Beyond low Tidal Volume Ventilation: Treatment Adjuncts for Severe Respiratory Failure in Acute Respiratory Distress Syndrome

Synopsis
This is a summary of trials, observational studies, and reviews of treatments for ARDS, an entity with a mortality of 40%, even in the modern era. Specifically, the authors break the discussion down into three persistent derangements despite low-stretch ventilation per the ARDSNet protocol: hypoxemia (PaO₂<60mmHg for an hour despite 100% FiO₂), respiratory acidosis (pH<7.20 for over an hour despite ‘modest’ increases in T_v and respiratory rate), and elevated plateau pressures (>30mmHg). The summary recommendations are as follows.

Increasing intrathoracic pressures – PEEP and recruitment maneuvers
For refractory hypoxemia, the recommended strategies to consider first are increasing the PEEP, by no more than 2cm H₂O q15min, and using recruitment maneuvers. The evidence for a high PEEP strategy is mixed; no study has shown a mortality benefit in a high PEEP cohort as compared with a similarly low-stretch control group and some evidence from a study using an aggressive PEEP/recruitment maneuver protocol (ART) has suggested an increase in mortality. However, a high-quality meta-analysis demonstrated some benefit and high PEEP is recommended by SCCM and ATS. Similarly, recruitment maneuvers have shown some potential for mild benefit, though an intensive strategy was shown to be associated with harm. High-frequency oscillatory ventilation (HFOV) was addressed in this summary and not recommended.

Neuromuscular Blockade
If the above strategies fail to improve oxygenation or the patient is also experiencing severe acidosis or elevated plateau pressures, the next recommendation is to attempt neuromuscular blockade, using cisatracurium for a time-limited course of 48 hours. This is based on evidence of decreased mortality from the ACURASYS trial, which compared paralysis to deep sedation control patients (HR 0.68, p=0.04).

Prone positioning
The authors recommend prone positioning for hypoxemia refractory to the above strategies, respiratory acidosis, or elevated plateau pressures, as this improves V/Q matching and provides a more uniform distribution of T_v. The evidence comes primarily from the PROSEVA trial, which demonstrated a significant mortality benefit (HR 0.39, p<0.001) to proning among patients with P/F<150mmHg. Of note, about 85% of these patients were paralyzed. Other trials and meta-analyses have clouded the picture a bit with heterogeneous strategies for T_v management, PEEP management, and duration of prone positioning; in the end, the authors recommend consideration of proning for at least 12-16/d.

Inhaled Pulmonary Vasodilators – prostaglandins and NO
The evidence is weak; though no mortality benefit has been shown with these adjuncts, multiple meta-analyses have demonstrated an improvement in P/F ratio. The authors note the potential risks of renal failure associated with NO and hypotension with inhaled prostaglandins, but do recommend consideration of NO (starting dose: 5ppm, uptitrating q30min to a max of 20) in those with refractory hypoxemia, particularly when accompanied by right heart failure. Though a specific recommendation for or against inhaled prostaglandins is not given here, these are commonly used at Penn.

Corticosteroids
The authors recommend steroid therapy (1mg/kg/d methylprednisolone x 3days) for hypoxemia refractory to everything described thus far, but prior to day 14 following ARDS diagnosis. However, the data behind this is very mixed, both in results and in timing of administration (early vs late). Perhaps most applicable to this discussion, a 2011 paper by Brun-Buisson et al showed harm associated with steroid administration in patients with viral pneumonia (HR for mortality 2.82 in a propensity score adjusted analysis, p=0.002).

Renal Replacement Therapy
Noting the potential for RRT to treat acidosis as well as manage volume status, the authors recommend consideration of this therapy in patients with refractory acidosis and/or volume overload, regardless of renal status. The evidence for this is not strong; a recent small randomized trial did show an association with improved oxygenation and increased ventilator-free days.
Extracorporeal Membranous Oxygenation (ECMO)

The two trials discussed here are the Conventional Ventilatory Support Versus ECMO for Severe Adult Respiratory Failure trial and the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial. The former demonstrated improved 6-month survival; however, the ‘intervention’ was transfer to an ECMO-capable institution (only 75% of patients in this group were actually cannulated and there may have been confounding by more uniform application of low-stretch protocols at tertiary referral centers). EOLIA addressed this by randomizing patients with severe ARDS to VV ECMO vs conventional ventilation strategies. Though no statistically significant mortality benefit was shown, a) results trended towards a benefit (35% mortality in ECMO group vs 46% in control group, p=0.09); and b) there was a 28% crossover rate from control to ECMO. Newer trials are ongoing; given both the abilities of ECMO to treat refractory hypoxemia and hypercarbia as well as the ability to use ‘ultraprotective’ ventilation strategies when on VV ECMO, the authors recommend its use for refractory cases. VA ECMO can be considered in patients with cardiac compromise.

The article itself has several useful figures, including 3 algorithms for treatment of hypoxemia, respiratory acidosis, and high plateau pressures, and a table summarizing the adjuncts described above.