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REVIEW ARTICLE

# The human microbiome in disease and pathology

JIM MANOS

Infection, Immunity and Inflammation, School of Medical Sciences, Faculty of Medicine and Health, The Charles Perkins Centre, The University of Sydney, Sydney, NSW, Australia

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This narrative review seeks to examine the relationships between bacterial microbiomes and infectious disease. This is achieved by detailing how different human host microbiomes develop and function, from the earliest infant acquisitions of maternal and environmental species through to the full development of microbiomes by adulthood. Communication between bacterial species or communities of species within and outside of the microbiome is a factor in both maintenance of homeostasis and management of threats from the external environment. Dysbiosis of this homeostasis is key to understanding the development of disease states. Several microbiomes and the microbiota within are used as prime examples of how changes in species composition, particularly at the phylum level, leads to such diverse conditions as inflammatory bowel disease (IBD), type 2 diabetes, psoriasis, Parkinson's disease, reflux oesophagitis and others. The review examines spatial relationships between microbiomes to understand how dysbiosis in the gut microbiome in particular can influence diseases in distant host sites via routes such as the gut–lung, gut–skin and gut–brain axes. Microbiome interaction with host processes such as adaptive immunity is increasingly identified as critical to developing the capacity of the immune system to react to pathogens. Dysbiosis of essential bacteria involved in modification of host substrates such as bile acid components can result in development of Crohn's disease, small intestine bacterial overgrowth, hepatic cancer and obesity. Interactions between microbiomes in distantly located sites are being increasingly being identified, resulting in a 'whole of body' effect by the combined host microbiome.

Key words: Bacterial-infection; bacteriology; biofilm; clinical microbiology; dysbiosis; gut–brain axis; gut–lung axis; gut-skin axis; microbiome; microbiota.

Jim Manos, The University of Sydney, Level 5East, The Charles Perkins Centre D17, NSW 2006 Australia.
e-mail: jim.manos@sydney.edu.au

## INTRODUCTION

Microbiomes exist in every human ecological niche that has been examined, the oral cavity, skin surface, intestinal tract, oesophagus, lungs and other. The microbiota they comprise include bacteria, archaea, viruses, phages and fungi. Bacteria tend to be the most prominent microbiota, particularly in terms of species.

Whether they are part of a microbiome or not, bacteria prefer to live in communities referred to as biofilms in most host settings and many environmental settings. This preference for 'community living' and their 'communication skills' gives them an advantage within a microbiome. In order to build a community, bacteria communicate and interact with one another via small molecules known as autoinducers to assess numbers of 'self' (intraspecies communication) and to determine whether other bacterial species are present in the community (interspecies communication) by the process known as quorum sensing (QS) [1]. With interspecies communication, several species can work in unison, contributing to the community and forming an enclosed microbiome. While microbiomes exist in all environments, this review will concentrate on the relationship between the bacterial community within microbiomes and disease pathology in the human host.

Looking briefly at some of the most prominent human microbiomes, the most studied is that of the intestinal tract (gut). The gut microbiota are integral to host digestion and nutrition, and they can generate nutrients from substrates which are not accessible to host processes, such as xyloglucans found in onions and lettuce. The bacterial species of the gut microbiome present a greater degree of diversity than microbiomes at other body sites. According to data accumulated by the Human Microbiome Project and the metagenomic analysis

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database MetaHIT, close to 3000 bacterial species have been isolated from human faeces. The species have been classified into 11 different phyla with Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes comprising over 90% of the gut microbiome [2,3].

It should be noted that niche-specificity often defines the composition of a microbiome within a larger host context. References are often made to the 'oral microbiome'; however, the general area of the oral cavity does not have a single microbiome but contains a number of niche-specific microbiomes: those of the teeth surfaces, gums, saliva, tongue, buccal mucosa, palate, subgingival and supragingival plaque and the throat and tonsils [4].

The Human Oral Microbiome Database (eHOMD) contains well-curated 16S rRNA gene reference sequences for oral species within the various niches described above, and these are linked to available genomes [5]. As of the end of 2021, the database contained 775 microbial species of which 57% were officially named and 30% had not yet been cultured. These are derived from 2074 oral/nasal genomes, representing 529 taxa that are currently deposited in the database. The phyla Firmicutes and Proteobacteria contain the largest number of genera, followed by Actinobacteria and Bacteroidetes.

In contrast to previously held beliefs, the healthy human lower respiratory tract is not sterile but contains microbial communities that are similar, but also distinct from, those of the upper respiratory tract [6,7]. The use of 16SrRNA and whole-genome sequencing has enabled identification of numerous individual operational taxonomic units (OTUs), some culturable and named, and others not. The size of the healthy lung microbiome is determined by the arrival of new species, usually by aspiration of highly concentrated oral secretions, and removal of species, largely by mucociliary clearance, rather than the different reproduction rates of its members, thus providing for a balanced ratio in microbial composition [6,8].

While studies of the microbiota in lung conditions such as cystic fibrosis, chronic obstructive pulmonary disease (COPD) and pneumonia are commonplace, the healthy lung microbiota have not yet been extensively examined. Early work by Charlson et al. with 16S rDNA sequencing of bronchiolar lavage (BAL) samples from the lower respiratory tract showed that the main bacterial species were skin commensals from the genera Staphylococcus, Streptococcus, Veillonella, Prevotella and Propionibacterium, but that species from soil and water-associated genera such as Burkholderia and Comamonada were also present [9], thus demonstrating that species acquisition from the host's nasopharynx, skin and the external environment were key features of the lung microbiome. This study also established that the healthy lung microbiome comprises members of the phyla Bacteroidetes, Proteobacteria, Firmicutes and Actinobacteria and OTUs from the genera Prevotella, Veillonella and Streptococcus. Questions over sampling techniques and potential bronchoscope contamination of samples led Dickson et al. to undertake a rigorous experimental study minimizing contamination and obtain a topographic outline of lower respiratory tract microbiota [10]. Results were consistent with previous studies showing that airway and lung bacterial communities resemble those of the oropharyngeal tract, with little evidence of site-specific enrichment by reproducing bacteria.

## DEVELOPMENT OF THE MICROBIOME AND NICHE-SPECIFIC DIVERSITY

Microbiome development beings early in life. Current indications are that the womb is not sterile, and the foetus during gestation is exposed to bacteria which do not adversely affect it and likely form the basis for microbiome development [11]. In a longitudinal study of 60 mother–infant pairs (dyads) sampled at birth, 4 and 6 weeks, Chu et al. showed that at all sampled sites (nostrils, skin, oral cavity, stool, vaginal fornix and vaginal opening), microbiome composition and function had diversified to become body-site specific by 6 weeks of age [12]. There is mounting evidence that this early colonization has a role in the establishment and maturation of developmental pathways within the first 2 years of life [13]. During and immediately after birth, the newborn is exposed to complex microbial communities in the external environment. The forces shaping the development of this early infant microbiota comprise the maternal microbiota, exposure to antibiotics, and whether the infant is breast or formula-fed [14]. Post-natal changes in infant diet are the main forces shaping the early microbiome; thus, most studies have centred on changes to the gut microbiome. As solid foods are introduced, the microbiome begins evolving from one that mainly comprises human milk oligosaccharide metabolizers such as Bifidobacterium sp. to a more diverse one that includes Bacteroides spp., to catabolize the starch-based sugars found in complex diets [15]. Studies of Danish and Spanish birth cohorts of infants demonstrated an increased prevalence with the introduction of solids in the species Atopobium, Clostridium, Akkermansia, Bacteroides,

Lachnospiraceae and Ruminococcus while both Escherichia and Staphylococcus spp. decreased in prevalence [16,17]. However, geographic and societal factors (including breast versus formula feeding) influence early microbiome composition, and studies of more diverse cohorts worldwide are needed to establish a baseline composition.

The composition of the faecal microbiome tends to mirror that of the diet in the infant stage, as the resident gut flora have yet to be fully established. A comparison of the maternal milk microbiome and gut and faecal microbiomes from 21 lactating women and their infants over 1 year was made by Williams et al., and findings suggest that even though the microbiomes were different between maternal milk and infant faeces, correlation analysis of the data suggests that these two bacterial communities are intimately linked [18].

Palmer et al. analysed species composition of stool samples collected from 14 infants and their mothers over a 1-year period (daily to 14 days, then weekly, then monthly from 4 to 6 months and then once at 1 year) using self-developed DNA microarrays and found that the vast majority of samples were dominated by just three of the 22 bacterial groups represented on the array [19]. Consistent with previous studies, it was found that aerobes were the first colonizers, and anaerobes were the later colonizers. The results were both qualitatively and quantitatively similar to those obtained by sequencing in other studies.

The composition of the skin microbiota of an infant at 6 weeks is far less divergent from that of the mother than at other body sites such as gut and oropharynx [12]. Nevertheless, the nasal cavity and the skin provide a rich and diverse habitat for acquisition of a number of species in infancy, starting with species commonly found in neonatal delivery wards [20]. Most early acquisitions originate from four phyla: Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%) and Bacteroidetes (6.3%). In the cohort of 129 newborns examined by Younge et al., bacterial species associated with the gut microbiome, including Escherichia, Enterobacter and Enterococcus, were also present on infant skin [20]. One of the best-known skin species (but not the most common) is *Staphylococcus epidermidis*, a commensal whose success in staying under the host immune radar is mainly due to its low cytotoxicity, which enables it to evade host defences and thus ensure an overall low host immune response. In newborns, however, *S. epidermidis* is a recognized cause of neonatal morbidity, possibly because host susceptibility may allow *S. epidermidis* to easily enter the bloodstream through indwelling catheters [21,22].

With further growth and contact with the environment, the number of skin microbiome species grows. Sequencing of the adult skin microbiome showed that the human skin microbiota comprises around 113 phylotypes that belong to six bacterial divisions and that its composition varies with the specific topographic skin site [23]. This finding is supported by subsequent whole-genome and 16S rRNA sequencing of a variety of skin sites by Oh et al. where the composition of a particular microbiome was primarily dependent on the physiology of the skin site and changes in the relative abundance of bacterial taxa were related to the microenvironment and whether it is moist (Corynebacterium sp., β-proteobacteria and Staphylococcus sp.) dry (Corynebacterium sp., β-proteobacteria and Flavobacterium sp.) or sebaceous (Propionibacterium and Staphylococcus spp.) [24,25]. Species abundance was also dependent on the individual, with two skin commensals showing divergence on this; *S. epidermidis* strains were significantly more site-driven with diminished inter-individual variation, while *Propionibacterium acnes* abundance was based more on the particular individual than the specific site.

The infant/child oral cavity undergoes a steady increase in the number of species detected, as shown in a recent longitudinal cohort study of 134 children over a period of 4 years (2 months to 4.5 years of age) with sampling at six time points and comparison with the maternal microbiome at one time point [26]. Just seven species (*Streptococcus mitis* group, *Gemella haemolysans, Streptococcus salivarius* group, *Rothia mucilaginosa, Staphylococcus caprae, Haemophilus parainfluenzae and Campylobacter concisus)* from the 40 comprising the core oral maternal microbiome were present in >90% of child samples at the first time point (1.9 months). By the third sampling (13.2 months), 28 species were present in all children, and by the last time point (48.6 months), 37 of 40 species were present in all children. In addition to this, other microbiome sources, including gut, skin, diet and vaginal delivery, may shape the early oral microbiome differently in different children [27,28].

Infants and children inhale a variety of microbial species from birth, and these generally persist longer in the nasopharynx due to their immature immune system. Gram-positive aerobes from the genera *Streptococcus* (mainly *Streptococcus salivarius* and *Streptococcus mitis*), *Dolosigranulum, Corynebacterium, Gemella, Granulicatella* and others are commonplace [29]. Non-pathogenic species amongst these will remain and develop communities as part of the nasopharyngeal microbiome. Little data exist on the developing microbiome of the

 

lower respiratory tract of children; however, it is understood that initial colonization of the lung and airways normally occurs in the pre- or perinatal period, and comparative studies of healthy children with children suffering from asthma and cystic fibrosis (CF) have attempted to highlight the changed microbial environment caused by lung disease. Recently Pust et al. compared the lung microbial diversity of children with and without CF aged between 3 weeks and 6 years and found that all children under four had similar core bacterial species ratios in the lungs (with 'core' species defined as present in ≥95% of samples). After the age of four, there was a significant divergence: while the number of species with significantly higher relative abundances in healthy children increased, there was no increase in CF children. Furthermore, healthy children consistently harboured more bacterial cells per human cell of all core species than CF children [30]. Lung microbiome studies in asthma have observed increase in the relative abundance of species belonging to the Proteobacteria in asthmatics over time, compared to non-asthmatics [7,31]. Thus, the infant lung microbiome appears to acquire a common set of core species probably from aspiration, and these form the common basic microbiota. The immune regulation in healthy children will maintain the beneficial and remove the pathogenic species; however, in disease states, the deficiencies in this regulation lead to establishment of pathogens amongst the lung microbiota from birth.

Thus by adulthood, the microbiome of most healthy adults appears to contain a 'core' set of species/OTUs that is present irrespective of diet, ethnic and cultural differences, as determined by both metagenomic [32] and culture isolation studies [33]. Looking at the species overall, more than 160 species have been identified [34]. The dominant gut phyla are the Firmicutes (mainly Gram-positive Clostridiodes sp.), Bacteroidetes (mainly Gram-negative species), Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia. Members of the Firmicutes and Bacteroidetes collectively represent around 90% of the bacterial species in the healthy gut microbiome, and this remains relatively stable in most situations [35]. While more than 200 different genera within the Firmicutes have been identified in the gut microbiome, including *Lactobacillus*, *Bacillus*, *Clostridium*, *Enterococcus* and *Ruminicoccus*, the vast majority (ca. 95%) belong to Clostridiodes sp. The main genera in the Bacteroidetes are *Bacteroides* and *Prevotella*. The Actinobacteria are proportionally less abundant and mainly consist of members of the genus *Bifidobacterium*.

## COMMUNICATION WITHIN THE MICROBIOME

Examples of biofilm communities where interspecies communication has been investigated include the intestinal tract (gut), the oral cavity and the vaginal tract. The mammalian gut is known to harbour hundreds of different bacterial species that need to coexist and interact with each other and with the host. The two phyla Firmicutes and Bacteroidetes are the most predominant phyla in the mammalian gut. A healthy mammalian gut microbiome is composed of an almost equal proportion of these two phyla and changes in the microbial population affecting the balance between them have been associated with several disease states including obesity, inflammation and pathogenic infections [36]. In the oral cavity, the commensal species *Streptococcus mitis* has been demonstrated to promote cross-species communication and surface polysaccharide production by the closely related pathogenic species *Streptococcus pneumoniae* within the oral microbiome [37]. The vaginal microbiome is dynamic and compositional changes in response to pregnancy, menstruation, external influences such as douching and sexual activity and disease states such as bacterial vaginosis. Additionally, compositional changes in microbiome exist between ethnic groups [38]. These differences have led researchers to postulate that no typical 'core' vaginal microbiome exists, instead its composition depends on the functional capabilities of specific species [39]. Lactobacillus sp. generally predominate as the normal flora; however, several species and taxon groups are considered to have over-lapping roles, so that removing or adding species has little effect on the overall function of the microbiome [40].

Evidence of a link between intraspecies communication and disease has been investigated in *Escherichia coli*, where the two-component quorum-sensing regulator QseBC is responsible for sensing signals emanating from the gut microbiome and responding to them. Catecholamines produced by the host are also involved in the sensing process. The histidine-kinase component (QseC) is activated by the presence of the stress-related autoinducer A-3, and the blocking of QseBC has been shown to reduce the virulence of enterohaemorrhagic *E. coli*, *Salmonella enterica* and *Legionella pneumophila* [41,42]. Blocking of QseBC has also been shown to reduce the motility of adherent-invasive *E. coli*, the causative agent of inflammatory bowel disease (IBD) and modulate the expansion of the microbiota responsible for colitis [43].

Most studies have focused on intraspecies communication; however, the roles of interspecies communication and host-bacterium communication are

becoming increasingly better understood. Interspecies communication also requires small molecules secreted by bacteria to communicate with other bacteria or the host. The end-result is the regulation of virulence factors or bacterial community composition, the regulation of gene expression in the host, or the supplementation of nutrients in the community as a whole [44].

## MICROBIOMES AND HOST PROCESSES

Microbiota within microbiomes have been demonstrated to intervene in host processes, including compound modification and host immunity, and the examples below demonstrate how such interventions can result in development of disease states.

### Bile acid modification

Modification of bile acids may contribute to bidirectional communication between the gut microbiota and the host. Both the host and gut bacteria modify the primary bile acids cholic acid and chenodeoxycholic acid at different stages, with host liver enzymes conjugating bile acids with either taurine or glycine. Upon release, the conjugated acids are deconjugated by gut species using microbial bile salt hydrolase, to remove taurine and glycine and enable their downstream processing in the colon into secondary bile acids by other species [45].

Alterations to the composition of gut microbiota have been demonstrated to affect bile acid modification and ultimately lead to disease states including IBD, Crohn's disease, small intestine bacterial overgrowth, liver cirrhosis, obesity and hepatic cancer [46–49]. Infection with hepatitis B virus (HBV) also leads to alterations in gut microbiota. HBV patients show a decreased abundance of species from Bifidobacteria and Lactobacillus and an increased abundance of species from Enterococcus and the Enterobacteriaceae, compared with the gut microbiome of healthy controls [50]. These changes can ultimately lead to the development of hepatic cancer.

The complex relationship between bile levels and gut microbiota has not yet been fully elucidated. Alterations in bile acid concentration can also alter physiologically significant bacterial species within the gut microbiome, and a reduction in bile acid concentration has been associated with bacterial overgrowth [51].

### Host immunity

Gut microbiota constitute a stimulus that drives the development of the immune system in its capacity to react to pathogens. Recent work by Song et al. sought to determine how bile acid-modifying bacteria regulate colonic regulatory T-cells expressing the transcriptional factor RORγ+ [52]. Using mouse diet studies, Song et al found that neither dietary alteration (rich or minimal diet) nor bile acid supplementation affected the level of bacteria such as Clostridiodes clusters IV or XIVα involved in secondary processing of bile acid in the mouse colon. Thus, gut bacteria quickly adapt to the dietary change and production of colonic bile acid is not affected.

The presence of proinflammatory cytokines largely depends on the response of the innate immune system to the presence of microbial products. An example of this is interleukin-36 cytokines, which are known to play a central role in bringing about psoriatic skin inflammation and can also act as mediators of gastrointestinal and pulmonary inflammation [53–55]. IL-36 also appears to be an important mediator of obesity-related metabolic disease, with work by Giannoudaki et al. showing that IL-36 works in concert with *Akkermansia muciniphila* in the gut microbiome against obesity. IL-36-deficient mice not only demonstrated an altered gut microbiome but an increased abundance of *A. muciniphila* and increased expression of colonic mucus [56].

Specific species within particular host microbiomes are known to modulate the host immune system, indicating that the presence of specific bacteria at a particular time in host development is important for normal functioning of host immunity. Studies comparing germ-free (GF) and specific-pathogen free (SPF) mice by Atarashi et al. showed that SPF mice underwent a marked induction compared to GF mice in a T-regulatory cell commonly found in the intestine. This induction was linked to the presence of Clostridiodes sp. in the mouse gut [57].

## MICROBIOMES IN DISEASE STATES

Disease states can result from compositional changes in microbiome speciation or abundance changes within microbiome species, both resulting in microbiome dysbiosis, or expression of virulence characteristics by a species within the microbiome. With regard to the third of these, there are studies showing that asymptomatic microbiome species can in certain circumstances express virulence characteristics indicative of pathogenesis. *Streptococcus agalactiae* is generally considered a part of the normal vaginal microbiome, with reported colonization rates of up to 36%. During pregnancy, however,

 

the foetal transmission of *S. agalactiae* can be fatal to the newborn and is a leading cause of morbidity and mortality in neonates [58]. The exact mechanism that results in this switch to a virulent phenotype is unknown; however, virulence is determined by the capsular serotype and virulence factors such as the polysaccharide capsule, encoded by the *cps* gene, protein C, which includes the Cα surface proteins (*bca* gene), Rib *(rib* gene) and Cβ (*bac* gene) [59]. Here, we examine a number of disease states resulting from activities within niche-specific microbiomes.

## Oesophageal diseases

The adult oesophageal microbiome largely comprises a balance between Streptococcus and Prevotella spp. However, changes related to age and disease state such as adenocarcinoma have been shown to result in enrichment with Gram-negatives such as Haemophilus, Veillonella and Rothnia spp., particularly in the early stages of adenocarcinoma development [60]. Prior studies had also suggested that the oesophageal microbiome in patients with reflux oesophagitis has high concentrations of Gram-negative species and that these are likely contributing to the pre-cancerous stage of adenocarcinoma development [61]. Another oesophageal disease state, Barratt's oesophagus, has also been investigated with regard to changes in microbiome composition and compared to adenocarcinoma by Lopetuso et al., and results from six Barratt's oesophagus and 10 adenocarcinoma samples indicated a shift from the normal dominant Gram-positive Streptococci to Gram-negatives such as *Prevotella*, *Actinobacillus* and *Veillonella,* though this change was not as marked as that seen in the adenocarcinoma samples [62]. The indications from this study were that the shift to Gram-negatives in the oesophageal microbiome becomes more prominent as the severity of disease increases.

Oesophageal diseases include eosinophilic oesophagitis, characterized by intraepithelial eosinophils in the squamous epithelium, defective desmosomes and dysregulated transforming growth factor beta (TGF-β) production, with mast cells, and cytokines IL-5 and IL-13, acting synergistically to generate the disease state. The eosinophils are activated and may in the process perpetuate the conditions required to maintain the disease while concurrently changing the microbiome composition through overexpression of anti-microbial products, including granule cationic proteins, defensins and DNA-containing extracellular traps [63,64]. Diet and food allergy also play a role in the development of eosinophilic oesophagitis, with established treatments comprising diets demonstrating favourable outcomes. However, a potential role for the microbiome in this disease has led researchers to explore links between changes in microbiome and development of eosinophilic oesophagitis.

A study by Harris et al. of microbiome composition and eosinophilic oesophagitis in 70 children (7+ years of age) and adults with a history of oesophageal narrowing, gelatin allergy and conditions leading to endoscopic complications indicating eosinophilic oesophagitis [64] in which 16SrRNA and whole-genome sequencing were utilized for species determination, pointed to a significant increase in Haemophilus sp. in untreated subjects compared to subjects without eosinophilic oesophagitis. Eosinophilic oesophagitis patients sampled before and after dietary changes were compared by Benitez et al. to a non-eosinophilic oesophagitis cohort and concluded that while overall bacterial load was significantly increased in eosinophilic oesophagitis, the diversity of species was not significantly greater that of the control group [65]. A recent study by Johnson et al. appears to confirm the lack of association between eosinophilic oesophagitis and microbiome diversity changes in the adult population [66].

## Gut diseases

The most widely studied human microbiome is that of the gastrointestinal tract (gut). Over the last two decades, studies have reported on the development of the infant gut microbiome and on changes in the gut microbiome in a number of disease states including diabetes and liver diseases, cancer, and more recently, neurodegenerative diseases. In the case of infants, studies have shown that the microbiome development process is affected by the mode of delivery (caesarean or natural), type of infant feeding (breast or formula), gestational age at birth, hospitalization and use of antibiotics [67]. The initial sterile gut is an oxidized environment favourable to colonization by facultative aerobes such as Lactobacillus, Prevotella and Sneathia sp. being amongst the most abundant. As oxygen is consumed, and the environment becomes more reduced, they are followed by anaerobes [67]. The acquisition of Bacteroides and Bifidobacterium sp., which are known to have an important role in the maturation of the immune response, is critical to development of a healthy gut microbiome [68]. A study by Backhed et al. showed that within 5 days of vaginal delivery, a diverse population comprising mainly maternal gut bacteria such as Escherichia, Bifidobacterium, Enterococcus and Bacteroides was evident, whereas infants delivered by caesarean section contained a larger proportion of maternal skin flora at the same time point [69].

Inflammatory bowel disease (IBD) a disease group that includes Crohn's disease and ulcerative colitis ultimately leads to gut microbiome dysbiosis and a reduction in species diversity. The result is a proliferation of facultative anaerobes plus invasive and adherent *E. coli* strains whose activity is most evident in areas where bacterial populations are highest (the colon) and also where faecal material accumulates (the terminal ileum and rectum) [70]. Additionally, the microbiome as a whole is altered in patients with IBD when compared with the microbiome of non-IBD subjects. An example is mutations in the host pattern recognition receptor nucleotide-binding oligomerization domain-containing protein 2 (NOD2), which are a risk indicator for Crohn's disease. NOD2 interacts with the peptidoglycan of both Gram-positives and Gram-negatives, and animal studies in NOD2 knockout mice showed a reduction in cytokine expression and increases in a specific mucosa-associated microbial dysbiosis with altered concentrations of gut mucosal bacteria [71]. Other animal studies have shown that the transfer of proinflammatory bacteria or microbiota from diseased mice to healthy mice induces bowel inflammation, and germ-free mice are not susceptible to ulcerative colitis [72]. There are some contradictory data on the significance of microbial changes in IBD, stemming from the human microbiome project [73]. 132 people including 27 without IBD were followed for 1 year and compared for faecal metagenomes, metatranscriptomes, metaproteomes, viromes, metabolomes, host exomes, epigenomes, transcriptomes and serological profiles in samples taken over this time. The recruitment of patients both during both the active and quiescent periods of disease allowed for collection of longitudinal data. These data demonstrated that no metagenomic species were significantly different between IBD and non-IBD subjects; however, metabolite pools were less diverse in individuals with IBD, paralleling previous observations showing a reduction in microbial diversity [74].

While a direct causal relationship between type 2 diabetes (T2D) and changes in the host microbiome have yet to be fully investigated, an increasing number of studies have linked progenitors of T2D: obesity [75–78] inflammation [79–81] and insulin resistance [82], to changes in the gut microbiome. The species composition of the human microbiome undergoes changes during obesity, with members of the Firmicute phyla increasing compared to those of the Bacteroidetes [83,84]. With regard to microbiomes in Non-Western diet populations, a Japanese population study identified a similar rise in the percentage of Firmicute to Bacteroidetes in the obese subjects and also identified five Firmicute species associated with obese subjects and five Bacteroidetes species associated with non-obese subjects [85]. These same changes are found in T2D [86,87]. Alterations to the composition of the gut microbiome can lead to increased intestinal permeability and ultimately, systemic inflammation. This chronic low-grade inflammatory state is a characteristic of diabetes and diabetic kidney disease identified by the inflammatory proteins circulating in the bloodstream [88].

There are specific species whose presence/absence has been identified in T2D. The bacterium *Faecalibacterium prausnitzii* has been shown to be elevated in the microbiota of T2D patients. Conversely, the species *A. muciniphila*, a mucus colonizer that can use mucin as its sole carbon and nitrogen source in times of caloric restriction, is at low levels within the type 2 diabetes gut microbiome [89].

## Oral diseases

Studies of niche-specific colonization in the oral cavity have demonstrated how individual microbiota relate to their specific site. The nostrils (nares) are most likely to be colonized by the proximally located skin colonizer *S. epidermidis* (a Firmicute), Corynebacterium sp., with *S. aureus* also present in about 25% of the population. *S. aureus* carriage in the nares is a risk for both food poisoning (*S. aureus* toxin) by infected food handlers and is also linked to an increased risk of *S. aureus* infection elsewhere on the body [90]. With respect to the nasal and oral cavities, an 16SrRNA sequencing study of the microbiota from 12 healthy adults showed that the dominant phyla in the nasal cavity were Actinobacteria (dominated by Corynebacteriaceae and Propionibacteriaceae), Firmicutes and Proteobacteria. A distinct difference in microbiome composition was detected between the nasal and oral cavities Streptococcaceae was the most abundant Firmicute genera in the oral cavity while Staphylococceae were not detected at all [91]. The microbiome of the pharynx is largely composed of benign Streptococcal species; however, the entry of pathogenic species likely leads to infectious disease conditions. These include *Streptococcus pneumoniae* and *Streptococcus pyogenes* causative agents for pneumonia, *Neisseria meningitidis* agent a cause of meningitis, and *Corynebacterium diphtheriae* causative agent of diphtheria.

Periodontitis (PDIS) is a common oral disease with potentially serious consequences for the gums and jawbone if untreated. It has inflammatory origins linked to the patient's distinctive oral microbiota and immune system. Specific periodontopathic species have been identified as linked to PDIS development, including *Tannerella*

 

*forsythia, Porphyromonas gingivalis* and *Treponema denticola,* and these bacteria were significantly associated with the clinical features of periodontitis; however, many more species within the oral microbiota are involved. A study of changes in microbiota in patients undergoing treatment for a treatable form of PDIS (Refractory PDIS) showed that successful treatment resulted in a significant reduction in numbers of *Porphyromonas endodontalis, Porphyromonas gingivalis*, Prevotella spp., *Tannerella forsythia*, Dialister spp., Selenomonas spp., *Catonella morbi*, Eubacterium spp., *Filifactor alocis*, *Parvimonas micra*, Peptostreptococcus sp. OT113, Fusobacterium sp. OT203, *Pseudoramibacter alactolyticus* and *Streptococcus intermedius* [92].

Saliva can contain pathogenic bacterial species in the microbiome in sufficient concentrations to cause disease in the host or others. Examples include Group A Streptococci such as *S. pyogenes*, responsible for a range of serious conditions including necrotizing fasciitis, septicaemia, toxic shock syndrome, erysipelas, cellulitis, acute postinfectious glomerulonephritis, rheumatic fever, tuberculosis and scarlet fever [93]. A comparison of six species of periodontopathic bacteria in whole saliva and subgingival plaque from 202 subjects by Umeda et al. found a clear relationship between the presence of *P. gingivalis*, *Prevotella intermedia*, *Prevotella nigrescens* and *T. denticola* in whole saliva and in samples taken from sites of periodontal damage, indicating a line of transmission between saliva and these sites [94,95].

## Lung diseases

With the knowledge that the healthy lower respiratory tract has an existing microbiome, it is possible to conceptualize the entry of species pathogenic to the lung environment.

The upper respiratory tract forms a reservoir of microbes acquired from the environment and is the main source for the lower respiratory tract. The immune defence system should be able to eliminate the majority of invaders in healthy individuals, with the assistance of the resident flora. An example of this is the dysbiosis caused by the lack of cross-membrane ion regulation in cystic fibrosis, which leads to a changed lung mucus environment, and a changed microbiome. This environment is conducive to bacterial growth to certain species, and indeed, microbial changes have been observed from infancy. In a 16S rRNA sequencing study of BAL samples taken from 21 CF infants and 10 non-CF infants at 1.8 and 5 months after birth, Frayman et al. found that microbial diversity was significantly reduced in the samples from CF infants compared to the non-CF controls [96]. Additionally, the genera Staphylococcus, Ralstonia and Methylobacterium showed the greatest increases in CF infants, while Fusobacterium, Neisseria and Escherichia/Shigella showed the greatest increases in non-CF infants, with total bacterial biomass closely linked to level of inflammation. A larger study of 136 paediatric CF, 45 paediatric non-CF and 10 adult CF BAL samples also found significantly higher total bacterial biomass in CF compared to non-CF samples ($p < 0.01$). The genera of highest abundance in CF patients were the typical pathogens associated with the disease (Pseudomonas, Staphylococcus, Stenotrophomonas, Haemophilus, Achromobacter and Burkholderia), and all except Haemophilus were absent in the non-CF cohort. An interesting finding was that 20% of all CF samples had seven additional genera of high abundance not normally associated with CF infection and pathogenesis (Streptococcus, Prevotella, Bordetella, Veillonella, Moraxella, Neisseria and Corynebacterium) [97].

The existence of a 'gut–lung axis' whereby a dysbiosis in microbiomes occurs concurrently in both gut and lung has been strengthened by the discovery of significant declines in the gut biomass of certain species, in particular *Bacteroides vulgatus, Bacteroides uniformis*, *F. prausnitzii*, *Bifidobacterium catenulatum* and *Bifidobacterium adolescentis* in CF children [98] and these changes are concurrent with the changes in the lung microbiome, evoking the idea of cross-talk between the two sites. A dysbiosis of the lung microbiome also occurs in bronchial asthma and this altered microbiome probably precedes manifestation of asthma. One hypothesis is that a lack of exposure in infancy to a range of environmental microorganisms leads to impaired immune system development and asthma [99]. As described above for CF, a dysbiosis in the gut microbiome can lead to a concurrent lung dysbiosis in asthmatics, and studies have investigated the influence of microbiota along the gut–lung axis in asthma. Studies of microbiota in children of preschool age by Stiemsma et al. showed evidence of gut bacterial dysbiosis, particularly a reduction of the genus Lachnospiraceae in favour of Clostridiodes, with a potential link to asthma [100]. Changes in the gut microbiome of adult asthmatics were examined through a metagenomic analysis of gut bacterial sequencing data from 36 asthmatic adults compared to 185 controls [101]. Butyrate-producing bacteria, such as *F. prausnitzii* and *Coprococcus eutactus,* were depleted in asthmatics. This was directly correlated to increases in the abundance of *Clostridium bolteae, Clostridium ramosum, Clostridium spiroforme* and also

*Eggerthella lenta,* the latter of which has also been identified as increased in IBD.

COPD is characterized by long-term airway inflammation, persistent respiratory symptoms and chronic airflow limitation, and sufferers undergo exacerbation due to inflammatory events in a similar manner to CF patients. In COPD, the microbial diversity pattern has been demonstrated to be different in sputum and more distal samples. Therefore, the favoured method of sampling the lung microbiome is one that samples the distal bronchi and alveoli such as BAL fluid. One early study of BAL samples from four COPD patients (two classified as 'moderate' and two as 'severe') indicated a greater loss of diversity in the severe disease cases compared to the mild; however, a similar loss of diversity was noted in one of three healthy test subjects. It should be noted though that the small number of test subjects here limits the strength of conclusions [102]. A study of 32 BAL samples (14 from moderate COPD, eight from severe COPD and 10 non-COPD controls) by Pragman et al. showed that members of the anaerobic Gram-negative phylum Fusobacteria were increased in the COPD samples, and this increase was reflected at all taxonomic levels down to the genera Leptotrichia and Fusobacterium, Prevotella, Haemophilus, Fusobacterium, Pseudomonas, Streptococcus, Veillonella and Porphyromonas [103]. 16S rRNA sequencing, coupled with shotgun metagenomics, was used to demonstrate that the COPD patients' gut contains an overrepresentation of the Proteobacteria, which include most pathogenic species, and this is coupled to a decline in the relative abundance of the Firmicutes [104].

### Skin diseases

Differences in microbiome composition between healthy and diseased states are a feature of several skin diseases, as shown in the examples below.

In patients with the skin disease psoriasis, a change in bacterial numbers compared to healthy controls was noted by Fahlén et al., where Proteobacteria sp. were present at significantly higher levels on the trunk of the body, while higher levels of Streptococcus and Propionibacterium sp. were present in lesions compared to healthy skin sites [105]. Further studies identified two distinct microbial groupings of species that dominate in psoriasis patients, a Proteobacteria-associated group and a Firmicute-Actinobacteria-associated group [106].

Significant shifts in the composition and diversity of the microbial communities within microbiomes are a feature of atopic dermatitis. Atopic dermatitis produces skin lesions, and the main species within these is *S. aureus*. However, *S. aureus* is not a common skin colonizer of people without atopic dermatitis. Research has shown that initial skin colonization with *S. aureus* is needed develop the lesions. Kong et al. found that more than 90% of atopic dermatitis patients are colonized with *S. aureus* on both lesional and non-lesional skin, compared with less than 5% of healthy individuals. Furthermore, the composition of the microbiome at the lesion site shows loss of diversity with *S. aureus* becoming the dominant species [107]. Additionally, anaerobic species such as *Clostridium* and *Serratia marcescens* are increased in abundance within these lesions [108].

Acne is a skin disease normally associated with puberty and the presence of *P. acnes* within the lesions is well known. However, *P. acnes* is present in the microbiome of sebaceous glands in healthy people, where it accounts for nearly 90% of the microbiota but does not cause acne. 16S rRNA sequencing of lesion strains has shown that only certain strains containing genes that likely contribute to their virulence are associated with acne, while other strains are associated with the healthy skin microbiome [109–111].

## AXES OF MICROBIAL ACTIVITY AND DISEASE

The gut–lung axis has been briefly described above, and mounting evidence indicates the existence of what appear to be other axes of regulated microbial activity, including between the gut and the brain, the gut and the skin and the brain and the skin. The influence of bacterial communities in these axes has led to their re-description as microbiota–gut–brain, microbiota–gut–lung, microbiota–gut–oral or microbiota–gut–skin axes. Further combinations of activity have recently been described between three sites, with the microbiome of the gut interacting with/affecting both brain and skin and interacting with/affecting lung and brain. Diseases including asthma, psoriasis, tuberculosis and neurological disorders have been linked with axes of microbial activity. Here, we examine the evidence for microbiotas within these axes influencing the course of pathology and disease development.

### The Gut–skin–microbiota axis

While cross-talk between the gut microbiome and distant sites via neurons of the sympathetic and parasympathetic nervous systems had long been suspected, a study by Levkovich et al. that showed that feeding certain gut lactobacilli to mice can markedly change the overall skin phenotype

 

provided early firm evidence of the existence of this long-distance effect [112]. The acquired evidence appears to show that microbes and the metabolites they secrete interact with immunological, neurological and metabolic pathways [113,114]. In a metagenomic study of gut bacteria from 30 psoriasis patients, Xiao et al. recently found that while the gut microbiota of the patients showed increased proportions in certain phyla and reductions in others, there were no significant changes in species diversity compared to healthy controls. Most interestingly, the gut microbiota of psoriasis patients significantly differentially expressed 15 kyoto encyclopaedia of genes and genomes (KEGG) biosynthetic pathways. These included upregulation of lipopolysaccharide (LPS) biosynthesis, the bacterial secretion and phosphotransferase systems and fructose and mannose metabolism; and downregulation of signalling through cell surface receptors (WNT signalling), apoptosis and sulphur metabolism pathways [115]. LPS contains a potent endotoxin component (Lipid A), responsible for the septic shock caused by circulating Gram-negative pathogens.

Evidence exists that the gut microbiome influences the lung through histamine secreted by gut microbiota. High levels of lung histamine are an indicator of asthma, and Barcik et al. showed that the highly-expressed bacterial histamine decarboxylase (HDC) from gut microbiome species was significantly elevated in adult patients with asthma compared to healthy controls ($n = 74$ for each; $p = 0.01$). The asthma patients categorized as 'severe' (as defined by medication use, medication dose and other parameters) had significantly higher bacterial loads of the histamine secreting species *Morganella morganii* ($p = 0.02$) [116]. Histamine is an immune response modulator, and in a subsequent study using *E. coli* modified to express *M. morganii* HDC, the group showed that this strain reduced lung eosinophilia and suppressed cytokine secretion from lung cells in a respiratory inflammation mouse model, while the parent bacterium, which does not secrete histamine, had no effect [117].

### The Gut–lung–microbiota axis

The gut–lung axis is an evolving area of investigation in the case of *Mycobacterium tuberculosis* infection. *M. tuberculosis* utilizes a range of carbon sources during the persistence phase, including short-chain fatty acids (SCFA) that are the main metabolic products of fermentation of nondigestible dietary fibres by the gut microbiota. These fatty acids act on immune and endothelial cells through activation of G-protein coupled receptors and also by inhibition of histone deacetylase [118]. Lachmandas et al. found that SCFAs significantly affected cytokine release and decreased production of proinflammatory cytokines TNF-α, IL-1? and IL-17 in a dose-dependent manner [119]. The role of gut SCFAs in lung infection was further demonstrated with microbiome studies of tuberculosis patient faeces, which showed a significant increase in the abundance of gut microbiome species producing the SCFAs butyrate and propionate, including *Eubacterium, Faecalibacterium*, *Phascolarctobacterium* and *Roseburia*. On the contrary, the non-SCFA-producing gut genera *Prevotella* and *Lachnospira* were significantly decreased in both the new and recurrent tuberculosis patients compared with non-tuberculosis controls [120,121].

### The Gut–brain–microbiota axis

Communication along the gut–brain axis is proposed to occur via the autonomic nervous system (ANS), comprising the sympathetic and parasympathetic systems [122]. Another two systems have also been proposed as additional lines of communication, the immune system and the enteric nervous system [123,124]. The microbiome–gut–brain axis has been intensively investigated with regard its role in anorexia nervosa (AN) [125–127], in neurodegenerative disorders such as Parkinson's disease (PD) [128–130] and neurodegenerative dementias such as Alzheimer's disease (AD) [131–133].

Microbiota, and in particular gut microbiota, can causally influence complex behaviours, such as anxiety, learning, stress and depression. All of these behaviours are linked to the development of AN [134,135]. Mack et al. conducted 16S rRNA analysis of the gut bacterial species in the faeces of 55 AN patients, including before and after treatment for weight gain in 44 of them, and compared these results to 55 normal-weight controls. A significant reduction in abundance of Bacteroidetes and a significant increase in Firmicute abundance were identified in AN patients compared to normal-weight controls [136]. Furthermore, after weight gain, the abundance of Bacteroidetes decreased even further while Firmicute abundance continued to grow, indicating that the initial dysbiosis is maintained despite weight gain. This persistence in the gut dysbiosis has also been noted in a recent study [137].

Different types of AD also appear to present a different gut microbiome composition. A recent study found that dysbiosis in the gut microbiome differed between restricting AD and binge-purging AD. While preliminary due to small sample size, the evidence showed that the restricting AD cohort had a significantly lower relative abundance of Actinobacteria, while the binge-purging cohort had

a significantly greater relative abundance of Bifidobacteria and Eubacteria and a significant decrease in the relative abundance of Odoribacter, Haemophilus and Pasteurella sp. [138]

Animal model studies have provided most of the evidence to-date for a connection between gut–brain microbiota and neurological conditions; however, there is cross-sectional study evidence that infection with the gastric mucosal pathogen *Helicobacter pylori* results in a more severe form of PD [139]. While the evidence is indirect and no mechanism has been identified, this evidence is strongly indicative of a link for the following reasons: (i) People with PD are up to three times more likely to be infected with *H. pylori* than people without PD; (ii) *H. pylori*-infected PD patients display worse motor functions than *H. pylori*-negative PD patients; (iii) Eradication of *H. pylori* leads to improved motor function in these PD patients compared to PD patients where *H. pylori* was not eradicated; and (iv) with respect to PD treatment, absorption of the drug levodopa has been demonstrated to increase when *H. pylori* is eradicated in PD patients [140]. The last two findings indicate that the *H. pylori* bacterium needs to be active and present for the effects to continue, and eradication will reduce PD symptoms. In a recent study of 40 patients with PD where 17 of 22 had eradicated *H. pylori* infection, those that eradicated *H. pylori* showed a significant decrease ($p = 0.040$) in 'off time' (when levodopa doesn't control the PD symptoms) and a significant increase ($p = 0.009$) in 'on time' (when the symptoms are under control) [141]. The route of signal transmission to the brain may involve the vagus nerve as a population-based study by Svensson et al. showed that patients that underwent a truncal vagotomy to treat peptic ulcer complication and pain were significantly less likely to develop PD over the ensuing 20+ years of observation compared to the general population [adjusted HR = 0.53; 95% CI: 0.28–0.99] [142].

AD results from the failure to remove amyloid-β from brain tissue where it then forms neurofibrillary plaques and tangles [143,144]. A combination of factors appear to play a role in how the gut–brain axis contributes to AD development. Firstly, the healthy Firmicutes/Bacteroidetes balance in the gut microbiome is disrupted in AD patients, with decreases in the Ruminococcus, Bifidobacteria, Clostridiodes, Mogibacteria, Turicibacteria and Peptostreptococcus families, while Bacteroides, Rikenella and Gemella are more abundant [145–147]. Secondly, the normally impermeable gut wall suffers damage due to continuous progressive inflammation, and this damage spreads to the central nervous system (CNS), where it can damage and cross the blood–brain barrier to cause neurodegenerative dementia in the brain. The source of this inflammation has not been definitively described, but the evidence is pointing towards it being a direct response certain bacterial metabolites leaking from the gut, such as LPS, SCFAs and amyloid, and disturbances in brain–gut communication. Marizzoni et al. studied 89 people in varying stages of dementia by positron emission tomography (PET) to measure biomarkers of metabolic activity in six brain regions (frontal cortex, temporal cortex, parietal cortex, posterior cingulate cortex, anterior cingulate cortex and precuneus) and globally. They then compared this to the subject's blood plasma levels of LPS and four SCFAs produced by gut bacteria: acetate, butyrate, propionate and valerate. The results showed that greater amyloid pathology by PET was significantly associated with increased levels of LPS and the SCFAs butyrate, valerate and acetate, but not propionate, at all regions tested ($p < 0.001$) [148].

With respect to particular species that may play a role in AD development, one species of Bacteroidetes, *Bacteroides fragilis*, produces a toxin BFT fragilysin. BFT has been shown to disrupt epithelial cells of GI tract barriers via cleavage of the synaptic zonula adherens protein E-cadherin, thus increasing leakage across the membrane [149]. Furthermore, *B. fragilis* LPS is known to be particularly inflammatory and a potent inducer of the proinflammatory transcription factor NF-kB (p50/p65) complex. This complex is known to trigger pathways leading to neurodegeneration [150].

While more evidence is needed, the pattern that is emerging with regard to the gut–brain axis and AD is that microbiome changes in the ageing gut lead to the emergence of species producing proinflammatory metabolites. These can leak out of damaged membranes and barriers to bring about changes in brain tissue resulting in AD pathology.

## DISCUSSION AND CONCLUSIONS

The significance of a healthy 'whole of body' microbiome, both in terms of species composition and species abundance, is most evident in the scale of its involvement in the manifestation of the disease states and syndromes outlined in this review. The bacteria within individual niche-specific microbiomes communicate both at the intra- and inter-species level, and this facilitates their responses to the host. Dysbiosis of the microbiota within niche-specific microbiomes can result in damage to the host and development of disease.

Dysbiosis can result from compositional change at the phylum level, where species belonging to the Bacteroidetes may be reduced compared to

 

Firmicute species, or from a change in abundance of one or more particular species. It may also result from the acquisition of virulence properties by specific bacterial species within a microbiome, and the activities of these virulent phenotypes subsequently change host pathology in the niche.

However as more recent studies have revealed, communication along axes that link host sites is equally important. A number of disease states have now been closely linked to axonal communication, and in some cases such as *H. pylori* and Parkinson's disease, the link was quite unexpected. The trend that is emerging with regard to axes of communication is that the links are widespread, and likely involve all or most niche-specific microbiomes working in concert to effect changes at host sites.

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## CONFLICT OF INTEREST

The author states that he has no conflict of interest.

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