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Human polymicrobial infections

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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 interdependencies seen between some periodontal pathogens or the infections resulting from virus-induced immunosuppression. Human metapneumovirus, for example, has been isolated with coronavirus in patients with severe acute respiratory syndrome and also with respiratory syncytial virus in bronchiolitis and other respiratory infections. Measles virus kills mainly because of secondary infections induced by immunosuppression, and an immunosuppressive factor produced by infected lymphoid cells might profoundly inhibit B-cell proliferation. 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. Many HIV-AIDS patients in Africa are also co-infected with malaria parasites or with *Mycobacterium tuberculosis*, 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.

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. 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.

In additive polymicrobial infections, two or more non-pathogenic micro-organisms together can cause bacteraemia, abdominal abscess or secondary peritonitis, lung abscess, odontogenic infections, brain abscess or subdural empyema, chronic otitis media or mastoiditis, liver infections, and soft-tissue infection or fasciitis. Many of these polymicrobial interactions occur within biofilms that form on natural or artificial surfaces within the human host. For example, *Pseudomonas aeruginosa* has multiple phenotypes 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

| Synergistic polymicrobial infections | Disease |
|-------------------------------------|---------|
| Human metapneumovirus with coronavirus or respiratory syncytial virus | SARS, bronchiolitis |
| Measles and Mycobacterium tuberculosis and Staphylococcus aureus | Measles |
| Epstein-Barr virus and retrovirus | Multiple sclerosis |
| HTLV-I, HTLV-II, and/or HIV-1, HIV-2 | AIDS |
| HTLV-I and HTLV-II | Respiratory and urinary tract infections |
| HIV and M tuberculosis | |
| HBV or HCV and HIV-1 | AIDS |
| HIV and enteric viruses, Acinetobacter species, M tuberculosis, Ehrlichia chaffeensis, Candida albicans, Histoplasma capsulatum, Cryptosporidium parvum, Trichomonas vaginalis, and others | |
| Lyme disease with babesiosis or ehrlichiosis | Lyme disease |
| Stenotrophomonas maltophilia and Aspergillus fumigatus | Pulmonary disease |

### Infections predisposing to polymicrobial disease:

| Influenza viruses, parainfluenza viruses, respiratory syncytial viruses, adenoviruses, measles viruses, rhinoviruses, and coronaviruses with | Respiratory disease |
| Streptococcus pneumoniae, Strept pyogenes, Haemophilus influenzae, Staph aureus, Neisseria meningitidis, M tuberculosis, or Rhodotorula pertussis | |
| Coronavirus and Escherichia coli | SARS |
| Respiratory tract viruses and bacterial infections | Orbs media |
| Vancilae stover virus and Strept pyogenes | Invasive group A streptococcal disease |

### Additive polymicrobial infections:

| Aerobic and anaerobic gram-positive and gram-negative bacteria and | Periodontal disease |
| Candida spp | |
| Prevotella-like bacteria | Caries |
| B pertussis, Strep pneumoniae, Staph aureus, H influenzae | Pertussis |
| Nocardia asteroides and Cryptococcus neoformans | Lung abscesses |
| Herpes zoster and tuberculosis | Tuberculosis |
| Pseudomonas aeruginosa, S maltophilia, Prentella oris, | Cystic fibrosis |
| Fusobacterium gondiiformans, Bacteroides fragilis, | |
| Leptotrichia-like spp, Abiotrophia defecta, Citrobacter freundiae, | |
| Lactobacillus viridans, and Sarcina ventriculi | |
| Aerobic and anaerobic gram-positive and gram-negative bacteria | Peritonitis |
| HBV, HCV, and HDV | Hepatitis |
| HCV and HIV | Hepatitis |
| Norwalk-like virus and Aperomonas sobria or E ecoli | Gastroenteritis |
| Schistosoma haematobium and S mansoni | Intestinal schistosomiasis |
| Combinations of Corynebacterium urealyticum, Gardnerella vaginalis, | Ureaplasma urealyticum, Dientheria intesinarius, Fusobacterium | |
| Anaerococcus lactoalcalolyticus, Bact vulgatus, Dialathia intesinarius, Fusobacterium | |
| nucleatum, Lactobacillus rhesus, Leptotrichia amnionii, P boccoli, | |
| P nomicolus, Rhinella aquae, and Strept intermedius, | |
| Staphylococcus spp, Streptococcus spp, and HACEK group | Endocarditis |

### Microbial interference:

| Flavivirus and HIV | AIDS |
| Strept pneumoniae and Staph aureus | Staph-aureus-related disease |

### Table: Combinations of microorganisms in human polymicrobial diseases

| Causal agents | Disease |
|----------------|---------|
| Synergistic polymicrobial infections | SARS, bronchiolitis |
| Measles | Measles |
| Multiple sclerosis | |
| AIDS | Respiratory and urinary tract infections |
| AIDS | |
| Lyme disease | Lyme disease |
| SARS | Pulmonary disease |

of HIV in vitro, and is associated with a decreased risk of death in HIV-positive people. 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. *Streptococcus pneumoniae* and *Staphylococcus aureus* colonize 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 and viridans group streptococci against *Staphylococcus aureus*.

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

Debby Bogaert and colleagues also find a negative correlation between co-colonisation of vaccine type *Streptococcus pneumoniae* and *Staphylococcus aureus* in 3085 healthy children. Co-colonisation with *Staphylococcus aureus* was lower with vaccine-type *Streptococcus pneumoniae* (23%) than with the non-vaccine-type (37%) or in children without *Streptococcus pneumoniae* (37%). Risk factors correlating with an increase in the carriage rate of *Streptococcus 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.

Overall, these results suggest that *Streptococcus pneumoniae* carriage protects against *Staphylococcus 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 *Streptococcus pneumoniae*. This could result in a shift towards their carriage of non-vaccine *Streptococcus pneumoniae* serotypes or towards higher carriage rates of *Staphylococcus aureus*, including meticillin-resistant *Staphylococcus 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. 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. Antiretroviral drugs reduce the incidence of tuberculosis to that observed immediately after HIV seroconversion. 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.

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

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 Streptococcus pneumoniae infection in healthy children may have adverse effects. Regev-Yochay and colleagues suggest that the mechanism of bacterial interference by Streptococcus pneumoniae carriage on Staphylococcus aureus carriage could be disrupted by vaccinating children with pneumococcal conjugate vaccines that reduce nasopharyngeal carriage of vaccine-type Streptococcus pneumoniae. Bogaert and colleagues suggest that children vaccinated with a 7-valent pneumococcal-conjugate vaccine became colonised with non-vaccine Streptococcus pneumoniae serotypes and had higher rates of Staphylococcus-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 Staphylococcus aureus carriage and the development of Staphylococcus-aureus-related disease.

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