Advances in Clinical Medicine 临床医学进展, 2024, 14(6), 8-17
Published Online June 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.1461738

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呼吸道合胞病毒感染对气道菌群定位和免疫微环境的影响

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收稿日期：2024年5月6日；录用日期：2024年5月29日；发布日期：2024年6月6日

摘　要

呼吸道合胞病毒(RSV)是2岁以内儿童呼吸道感染的主要病原，尤其是小于6月的婴儿。目前针对RSV感染的治疗尚无特效治疗方法。婴儿生后呼吸道快速定植各种菌群，通过直接或间接的作用，对宿主健康有着重要影响。目前，RSV感染患儿其气道菌群变化及其局部的免疫微环境变化尚不完全清楚。因此本文针对RSV感染患儿其气道菌群变化和气道局部的免疫微环境变化进行概述性综述，期望从气道菌群角度对RSV防治提供一定的理论基础。

关键词

呼吸道合胞病毒，气道菌群，免疫微环境，概述性综述

Effect of Respiratory Syncytial Virus Infection on Airway Flora Localization and the Immune Microenvironment

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Received: May 6th, 2024; accepted: May 29th, 2024; published: Jun. 6th, 2024

Abstract

Respiratory syncytial virus (RSV) is the main cause of respiratory infections in children up to 2 years, especially in infants younger than 6 months. There is no specific treatment for RSV infection.

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文章引用：甘丽丹，邓昱，刘恩梅．呼吸道合胞病毒感染对气道菌群定位和免疫微环境的影响[J]．临床医学进展，2024, 14(6): 8-17. DOI: 10.12677/acm.2024.1461738

The rapid colonization of various microflora in the respiratory tract of infants after birth has an important impact on host health through direct or indirect effects. At present, the changes in airway flora and local immune microenvironment in RSV-infected infants are not fully understood. Therefore, this paper provides an overview of the changes in airway flora and the local immune microenvironment in RSV-infected children, with the expectation that it would provide a theoretical basis for the prevention and treatment of RSV from the perspective of airway flora.

Keywords

Respiratory Syncytial Virus, Airway Flora, Immune Microenvironment, Scoping Review

1. 引言

病毒感染是引起急性呼吸道感染的最常见原因，其中呼吸道合胞病毒(respiratory syncytial virus, RSV)是最常见的病毒病因，大部分儿童在 2 岁以内都会经历 RSV 感染，尤其是在小于 6 个月的婴儿中。RSV 感染的患儿中，约 3%需要住院治疗[1]。因为病毒的特性，目前针对 RSV 感染只能对症处理，由此引起了全球巨大的经济负担[2]。

小儿气道不同解剖位定植有不同的细菌菌群，有多种共生菌和致病菌共存，如肺炎链球菌、流感嗜血杆菌、卡他莫拉菌和金黄色葡萄球菌等[3]。在功能上，不同解剖位为了维持相应部位的动态平衡，需要保持不同的细菌负荷[4]。Jake G. Natalini 等研究显示肺部微生物组表现出低生物量，并受微生物迁移和清除的动态通量控制，导致细菌负荷和微生物组组成在本质上是流动的而不是固定的。这种下呼吸道的低生物量使得下呼吸道能够执行最关键的功能：氧气和二氧化碳的交换[5]。随着目前研究对气道菌群的逐渐深入，RSV 感染会破气道菌群－宿主之间的平衡性，最终影响疾病的发生机制。气道菌群可与宿主共同构成呼吸道微环境，与宿主免疫系统相互作用，在免疫应答、免疫耐受和免疫成熟等免疫稳态方面起着重要的作用[6]。

RSV 感染患儿其气道菌群变化及其局部的免疫微环境变化尚不完全清楚。了解 RSV 感染患儿气道菌群多样性及其与宿主间的相互反应，可能是治疗 RSV 感染的策略。本研究拟综述 RSV 感染患儿气道菌群的变化及总结气道局部免疫微环境的变化，有利于从呼吸道菌群角度为防治 RSV 感染提出新的策略及新的干预靶点。

2. 方法

2.1. 搜索策略

本我们做了一个系统性检索，综合检索了 CBM (China Biology Medicine)，CNKI (China National Knowledge Infrastructure)，EMBASS，PUBMED，Web of Science，Wan Fang Data，The Cochrane Library，WHO，Google Scholar 及 Biorxiv，Medrxiv 两个预印平台。呼吸道合胞病毒关键词为：Respiratory Syncytial Virus Infection* OR Respiratory Syncytial Virus* OR Chimpanzee Coryza Agent* OR RSV，菌群关键词为：Microbiota* OR Microbial Communit* OR Microbial Community Composition* OR Microbial Community Structure* OR Microbiome* OR Microorganism* OR Microbiology OR Germ OR Microbial OR microbe* OR

bacterium OR bacteria。

2.2. 纳入和排除标准

1) 纳入标准：检索到的所有 0~18 岁 RSV 感染患儿及其气道菌群研究的文章，包括指南、综述、基础研究、流行病学研究和评论、通讯文章和出示数据的摘要等。不限时间和语言。

2) 排除标准：对未获取全文，联系作者在 14 天内未能获得全文或数据的文章。

2.3. 文章筛选和数据提取

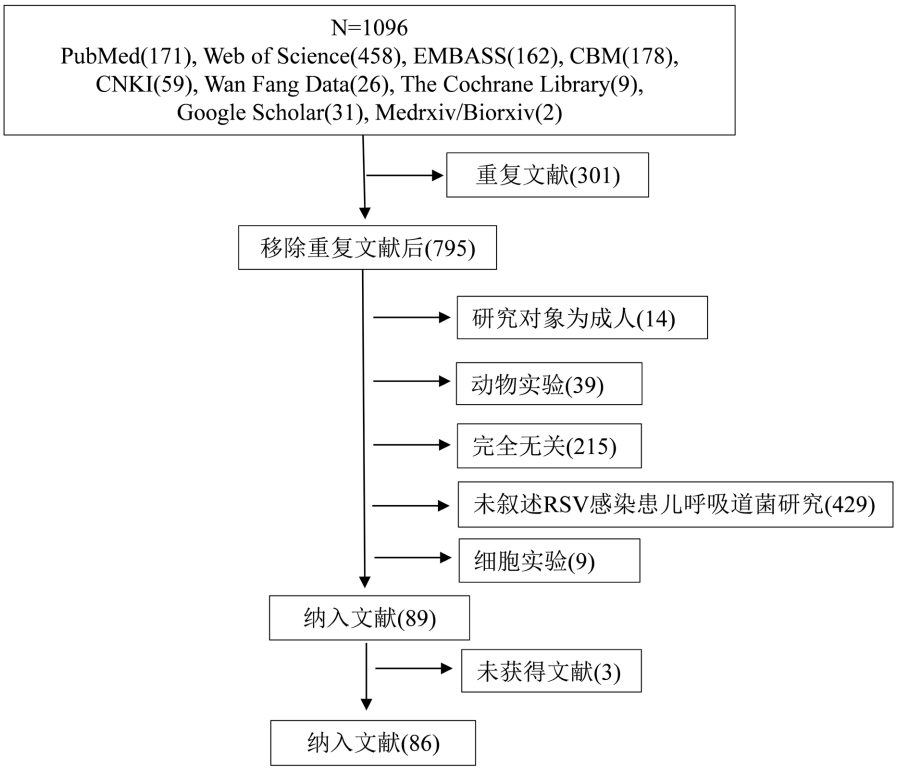
由两名独立评审员进行数据提取。两名评审员之间的差异将通过协商一致来解决。我们将提取以下数据：标题、第一作者、第一作者所在国家、文章发表时间、第一作者所在国家、样本来源及呼吸道免疫因子等方向进行总结分析；相关的文本，表格和数字将被作为为数据提取侧重点。我们将与本研究的作者联系，提供不完整的报告数据。如果研究作者在 14 天内没有回应，我们将使用现有数据进行分析。

2.4. 数据分析

对纳入的文献进行描述性分析。表格由 GraphPad Prism 8 制作完成，通过概述性综述的方式，寻找出目前此领域所存在的研究空白。

3. 结果

3.1. 文献筛选结果



*CBM (China Biology Medicine)、CNKI (China National Knowledge Infrastructure)

Figure 1. Flow chart of literature screening
图 1. 文献筛选流程图

在网站上一共检索出 1096 篇文献，排除 301 篇重复文献后对 795 篇文献进行初筛，排除成人研究 14 篇、动物试验 39 篇、完全无关 215 篇、未叙述 RSV 感染患儿呼吸道菌研究 405 篇、完全无关 215 篇、细胞实验 9 篇后进行再次筛选，其中 3 篇无全文且摘要无数据，在联系作者后未获得回应的文章 3 篇排除，最后纳入文献 86 篇。具体筛选流程见图 1。

3.2. 纳入文献特征

在 86 篇文章中，此领域文献逐渐呈现出一个增长趋势。具体文献发表时间见图 2。研究主要集中在欧美国家，国内尚缺乏此领域的研究。发展中国家和发达国家存在较大的研究差距，在发展中国家有必要开展此领域的相关研究，详见图 3。

3.3. RSV 感染患儿样本来源与呼吸道菌群组成分析

由总结可知，气道菌群在不同的解剖位有不同的组成[7]，鼻部主要以 *Streptococcus spp* (链球菌)、*Haemophilus spp* (嗜血杆菌)、Moraxella (莫拉菌)分布为主，鼻部有着最丰富的细菌物种。鼻咽部主要以 Moraxella、Staphylococcus (金黄色葡萄球菌)、Corynebacterium (棒状杆菌)、*Haemophilus spp*、*Streptococcus spp* 分布，肺部主要是以 *Streptococcus spp* 为主[8] [9]。在气道各个解剖位中，肺炎链球菌、流感嗜血杆菌、金黄色葡萄球菌及卡它莫拉菌是检出最多的细菌菌群。Rosas-Salazar C 等[10]首先研究了 50 例肺炎患儿和 50 名正常儿童鼻咽部菌群变化，结果表明肺炎患儿鼻咽菌群的丰度和多样性显著低于正常儿童。图 4 总结了 RSV 感染标本中不同样本来源其呼吸道菌群种类。

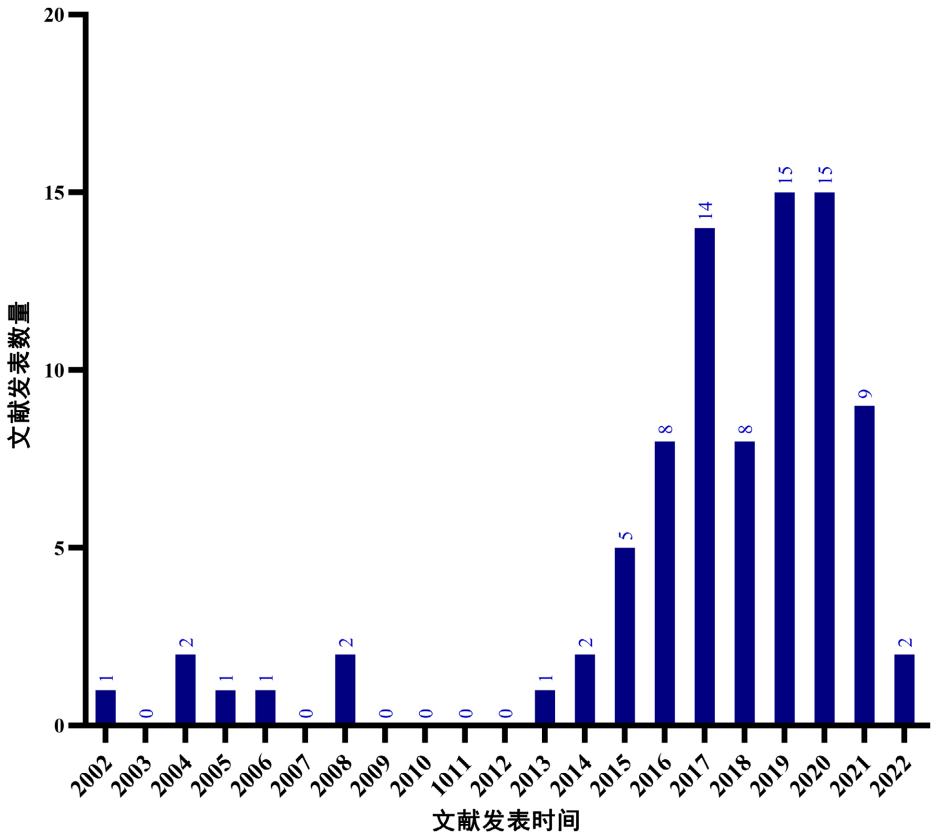


Figure 2. Analysis of temporal trends in the included literature
图 2. 纳入文献时间趋势分析

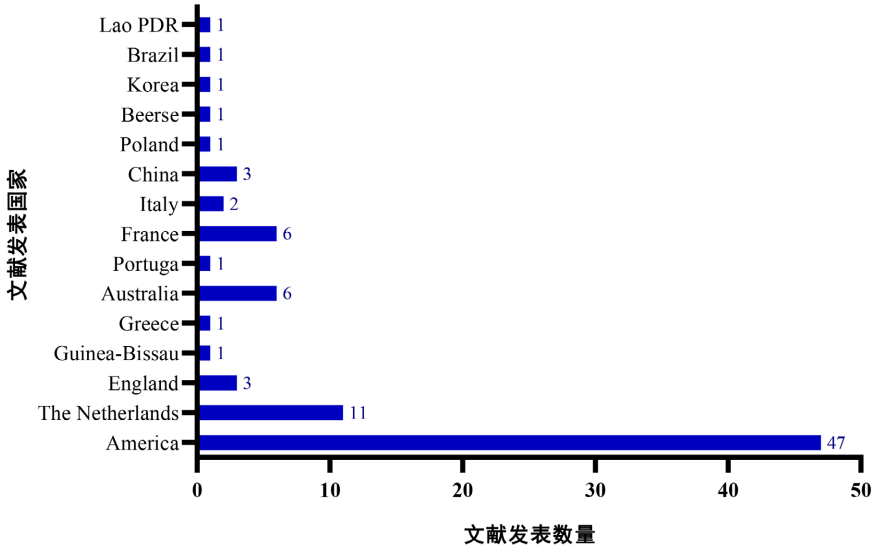


Figure 3. Geographical analysis of publications in the included literature
图 3. 纳入文献地域分析

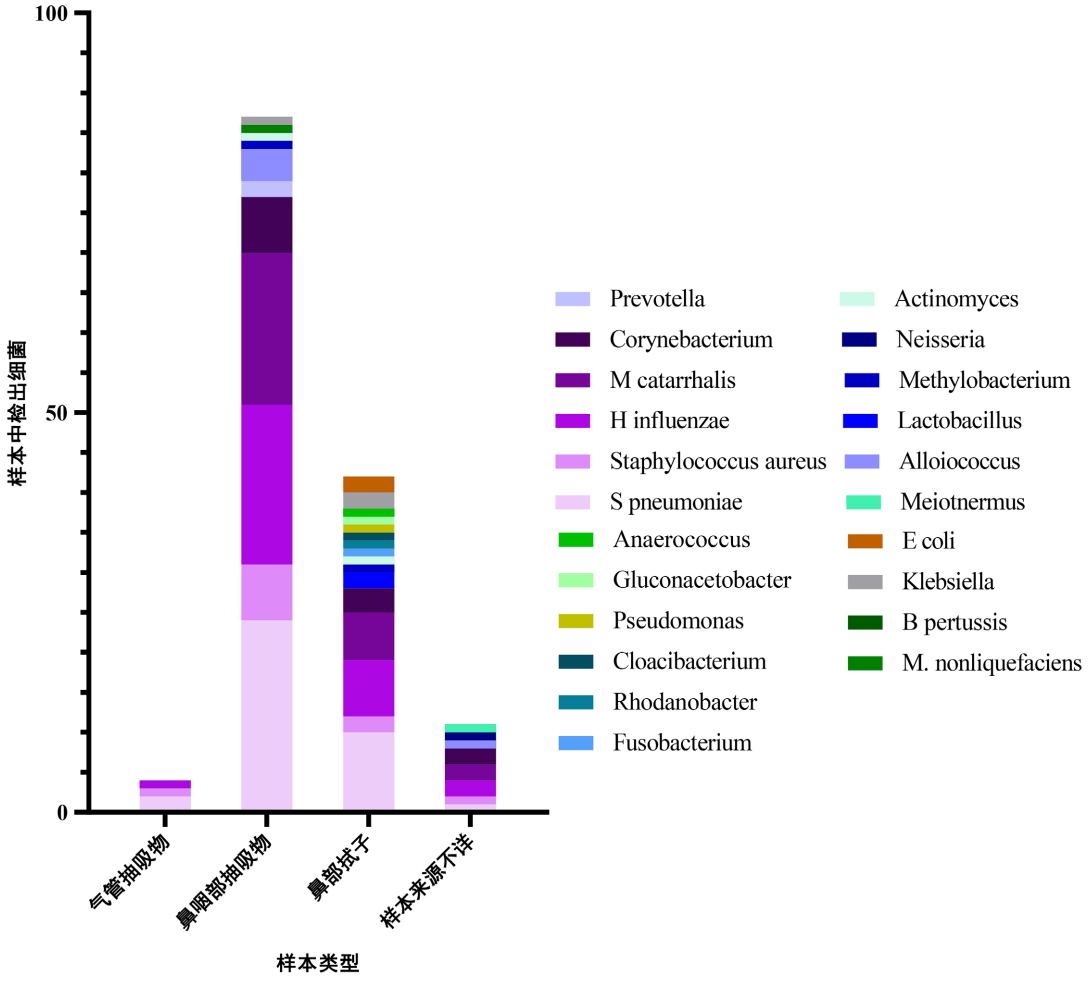


Figure 4. Bacterial flora detected in specimens from different sources included in the literature
图 4. 纳入文献中不同来源标本所检出菌群

由图中所示初步分析，当呼吸道存在 RSV 感染时，上下气道之间的呼吸道优势菌群变得相似，间接表明上呼吸道菌群可能是下呼吸道菌群的来源，导致下呼吸道感染症状[11]。在功能上，下呼吸道的条件在氧张力、蛋白质含量、表面活性剂的存在和其他环境因素方面与其他粘膜不同[12]。为了保持较低的细菌负荷，以促进气体交换，主要依赖于促进到达下呼吸道的菌群清除的机制，包括机械机制，如粘膜纤毛清除和咳嗽，以及先天和适应性宿主免疫反应[13]。无论是上呼吸道还是下呼吸道，都分布有致病菌和共生菌，包括细菌、真菌病毒等，*Moraxella*、*Haemophilus spp*、*Streptococcus spp* 是其主要的优势菌属[14]。当 RSV 侵入呼吸道，其呼吸道定植的菌群含有更多的迁移基因、鞭毛组装基因和/或嵌合反应基因，从而导致细菌诱导的粘液纤毛改变和免疫调节代谢物的分泌限制宿主反应，呼吸道的微生物菌群对呼吸道环境产生直接影响[15]。其次，呼吸道菌群也可能通过对上皮细胞的直接作用促进病毒感染，也可以直接与病毒病原体相互作用，比如一些肠道病毒结合细菌脂多糖(LPS)以使其进入靶细胞或诱导使其逃避机体免疫反应[16]。另一方面，急性 RSV 感染期间发生的大多数症状是由于宿主的炎症反应过强[17]。当 RSV 感染机体后，由于呼吸道微生物与免疫系统之间的相互作用，间接影响了呼吸道疾病的临床结局。

3.4. RSV 感染患儿对气道局部免疫微环境的影响

当 RSV 作为外来病原侵入机体后，RSV 感染气道上皮细胞，气道上皮完整性消失，其气道上皮细胞表达 RSV-G 蛋白(主要是作为肺炎链球菌和流感嗜血杆菌的受体)，使细菌粘附和毒力增强，从而导致细菌在局部增殖[18]。在婴儿 RSV 急性呼吸道感染期间，气道菌群与机体的局部免疫应答相关，影响 RSV 感染性疾病的严重程度及预后[19] [20] [21]。细胞因子是一组由激活的淋巴细胞、巨噬细胞和中性粒细胞等细胞分泌的信号分子，是体液免疫及细胞免疫的重要组成部分，通过结合靶细胞膜上的特定受体结合来发挥生物学效应[22]。为了识别 RSV 感染患儿气道菌群与局部免疫因子之间的关联，进一步了解 RSV 感染对宿主免疫微环境的影响，我们对纳入的文献从气道菌群与局部免疫因子之间关系为角度进行了总结。图 5 展示了 RSV 感染患儿气道主要菌群与局部免疫因子之间的关系。一种菌属之间可与多种免疫因子之间存在相互作用，主要是与具有抗病毒、抗炎和促炎功能的介质相关，影响 RSV 疾病长期和短期结局的发展。由图可知，克雷伯杆菌(Klebsiella)和莫拉菌属(Moraxella)与 2 型(IL-13、IL-4)、3 型(IL-17A)、促炎因子(TNF-α, IL-1β, IL-6, IL-8)和单核细胞趋化蛋白(monocyte chemoattractant protein 1, MCP-1)水平之间呈正相关，嗜血杆菌属(Haemophilus)与 IL-17A，TNF-α，IL-1b，IL-6，MCP-1 水平呈正相关，链球菌属(Streptococcus)与 TNF-α 和 IL-8 呈正相关[23] [24]。通过总结提示 RSV 与气道菌群的相互作用可能调节宿主的免疫反应，主要是通过激活抗病毒、抗炎和促炎功能的相关介质来决定病情轻重。对 RSV 急性呼吸道感染的免疫反应是多方面的，主要取决于抗病毒、抗炎(如与调节性 T 细胞相关的)、促炎(如与 1 型和 3 型相关的)和抗病毒之间的微妙平衡[25] [26] [27]。

有研究表明，黏附分子的上调可能会增强促炎信号，流感嗜血杆菌与 RSV 之间对 ICAM-1 有协同作用，随后 IL-6 与 IL-8 的产生增加[28]。呼吸道菌群与宿主免疫之间的相互反应，对呼吸道疾病有一定的指示作用[29] [30] [31]。人类数据表明，微生物暴露在出生后几天到几周内就开始了，对免疫系统的成熟有重要影响。在一项对婴儿下呼吸道样本的研究中，微生物群落组成的差异与宿主免疫的明显变化相关[32]。呼吸道菌群与机体间通过抗炎、促炎的相互作用产生免疫因子及生后肺部微生物的变化影响免疫球蛋白和先天免疫反应的调节，被认为是下呼吸道免疫成熟发生的机制之一[33]。生命早期，链球菌属、嗜血杆菌属、莫拉菌属的定植与呼吸道道感染增加有关，而鼻咽部棒状杆菌属、差异球菌属与更低的呼吸道疾病发病率有关[34] [35] [36]。呼吸道菌群可通过影响 RSV 诱导的免疫应答，潜在调节呼吸道疾病的严重程度[37]。微生物生态失调存在于各种肺部疾病中，如囊性纤维化、慢性阻塞性肺病和特发性肺纤维化，其中细菌组成的多样性降低与疾病进展有关。然而，微生物生态失调本身是疾病的原因还是疾病过

程的结果尚不清楚。例如，在肺部疾病中，肺部结构的病理生理变化和粘液清除机制受损可能会导致微生物生态失调。或者，生态失调可能通过上调炎症信号(如 NF-κB、Ras、IL-17 和 PI3K)或抑制肿瘤坏死因子(TNF)和 IFNγ 的产生来响应下气道病原体[38]。在 RSV 感染期间，呼吸道相关菌群通过增强 Toll-like 样受体通路及中性粒细胞和巨噬细胞相关的免疫应答的方式增强宿主反应，在临床上与 RSV 疾病严重程度相关[39] [40] [41]。中性粒细胞可以在吞噬作用后迅速杀死病原体，从而最大限度地提高宿主的免疫应答，其中包括颗粒酶、活性氧以及 NETs。NETs (Neutrophil extracellular traps)，中性粒细胞胞外诱捕网，负责捕获和杀死细胞外病原体。但是由于 NETs 的成分是非特异性的，NETs 可能导致不受控制的炎症反应，导致组织病理学[42] [43] [44] [45]。

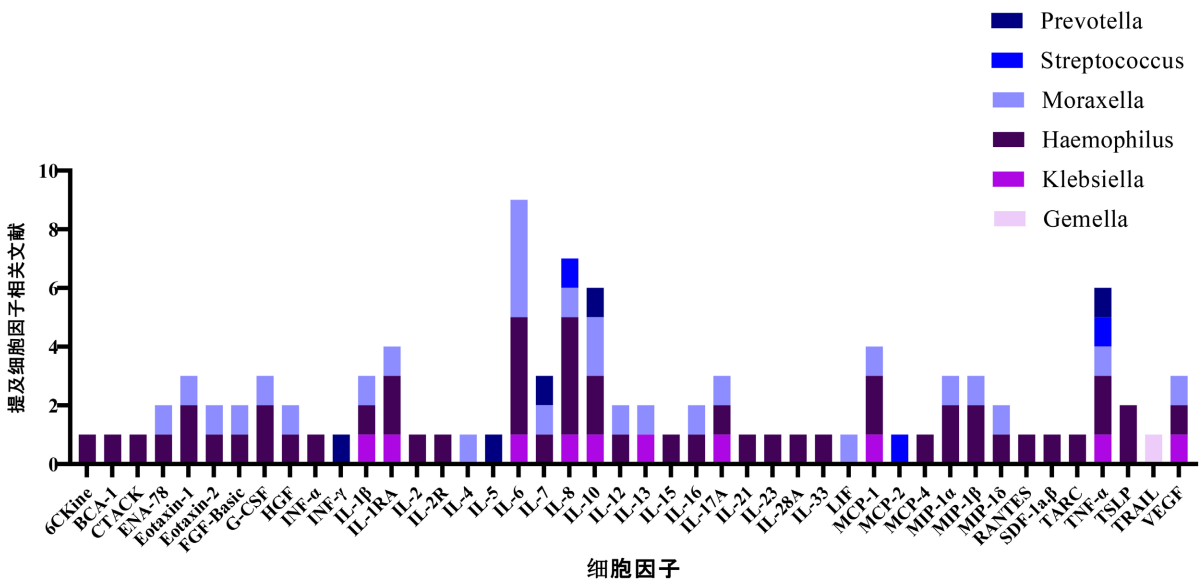


Figure 5. Relationship between airway flora and local immune factors
图 5. 气道菌群与局部免疫因子间的关系

4. 小结与展望

综上所述，近年来关于 RSV 感染患儿其气道菌群的研究逐年呈上升趋势。由于地域、经济、政治的影响，此领域的研究主要集中在发达国家。气道不同解剖位其菌群多样性有所不同，从鼻部延申至肺部的过程中，菌群多样性逐渐减低，即从上呼吸道至下呼吸道，菌群数量逐渐减少。RSV 感染破坏了气道菌群与宿主之间的平衡，通过激活抗病毒、抗炎和促炎功能的细胞因子发挥免疫调节作用，使机体对疾病状态变得易感。

未来的研究方向有必要探索 RSV 感染与气道菌群的动态特性，特别是因为它与宿主免疫调节和多种不同疾病过程的发病机制有关。新的临床应用需要解释气道菌群的进化性质。

致　谢

我衷心地向邓昱副教授表示深切地谢意，是她一直以来在热心地关注我的工作。我要感谢她在我整个工作过程中提供建议和支持。也衷心地感谢刘恩梅教授对文章提出地宝贵建议。

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