (converted from 2002 CAD)[2]	ICU LOS	**10 days** (Italy)[1] to **35 days** (Int.)[4]
Post discharge costs	**~$41,000** by year 5 (converted from 2009 CAD)[2]	Hospital LOS (median) Hospital admissions	**17 days** (Italy, Int.)[1,4] **0.28%** of all admissions (USA)[6]
ICU costs attributable to mechanical ventilation	**$31,574** (2005 USA)[2]	Patients with hospitalisations post-initial discharge	**39%** (Canada)[2]
Hospital costs attributable to mechanical ventilation	**$47,158** (2005 USA)[2]	Patients requiring prolonged ventilation (≥96 hours)	**39%** (USA)[2]

All costs are in US dollars but have not been standardised to the same year
CAD = Canadian Dollars; Int. = International; LOS = Length of stay

12. What are the costs associated with ARDS?

Economic evaluations:

- **Simvastatin** significantly increased QALY gain (incremental QALYs = 0.064) and cost savings (incremental total costs = -£3,601) compared to placebo.[1]
- **Veno-venous extracorporeal membrane oxygenation** compared with lung protective ventilation: ICER = $36,001/QALY.[2]
- Intervention to increase use of **prone positioning** from 16% to 65%: ICER = $38,648/QALY (societal perspective).[3]
- ICER per QALY gained for providing rather than withholding **ventilator support and aggressive care** varies according to prognosis: [4]
  - 70% likelihood of 2-year survival: ICER = $29,000/QALY;
  - 51% to 70% likelihood of 2-year survival: ICER = $44,000/QALY;
  - ≤50% likelihood of 2-year survival: ICER = $110,000/QALY.
- **High-frequency oscillatory ventilation:**
  - ICER = £88,790/QALY (societal), ICER = £78,260/QALY (healthcare perspective) vs conventional ventilation in the UK.[5]
  - ICER = $36,257/QALY vs conventional ventilation in USA. [6]

13. What is the unmet need in ARDS?

- **Difficulties in diagnosis** hamper effective management of ARDS.[1]
- Poor **communication of prognosis** creates inaccurate expectations among surrogates.[2]
- **Caregivers** experience more emotional distress and poor health-related quality of life:
  - Caregivers' psychological wellbeing is improved as a result of being able to provide care and having more mastery and social support. [3]
- **Complicated procedures**
  - One study reported a lack of confidence and practical skills in using prone positioning during mechanical ventilation among critical care nurses, respiratory therapists and physicians.[4]
- **Patient preferences**
  - No discussion of patients' values and preferences occurred in roughly one quarter of ICU family conferences.[5]
  - Clinicians rarely made treatment recommendations that were explicitly grounded in patient values and preferences.[5]
- **Long-term impact**
  - PTSD, psychological well-being, delayed return to work.[6]

Methodology

Identification:

- We conducted a systematic search of Medline and Embase via embase.com, Cochrane, heoro.com on 11 April 2020 (search strategy reported in Evidence Map).
- We identified relevant HTAs and guidelines from: NICE, SIGN, SMC, ICER, CADTH, AHRQ, FDA, EMA.
- We identified ongoing trials at clinicaltrials.gov.

Screening:

- Abstracts were double-screened for relevance to 1 or more of the topics in this presentation.
- Abstracts were shortlisted for inclusion in the Evidence Map using basic prioritisation criteria:
  - Any relevant primary publications from 2000 onwards;
  - Any relevant ongoing clinical trial records with a completion date of 2019 onwards.

Data summary:

- Data from included abstracts were summarised to find the range of values reported by location and topic.
- Freely available SLRs, HTAs and guidelines were retrieved and examined for relevant data.

Useful Publications:

Guidelines and regulatory

- Griffiths, M.J.D., et al. (2019). "Guidelines on the management of acute respiratory distress syndrome." BMJ Open Respiratory Research 6(1).

Epidemiology

- Belenkiy, S.M., et al. (2014). "Acute respiratory distress syndrome in wartime military burns: Application of the Berlin criteria." Journal of Trauma and Acute Care Surgery 76(3): 821-827.
- Bellani, G., et al. (2016). "Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries." Jama 315(8): 788-800.
- Chaiwat, O., et al. (2009). "Early packed red blood cell transfusion and acute respiratory distress syndrome after trauma." Anesthesiology 110(2): 351-360.
- Máca, J., et al. (2017). "Past and present ARDS mortality rates: A systematic review." Respiratory Care 62(1): 113-122.
- Mohananey, D., et al. (2016). "Effect of antiplatelet therapy on mortality and acute lung injury in critically ill patients: A systematic review and meta-analysis." Annals of Cardiac Anaesthesia 19(4): 626-637.
- Pfeifer, R., et al. (2017). "Incidence of adult respiratory distress syndrome in trauma patients: A systematic review and meta-analysis over a period of three decades." Journal of Trauma and Acute Care Surgery 83
- Rodriguez-Morales, A.J., et al. (2020). "Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis." Travel Medicine and Infectious Disease.
- Simou, E., et al. (2018). "The Effect of Alcohol Consumption on the Risk of ARDS: A Systematic Review and Meta-Analysis." Chest 154(1): 58-68.

Diagnosis and classification

- Caser, E.B., et al. (2014). "Impact of distinct definitions of acute lung injury on its incidence and outcomes in Brazilian ICUs: prospective evaluation of 7,133 patients*." Crit Care Med 42(3): 574-582.
- Costa, E.L.V. and Amato, M.B.P. (2013). "The new definition for acute lung injury and acute respiratory distress syndrome: Is there room for improvement?" Current Opinion in Critical Care 19(1): 16-23.
- Frohlich, S., et al. (2013). "Comparison of the accuracy of the AECC and berlin definitions in diagnosing ards." American Journal of Respiratory and Critical Care Medicine 187.
- Wayne, M.T., et al. (2019). "Electronic sniffer systems to identify the acute respiratory distress syndrome." Annals of the American Thoracic Society 16(4): 488-495.

Treatments and efficacy

- Chacko, B., et al. (2015). "Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)." Cochrane Database of Systematic Reviews (1).
- Cho, Y.J., et al. (2016). "Clinical practice guideline of acute respiratory distress syndrome." Tuberculosis and Respiratory Diseases 79(4): 214-233.
- Del Sorbo, L., et al. (2017). "Mechanical ventilation in adults with acute respiratory distress syndrome: Summary of the experimental evidence for the clinical practice guideline." Annals of the American Thoracic Society 14: S261-S270.
- Dushianthan, A., et al. (2019). "Immunonutrition for acute respiratory distress syndrome (ARDS) in adults." Cochrane Database of Systematic Reviews (1).
- Galvin, I.M., et al. (2013). "Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome." The Cochrane database of systematic reviews 7: CD003707.
- Gebistorf, F., et al. (2016). "Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults." Cochrane Database of Systematic Reviews (6).
- Gong, M.N., et al. (2010). "Body mass index is associated with the development of acute respiratory distress syndrome." Thorax 65(1): 44-50.
- Griffiths, M.J.D., et al. (2019). "Guidelines on the management of acute respiratory distress syndrome." BMJ Open Respiratory Research 6(1).
- Hodgson, C., et al. (2016). "Recruitment manoeuvres for adults with acute respiratory distress syndrome receiving mechanical ventilation." The Cochrane database of systematic reviews 11: CD006667.
- Kasenda, B., et al. (2016). "Multivariable fractional polynomial interaction to investigate continuous effect modifiers in a meta-analysis on higher versus lower PEEP for patients with ARDS." BMJ Open 6(9): e011148.
- Lewis, S.R., et al. (2019). "Pharmacological agents for adults with acute respiratory distress syndrome." Cochrane Database of Systematic Reviews (7).
- Mora-Arteaga, J.A., et al. (2015). "The effects of prone position ventilation in patients with acute respiratory distress syndrome. A systematic review and metaanalysis." Medicina Intensiva 39(6): 352-365.
- Papazian, L., et al. (2019). "Formal guidelines: management of acute respiratory distress syndrome." Annals of Intensive Care 9(1).
- Petrucci, N. and De Feo, C. (2013). "Lung protective ventilation strategy for the acute respiratory distress syndrome." Cochrane Database of Systematic Reviews (2).
- Ruan, S.Y., et al. (2014). "Exploring the heterogeneity of effects of corticosteroids on acute respiratory distress syndrome: A systematic review and meta-analysis." Critical Care 18(2).
- Santa Cruz, R., et al. (2013). "High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome." Cochrane Database of Systematic Reviews (6).
- Sud, S., et al. (2016). "High-frequency oscillatory ventilation versus conventional ventilation for acute respiratory distress syndrome." Cochrane Database of Systematic Reviews 2016(4).

Quality of Life

- Deja, M., et al. (2006). "Social support during intensive care unit stay might improve mental impairment and consequently health-related quality of life in survivors of severe acute respiratory distress syndrome." Crit Care 10(5): R147.
- Dinglas, V.D., et al. (2016). "One-year outcomes of rosuvastatin versus placebo in sepsis-associated acute respiratory distress syndrome: prospective follow-up of SAILS randomised trial." Thorax 71(5): 401-410.
- Dodoo-Schittko, F., et al. (2017). "Determinants of quality of life and return to work following acute respiratory distress syndrome - A systematic review." Deutsches Arzteblatt International 114(7): 103-109.
- Dowdy, D.W., et al. (2006). "Quality of life after acute respiratory distress syndrome: A meta-analysis." Intensive Care Medicine 32(8): 1115-1124.
- Wilcox, M.E., et al. (2020). "Long-Term Quality of Life After Extracorporeal Membrane Oxygenation in ARDS Survivors: Systematic Review and Meta-Analysis." Journal of Intensive Care Medicine 35(3): 233-243.

Costs

- Angus, D.C., et al. (2006). "Healthcare costs and long-term outcomes after acute respiratory distress syndrome: A phase III trial of inhaled nitric oxide." Critical Care Medicine 34(12): 2883-2890.
- Bellani, G., et al. (2016). "Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries." Jama 315(8): 788-800.
- Bice, T., et al. (2013). "Cost and health care utilization in ARDS--different from other critical illness?" Semin Respir Crit Care Med 34(4): 529-536.
- Fuller, B.M., et al. (2012). "Lower tidal volume at initiation of mechanical ventilation may reduce progression to acute respiratory distress syndrome: A systematic review." Critical Care 17(1).
- Ho, A.T.N., et al. (2020). "Neuromuscular blockade in acute respiratory distress syndrome: A systematic review and meta-analysis of randomized controlled trials." Journal of Intensive Care 8(1).
- Kamdar, B.B., et al. (2017). "Joblessness and lost earnings after acute respiratory distress syndrome in a 1-year national multicenter study." American Journal of Respiratory and Critical Care Medicine 196(8): 1012-1020.

Unmet needs

- Cameron, J.I., et al. (2006). "Well-being in informal caregivers of survivors of acute respiratory distress syndrome." Crit Care Med 34(1): 81-86.(2).
- Chiarchiaro, J., et al. (2015). "Quality of communication in the ICU and surrogate's understanding of prognosis." Crit Care Med 43(3): 542-548(3).
- Mourad, B., et al. (2019). "A novel application of healthcare simulation: Developing and implementing a prone ventilation protocol for severe acute respiratory distress syndrome (ARDS)." American Journal of Respiratory and Critical Care Medicine 199(9)(4).

Evidence Maps

1. Select the first category to be included in the Evidence Map. This will show as a series of rows in the Map

First dimension

Outcomes

2. Then select the second category to be shown as the columns of the Map, or leave blank

Second dimension

Study methodologies

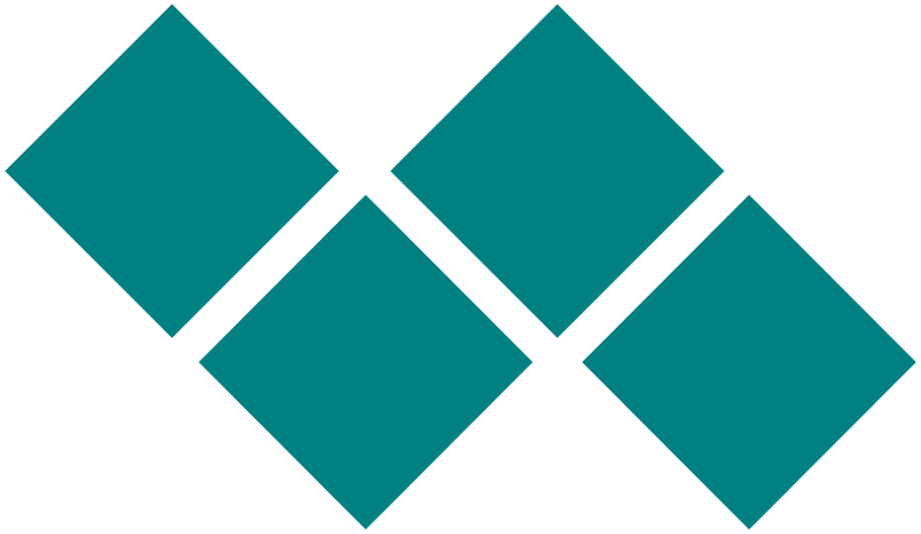
3. Click on a cell in the Map, then click the Show Citation button below to see the relevant citations for that cell

	Show Citations
Row	Adverse Event Rate
Column	Clinical Trial

See Abbreviations

	Case-control	Clinical Trial	Cohort	Pooled Analysis	RCT	SLR
Adverse Event Rate	8	88	1	1	45	0
Disease Severity Score	11	6	3	2	29	0
Discontinuations	0	3	7	0	45	1
Mortality Rate	0	9	3	1	32	0
Response Rate	0	26	34	12	45	3
Time-to-response	0	55	6	1	15	0
QoL	2	44	6	3	21	0
QoL by Intervention	0	7	0	1	8	0

- Clear and concise overview of the evidence available
- Abstracts indexed to standard and custom categories
- Switch between table view and citation lists
- Abbreviations and Key included for clarity
- Search terms and screening criteria also included



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