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ARDS: WHATS WITH THE NAME CHANGE?

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INTRODUCTION

Acute respiratory distress syndrome is an alveolar disorder characterized by a permeability pulmonary oedema leading to hypoxemia that is refractory to usual oxygen therapy.[1] Although ARDS has been defined and treated since 1967, mortality of ARDS has remained persistently high.

The purpose of this booklet is to provide an update by addressing the controversies regarding changing definitions in the recent years to the Berlin definition, and to explore current evidence for the use of treatment modalities available.

EPIDEMIOLOGY

The incidence of ARDS varies widely due to changes in definitions, different demographics and healthcare systems.

Older US studies using the AECC definition ranged from 64 to 78,9 cases/100000 person-years, compared to European estimates of 17cases/100000. Australian/New Zealand [34cases/100000] also showed a lower estimate.[2]

The recent "Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure"[LUNG SAFE] study was an international multicentre prospective study in which the primary outcome was ICU incidence of ARDS using the new Berlin definition. It was performed in 459 ICUs from 50 countries.

Among ICUs, the period prevalence of ARDS was 10.4% of ICU admissions.
30% of these patients had mild ARDS, 46,6%moderate ARDS and 23.4% had severe ARDS.[3]

PATHOGENESIS [4.5]

The hallmark of ARDS is diffuse alveolar damage with injury to lung capillaries. Two pathways may lead to ARDS namely pulmonary [direct] insults, that directly damage lung parenchyma, and extra pulmonary [indirect], that releases an acute systemic inflammatory response. [2]

Neutrophil accumulation and activation are key in the pathogenesis of ARDS. Following lung injury, either direct or indirect, these neutrophils release proteases, cytokines and reactive oxygen species and cause pathological vascular permeability with diffuse alveolar-capillary damage. Alveolar collapse occurs as a result in a decrease in the production of surfactant.

Classically the pathology of ARDS was described in three phases, the early exudative phase, the late proliferative phase and very late fibrotic phase. [2]

It is now understood that there is significant overlap between the phases, both pathologically and histologically.

Early exudative phase: diffuse alveolar damage, protein rich alveolar oedema
Late Proliferative phase: hyaline membrane formation, cellular alveolar infiltrates and reduced lung compliance

Late Fibrotic phase: Extracellular matrix deposition, chronic inflammation, diffuse fibrosis with honeycombing.

RISK FACTORS

Risk factors for ARDS can be divided into direct lung injury factors and indirect lung injury factors.

Pneumonia, gastric aspiration, pulmonary contusion, fat embolism and inhalational injury are all direct lung injury factors.[6]

Indirect lung injury factors include sepsis, trauma, blood transfusion, burns and acute pancreatitis.[6]

CHANGING DEFINITIONS: WHATS IN A NAME? [7,8,9,10,11]

A reliable definition is essential for clinical trials, biological studies and is needed for clinicians to make a diagnosis and initiate treatments that will improve outcomes.

Aashbough and colleagues first defined Acute Respiratory Distress Syndrome in 1967.
"A cohort of twelve patients were described with severe acute respiratory failure, having severe hypoxaemia refractory to supplemental oxygen, which responded to application of PEEP".[7]

1994 saw the American European Consensus Conference's [AECC] definition coming to the forefront.

The AECC defined ARDS as "acute onset of hypoxaemia [PA02/FI02 ≤200mmHg], with bilateral infiltrates on frontal chest x-ray in the absence of left atrial hypertension [PAWP ≤18mmHG]." [9]

A new term, Acute Lung Injury [ALI], was also coined, encompassing the same variables but with a higher cut off for hypoxaemia, namely Pa02/Fi02 ≤300mmHg.

These definitions performed well for over two decades, aiding clinicians to treat patients and allowing researchers to acquire data in ARDS. [8]

As time passed however, a number of potential issues arose[9]

- When the definition criteria were strictly applied on a daily basis, the sensitivity was 84% and specificity was much lower at only 51%.
- ALI was frequently missed by clinicians especially in those with milder hypoxaemia.
- The definition did not define specific time frames when labelling it acute.
- The hypoxaemia criterion did not take into account varying Fi02 and other ventilator settings including PEEP.
- Chest X-ray criteria had only moderate inter observer reliability even when applied by experts.
- The definition included PAWP ≤18mmhg, the relevance of which was challenged, as the use of pulmonary artery catheters had declined worldwide. There was also a recognition that hydrostatic oedema and ARDS could co-exist resulting in higher PAWP.

For these reasons a task force initiated by the European Society of Intensive Care Medicine was created to review the definition and the new Berlin definition of ARDS was born in 2012.

THE BERLIN DEFINITION [6,9,10.11]

The New Berlin definition is an evolution rather than a revolution to the original 1994 definition. The goal of the new definition was to try and improve reliability, feasibility, face and predictive value.

It maintains a link to the prior definition while including diagnostic criteria of timing, chest imaging, origin of oedema and hypoxaemia and PEEP.

Table 1. ARDS Berlin definition.

The Berlin definition of acute respiratory distress syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities — not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mmHg < PaO_2/FIO_2 ≤300 mmHg with PEEP or CPAP ≥5 cmH_2O[c]
Moderate	100 mmHg < PaO_2/FIO_2 ≤200 mmHg with PEEP ≥5 cmH_2O
Severe	PaO_2/FIO_2 ≤100 mmHg with PEEP ≥5 cmH_2O

Abbreviations: CPAP, continuous positive airway pressure; F_IO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; [a]Chest radiograph or computed tomography scan; [b]If altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2_(barometric pressure/760)]; [c]This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

TABLE 1: Ranieri VM, rubenfeld GD, Thompson BT et al Acute Respiratory Distress syndrome the Berlin definition, JAMA 2012;307 THE ARDS BERLIN DEFINITION

Whats changed in the new definition?

The new definition sought to address issues previously found with the AECC definition by reviewing the following criteria:

- **Time Period:** A specific time frame of "within one week of known clinical insult or worsening/new respiratory symptoms.

- **Oxygenation and Severity**: ARDS is graded into mild, moderate and severe using Pa02/Fi02 thresholds with a minimum PEEP of ≥5cmH20.This severity orientated method provides better separation for prognosis and treatment options.

- The term Acute Lung Injury was abolished as these patients now fall into the mild category of ARDS. By classifying this group as ARDS, it is hoped that fewer patients will be missed and lung protective strategies will be instituted earlier in the evolution of the syndrome, decreasing mortality.

- **PAWP**: Pulmonary artery wedge pressures are no longer included in the Definition due to its decline in clinical use and understanding that Left Ventricular Failure can co-exist with other causes of ARDS

- **XRAY Criteria**: To help address the issue of inter-observer reliability with chest x-ray, the Berlin criteria are more explicit specifying "bilateral opacities consistent with pulmonary oedema, not fully explained by effusions or lobar collapse". A series of example x-rays are also included. Were possible if Ct is available, it may replace chest x-ray.

- **PREDICTIVE VALIDITY**: Compared with the AECC definition the Berlin definition has "better predictive validity for mortality, with an area under the receiver operating curve if 0,577 vs 0.536."

Issues with the Berlin Definition [3,6,9.10,11,12.13]

- The Berlin definition was tested against autopsy results. In a 712 patient autopsy series, of patients that met the clinical diagnosis for ARDS, only 45% had Diffuse Alveolar Damage [DAD.] The finding increased to 58% in the most severe subset. If however the findings of pneumonia without DAD were added, then DAD or pneumonia or both, were identified in 88% of ARDS cases. These findings perhaps suggest the pneumonia being one of the commonest causes of ARDS should be included in histopathological definitions.

- Furthermore there is a suggestion that given the above findings, that lung biopsy would give a definitive diagnosis, but the logistics and patient selection in terms of selection for fitness for biopsy and histology would be difficult in the ICU population.

- Imaging Criteria: X-ray findings are still included in the definition. Although there have been endeavours to increase reliability for this criteria, there is still room for error and missed diagnosis. CT scan findings have faired better and would appear more reliable but not widely available to all centres and hence were not included in the diagnosis.

- The cut-off for severity may mean that a small percentage of patients with early evolving ARDS may be missed.

- The findings of the LUNG SAFE study showed that" clinical recognition of ARDs with the Berlin Definition ranged from 51,3% in mild ARDs to 75% in severe ARDS." This indicates that even with the Berlin definition the syndrome appears to be "under-recognized and undertreated". [3]

- Absence of biomarkers in definition: The definition does not include biomarkers which is an emerging field and may possibly lead to early diagnosis.

BI0MARKERS [13]

The Future of ARDS diagnosis?

Various trials have demonstrated the importance of biomarkers in the future for diagnosis. Below are biomarkers likely to come into the use in the future.

Clara cell secretory protein (CCSP, CC16):

Clara cells are non-ciliated epithelial cells mainly found in the epithelium of terminal bronchioles and respiratory bronchioles.

In a prospective multicentre trial looking at 78ARDS cases, CC16 serum levels, duration of ventilation and 28day mortality were examined. It was found that CC16 levels were higher in non survivors at day 2. In addition the level of CC16 correlated with the number of ventilated days and failing organs. [13]

It concluded that "higher initial CC-16 serum level was associated with increased risk of death, fewer ventilator- free days and increased frequency of non- pulmonary multiple organ failure and that CC-16 was a valuable biomarker of ARDS that may help predict outcome."[13]

Similar retrospective research by Determann et al showed that "Plasma CC16 had a good diagnostic capacity for acute lung injury (ALI)/ARDS"[13]

Pulmonary surfactant-associated protein D (SP-D:)[13]

SP is a surface-active lipoprotein complex formed by type II alveolar epithelial cells and Clara cells. Research has shown that SP-D increases in the early stage of ALI and/or ARDS, and maybe helpful in early diagnosis. Just like CC16, its levels correlated with mortality rate and length of hospital stays, Research has been scarce on this particular biomarker and more prospective controlled studies are expected.

Inflammatory cell activation markers:[13]

Important inflammatory markers include Interleukin 8, tnf, Matrix metalloproteinase-9 (MMP-9) and ferritin.

The diagnostic value of Interleukin-8 for ARDS induced by different factors has not been fully determined, but it has a good predictive value for ARDS caused by infection and may also help to predict prognosis.

Currently, research on TNF-α are mostly concerned with animal studies. More prospective clinical studies are needed to further clarify the role of TNF-α in the early diagnosis and prognosis of ALI/ARDS.

TREATMENT MODALITIES

Since ARDS was first described, there has been numerous trials and studies into various therapies. Despite large amounts of study and literature, there is a paucity of effective treatments other than lung protective strategies.

The current modalities available can be broadly divided into ventilatory and non ventilatory strategies.

VENTILATORY TREATMENTS [5,10,14,15,16,17]

The optimal ventilatory treatment for ARDS remains to be defined.
Multiple physiological factors including, trans-pulmonary pressures, lung mechanics, body habitus, hemodynamics, and lung recruitability can influence the risks and benefits of ventilation. Thus the approach to the ARDS patient should be individualized taking into the account the varying physiological and biological differences between patients.

Lung Protective Ventilation [10,14,15,16]:

Remains the cornerstone for treating patients with ARDS. The aim is to prevent ventilator induced lung injury[VLI], i.e. avoid volutrauma, barotrauma, atelectrauma and biotrauma, which in itself is not really a treatment for ARDS alone but rather a strategy to prevent VLI.

Landmark NHLBI Ardsnet trial in 2000 compared low tidal volume ventilation to high tidal volume ventilation, and Pplat ≤30cmh20 vs 50cmh2o. The study demonstrated reduction in 28 day mortality, increase in ventilator free days and non-pulmonary organ failure free days.

A study in 2010 by Determann et al were able to produce similar results when comparing conventional ventilation to low volume strategies. The study was terminated early for safety concerns as the occurrence of lung injury was higher in the conventional tidal volume group.

The IMPROVE trial, examined 400 patients undergoing abdominal surgery and compared low tidal volume to high tidal volume ventilation. In this study the low tidal volume group required significantly less respiratory support [5 vs 17%] and had shorter lengths of hospital stays. Numerous other studies and reviews have been done all which have similar outcomes. Based on these findings being reproducible in multiple studies, low tidal volume ventilation and other lung protective measures have become the standard of care for ARDS patients.

Current ARDs net guidelines for ventilation[17]

- TIDAL VOLUME 6ML/KG
- P PLAT < 30CMH2O
- PEEP ≥5CM H20
- RESP RATE 18-25/MIN
- Permissive hypercarbia
- Spo2 88-92%
- Ph>7.2

PEEP and Recruitment Manouveres:

The open lung approach- multiple studies comparing high and low peep strategies: ALVEOLI, ARMA, LOV, EXPRESS, LOV. The theory is that cyclic opening and closing of small airways and alveolar units can also lead to lung injury [atelectrauma] and use of PEEP may prevent this

The ALVEOLI trial compared lower vs higher levels of PEEP but was stopped early due to futility, showing a trend to worse outcome in the higher PEEP arm. There were possible imbalances in the treatment group compared to the control group, such as higher age, APACHE II scores and lower pa02/Fi02 scores in the treatment group. Similar results were however found in the LOV trial.

A French multicentre trial [EXPRESS study] compared different peep titrations while keeping PPLAT <30cmh20 while ventilating with low tidal volumes. The open lung approach had significantly more ventilator free and organ failure free days, but 28day and 69 day mortality was not different from the control group.

Meta-analysis of the various studies comparing higher vs lower peep showed no difference in mortality when applied in mild ARDS. The subgroup of severe ARDS did show some benefit however. There is also concern about increasing cardiovascular instability with increasing PEEP. Thus, how much PEEP and when to increase PEEP, still remains controversial.

Recruitment manoeuvers aim to overcome chest wall elastance and impart a distending pressure that opens collapsed alveoli. Various recruitment manoeuvers including sustained inflation pressures, sigh, stepwise increase in PEEP with fixed Pplat, prolonged stepwise increase in PEEP with constant driving pressure. Of importance, whatever recruitment manoeuver is employed, is to monitor the response to recruitment- look for change in 02, lung compliance and end tidal co2. PEEP needs to be set following the manoeuver in order to prevent de-recruitment.

High frequency oscillatory ventilation [HFOV]

In theory, HFOV contains the main principles of lung protection, extremely small tidal volumes at a high mean airway pressure at high frequencies with the goal of avoiding tidal overstretch and recruitment.

Recent large clinical trials have however failed to show any improvement in survival and has questioned the safety of HFOV. The OSCAR study showed no difference in mortality when comparing HFOV to conventional ventilation. The OSCILLATE study was stopped early due to excess mortality in the HFOV arm

Currently there is not enough evidence to show any benefit of using HFOV in ARDS

VENTILATORY ADJUNCTS [5,10,16,17]

Proning

ARDS causes compression atelectasis due to increased lung mass and collapse of dependant lung zones. Collapse may be worsened by cardiac compression and increased abdominal pressure.

The prone position itself aids ventilation by decreasing chest wall compliance, redistribution and recruitment of dorsal lung regions, and relieving cardiac compression.

Possible practical issues with instituting prone positioning are the potential of loss of invasive lines and monitors during the actual turning procedure, and the fact that access to the airway in the patient with accidental extubation may be difficult due to positioning. Nursing may also prove difficult if staff are untrained.

The PROSEVA trial showed marked mortality reduction in patients with severe ARDS at 28days and 90 day mortality. Though these results may seem dramatic, a meta-analysis in 2014 of 9 RCT's made similar conclusions, possibly strengthening the case for Proning and for further study in this area.

ECMO [18]

There is growing evidence that venovenous ECMO can prevent life threatening hypoxaemia and hypercapnia and facilitate lung protective ventilation in severe ARDS. The 2009 CESAR study showed reduced mortality and demonstrated increased survival without severe disability. A study looking at patients with H1N1 showed good outcomes in ECMO. Current controversies revolving around ECMO are the cost, when it should be instituted and the risk of complications.

The ELOIA and SUPERNOVA trials that are currently ongoing may hopefully provide more clarity into the use of ECMO and ARDs.

NON VENTILATORY MEASURES

Fluid Therapy[19]

Remains controversial- Fluid therapy is usually one of the 1st principles in resuscitation in critically ill patients, with ARDS literature trending towards a conservative rather than liberal strategy. Basic physiological principles using Starling's Law, indicate that decreased oncotic pressure and increased hydrostatic pressure increase extravascular lung water. ARDS patients display alveolar capillary barrier dysfunction which leads to pulmonary oedema.

The FACTT trial comparing liberal[cvp <8cmh20] to conservative strategies[cvp<4cmh20] showed no difference in 60day mortality but the conservative group demonstrated more vent free days, improved oxygenation index at 28days and no increase in shock or dialysis requirements.

The FACTT LITE, a retrospective analysis of patients in ALTA and EDEN trials compared patients treated with a "lite strategy [cvp 4-8], to FACTT conservative strategy [cvp<4]]. There was no difference in 60 day mortality but patients in the Lite group demonstrated less organ dysfunction and shock.

A conservative fluid strategy thus appears beneficial to improving pulmonary outcome. There is however risk of underperfusing other vital organs when restricting fluid therapy. Current trends in ARDS trials and treatments lean towards restrictive strategies, with no clear guideline as to exactly how much or type of fluid should be used.

DRUG THERAPIES [20]

Neuromuscular Blockade

Lung Protective ventilation can for the majority of patients be performed without neuromuscular blockade. There is however literature that indicates that instituting neuromuscular blockade for ARDs treatment for shorter periods may improve outcome by improving ventilator synchrony and improving compliance.

This may appear to be in conflict to the trend to move away from neuromuscular blockade due to critical illness myopathy.

Leading study is the ACURAYS study which randomized patients with severe ARDs to receive cisatracurium within 48hrs and for 48hrs only. A survival benefit was found and there were better outcomes in terms of ventilator free days and incidence of barotrauma. Meta-analysis of similar studies also demonstrated reduced mortality, more vent free days and less barotrauma.

A potential drawback is that this study looked at cisatracurium only, other agents such as pancuroniumm and vecuronium may indeed put patients at risk of critical illness myopathy. The negative potential protective effects of neuromuscular drugs thus needs to be investigated further.

Statins

Statins have multiple effects besides reducing cholesterol. These pleotropic effects include anti-inflammatory effects and endothelial function modulation.

Their effect on pulmonary inflammation was initially found in preclinical study, were simvastatin demonstrated anti-inflammatory actions during a LPS model of ARDS in healthy volunteers.[20]

HARP a small phase 2 trial suggested a potential role for simvastatin as it showed benefit in the intervention group.

Subsequent trials have however not supported this finding.
HARP 2 showed no difference in 28day mortality and no difference in ventilator free days or non-pulmonary organ failure free days.

The SAILS trial assessing rosuvastatin for sepsis associated ARDS was stopped early due to futility.

Steroids

Given their marked anti-inflammatory properties and the reduction of TNF and other pro inflammatory cytokines, by inference it would appear that steroid therapy should improve outcomes in ARDS patients.

There have been multiple studies investigating varying doses of steroids, different times of initiation and duration of treatment and found the following:

High dose steroid therapy did not prevent ARDS or reduce mortality once developed.
"Moderate dose therapy in the ARDSnet trial showed no effect with prolonged treatment with steroids when compared to placebo. In addition it demonstrated harm when initiated in patients after 14days of ARDs with increased 60 and 180day mortality."[20]

Low dose therapy for ARDs remains unclear, with at least one study demonstrating a reduction in severity of lung injury after 7 days of treatment.

Multiple systematic reviews and meta analysis have been done and still the use of steroids in ARDS remains unclear. A potential reason for this is that many of the studies are from the pre lung protective ventilation era, where injurious lung ventilator strategies were used.
Further trials are thus needed to evaluate the efficacy of steroids in combination with newer lung protective strategies.

B_2 Agonists

Experimental studies indicated that B2 agonists could accelerate alveolar fluid clearance, offer cytoprotection and decrease permeability.

This results were not reproducible in multicentre trials however.
Two multicentre trials, one looking at aerosolizd salbumtamol [ALTA TRIAL] and the other at IVI salbutamol [BALTI 2] were stopped early, the former due to futility and the latter due to excessive mortality.

Heparin

In ARDS, there is fibrin deposition throughout the alveolus which impairs oxygenation. Experimental data indicates that heparin may reduce fibrin deposition. A small study suggested that nebulized heparin may increase the number of ventilator free days. This study has prompted further research to investigate heparin and its impact in the long term.[20]

Aspirin

Platelets become activated during ARDS, forming micro thrombi and attracting inflammatory cells to injured lung.
Observational data indicates that "Aspirin's antiplatelet effect may be associated with a reduction in subsequent ARDS incidence".[20] This however requires further study.

Nitric Oxide

A systematic review and meta-analysis investigating the effect of nitric oxide on oxygenation and mortality has found it to be ineffective.[20]

NOVEL TREATMENT THERAPIES [20,21]

Stem Cell Therapy[21]

Regenerative medicine is an exciting new development in medicine. While their precise mechanisms appear unclear, Stem cells have reparative, anti-inflammatory and immuno modulatory effects. Animal models of ARDS have shown survival to increase when treatment was delivered directly to the bronchial tree. The optimal route of administration and dosages are not yet known. Clinical trials are needed in this emerging field.

Growth Factor[21]

Keratinocyte growth factor [KGF], is an epithelial growth factor that plays an important role in lung injury repair, by increasing type II alveolar cell proliferation, reducing endothelial permeability and improving alveolar fluid clearance. Results are awaited for a phase II trial investigating the efficacy and safety of intravenous KGF in ARDS.[21]

Vitamin D[21]

This vitamin is currently being tested in patients at risk of developing ARDS following oesophagostomy. Animal models have demonstrated that vitamin D can decrease neutrophil recruitment to the lung.[21.]

CONCLUSION

Despite evolution of definitions and remarkable advancements in understanding of pathogenesis and treatment options, there are few therapeutic measures that have strong evidence.

Most patients die of multi-organ failure rather than of respiratory failure alone. This indicates ARDS involvement in non-pulmonary organ failure by possible neurological biochemical and inflammatory reactions.

Early recognition of ARDS, identifying patients at risk of developing ARDS and the avoidance of aggravating factors may help decrease the burden of this syndrome. Even with the revised Berlin definition, clinical recognition of the syndrome is often missed, thus ongoing review of definitions and diagnostic criteria is required.

There is thus a clear need for ongoing research and constant evolution of the definition itself as well as treatment options.

REFERENCES

1. Koh: An update in Acute Respiratory Distress Syndrome. Journal of intensive care 2014 2:2
2. A J Walkey, R Summer, Vu Ho, P Alkana, Acute Respiratory distress syndrome: epidemiology and management approaches. Clinical Epidemiology 2012:4 159-169
3. G Bellani, J Laffey, T Pham, E Fan, L Brochard, A estena, L Gattinoni, F van haren, A Larsen, d McAuley, M Ranieri, G Rubenfeld, BT Thompson, H Wrigge A Slutsky, A Pesenti: Epidemiology, Patterns of Care and Mortality for Patients with Acute Respiratory Distress Syndrome in Intensive Care units in 50 Countries. JAMA Feb 23 2016 Vol 315, No 8.
4 C Evans Ventilation in ARDs Dept of Anaesthesia ukzn 2009
5. T Kisten ARDS Evidence based strategies to improve outcome Part II Refresher Course Dept of Anaesthesia UCT
6. Ionnnis Pneumatikos, MD, PhD, FCCP Vasilios E. Papaioannou, MD, MSc, PhD The new Berlin definition: What is, finally, the ARDS? PNEUMON Number 4, Vol 25, Dec 2012
7. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults. Lancet 2:319–323
8. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R (1994) The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824
9. Niall D. Ferguson Eddy Fan Luigi Camporota Massimo Antonelli Antonio Anzueto Richard Beale Laurent Brochard Roy Brower Andre ´s Esteban Luciano Gattinoni Andrew Rhodes Arthur S. Slutsky Jean-Louis Vincent Gordon D. Rubenfeld B. Taylor Thompson V. Marco Ranieri [2012] The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material Intensive Care Med (2012) 38:1573–1582
10. Fanelli et al J Thorac Dis 2013;5(3):326-334.Acute Respiratory distress syndrome: new definition, current and future therapeutic options
11. Topics in acute respiratory distress syndrome: the patient needs our tender loving and care S. John Wort, Laura Price and Stefano Nava Eur Respir Rev 2014; 23: 157–16
12. B Taylor Thompson, Michael A Mathay: The Berlin Definition of ARDS versus Pathological Evidence of Diffuse Alveolar Damage AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 187 2013
13. Biomarkers in the diagnosis and prognostic assessment of acute respiratory distress syndrome Jing Yan, Qun Rao Journal of Translation Medicine / OCT-DEC 2014 / VOL 2| ISSUE 4
14. Determann et al Ventilation with lower tidal volumes as compared to vonventional tidal volumes for patients without acute lung injury: a preventative randomized controlled trial. Crit Care 2010 14(1)
15. Fuller BM, Mohr NM, Drewry Am, Carpenter CR. Lower tidal volume at initiation of mechanical ventilation may reduce progression to acute distress syndrome: a systematic review Crit Care 2013. Jan 18; 17(1)
16. Berngard SC, Beitler JR, Malhotra A, Personalizing mechanical ventilation for acute respiratory distress syndrome. J Thorac Dis 2016; 8 (3):E172-174
17. www.ardsnet.org
18. Simon J. Finney, Extracorporeal support for patients with acute respiratory distress syndrome Eur Respir Rev 2014; 23: 379–3891
19. GS Martin, Fluid management in acute lung injury and ARDS NETH J CRIT CARE - VOLUME 16 - NO 1 - FEBRUARY 2012
20. Boyles et al, Pharmacological treatments in ARDs: a state of the art update. BMC Medicine 2013 11: 166
21. Mairead Hayes, Gerard Curley, and John G. Laffey, Mesenchymal stem cells – a promising therapy for Acute Respiratory Distress Syndrome F1000 Medicine Reports 2012, 4:2