

NRS Roadmap Intensive Care

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1. **Inventory of Dutch research efforts in this field over the past five years (2008-2013) by ISI web of knowledge**

- COPD
- Asthma
- Non-cardiogenic pulmonary hypertension (PH)
- ARDS
- VIDDD

We used the following search strategy within the Web of Science for each field :

- topic: COPD, asthma, pulmonary hypertension NOT congestive heart, ARDS and ventilator-induced diaphragm dysfunction (VIDDD)
- topic: intensive care
- address: Netherlands
- year of publication: 2009-2013

Afterwards filters were set to:

- document types: article

Respiratory failure is very common in critically ill patients.and reasons for this is can be divided in three main categories:

- Exacerbation of existing pulmonary disease
- Newly developed pulmonary diseases before ICU admission
- Pulmonary dysfunction as complication of ICU treatment

Summary

The first category consists of the pulmonary failure due to the following diseases (and their exacerbations):

- COPD (constructive obstructive pulmonary disease)
- Asthma
- ILD (interstitial lung disease)
- Pulmonary hypertension (not due to congestive heart failure)

The second category contains a large number of diseases, including:

- Acute respiratory distress syndrome (ARDS)
- Severe community acquired pneumonia (SCAP)
- Pulmonary embolism

The third group, pulmonary failure associated with ICU treatment, consists of the following diseases:

- Ventilator induced lung injury (VILI)

- Ventilator-induced diaphragm dysfunction (VIDD)
- ventilator-associated pneumonia (VAP)

The body of research on the first group is limited and is ideal subject for multidisciplinary research between intensivists and pulmonologists. In this roadmap we focussed on existing research on the subject of intensive care medicine in combination with COPD, asthma and pulmonary hypertension. The number of hits on Dutch research on the subject intensive care and ILD was limited to one publication (web of Science) and excluded for further analysis.

ARDS is a major reason for ICU admission and is associated with high morbidity and mortality. ARDS is a common indication for intensive care treatment and is together with VIDD included in the analysis.

The SCAP and VAP are severe pulmonary infections treated by the ICU physician. However, research is often a collaboration between intensivists and infectious disease doctors. There is extended research of Dutch origin on VAP (de Smet, Oostdijk), but also on viral and fungal pulmonary diseases.

Table 1: Results of Web of Science search on patients with a pulmonary disease on the ICU

	Articles	Times cited	Average citation/item	Basic research	Clinical research
COPD	10	138	13.8	0	10
Asthma	10	191	19.10	0	10
PH	13	62	4.77	1	12
ARDS	15	145	9.67	0	15
VIDD	4	51	12.75	4	0

Remarks on COPD & Intensive Care:

- Topics of cited articles are smoking cessation (n = 4), outcome (n = 2) and others (n = 4). Smoking cessation is excluded for further analysis (intensive care is only an endpoint in these studies).

Remarks on Asthma & Intensive Care:

- Asthma in children (n = 5), guidelines (n = 2) + 3 ???? (maakt 10)

Remarks on Pulmonary hypertension & Intensive Care

- Pulmonary hypertension in children (n = 8), clinical experimental research (n = 3), guideline (n = 1), topic is not pulmonary hypertension (but abdominal hypertension) (n =1)

Remarks on ARDS:

- Top 3 cited articles published by (adult patients)
 UMC Utrecht, Dept. Intensive Care Medicine
 AMC Amsterdam, Dept. Intensive Care Medicine/ LEICA
 UMCG Groningen, Dept. Neuroscience

After review of the found articles in the Web of Science we performed a second search on the subject ARDS without the limitation intensive care, as we doubt whether the research groups within the field of ARDS were sufficiently identified by

the search above. 66 articles were found produced by UMC Utrecht, AMC Amsterdam, VUMC Amsterdam and EMC Rotterdam.

Remarks on VIDD:

- All articles are published by Radboud UMC

2. Visibility Dutch research judged by international experts (see also appendix)

Areas with good visibility	Areas with less visibility

3. Research needs

Facts and Figures (2013)

Facts and needs COPD

An increasing number of patients is diagnosed with COPD. Many patients with COPD suffer of several other co-morbidities (especially cardio-vascular) and reach a higher age (CBS Statline). This makes these patients at risk for the need for IC treatment.

Burden of the research on COPD is done in outpatient setting or in-hospital, with intensive care admission as an exclusion criteria or an endpoint. This makes it unsure whether interventions found to be beneficial in these studies are also applicable in the ICU setting. Within the intensive care literature main focus of research in patients with COPD is on non-invasive mechanical ventilation, and the ventilator-patient synchrony during invasive ventilation. Evidence based medicine on subjects as the use of (outpatient) medication for the treatment of COPD in ICU is limited. The same counts for IC-admission criteria for patients with COPD, criteria for withholding ICU-therapy in these patients and long-term prognosis. An interesting topic demanding a multicenter effort is the use of CO₂-removers in patients with an exacerbation COPD treated in the intensive care unit.

Facts and needs asthma

The intensive care literature on asthma is mainly focused on the initial presentation in the emergency department, but even within this field the level of evidence is low. Best evidence is found for emergency and ICU therapy in *children* with asthma. Collaboration with other research groups in the field of emergency and pulmonary medicine, for example those described in the NRS

Roadmap Asthma, could increase the level of evidence in the treatment of respiratory failure due to an exacerbation asthma.

Facts and needs pulmonary hypertension

Pulmonary hypertension is a common finding in the ICU, but mainly originates from congestive heart failure, and there is a lot of research available on this subject. Non-cardiogenic pulmonary hypertension due to conditions such as COPD, ILD, pulmonary embolism, auto-immune disease or obesity is seen in an increasing number of patients due to changes in the demographics of the population (like more COPD, higher BMI). Intensive care literature on pulmonary hypertension is mainly focused on cardiogenic pulmonary hypertension. The NRS Roadmap Pulmonary Hypertension describes research efforts in this area; it would be interesting to broaden this field with collaboration with intensive care researchers, especially on the subject of pharmacologic interventions

Facts and needs ARDS

ARDS is an indication for ICU admission and is also an important complication of mechanical ventilation (due to VILI), nevertheless it still is a relatively uncommon diagnosis. The pathophysiological model of ARDS is of inflammatory origin. Clinical research in the field of ARDS requires multicenter studies. Basic research could benefit of collaboration of researchers working on ARDS and, for example, COP or ILD. International research is focused on mechanical ventilation (ARDS network studies); the use of ECMO is an area with increasing interest. In the Netherlands the number of adult patients on ECMO is increasing, but still limited. A joint-effort of the ECMO centers is crucial to increase the level of evidence of this life-saving therapy.

Facts and needs ILD

Patients with a known interstitial lung disease at admission are relatively rare in the ICU, while the number of patients with ILD in the population is increasing (CBS Statline). Furthermore, cryptogenic organizing pneumonia (COP) is a more common complication of, for example, SCAP. Research efforts within the field of ILD (including COP) and intensive care medicine are very limited in the Netherlands, but there are strong research groups working on ILD and COP outside the Netherlands (see Roadmap ILD). Collaboration between these two groups would make it possible to increase level of evidence for intensive care therapy for patients with ILD.

Euro costs²

Unmet needs

References

4. Summary of SWOT analysis

Table 3 shows the SWOT-analysis for Dutch research on the subject of pulmonary diseases on the ICU. Due to the limited number of publications strength and weakness are the same for all 4 diseases. Major threats are, especially for this roadmap, the lack of collaboration between research groups, as the numbers of patients is limited, and the lack of collaboration between pulmonologists and intensive care physician, though this is also an opportunity to strengthen multidisciplinary research, and care.

Disease	Strength	Weakness	Opportunities	Threats
COPD	Many patients	Not a focus of current research	Joint-research between centers and pulmonologists and intensive care specialists; admission criteria, invasive mechanical ventilation, pharmacologic interventions, CO ₂ -removal	Competition instead of collaboration between research groups AND between pulmonologists and intensive care physicians
Asthma	NRS Roadmap	Limited number of patients; not a focus of current research	Collaboration between research groups IC, pulmonary medicine and emergency medicine; pharmacologic treatment respiratory failure	Lack of funding
PH	NRS Roadmap	Not a focus of current research	Collaboration with NRS Roadmap PH Joint-multicenter research, collaboration between research groups on ILD/COP and ARDS, national research on ECMO	Fragmentation of patient groups (for example: ECMO patients)
ARDS	Strong IC-research groups Strong ILD/COP research groups	Limited number of patients; little collaboration	Collaboration between pulmonologists and intensive care specialists	
VIDD	Strong IC- research group	Unknown disease		

Table 3: SWOT analysis on research in the Netherlands on COPD, asthma, ILD and non-cardiogenic pulmonary hypertension in the ICU.

Relevance of research judged by 5 international experts (order of importance):

See Table *Relevance of research judged by international experts* in appendix

	Mean
Phenotyping and Severity	
Biological mechanisms	
Environment and lifestyle	
Development and ageing	
Prevention	
Diagnosis monitoring	
Therapy medical	
Therapy non-medical	
Biobanking	
Data management clinical studies	
Implementation and care	

5. Description of the interface of asthma with other Roadmap areas

The roadmap Intensive Care is an extension of the roadmaps on COPD, asthma, ILD and pulmonary hypertension, though its areas of interest are solely focussed on the critically ill patient. This counts for clinical research, but also for basis research, in which the interaction between intensive care therapy or critically illness and the underlying disease is the primary area of interest.

6. Priorities for Dutch research in the area for 2014-2019

- Defining priorities in areas of interest, both basic and clinical
- Creating funding for research on pulmonary dysfunction and intensive care medicine
- Starting multicenter national research projects, especially in case of small patient populations on the ICU (ILD, asthma) or rare complex therapies (CO₂-removal, ECMO)
- Starting multidisciplinary collaboration research projects between intensive care specialists, pulmonologists (and emergency doctors in the case of asthma)
- Participation in international studies on this subject

7. What is needed to let the research priorities listed be successful?

- National collaboration between ICU research group
- Collaboration between intensive care and pulmonary research groups
- Collaboration with attached roadmaps
- Formation of national fund for ICU-research on these subjects

8. What do patients want?

There is no intensive care patient platform, society or other institution which represents the intensive care patients in general, nor intensive care patients with a pulmonary disease. Intensive care therapy is out of the focus of the patient organizations as the Longfonds. This is one of the reasons making funding of IC-research difficult.

Table 1 . Top 10 most cited basic research initiated by a Dutch group:

Theme	Article	Citations	
		Total	Mean/ yr
PH	Vos RM, Chahbouni A, Sinjewel A, et al. Quantitative analysis of sildenafil and desmethylsildenafil in human serum by liquid chromatography-mass spectrometry with minimal sample pretreatment. Epub. 2008; 876(2): 283-287	6	
ARDS	Rockx B, Baas T, Zornetzer GA, et al. Early upregulation of acute respiratory distress syndrome-associated cytokines promotes lethal disease in an aged-mouse model of severe acute respiratory syndrome coronavirus infection. J Virol. 2009; 14: 7062-7074	32	
VIDD	Brander L, Sinderby C, Lecomte F, et al. Neurally adjusted ventilatory assist decreases ventilator-induced lung injury and non-pulmonary organ dysfunction in rabbits with acute lung injury. Intensive Care Med. 2009; 35: 1979-1989.	34	
VIDD	van Hees HW, Schellekens WJ, Andrade Acuña GL, et al. Titin and diaphragm dysfunction in mechanically ventilated rats. Intensive Care Med. 2012; 38: 702-709.	5	

Table 2. Top 10 most cited clinical research initiated by a Dutch group:

Theme	Article	Citations	
		Total	Mean/ yr
COPD	Snijders D, van der Eerden M, de Graaff C, et al. The influence of COPD on mortality and severity scoring in community-acquired pneumonia. <i>Respiration</i> . 2010; 79: 46-53	10	
COPD	Veelo DP, Dongelmans DA, Binnekade JM, et al. Adaptive support ventilation: a translational study evaluating the size of delivered tidal volumes. <i>Int J Artif Organs</i> . 2010; 33: 302-309	4	
COPD	van Ranst D, Otten H, Meijer JW, et al. Outcome of pulmonary rehabilitation in COPD patients with severely impaired health status. <i>Int J Chron Obstruct Pulmon Dis</i> . 2011; 6: 647-657	2	
Asthma	van den Bosch GE, Merkus PJ, Buysse CM, et al. Risk factors for pediatric intensive care admission in children with acute asthma. <i>Respir Care</i> . 2012; 57: 1391-1397	2	
Asthma	Koninckx M, Buysse C, de Hoog M. Management of status asthmaticus in children. <i>Paediatr Respir Rev</i> . 2013; 14: 78-85	1	
Asthma	Eber E, Aurora P, Lødrup Carlsen KC, et al. Paediatrics in Amsterdam. <i>Eur Respir J</i> . 2012; 40: 215-226	1	
PH	Keijzer R, Puri P. Congenital diaphragmatic hernia. <i>Semin Pediatr Surg</i> . 2010; 19: 180-185	30	
PH	Top AP, Ince C, Schouwenberg PH, et al. Inhaled nitric oxide improves systemic microcirculation in infants with hypoxemic respiratory failure. <i>Pediatr Crit Care Med</i> . 2011; 12: 271-274	6	
PH	Richir MC, van Leeuwen PA, van den Berg A, et al. Plasma ADMA concentrations at birth and mechanical ventilation in preterm infants: a prospective pilot study. <i>Pediatr Pulmonol</i> . 2008; 43: 1161-1166	5	
ARDS	van der Heijden M, van Nieuw Amerongen GP, Koolwijk P, et al. Angiopoietin-2, permeability oedema, occurrence and severity of ALI/ARDS in septic and non-septic critically ill patients. <i>Thorax</i> . 2008; 63: 903-909	52	
ARDS	Kesecioglu J, Beale R, Stewart TE, et al. Exogenous natural surfactant for treatment of acute lung injury and the acute respiratory distress syndrome. <i>Am J Respir Crit Care Med</i> . 2009; 10: 989-994	34	
VIDD	Schellekens WJ, van Hees HW, Vaneker M, et al. Toll-like receptor 4 signaling in ventilator-induced	8	

	diaphragm atrophy. Anesthesiology. 2012; 117: 329-338		
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Table 3. Top 10 most cited collaborative international basic research (excl. reviews, guidelines):

Theme	Article	Citations	
		Total	Mean/ yr
ARDS	Narasaraju T, Yang E, Samy RP, et al. Excessive neutrophils and neutrophil extracellular traps contribute to acute lung injury of influenza pneumonitis. Am J Pathol. 2011; 179: 199-210	60	

Table 4. Top 10 Most cited collaborative international clinical research (excl, reviews, guidelines):

Theme	Article	Citations	
		Total	Mean/yr
	Van Kerkhove MD, Vandemaele KA, Shinde V, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Med. 2011; 8	92	
	Thébaud B, Tibboel D. Pulmonary hypertension associated with congenital diaphragmatic hernia. Cardiol Young. 2009; 1: 49-53	6	

Table 5: Top 10 best cited review and guideline papers with Dutch collaborators:

Theme	Article	Citations	
		Total	Mean/ yr
Asthma	Soar J, Perkins GD, Abbas G, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. Resuscitation. 2010; 81: 1400-1433	87	
COPD	Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections--full version. Clin Microbiol Infect. 2011; 6	62	
ARDS	Meduri GU, Marik PE, Chrousos GP, et al. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. Intensive Care Med. 2008; 34: 61-69	59	

APPENDIX

Opinions of international key opinion leaders

Questions were sent to international experts in the field about the visibility of Dutch Intensive Care research.

Question 1

Which research topics and groups in Intensive Care research are visible and have impact on pulmonary physicians and researchers outside the Netherland?

Expert 1

Question 2

Which research topics in Intensive Care research are less visible to physicians and researchers outside the Netherland?

Expert 1

Relevance of research judged by international experts (order of importance)

Research performed in the Netherlands in the field of **Intensive Care**

0= no relevant research

5= excellent research, international top level

	1	Mean
Phenotyping and Severity	4	
Biological mechanisms	4	
Environment and lifestyle	0	
Development and ageing	3	
Prevention	0	
Diagnosis monitoring	4	
Therapy medical	4	
Therapy non-medical	3	
Biobanking	2	
Data management clinical studies	2	
Implementation and care	4	