Centre Hospitalier Universitaire de Nice
UNIVERSITÉ CÔTE D'AZUR

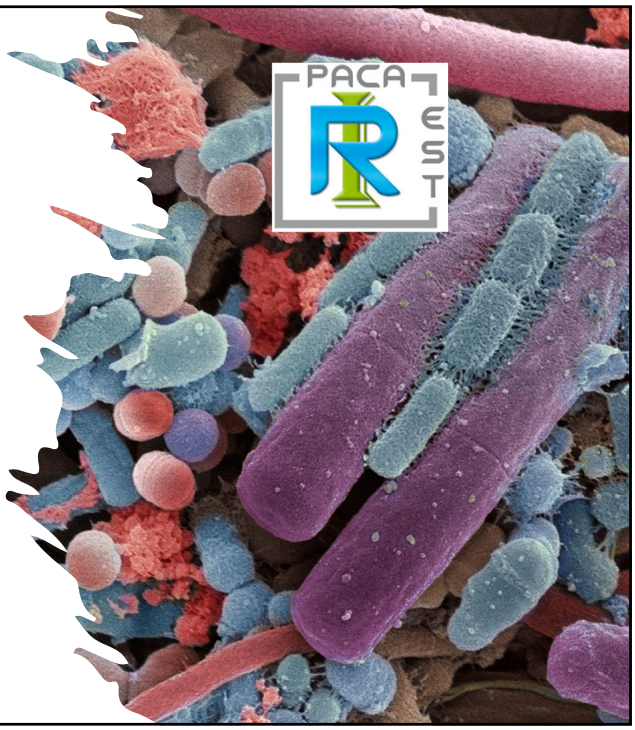
Microbiote respiratoire

Dr Matthieu Buscot

SMIT, CHU de Nice

Journée RésO-InfectiO-PACA-Est du 29/04/2022

« Infectiologie : approche diagnostique et thérapeutique en Soins Critiques »



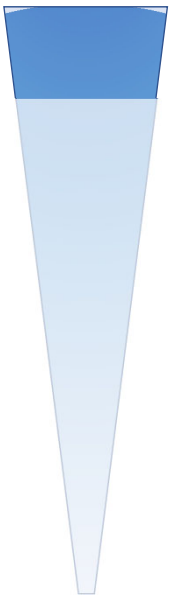
Plan

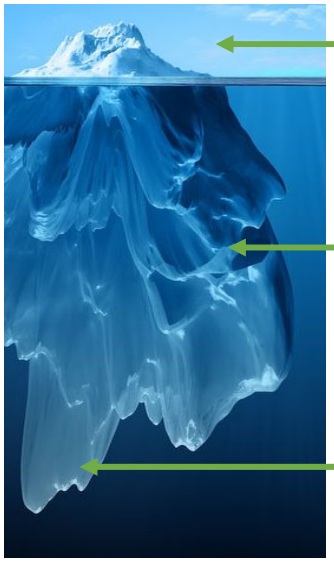
1. Les poumons sont-ils stériles?
2. D'où vient le microbiote pulmonaire (MP) ?
3. Quelles interactions du MP avec l'hôte?
4. Comment le MP est altéré en situation pathologique?

1. Les poumons sont-ils stériles?

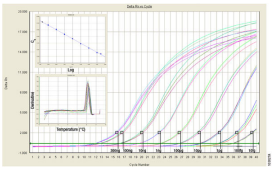
Cultures

Biomasse détectable





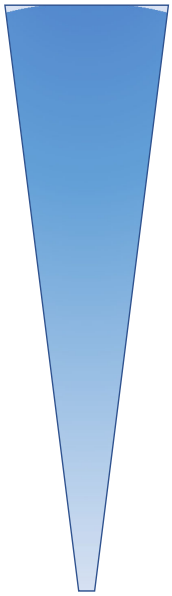
Cultures



PCR 16S
+/- séquençage

Metagenomique
NGS

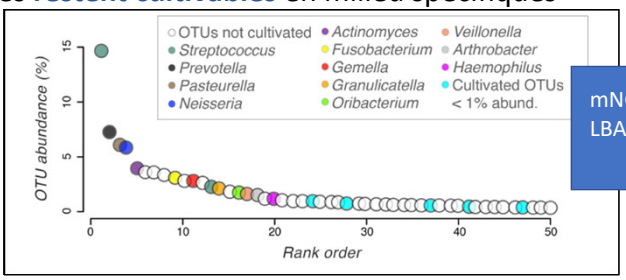
Biomasse détectable



Microbiote physiologique des voies respiratoires

Les poumons sont-ils stériles?

- mNGS : présence de bactéries **tout le long de l'arbre respiratoire**
  - **Biomasse décroissante** entre le pharynx et les alvéoles (facteur 10^{-3})
  - **Densité faible** : 10^3 à 10^5 bactéries/g (vs 10^{11} à 10^{12} dans l'intestin)
- **Variabilité intra-individuelle** faible (mais interindividuelle élevée)
- Certaines espèces **restent cultivables** en milieu spécifiques



mNGS réalisé sur des LBA chez des patients sains

Venkataraman A, et al. Application of a Neutral Community Model To Assess Structuring of the Human Lung Microbiome. McFall-Ngai MJ, éditeur. mBio. 27 févr 2015;6(1):e02284-14.

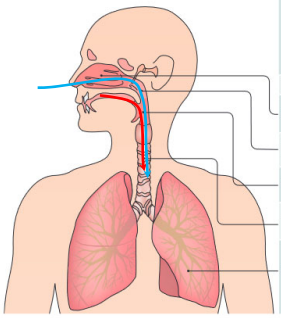
2. D'où vient le microbiote pulmonaire?

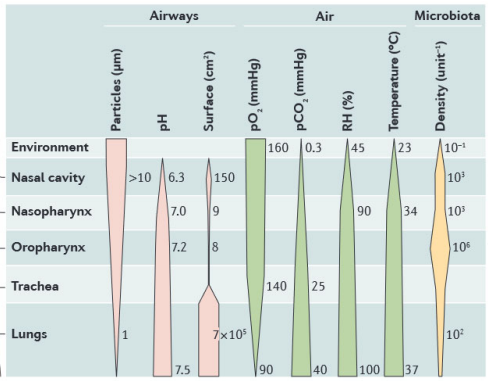
D'où vient le microbiote pulmonaire ?
Les microbiotes adjacents

MICROBIOME

The microbiota of the respiratory tract: gatekeeper to respiratory health

Wing Ho Man[1,2], Wouter A.A. de Steenhuijsen Piters[1,3]* and Debby Bogaert[1,3]*





Nat Rev Microbiol. mai 2017;15(5):259-70.

D'où vient le microbiote pulmonaire ?
Le nez ?

- Plus proche de celui de la **peau**
- Human Microbiome Project Consortium (https://hmpdacc.org)
  - Propionibacteria : *P. acnes ++*
  - Corynebacteria : *C. accolens, C. kropenstedtii*…
  - Staphylococcus : *S. aureus, and S. epidermitidis*
  - Moraxella : *M. catarrhalis*…
- Dysbiose : tabagisme, rhinite chronique

Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature 486, 207–214 (2012).

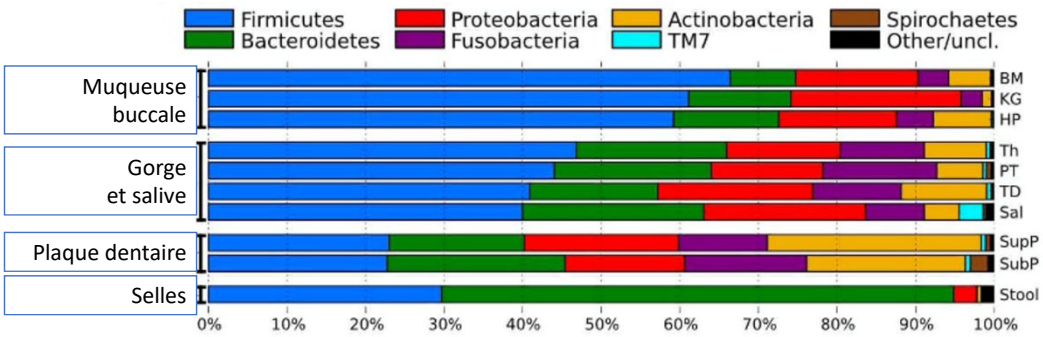
D'où vient le microbiote pulmonaire ?
La bouche

- Nombreuses micro-niches écologiques différentes :
  - Plaque dentaire, sillon gingival, joues
  - Langue, palais dur et mou
  - Amygdales
- 16S+Seq : eHOMD V3, https://www.homd.org/
- **774 espèces orales** :
  - 58% nommée officiellement
  - 16% non nommées mais cultivables
  - 26% phylotypes connus mais non cultivables

Dewhirst FE, et al. The Human Oral Microbiome. J Bacteriol. oct 2010;192(19):5002-17.

D'où vient le microbiote pulmonaire ?

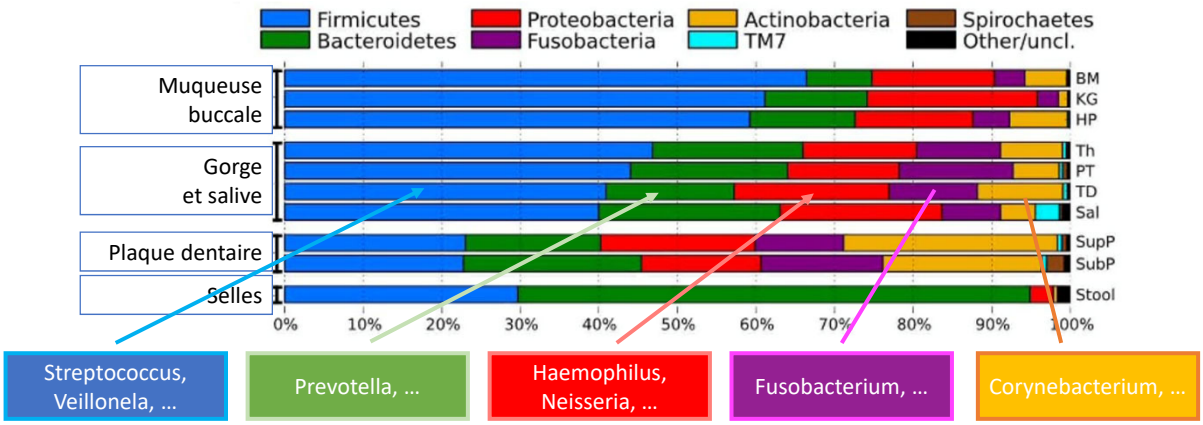
La bouche



Segata N, etal. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. Genome Biology. 2012;13(6):R42.

D'où vient le microbiote pulmonaire ?

La bouche



Segata N, etal. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. Genome Biology. 2012;13(6):R42.

D'où vient le microbiote pulmonaire ?

La bouche

Application of a Neutral Community Model To Assess Structuring of the Human Lung Microbiome

Arvind Venkataraman,[a,b] Christine M. Bassis,[b] James M. Beck,[c,d] Vincent B. Young,[b,f] Jeffrey L. Curtis,[a,e] Gary B. Huffnagle,[a,f] Thomas M. Schmidt[b,f]

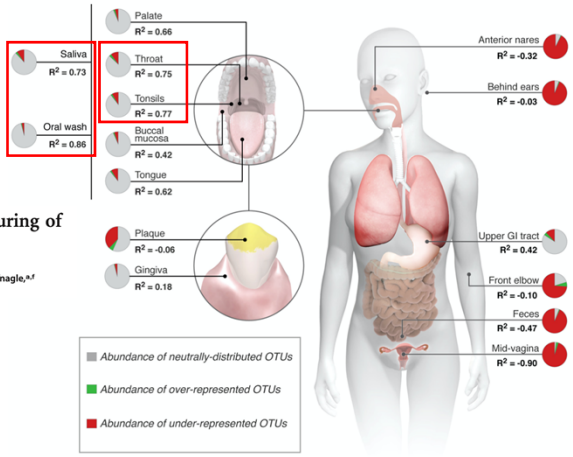
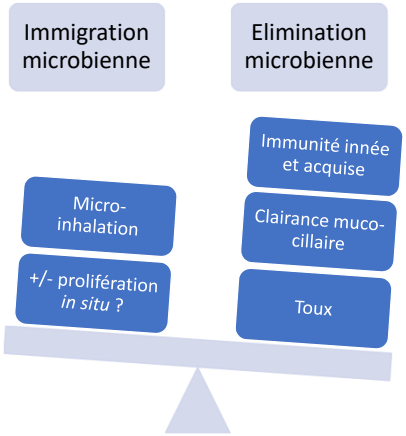


FIG 3 The neutral model applied to each body site as a potential source of microbes for the lung microbiome. Shown are the abundance of neutrally distributed, overrepresented, and underrepresented OTUs in lungs from each body site and the associated goodness of fit of the neutral model (R^2).

Venkataraman A, et al. Application of a Neutral Community Model To Assess Structuring of the Human Lung Microbiome. McFall-Ngai MJ, éditeur. mBio. 27 févr 2015;6(1):e02284-14.

D'où vient le microbiote pulmonaire ?

Déterminants écologiques



D'où vient le microbiote pulmonaire ?

Déterminants écologiques

3. Quelles sont les interactions du microbiote pulmonaire avec l'hôte?

Quelques concepts… beaucoup de chemin à parcourir !

Interactions MP – Hôte

« Immuno-écologie pulmonaire »

nature immunology
REVIEW ARTICLE
https://doi.org/10.1038/s41590-019-0451-9

The influence of the microbiome on respiratory health

Tomasz P. Wypych*, Lakshanie C. Wickramasinghe and Benjamin J. Marsland*

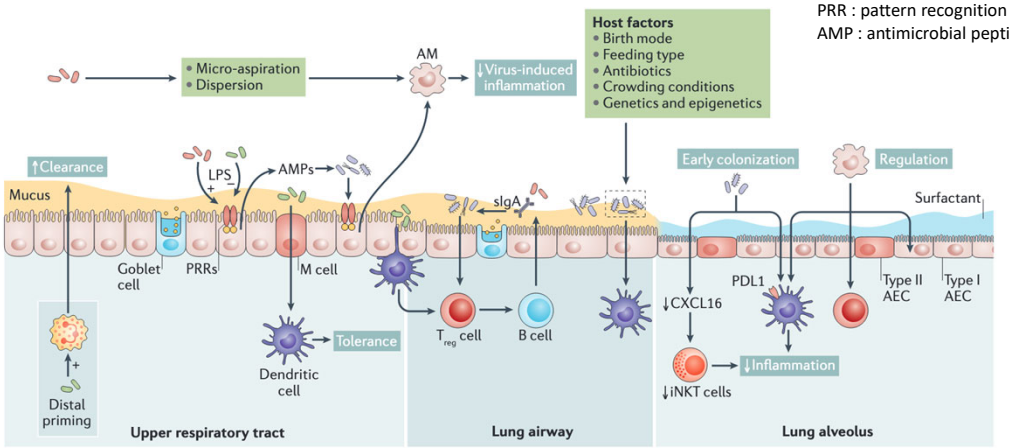
Développement physiologique des voies aériennes
- *Tolérance aux allergènes*
- *Réduction de l'inflammation viro-induite*
- *Maturation du système immunitaire*

Microbiote pulmonaire « normal » :
Streptococcus, Prevotella, Neisseria, Veillonella, Porphyromonas, Fusobacterium…

Homéostasie inflammatoire
- *Tolérance vis-à-vis de la flore résidante*
- *Elimination de la flore « pathologique » pro-inflamamtoire ; i.e. Haemophilus, Staphylococcus*

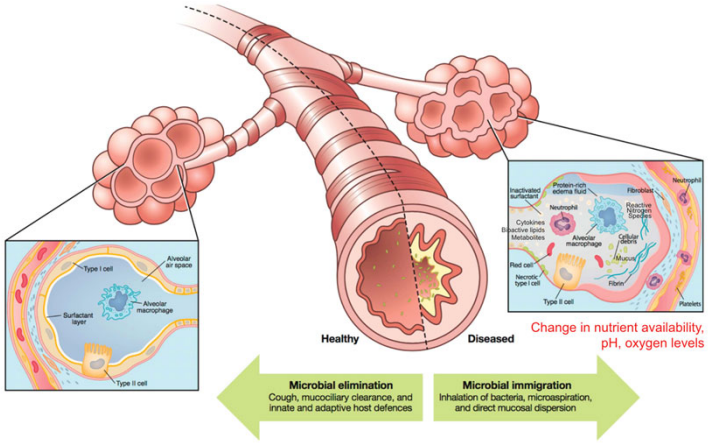
Concept d'immuno-écologie pulmonaire

PRR : pattern recognition receptor
AMP : antimicrobial peptide

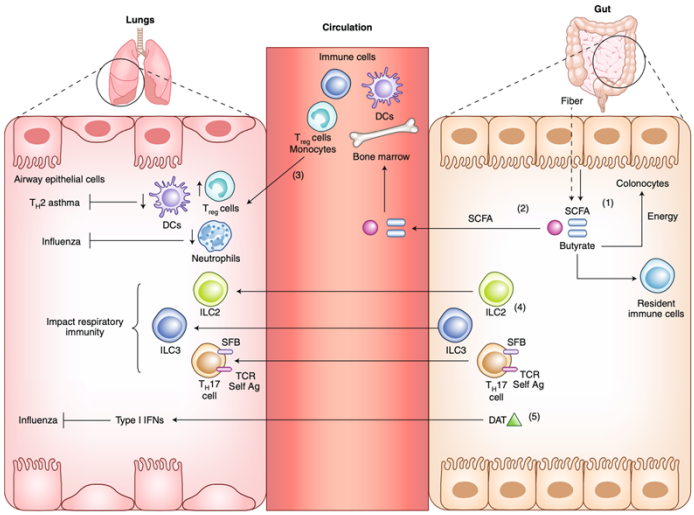


Man WH, et al. The microbiota of the respiratory tract: gatekeeper to respiratory health. Nat Rev Microbiol. mai 2017;15(5):259-70.

Relation inflammation – dysbiose pulmonaire



Axe poumon – intestin *(lung – gut axis)*



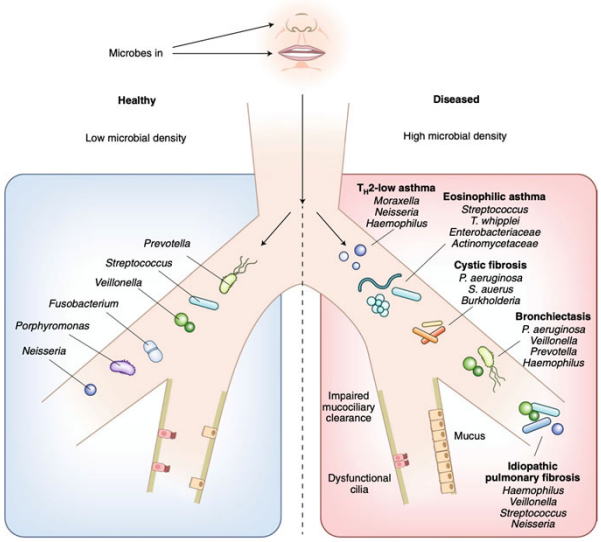
SCFA : acide gras à chaine courte
DAT : desaminothyrosine

Wypych TP, et al. The influence of the microbiome on respiratory health. Nat Immunol. oct 2019;20(10):1279-90.

4. Altération du microbiote pulmonaire (« dysbiose ») et situations pathologiques

Quelques exemples… et beaucoup de questions !

Dysbiose pulmonaire en situation pathologique

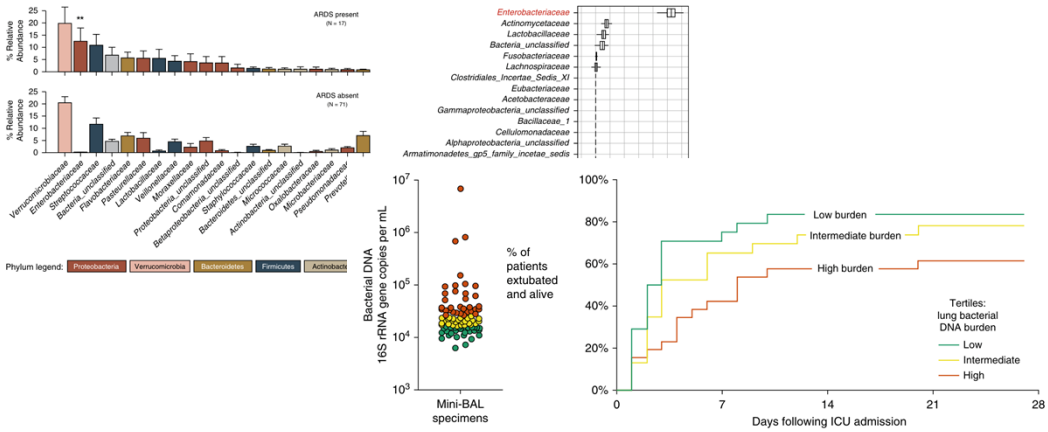


Wypych TP, et al. The influence of the microbiome on respiratory health. Nat Immunol. oct 2019;20(10):1279-90.

ORIGINAL ARTICLE

Lung Microbiota Predict Clinical Outcomes in Critically Ill Patients

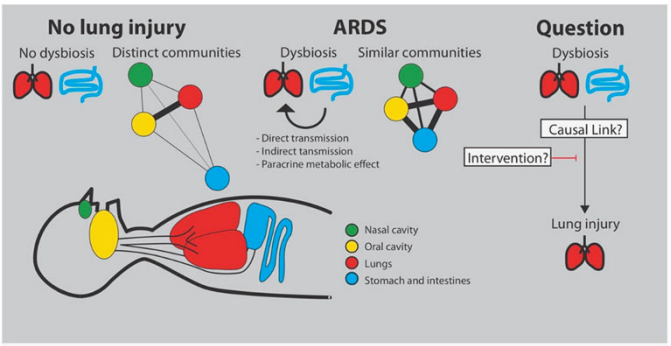
Robert P. Dickson[1,2,3], Marcus J. Schultz[4,5,6], Tom van der Poll[7], Laura R. Schouten[4,5], Nicole R. Falkowski[1], Jenna E. Luth[1], Michael W. Sjoding[1,3,8], Christopher A. Brown[1], Rishi Chanderraj[1,9], Gary B. Huffnagle[1,2], and Lieuwe D. J. Bos[4,5,10]; on behalf of the BASIC Consortium



Dickson RP, et al. Lung Microbiota Predict Clinical Outcomes in Critically Ill Patients. Am J Respir Crit Care Med. 1 mars 2020;201(5):555-63.

Dysbiose pulmonaire en situation pathologique

SDRA

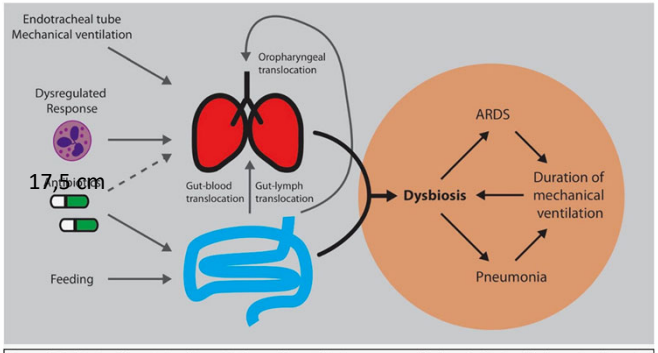


Legend: *In the absence of lung injury [left], there is little dysbiosis of the lung microbiome and nasal, oral, lung and gut microbiome show distinct communities. During ARDS [middle] the lung microbiome is enriched for gut bacteria that may be transmitted from gut to lung directly via de oropharynx, indirectly via the blood or lymphatic system or may influence regional growth conditions favouring gut bacteria through paracrine metabolic effects. The main question [right] is if these is a causal link between dysbiosis of the lung microbiome and development of lung injury and if this is a treatable trait.*

Martin-Loeches I, Dickson R, Torres A, Hanberger H, Lipman J, Antonelli M, et al. The importance of airway and lung microbiome in the critically ill. Critical Care. 31 août 2020;24(1):537.

Dysbiose pulmonaire en situation pathologique

SDRA



Legend: *Dysbiosis of the gut microbiome is influneced by antibiotic exposure and feeding. Dysbiosis of the lung microbiome is influenced by endotracheal intubation and mechanical ventilation and changes with the local host response. The influence of antibiotics on the lung microbiome during critical illness is plausbile but not supported by data. Dysbiosis of the gut microbiome may induce changes in the lung microbiome through oropharyngeal translocation or gut-blood (or gut-lymph) translocation. Dysbiosis of the lung and/or gut microbiome may influence the development of ARDS and pneumonia and might drive prolonged duration of mechanical ventilation, which in turn may induce further dysbiosis.*

Martin-Loeches I, Dickson R, Torres A, Hanberger H, Lipman J, Antonelli M, et al. The importance of airway and lung microbiome in the critically ill. Critical Care. 31 août 2020;24(1):537.

Pour conclure

Que retenir en pratique?

- Les poumons ne sont **pas stériles**
- Le microbiote pulmonaire semble impliqué dans le **maintien de l'homéostasie immunitaire muqueuse** : beaucoup de mécanismes restent à expliquer
- Association entre dysbiose pulmonaire et situations pathologiques (ARDS…) : mais **cause ou conséquence**?
- Difficultés : **collecte de spécimens chez le sujet sain** (LBA), nécessité d'étudier la réponse immunitaire associée au microbiote.
  - **Impact des nouvelles technologies** moins invasives: nanorod-PCR, microchromatographie en phase gazeuse de l'air exhalé…
- Microbiote pulmonaire = **cible thérapeutique? Biomarqueur?**

Merci de votre attention

Bibliographie

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TABLE 2

Description of media used in this study[a]

Medium	Targeted organism(s)
Tryptic soy agar	Many heterotrophic bacteria
Mannitol salt agar	*Staphylococcus* sp.
CDC kanamycin-vancomycin laked blood agar	Pigmented *Prevotella* spp., some *Porphyromonas* spp.
Mitis salivarius agar	*Streptococcus* spp.
Chocolate bacitracin agar	*Haemophilus* spp., *Campylobacter* spp., and other Gram-negative capnophiles
Enterococcosal agar	*Enterococcus* spp.