



# LUND UNIVERSITY

## Inhaled corticosteroids in chronic obstructive pulmonary disease a two-edged sword

Riesbeck, Kristian

*Published in:*  
American Journal of Respiratory and Critical Care Medicine

*DOI:*  
[10.1164/rccm.201605-0942ED](https://doi.org/10.1164/rccm.201605-0942ED)

2016

*Document Version:*  
Peer reviewed version (aka post-print)

[Link to publication](#)

*Citation for published version (APA):*  
Riesbeck, K. (2016). Inhaled corticosteroids in chronic obstructive pulmonary disease a two-edged sword. *American Journal of Respiratory and Critical Care Medicine*, 194(10), 1177-1178.  
<https://doi.org/10.1164/rccm.201605-0942ED>

*Total number of authors:*  
1

### General rights

Unless other specific re-use rights are stated the following general rights apply:  
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00

## Inhaled corticosteroids in COPD – a two-edged sword

The field of immunology is constantly expanding, and although focus has slightly turned from T cell- to more B cell-oriented research, new knowledge on unconventional T cells is still garnered. One example of this is the relatively recently discovered MR1-restricted T cells designated "mucosal associated invariant T" (MAIT) cells (1). Intriguingly, MAIT cells comprise 5-10 % of the total pool of CD3<sup>+</sup> T cells in peripheral blood. As a result of development of monoclonal antibodies, the CD161<sup>+</sup> MAIT cell subset has been defined as having an invariant T cell receptor designated TCR V $\alpha$ 7.2 that recognizes the MR1 molecule on antigen-presenting cells, for example, B cells.

MR1 is attached to  $\beta$ 2 microglobulin, and therefore is designated as "MHC (HLA) class I-like". The MR1 molecule is non-polymorphic, which is in bright contrast to the classical MHC molecules. This means that there are only a few compounds/ molecules that actually are loaded on MR1 and consequently presented for the MAIT cell subset. Importantly, it is now known based upon refolding experiments and crystallization that it is mainly riboflavin (vitamin B2) derivatives that are bound to MR1 (2).

The human host does not produce riboflavin itself but here bacteria come into the picture (3). Upon a bacterial infection and consequently increased densities of MR1 on antigen presenting cells, MAIT cells become important players. They then can promote inflammation by inducing a mixture of T helper (Th) cytokines, and interferon (IFN)- $\gamma$ , reflecting a Th1 profile, has been shown to be produced by MAIT cells originating from the lung (4). MAIT cells have also the capacity to directly kill epithelial cells that are infected with bacteria by using granzymes. Hence MAIT cells can be attributed to the innate immune system despite they do not sense infections by all microbes (5); viruses and a few Gram-positive bacteria, amongst others, group A streptococci are exceptions, and are not under attack since they cannot produce riboflavin metabolites.

In parallel to other Gram-negative bacteria, the coccobacillus *Haemophilus influenzae* possesses a riboflavin synthesis pathway (6), which indirectly (via MR1) may trigger MAIT cells. The bacterium also resides intracellularly in bronchial epithelial cells (7), which further would be a suitable target for the cytotoxic MAIT cells. Since the introduction of a vaccine against encapsulated *H. influenzae* type b (Hib), the incidence of invasive disease including meningitis and sepsis by *Haemophilus* has significantly decreased. Non-typeable, that is, non-encapsulated *H. influenzae* (NTHi) has in parts occupied the niche of Hib's, and might even break more ground after introduction of pneumococcal vaccines in child immunization programmes recent years. Despite NTHi is a commensal in pre-school children, it is one of the major causes of mucosal infections in the airways. The pathogen is associated with acute otitis media in pre-school children, sinusitis in adults, and finally exacerbations in patients with chronic obstructive pulmonary disease (COPD) (8). In fact, COPD patients are particularly vulnerable since NTHi maintains a chronic inflammation in this group of patients also during stable disease (9). Moreover, NTHi is overrepresented in patients with poorly controlled asthma (10).

The current opinion is that COPD patients administered inhaled corticosteroids (ICS) have an elevated risk of pneumonia albeit there is a reduced incidence of acute exacerbations and no increased risk of mortality (11). In the present issue of the *Journal* (pp. XX-YY), Hinks and collaborators reveal the mechanisms behind those clinical observations in COPD patients (GOLD stage 2) with emphasis on ICS-dependent effects on the peripheral and bronchial MAIT cell populations. The authors also shed light upon the importance of MAIT

cells with respect to the commonly found bacterial species NTHi. Interestingly, when peripheral blood T cells (CD3<sup>+</sup>) were analysed, a decreased percentage of MAIT cells was found in COPD patients on ICS as compared to healthy control individuals not receiving any ICS. In parallel, bronchial biopsies from COPD patients also revealed less MAIT cells in the lung tissue. Analyses of bronchoalveolar lavage (BAL) and sputum did not, however, confirm the findings with peripheral blood and lung tissue, a phenomenon the authors suggest to be related to differences in MAIT phenotypes in various anatomical compartments.

The capacity of NTHi to activate either lung macrophages or blood monocyte derived macrophages was also determined. Here, NTHi significantly increased MR1 and HLA-DR (class II) density on the cell surface, whereas no effect was seen with HLA-ABC (class I). There was not any *de novo* production of MR1 mRNA but only a presumed NTHi-dependent post-transcriptional effect. In contrast to whole cell NTHi, pro-inflammatory cytokines or purified LPS in addition to influenza virus did not increase MR1 expression. The authors next harvested monocyte-derived macrophages (MR1<sup>+</sup>) that had been pre-stimulated with NTHi, and added these cells to MAIT cells, CD4<sup>+</sup> or CD8<sup>+</sup> T cells followed by flow cytometry analysis after intracellular staining of IFN- $\gamma$ . In these experiments, all T cell subsets responded with a Th1 profile albeit only MAIT cells were activated via MR1 as proven with a neutralizing monoclonal antibody. Finally, to translate their observations on NTHi-dependent upregulation of MR1 that in turn triggered MAIT cells, Hinks and collaborators investigated the effect of fluticasone and budesonide on MR1 expression and IFN- $\gamma$ -secreting MAIT cells. The effectiveness of both steroids was verified, that is, the antigen-presenting MR1 and pro-inflammatory cytokine release was efficiently inhibited in these experiments.

In this study, there are as expected large variations in cellular responses between subjects implying confounding factors. The genotypes of patients' are most likely highly heterogeneous explaining differences in immune responses mounted, and further research on and stratification of COPD is thus required (12). If we evaluate individual patients in a clinical setting, another factor is that the lung microbiome may differ, a research field that has attracted much interest lately (13). Moreover, polymicrobial infections are common, an aspect that will further complicate the picture. It is indisputable, however, that NTHi is a key player in promoting inflammation in COPD patients, and due to the highly variable genome, NTHi may induce various responses. As yet it has, however, been difficult to find precise disease-causing patterns in this highly heterogeneous species (14).

Parallels that can be drawn between COPD and asthma patients on ICS therapy are striking despite the latter group seems to carry more different T cell phenotypes (1). Patients with severe asthma, presumably receiving more corticosteroids have markedly decreased levels of MAIT cells in peripheral blood as well as in bronchial biopsies. This may be one explanation as to why particularly patients with severe asthma also run an increased risk of pneumonia and sepsis (15).

In conclusion, although this highly interesting study is mainly based upon experiments done *ex vivo* it paves the way for further investigations on the innate T cell defense directed against bacteria such as NTHi that dwell in the lower respiratory tract. A customized therapy based upon a combination of patient genetics with focus on innate immune parameters, the microbiome status, and finally GOLD stage will be a future challenge in the era of personalized medicine.

## References

1. Hinks TS. Mucosal-associated invariant T cells in autoimmunity, immune-mediated diseases and airways disease. *Immunology* 2016;148:1-12.
2. Kjer-Nielsen L, Patel O, Corbett AJ, Le Nours J, Meehan B, Liu L, Bhati M, Chen Z, Kostenko L, Reantragoon R, *et al.* MR1 presents microbial vitamin B metabolites to MAIT cells. *Nature* 2012;491:717-23.
3. Howson LJ, Salio M, Cerundolo V. MR1-Restricted Mucosal-Associated Invariant T Cells and Their Activation during Infectious Diseases. *Front Immunol* 2015;6:303.
4. Leeansyah E, Loh L, Nixon DF, Sandberg JK. Acquisition of innate-like microbial reactivity in mucosal tissues during human fetal MAIT-cell development. *Nat Commun* 2014;5:3143.
5. Le Bourhis L, Dusseaux M, Bohineust A, Bessoles S, Martin E, Premel V, Coré M, Sleurs D, Serriari NE, Treiner E, *et al.* MAIT cells detect and efficiently lyse bacterially-infected epithelial cells. *PLoS Pathog* 2013;9(10):e1003681.
6. Saeed-Kothe A, Yang W, Mills SD. Use of the riboflavin synthase gene (ribC) as a model for development of an essential gene disruption and complementation system for *Haemophilus influenzae*. *Appl Environ Microbiol* 2004;70:4136-43.
7. Ahrén IL, Williams DL, Rice PJ, Forsgren A, Riesbeck K. The importance of a beta-glucan receptor in the nonopsonic entry of nontypeable *Haemophilus influenzae* into human monocytic and epithelial cells. *J Infect Dis* 2001;184:150-8.
8. Van Eldere J, Slack MP, Ladhani S, Cripps AW. Non-typeable *Haemophilus influenzae*, an under-recognised pathogen. *Lancet Infect Dis* 2014;14:1281-92.
9. Tufvesson E, Bjermer L, Ekberg M. Patients with chronic obstructive pulmonary disease and chronically colonized with *Haemophilus influenzae* during stable disease phase have increased airway inflammation. *Int J Chron Obstruct Pulmon Dis* 2015;10:881-9.
10. Simpson JL, Daly J, Baines KJ, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, Hugenholtz P, Willner D, *et al.* Airway dysbiosis: *Haemophilus influenzae* and *Tropheryma* in poorly controlled asthma. *Eur Respir J* 2016;47:792-800.
11. Festic E, Bansal V, Gupta E, Scanlon PD. Association of Inhaled Corticosteroids with Incident Pneumonia and Mortality in COPD Patients; Systematic Review and Meta-Analysis. *COPD* 2015;8:1-15.
12. Malhotra R, Olsson H. Immunology, genetics and microbiota in the COPD pathophysiology: potential scope for patient stratification. *Expert Rev Respir Med* 2015;9:153-9.
13. Einarsson GG, Comer DM, McIlreavey L, Parkhill J, Ennis M, Tunney MM, Elborn JS. Community dynamics and the lower airway microbiota in stable chronic obstructive pulmonary disease, smokers and healthy non-smokers. *Thorax* 2016 May 4. pii: thoraxjnl-2015-207235. doi: 10.1136/thoraxjnl-2015-207235. [Epub ahead of print] PubMed PMID: 27146202.

14. Jalalvand F, Riesbeck K. *Haemophilus influenzae*: recent advances in the understanding of molecular pathogenesis and polymicrobial infections. *Curr Opin Infect Dis* 2014;27:268-74.
15. Torres A, Blasi F, Dartois N, Akova M. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. *Thorax* 2015;70:984-9.

Figure 1. Non-typeable *Haemophilus influenzae* in the lung from a COPD patient. Courtesy of Dr. Matthias Mörgelin (Lund University, Sweden).

