ARDS-ICU CHALLENGING DIAGNOSIS

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OVERVIEW

- PATHOPHYSIOLOGICAL MODEL OF ARDS
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- NONEFFECTIVE VS. EFFECTIVE TREATMENT
- CURRENT TREATMENT STRATEGIES
- PULMONARY INFECTIONS COMPLICATING ARDS

PATHOPHYSIOLOGICAL MODEL OF ARDS

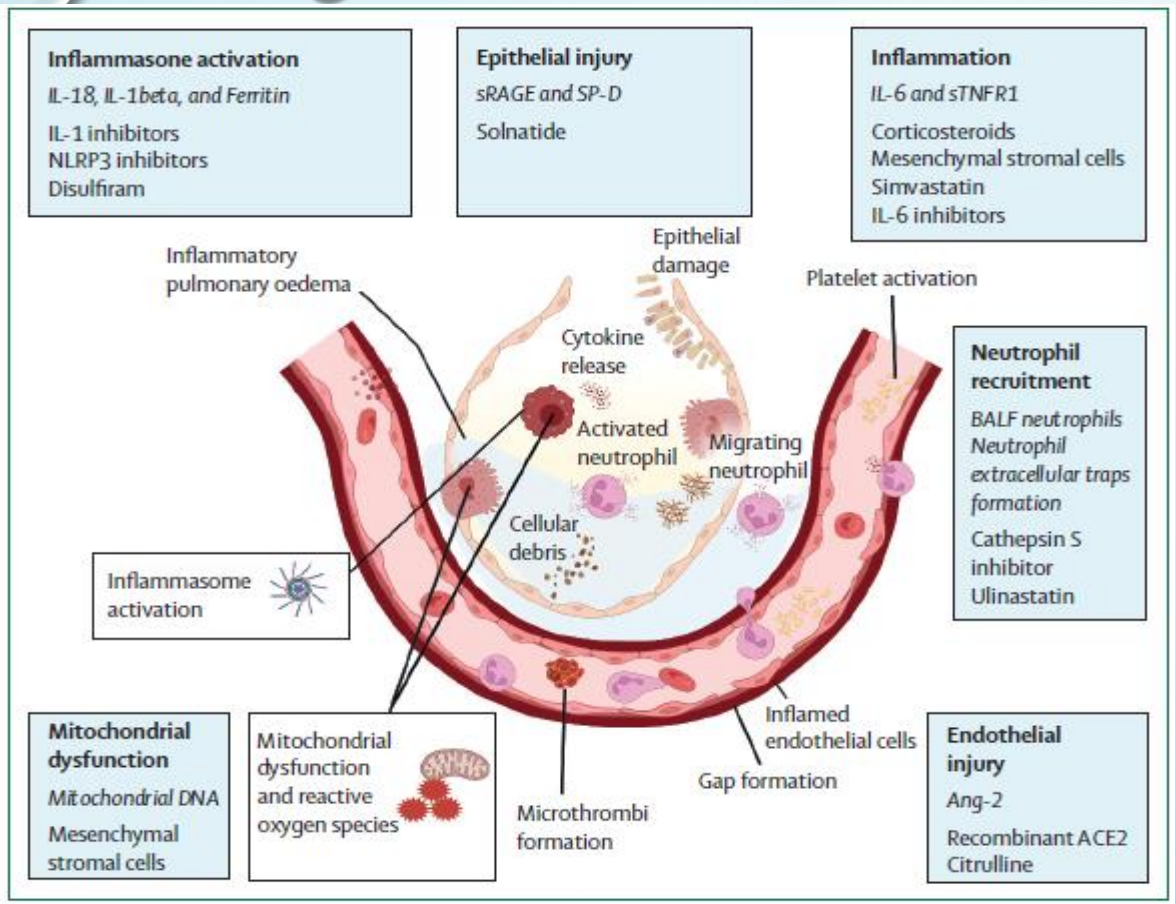


Figure 2: **Potential treatable traits in ARDS, a pathophysiological model**
Treatable traits could be identified by biomarkers (in italics), which align with underlying pathophysiological mechanisms and could be targeted by specific therapeutics or interventions. Biomarkers illustrated are biological markers (ie, obtained from biological samples). Alternative biomarkers might also include imaging, physiology, and clinical data, when they reflect an underlying pathophysiological process that could be responsive to therapy. The pathophysiological model illustrated here probably does not account for the complexities of interactions between pathophysiological mechanisms and individual patient responses. Integration of multiple modalities of information (eg, clinical features, imaging, physiology, biological tests, and multiomics data) might delineate further subphenotypes that could more reliably predict responsiveness to therapies and interventions.
BALF=bronchoalveolar lavage fluid.

Gorman EA, O'Kane CM, McAuley DF. Acute respiratory distress syndrome in adults: diagnosis, outcomes, long-term sequelae, and management. Lancet. 2022 Oct 1;400(10358):1157-1170.

TIMELINE OF ARDS CRITERIA

	Previous criteria AECC	Current criteria Berlin	Short-term possible revisions	Future areas of research
	1994	2012	2022+	Onwards
Timing	Acute, not specified	New or worsening within 7 days		
Chest imaging	Bilateral infiltrates on chest radiograph	Bilateral infiltrates on chest radiograph (or CT)	Ultrasound	
Oxygenation	PaO_2/FiO_2 Acute lung injury <300 mm Hg ARDS <200 mm Hg	PaO_2/FiO_2 Mild >200 mm Hg to ≤300 mm Hg Moderate >100 mm Hg to ≤200 mm Hg Severe ≤100 mm Hg	SpO_2/FiO_2 ratio	
PEEP	Not specfied	Minimum PEEP 5 cm H_2O (continuous positive airway pressure in mild ARDS)	High-flow nasal oxygen, no requirement for minimum PEEP	
Origin of oedema	Pulmonary artery wedge pressure ≤17 mm Hg	Not fully explained by cardiac failure		
Biological markers	None	None		

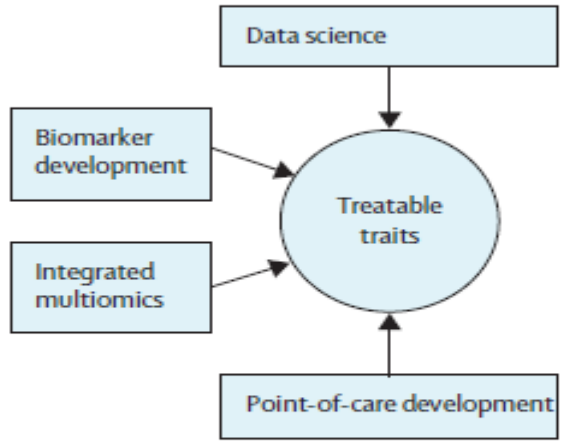


Figure 1: **Timeline of ARDS criteria and future directions**
The first consensus ARDS criteria were the AECC in 1994, followed by the Berlin Consensus Criteria in 2012. ARDS criteria are being revised and potential revisions are illustrated. The future of ARDS in the era of precision medicine strives towards identifying treatable traits. AEEC=American–European Consensus Criteria. PaO_2=partial pressure of arterial oxygen. FiO_2=fraction of inspired oxygen. SpO_2=oxygen saturation. ARDS=acute respiratory distress syndrome. PEEP=positive end expiratory pressure.

Gorman EA, O'Kane CM, McAuley DF. Acute respiratory distress syndrome in adults: diagnosis, outcomes, long-term sequelae, and management. Lancet. 2022 Oct 1;400(10358):1157-1170.

GUIDELINE RECOMMENDATIONS FOR ARDS MANAGEMENT

	The Intensive Care Society and the Faculty of Intensive Care Medicine[49]	The French Intensive Care Society[50]	The American Thoracic Society, European Society of Intensive Care Medicine, and the Society of Critical Care Medicine[51]	WHO living guideline (COVID-19 ARDS)[14]
Non-invasive ventilation	--	--	--	Conditional recommendation in mild ARDS
Lung protective ventilation	Recommended	Recommended	Recommended	Recommended
Prone positioning	Recommended in moderate-to-severe ARDS	Recommended PaO_2/FiO_2 ratio <150 mm Hg.	Recommended in severe ARDS	Recommended PaO_2/FiO_2 ratio <150 mm Hg
High positive end expiratory pressure strategy	Recommended in moderate-to-severe ARDS.	Recommended in moderate-to-severe ARDS	Recommended in moderate-to-severe ARDS	Conditional recommendation for moderate-to-severe ARDS
Driving pressure	--	No recommendation due to insufficient evidence	Research recommendation	Consider driving pressure as part of an individualised positive end expiratory pressure titration strategy
Spontaneous ventilation	--	No recommendation due to insufficient evidence	Research recommendation	--
Recruitment manoeuvres	--	Not recommended	Not routinely recommended	--
High-frequency oscillatory ventilation	Not recommended	Not recommended	Not recommended	--
Extracorporeal membrane oxygenation	Recommended in severe ARDS	Recommended when PaO_2/FiO_2 ratio is <80 mm Hg or lung protective ventilation is not possible	Research recommendation	Conditional recommendation for when PaO_2/FiO_2 ratio is <80 mm Hg despite lung protective ventilation
Extracorporeal carbon dioxide removal	Research recommendation	No recommendation due to insufficient evidence	Research recommendation	--
Conservative fluid strategy	Recommended	--	--	Recommended
Neuromuscular blockade	Recommended in early moderate to severe ARDS	Recommended in early ARDS with a PaO_2/FiO_2 ratio of <150 mm Hg	--	Not routinely recommended for all patients
Inhaled vasodilators	Not recommended	Can be used when hypoxaemia persists despite lung protective ventilation and prone position, and before extracorporeal membrane oxygenation	--	--
Corticosteroids	Research recommendation	--	--	Recommended
Other pharmacological agents	--	--	--	IL-6 receptor blockers (eg, tocilizumab or sarilumab) or baricitinib (Janus kinase inhibitor) is a strong recommendation; monoclonal antibodies (casirivimab and imdevimab) is a conditional recommendation for patients who are seronegative

ARDS=acute respiratory distress syndrome. PaO_2=partial pressure of arterial oxygen. FIO_2=fraction of inspired oxygen.

Table: **Guideline recommendations for ARDS management**

Gorman EA, O'Kane CM, McAuley DF. Acute respiratory distress syndrome in adults: diagnosis, outcomes, long-term sequelae, and management. Lancet. 2022 Oct 1;400(10358):1157-1170.

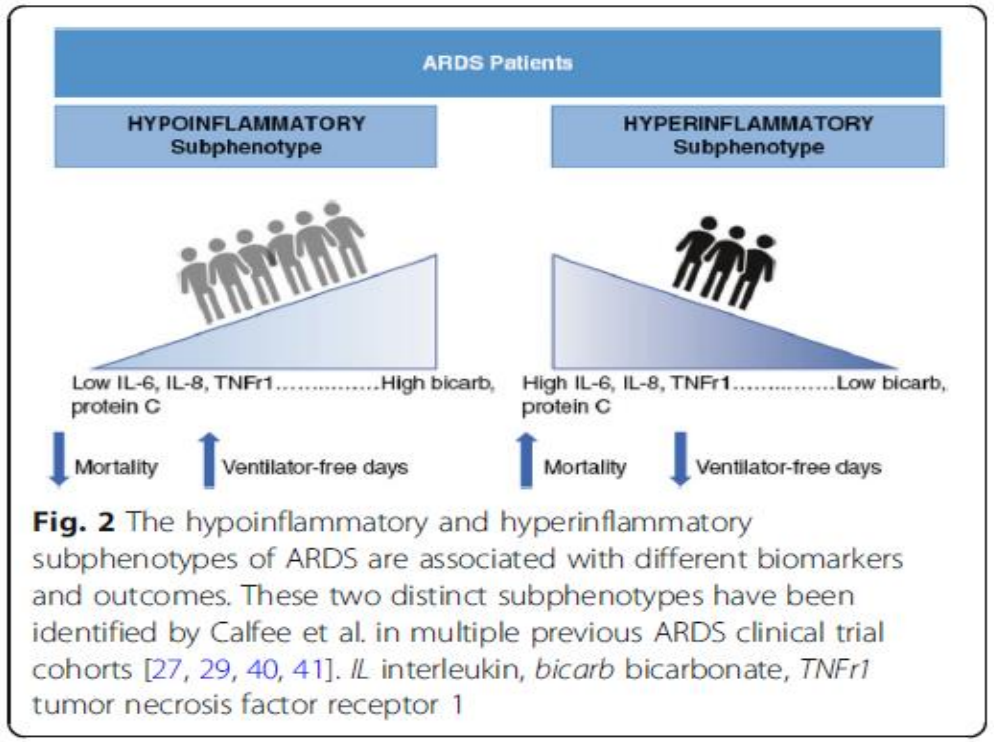


Fig. 2 The hypoinflammatory and hyperinflammatory subphenotypes of ARDS are associated with different biomarkers and outcomes. These two distinct subphenotypes have been identified by Calfee et al. in multiple previous ARDS clinical trial cohorts [27, 29, 40, 41]. *IL* interleukin, *bicarb* bicarbonate, *TNFr1* tumor necrosis factor receptor 1

SUBPHENOTYPE-SPECIFIC TREATMENT

Table 3 Subphenotype-specific treatment response in the reanalyses of outcomes in four different clinical ARDS trials

Intervention/trial cohort analyzed	Outcome	Hypoinflammatory subphenotype response		Hyperinflammatory subphenotype response	
		Intervention	Control	Intervention	Control
High vs. low PEEP/ ALVEOLI* [27]	90-day mortality	24% high PEEP	16% low PEEP	42% high PEEP	51% low PEEP
Conservative vs. liberal fluid strategy/ FACCT* [29]	90-day mortality	18% conservative fluid strategy	26% liberal fluid strategy	50% conservative fluid strategy	40% liberal fluid strategy
Simvastatin/ HARP-2 [40]	28-day survival	No difference		Improved survival with simvastatin (p = 0.008)	
Rosuvastatin/SAILS [41]	90-day mortality	No difference		No difference	

PEEP positive end-expiratory pressure; *p value <0.05 for interaction between treatment and subphenotype

Wilson and Calfee Critical Care (2020) 24:102

BARRIERS TO DIAGNOSIS

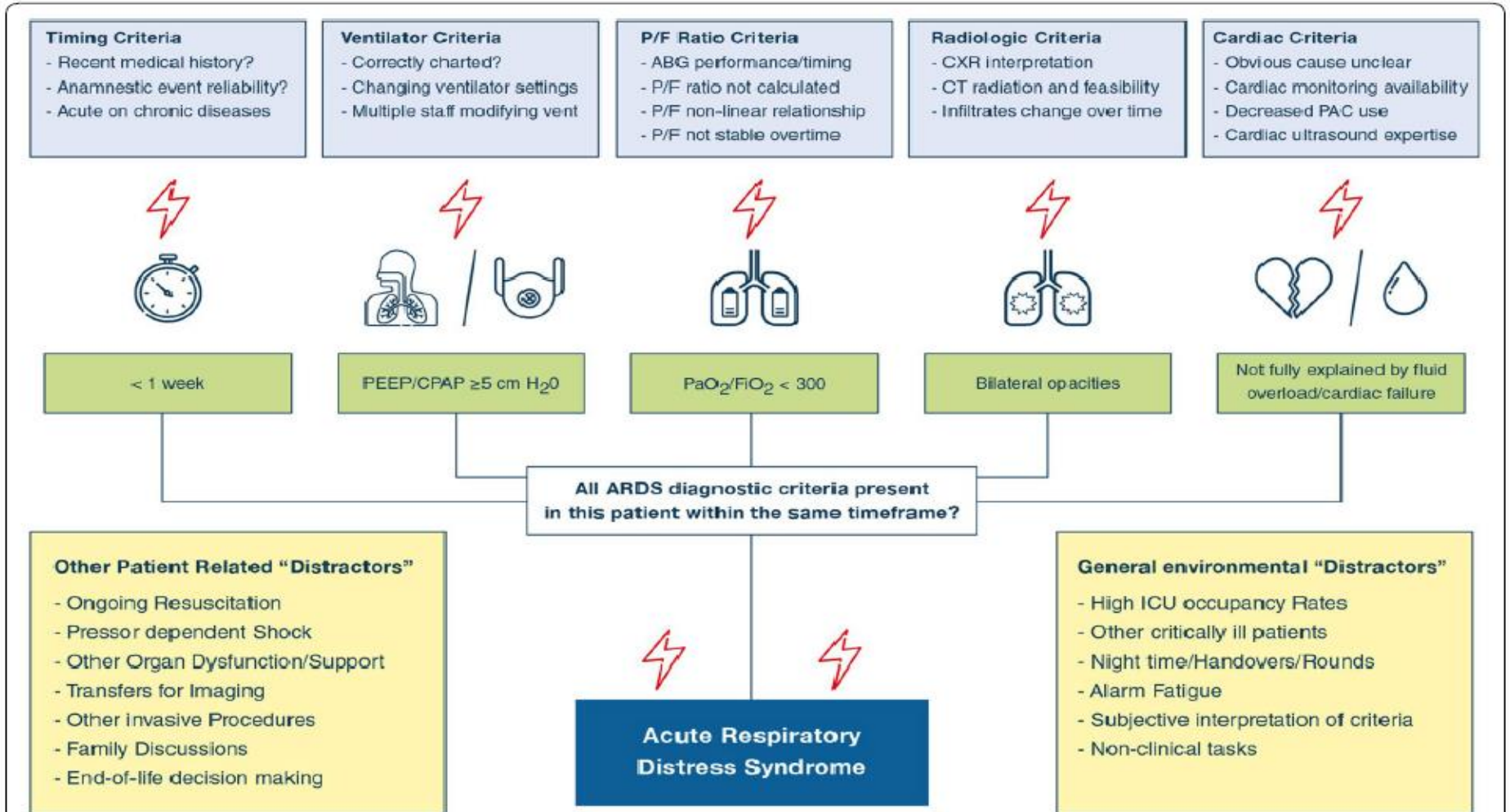
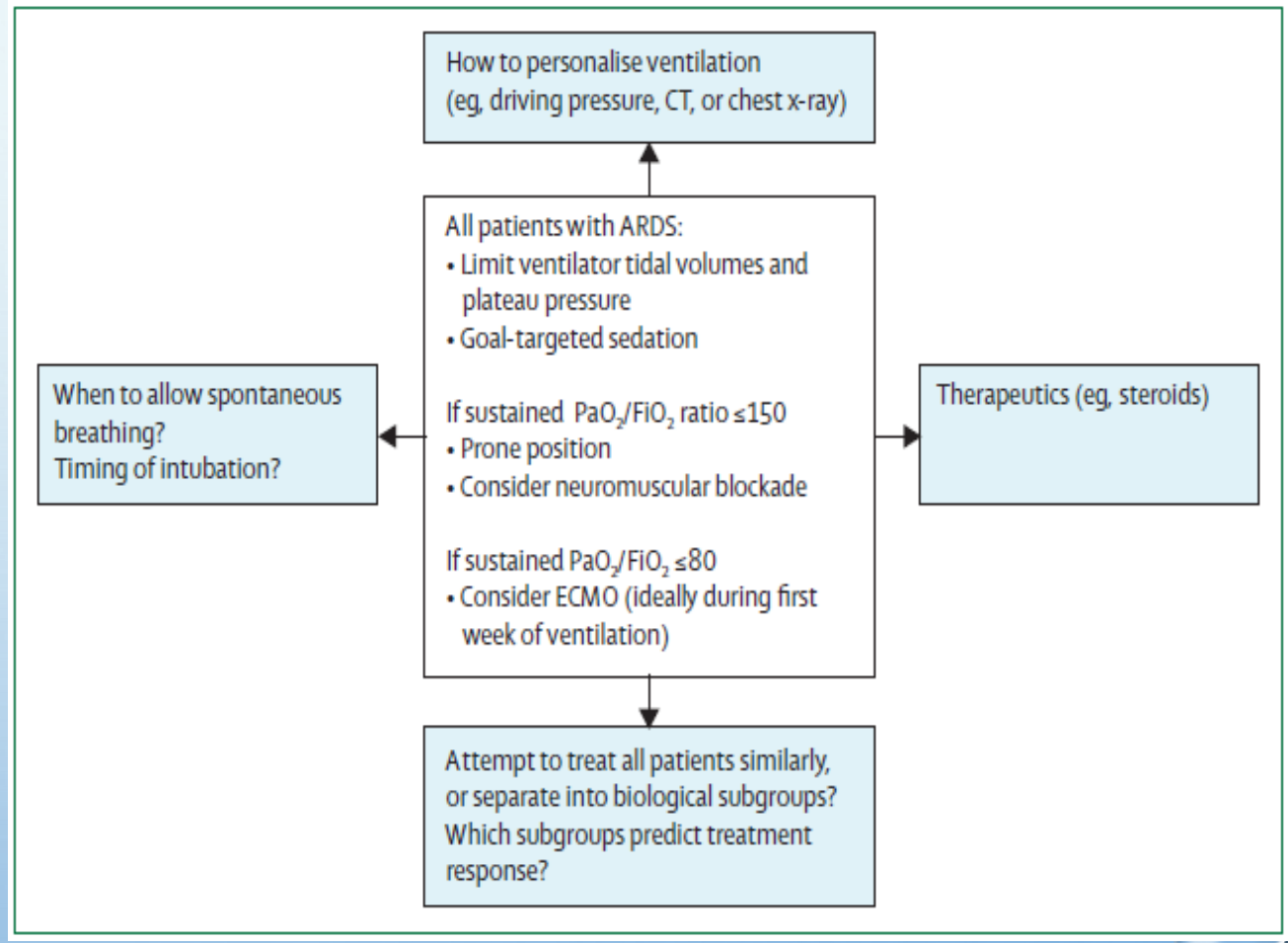


Fig. 1 Barriers to the diagnosis of ARDS. Each item of the ARDS definition poses specific challenges that can impair ability to diagnose ARDS. In addition, other patient-specific issues and the general ICU environment may constitute further barriers to ARDS recognition. *ABG* arterial blood gas, *CXR* chest X-ray, *CT* computed tomography, *PAC* pulmonary artery catheter, *PEEP* positive end expiratory pressure, *CPAP* continuous positive airway pressure

Bellani G, Pham T, Laffey JG. Missed or delayed diagnosis of ARDS: a common and serious problem. Intensive Care Med. 2020 Jun;46(6):1180-1183.

1. HFNC AND NIV
2. IMV
3. PRONE POSITIONING
4. NEUROMUSCULAR BLOCKADE
5. ECMO
6. OTHER RESCUE THERAPIES
7. SUPPORTIVE CARE (FLUIDS)
8. ANTI-INFLAMMATORY THERAPY
9. EXPERIMENTAL TRIALS



Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. Lancet. 2021 Aug 14;398(10300):622-637.

NONEFFECTIVE VS. EFFECTIVE TREATMENT

	Potential mechanisms	Key studies	Comments
Activated protein C	Anticoagulant, anti-inflammatory	Liu et al[138]	..
Anti-endotoxin antibodies	Bind endotoxin and thereby reduce inflammatory response	Bigatello et al[139]	..
Aspirin	Anti-inflammatory via antiplatelet effects	Kor et al[140]	Did not reduce ARDS development in patients at high risk
β-agonists	Improved alveolar fluid clearance	Matthay et al,[141] Gao Smith et al[142]	..
Ibuprofen	Anti-inflammatory, via inhibition of cyclooxygenase	Bernard et al[143]	Did not reduce ARDS development in sepsis
Interferon β-1a	Improve pulmonary endothelial barrier function	Ranieri et al[144]	..
Keratinocyte growth factor	Promote epithelial repair	McAuley et al[145]	..
Ketoconazole	Anti-inflammatory	The ARDS Network[146]	..
Lisofylline	Anti-inflammatory	The ARDS Network[147]	..
Neutrophil elastase inhibitor (eg, sivelestat)	Anti-inflammatory	Zeiher et al,[148] Iwata et al[149]	..
Nitric oxide (inhaled)	Pulmonary vasodilatation, improve V/Q mismatch	Gebistorf et al[150]	Improved oxygenation; increased acute kidney injury
Omega-3 fatty acids	Anti-inflammatory	Rice et al[134]	..
Procysteine and N-acetylcysteine	Reduction in oxidant injury via restoring glutathione	Bernard et al[151]	..
Prostaglandin E1	Pulmonary vasodilatation, improve V/Q mismatch	Fuller et al,[152] Vincent et al[153]	..
Statins (eg, simvastatin, rosuvastatin)	Anti-inflammatory; endothelial stabilisation	McAuley et al,[154] Truwit et al[155]	..
Surfactant	Promote epithelial repair, reduce atelectrauma	Spragg et al[156]	Effective in neonatal respiratory distress syndrome

ARDS=acute respiratory distress syndrome. V/Q=ventilation–perfusion.

Table 1: **Selected pharmacotherapies found to be ineffective for ARDS in human clinical trials**

CURRENT TREATMENT STRATEGIES

	Proposed mechanism	Clinical settings for use	Potential risks	Key studies
ECMO	Allow ultraprotective ventilation; rescue oxygenation	Severe and persistent hypoxaemia ; severe and persistent acidosis; refractory elevated inspiratory plateau pressure; first 7 days of mechanical ventilation with reversible cause	Bleeding, vascular access complications, thrombocytopenia, stroke; only available at referral centres	Peek et al,[167] Combes et al[168]
Higher PEEP strategies	Recruit collapsed alveolar units, thereby improving compliance and oxygenation	Refractory hypoxaemia	Decreased preload leading to hypotension; barotrauma	Mercat et al,[106] Meade et al,[107] Brower et al[108]
Recruitment manoeuvre	Recruit collapsed alveolar units, thereby improving compliance and oxygenation	Refractory hypoxaemia , particularly in patients who seem PEEP responsive	Decreased preload leading to hypotension; barotrauma	Brower et al,[108] Cavalcanti et al[109]
Inhaled pulmonary vasodilators	Improve V/Q matching, reduce pulmonary vascular pressures	Refractory hypoxaemia	Associated with acute kidney injury; development of tachyphylaxis	Gebistorf et al[150]
Corticosteroids	Decrease inflammation	Refractory hypoxaemia	Immunosuppression, critical illness myopathy or neuropathy; increased duration of viral shedding in influenza or SARS-CoV-1; conflicting data on benefits; late administration associated with harm	Lewis et al,[157] Villar et al,[169] Steinberg et al,[170] Bernard et al[171]
CRRT	Additional fluid removal and acid clearance; theoretical cytokine clearance	Refractory acidosis in setting of plateau pressure limitation	Risks of vascular access, bleeding	..

Not recommended: high-frequency oscillatory ventilation.[172,173] ARDS=acute respiratory distress syndrome. CRRT=continuous renal replacement therapy. ECMO=extracorporeal membrane oxygenation. PEEP=positive-end expiratory pressure. V/Q=ventilation–perfusion.

Table 2: **Rescue therapies for ARDS**

Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. Lancet. 2021 Aug 14;398(10300):622-637.

PULMONARY INFECTIONS COMPLICATING ARDS

- PULMONARY INFECTION IS ONE OF THE MAIN COMPLICATIONS OCCURRING IN PATIENTS SUFFERING FROM ARDS
- DYSREGULATION OF LUNG IMMUNE DEFENSES AND MICROBIOTA MAY PLAY AN IMPORTANT ROLE IN ARDS PATIENTS
- ALTHOUGH BACTERIA ASSOCIATED WITH VAP IN ARDS PATIENTS ARE SIMILAR TO THOSE IN PATIENTS WITHOUT ARDS, ATYPICAL PATHOGENS (*ASPERGILLUS*, HSV AND CMV) MAY ALSO BE RESPONSIBLE FOR INFECTION IN ARDS PATIENTS

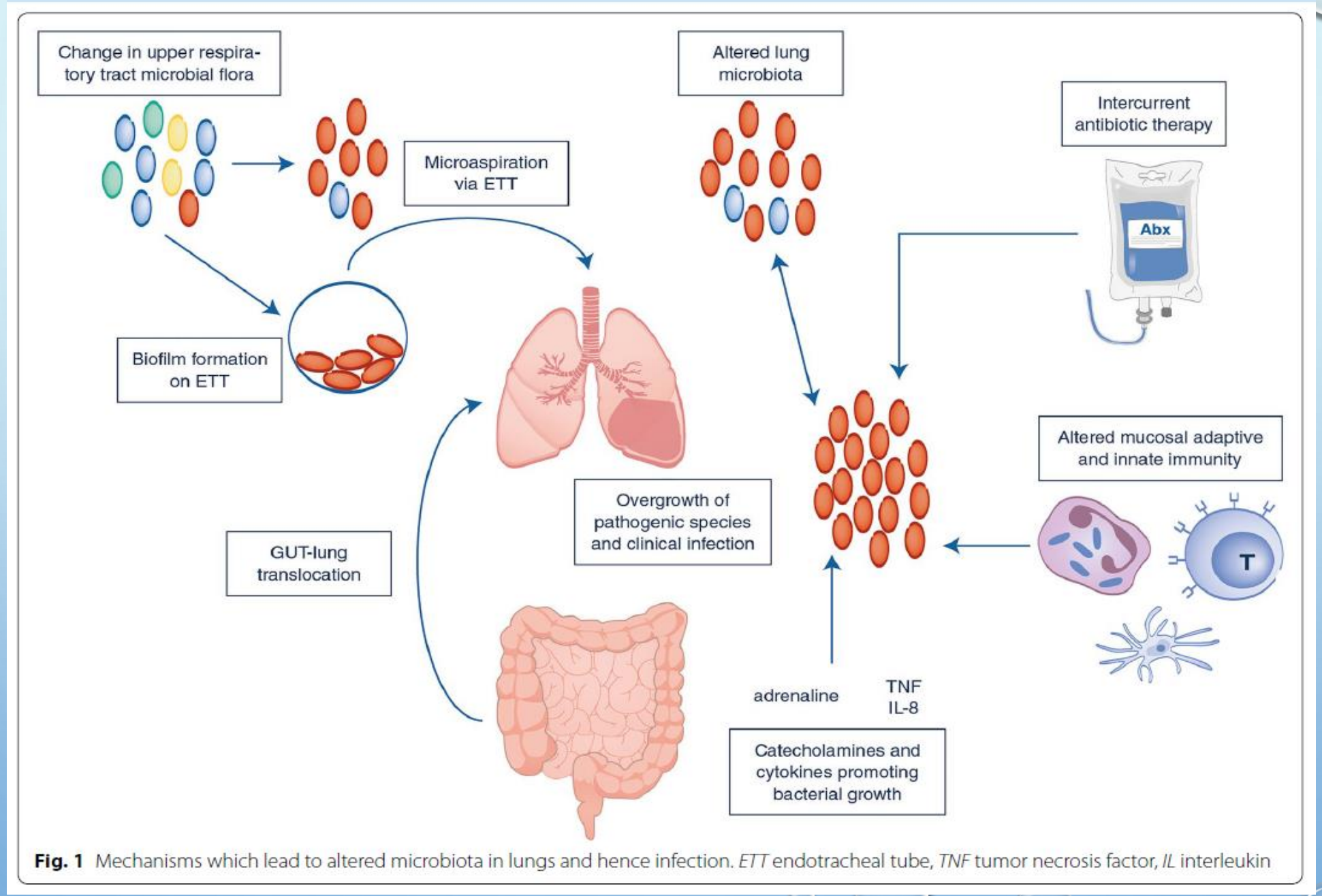


Fig. 1 Mechanisms which lead to altered microbiota in lungs and hence infection. *ETT* endotracheal tube, *TNF* tumor necrosis factor, *IL* interleukin

Luyt CE, et al. Pulmonary infections complicating ARDS. Intensive Care Med. 2020 Dec;46(12):2168-2183.

Table 1 Summary of host-based biomarkers for diagnosis of pneumonia in ARDS

Marker	Performance
Alveolar	
Interleukin-1/interleukin-8	Validated in multi-center cohort [54] but did not influence practice in an RCT [55]
sTREM-1	Initial report, but not validated in follow-up study [113, 114]
Exhaled breath markers	Experimental with technical variation currently limiting implementation [115]
Pentraxin-3	Meta-analysis suggested alveolar levels superior to plasma levels with moderate diagnostic performance, no RCT testing influence on practice [116]
Combination 'bio-score'	May be superior to individual markers, but remains to be validated [117]
Peripheral blood	
C-reactive protein	May be useful predictor of VAP, but non-specific and raised in both sterile and infective inflammation [118]
Procalcitonin	Lacks sensitivity for diagnosis of pneumonia, but can significantly shorten antibiotic duration [118]
Pro-adrenomedullin	Limited utility in diagnosis of pneumonia, but useful as marker of severity [118]
Pentraxin-3	Less effective as a diagnostic than alveolar levels [116]
Presepsin	No reports in VAP
Neutrophil CD64	Role in pneumonia uncertain [8]
Monocyte HLA-DR	Markers of monocyte deactivation and predictor of infection, but poor discriminant value for diagnosis of infection [8]

ARDS acute respiratory distress syndrome, *RCT* randomized controlled trial, *sTREM* soluble triggering receptor expressed on myeloid cells, *VAP* ventilator-associated pneumonia, *HLA* human leukocyte antigen

Luyt CE, et al. Pulmonary infections complicating ARDS. Intensive Care Med. 2020 Dec;46(12):2168-2183.

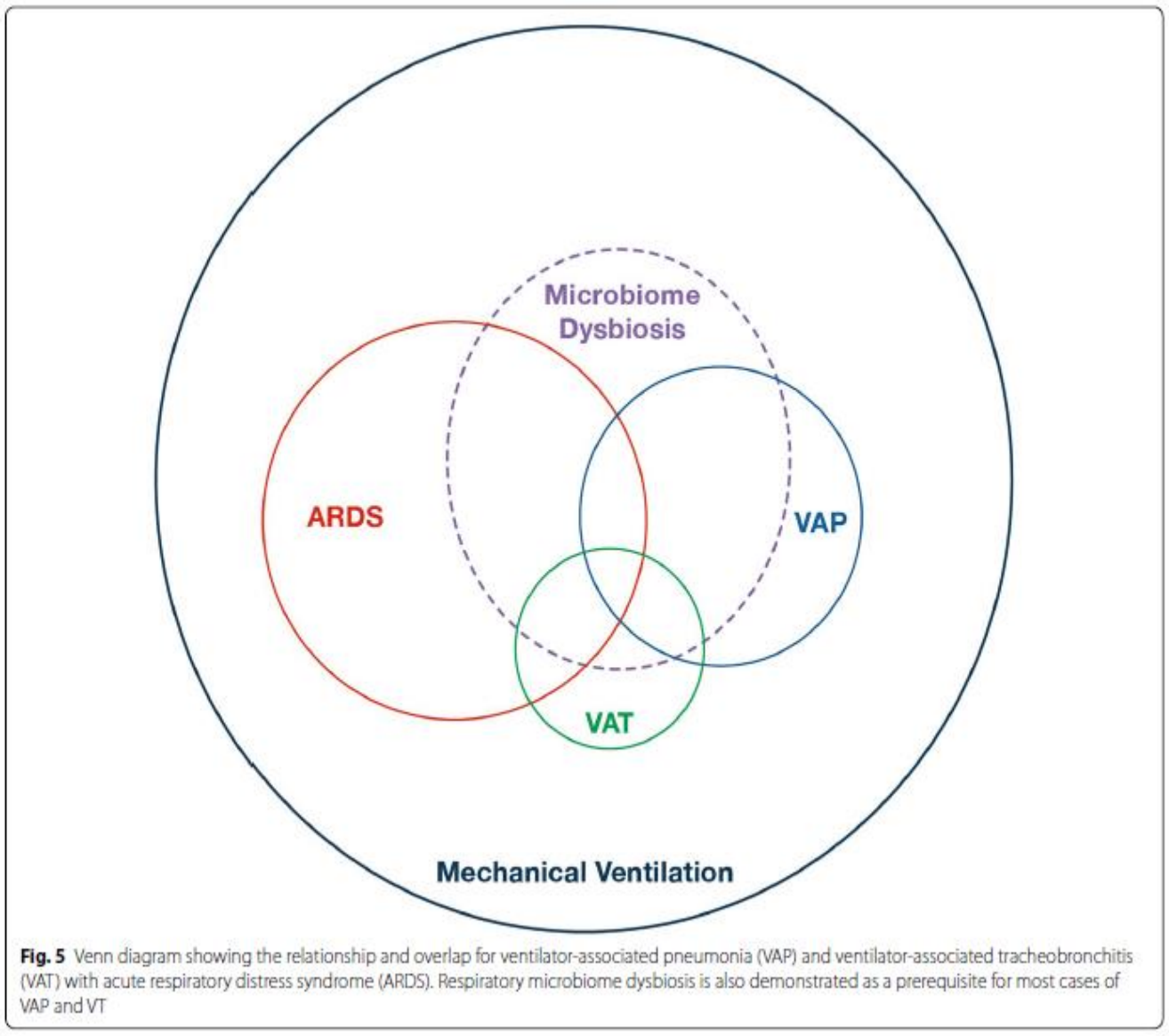


Fig. 5 Venn diagram showing the relationship and overlap for ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT) with acute respiratory distress syndrome (ARDS). Respiratory microbiome dysbiosis is also demonstrated as a prerequisite for most cases of VAP and VT

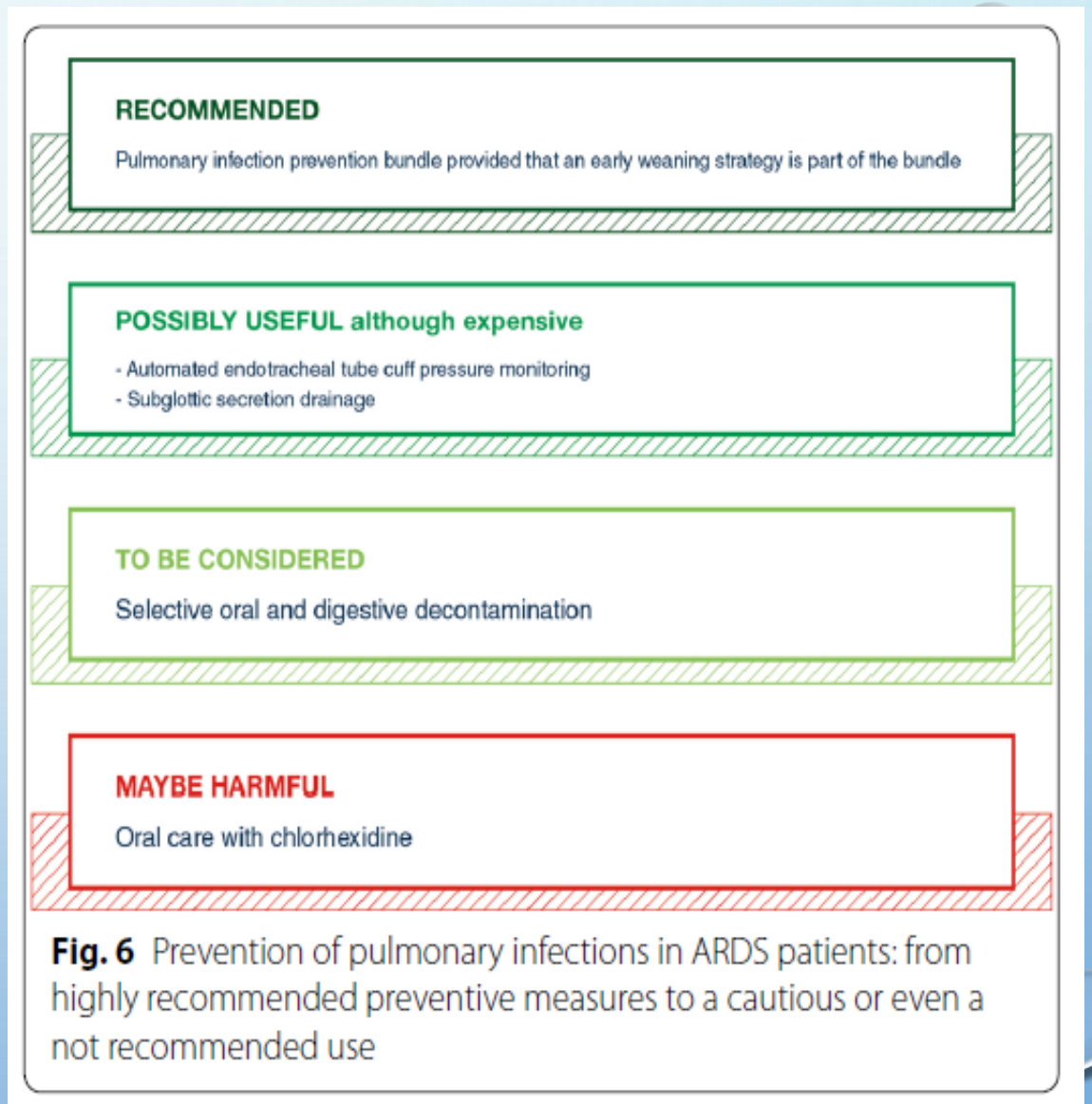


Fig. 6 Prevention of pulmonary infections in ARDS patients: from highly recommended preventive measures to a cautious or even a not recommended use

Luyt CE, et al. Pulmonary infections complicating ARDS. Intensive Care Med. 2020 Dec;46(12):2168-2183.

THANK YOU FOR YOUR ATTENTION!