Human polymicrobial infections

Kim A Brogden, Janet M Guthmiller, Christopher E Taylor

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Department of Periodontics and Dows Institute for Dental Research, College of Dentistry, University of Iowa, Iowa City, IA 52242, USA (K A Brogden PhD, J M Guthmiller PhD); **and National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA** (C E Taylor ScD)

Correspondence to:
Prof Kim A Brogden
kim-brogden@uiowa.edu

Context **Polymicrobial diseases, caused by combinations of viruses, bacteria, fungi, and parasites, are being recognised with increasing frequency. In these infections, the presence of one micro-organism generates a niche for other pathogenic micro-organisms to colonise, one micro-organism predisposes the host to colonisation by other micro-organisms, or two or more non-pathogenic micro-organisms together cause disease.**

Starting point **Recently, Gili Regev-Yochay (*JAMA* 2004; 292: 716–20) and Debby Bogaert (*Lancet* 2004; 363: 1871–72), and their colleagues, suggested another interaction: microbial interference—the ability of *Streptococcus pneumoniae* carriage to protect against *Staphylococcus aureus* carriage, and the inverse effect of pneumococcal conjugate vaccination on the increased carriage of *Staph aureus* and *Staph-aureus*-related disease. *Strep pneumoniae* carriage protected against *Staph aureus* carriage, and the bacterial interference could be disrupted by vaccinating children with pneumococcal conjugate vaccines that reduced nasopharyngeal carriage of vaccine-type *Strep pneumoniae*.**

Where next **The medical community is recognising the significance of polymicrobial diseases and the major types of microbial community interactions associated with human health and disease. Many traditional therapies are just starting to take into account the polymicrobial cause of diseases and the repercussions of treatment and prevention.**

Polymicrobial diseases, which are recognised with increasing frequency, are acute and chronic diseases caused by various combinations of viruses, bacteria, fungi, and parasites. Generally the presence of one micro-organism generates a niche for other pathogenic micro-organisms to colonise, the presence of one micro-organism predisposes the host to colonisation by other micro-organisms, or two or more non-pathogenic micro-organisms together cause disease (table). These concepts sparked interest at a conference sponsored by the American Society for Microbiology (Oct 19–23, 2003, Lake Tahoe, Nevada).

Polymicrobial infections also include an interaction called microbial interference: the presence of one micro-organism generates a niche in the host that suppresses the colonisation of other micro-organisms. Microbial interference can occur between potential pathogens or between probiotic organisms and pathogens.

In synergistic polymicrobial infections, one micro-organism generates a niche favourable for the infection and colonisation of other, often pathogenic micro-organisms, similar to the metabolic interdependancies seen between some periodontal pathogens[1] or the infections resulting from virus-induced immunosuppression. Human metapneumovirus, for example, has been isolated with coronavirus in patients with severe acute respiratory syndrome[2] and also with respiratory syncytial virus in bronchiolitis[3] and other respiratory infections.[4] Measles virus kills mainly because of secondary infections induced by immunosuppression,[5] and an immunosuppressive factor produced by infected lymphoid cells might profoundly inhibit B-cell proliferation.[6] Patients with human T-lymphotropic virus type I (HTLV-I) had increased incidences of bladder and kidney infection, and patients with HTLV-II had increased incidences of acute bronchitis, bladder and kidney infection, arthritis, and asthma.[7] Many HIV-AIDS patients in Africa are also co-infected with malaria parasites or with *Mycobacterium tuberculosis*,[8] and with other viruses, bacteria, fungi, and protozoans. The role of Epstein-Barr virus and retrovirus resulting in multiple sclerosis is still to be determined.[9]

The presence of one micro-organism can predispose the host to colonisation or infection by a second organism, often consecutively. Respiratory tract viruses destroy respiratory epithelium (increasing bacterial adhesion), induce immunosuppression causing bacterial superinfections, or upregulate the expression of molecules that bacteria use as receptors.[10] Specific viruses and bacteria involved in these infections are shown in the table. Respiratory tract viruses also have a pivotal role in predisposing the middle ear to bacterial infections resulting in otitis media.[11,12]

In additive polymicrobial infections, two or more non-pathogenic micro-organisms together can cause bacteraemia, abdominal abscess or secondary peritonitis,[13] lung abscess, odontogenic infections, brain abscess or subdural empyema, chronic otitis media or mastoiditis, liver infections,[14,15] and soft-tissue infection or fasciitis.[16] Many of these polymicrobial interactions occur within biofilms that form on natural or artificial surfaces within the human host.[17] For example, *Pseudomonas aeruginosa* has multiple phenotypes[18] during biofilm development. On average, over 525 proteins changed between each of the stages of biofilm development. Understanding the physical and chemical interactions between micro-organisms in these polymicrobial communities will help to define potential new targets for disrupting biofilm-community development and, in cystic fibrosis, affect the ecology of biofilms in the airways of patients.

In microbial interference, pathogens or probiotic organisms generate a niche (or occupy sites) in the host that suppresses the colonisation of other micro-organisms. Examples include both viruses and bacteria. GB virus C, a flavivirus which is not known to be pathogenic in human beings, replicates in lymphocytes, inhibits the replication

Causal agents	Disease
Synergistic polymicrobial infections	
Human metapneumovirus with coronavirus or respiratory syncytial virus	SARS, bronchiolitis[2–4]
Measles and *Mycobacterium tuberculosis* and *Staphylococcus aureus*	Measles[5]
Epstein-Barr virus and retrovirus	Multiple sclerosis[9]
HTLV-I, HTLV-II, and/or HIV-1, HIV-2	AIDS[30]
HTLV-I and HTLV-II	Respiratory and urinary tract infections[7]
HIV and *M tuberculosis*	AIDS[8]
HBV or HCV and HIV-1	AIDS[31]
HIV and enteric viruses, *Acinetobacter radioresistens*, *M tuberculosis*, *Ehrlichia chaffeensis*, *Candida albicans*, *Histoplasma capsulatum*, *Cryptosporidium parvum*, *Trichomonas vaginalis*, and others	AIDS
Lyme disease with babesiosis or ehrlichiosis	Lyme disease
Stenotrophomonas maltophilia and *Aspergillus fumigatus*	Corneal infection
Infections predisposing to polymicrobial disease	
Influenza viruses, parainfluenza viruses, respiratory syncytial viruses, adenoviruses, measles viruses, rhinoviruses, and coronaviruses with *Streptococcus pneumoniae*, *Strep pyogenes*, *Haemophilus influenzae*, *Staph aureus*, *Neisseria meningitidis*, *M tuberculosis*, or *Bordetella pertussis*	Respiratory disease[10]
Coronavirus and *Escherichia coli*	SARS
Respiratory tract viruses and bacterial infections	Otitis media[11,12]
Varicella-zoster virus and *Strep pyogenes*	Invasive group A streptococcal disease[32]
Additive polymicrobial infections	
Aerobic and anaerobic gram-positive and gram-negative bacteria and *Candida* spp	Periodontal disease[33]
Prevotella-like bacteria	Caries
B pertussis, *Strep pneumoniae*, *Staph aureus*, *H influenzae*	Pertussis[34]
Nocardia asteroides and *Cryptococcus neoformans*	Lung abscesses
Herpes zoster and tuberculosis	Tuberculosis
Pseudomonas aeruginosa, *S maltophilia*, *Prevotella oris*, *Fusobacterium gonidoformans*, *Bacteroides fragilis*, *Leptotrichia*-like spp, *Abiotrophia defecta*, *Citrobacter murliniae*, *Lautropia mirabilis*, and *Sarcina ventriculi*	Cystic fibrosis[25]
Aerobic and anaerobic gram-positive and gram-negative bacteria	Peritonitis[13]
HBV, HCV, and HDV	Hepatitis[14,15]
HCV and HIV	Hepatitis[14,15]
Norwalk-like virus and *Aeromonas sobria* or *E coli*	Gastroenteritis
Schistosoma haematobium and *S mansoni*	Intestinal schistosomiasis
Combinations of *Corynebacterium urealyticum*, *Gardnerella vaginalis*, *Anaerococcus lactolyticus*, *Bact vulgatus*, *Dialister invisus*, *Fusobacterium nucleatum*, *Lactobacillus iners*, *Leptotrichia amnionii*, *P buccalis*, *P ruminicola*, *Rahnella aquatilis*, and *Strep intermedius*	Urinary tract infection
Staphylcoccus spp, *Streptococcus* spp , and HACEK group	Endocarditis
Microbial interference	
Flavivirus and HIV	AIDS[19]
Strep pneumoniae and *Staph aureus*	*Staph-aureus*-related disease[20,21]

SARS=severe acute respiratory syndrome, HACEK=*Haemophilus* spp, *Actinobacillus* spp, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

Table: **Combinations of micro-organisms in human polymicrobial diseases**

of HIV in vitro, and is associated with a decreased risk of death in HIV-positive people.[19] HIV-infected individuals co-infected with GB virus C had lower mortality rates, higher baseline CD4+ T-cell numbers, a slower rate of decline of CD+ T cells, and lower plasma HIV RNA levels than HIV-positive individuals without GB virus C.

Two recent studies show that the carriage of *Streptococcus pneumoniae* suppresses the carriage of *Staphylococcus aureus* in vaccinated and unvaccinated healthy children.[20,21] *Strep pneumoniae* and *Staph aureus* colonise the upper respiratory tract of children, although not at the same rates of carriage and not necessarily at the same time. This inverse relation suggests that one organism interferes with the colonisation of the other, and the mechanisms may be similar to that reported for bacterial interference by *Corynebacterium* spp[22] and viridans group streptococci[23] against *Staph aureus* in the nasal cavity.

Gili Regev-Yochay and colleagues[21] recently assessed the possible association between *Strep pneumoniae* and *Staph aureus* by studying prevalence and risk factors for carriage in 790 children aged 5 days to 40 months.[21] The carriage rate of *Staph aureus* was lower in children with *Strep pneumoniae* (6·5%) than in children without (12·9%), and the carriage rate of *Strep pneumoniae* was seen to be lower in children with *Staph aureus* (27·5%) than in children without (44·8%). In children aged 3 months or below, the highest carriage rate of *Staph aureus* (30%) coincided with the lowest carriage rate of *Strep pneumoniae* (9%). Similarly, in children aged 7–40 months, the highest carriage rate of *Strep pneumoniae* (50%) coincided with the lowest carriage rate of *Staph aureus* (5–9%).

Debby Bogaert and colleagues[20] also find a negative correlation between co-colonisation of vaccine type *Strep pneumoniae* and *Staph aureus* in 3085 healthy children. Co-colonisation with *Staph aureus* was lower with vaccine-type *Strep pneumoniae* (23%) than with the non-vaccine-type (37%) or in children without *Strep pneumoniae* (37%). Risk factors correlating with an increase in the carriage rate of *Strep pneumoniae* were age (>3 months), having young siblings, attending day care, having a respiratory tract infection at screening, previous steroid treatment, passive and active smoking, and sporting and social activities.[20,21]

Overall, these results suggest that *Strep pneumoniae* carriage protects against *Staph aureus* carriage, and the mechanism of bacterial interference could be disrupted by vaccinating children with pneumococcal conjugate vaccines that reduce nasopharyngeal carriage of vaccine-type *Strep pneumoniae*. This could result in a shift towards their carriage of non-vaccine *Strep pneumoniae* serotypes or towards higher carriage rates of *Staph aureus*, including meticillin-resistant *Staph aureus*.

Novel methods of diagnosis and treatment

Recent technological advances have enhanced the identification and characterisation of the vast microbial diversity colonising the human body (commensals and pathogens). Metagenomic analyses are being used to describe polymicrobial ecosystems, flowcells are being used to study microbial interactions in biofilms, and other molecular methods are being used to identify unique microbial species and phylotypes in complex ecosystems[24,25]. However, many of these techniques have not yet reached laboratories in a scale to assist clinicians in practice.

Traditional therapies are generally targeted at individual causative agents without consideration for effect on a polymicrobial cause or on individual members of microbial communities. In some cases, there are beneficial consequences. In Africa, HIV infection is concentrated in patients with tuberculosis.[26] Antiretroviral drugs reduce the incidence of tuberculosis to that observed immediately after HIV seroconversion.[26] In other cases, broad-

spectrum antibiotics may kill polymicrobial anaerobic flora and reduce colonisation resistance of the intestinal tract, particularly for acquisition of multiresistant bacteria such as vancomycin-resistant enterococci.[27]

Probiotics also use microbial interference as a mechanism for novel prophylactic or therapeutic management of polymicrobial diseases. Treatment of patients with *Saccharomyces boulardii*, lactobacilli, or enterococci prevents or reduces the duration of gastroenteritis caused by bacteria and rotaviruses,[28] and treatment with other lactobacilli, such as *L fermentum*, *L rhamnosus*, or *L crispatus*, has the potential to reduce vaginal infections.[29]

The medical community is recognising the significance of polymicrobial diseases and the major types of microbial community interactions associated with human health and disease. Many traditional therapies are just starting to take into account the polymicrobial cause of diseases and the repercussions of treatment and prevention. The use of vaccines to control *Strep pneumoniae* infection in healthy children may have adverse effects. Regev-Yochay and colleagues[21] suggest that the mechanism of bacterial interference by *Strep pneumoniae* carriage on *Staph aureus* carriage could be disrupted by vaccinating children with pneumococcal conjugate vaccines that reduce nasopharyngeal carriage of vaccine-type *Strep pneumoniae*. Bogaert and colleagues[20] suggest that children vaccinated with a 7-valent pneumococcal-conjugate vaccine became colonised with non-vaccine *Strep pneumoniae* serotypes and had higher rates of *Staph-aureus*-related acute otitis media after vaccination. Both conclude that more work is needed to ascertain the potential effects of pneumococcal conjugate vaccination on both *Staph aureus* carriage and the development of *Staph-aureus*-related disease.

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