Viral and Bacterial Co-Infection and Its Implications

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The first understanding of the viral/bacterial co-infection contribution to disease exacerbation came from studying the role of bacterial secondary infections during influenza pandemics. In the case of influenza virus, secondary infection has been substantially documented as ranging from 2% to 65% during a given epidemic [1]. Staphylococcus aureus, Streptococcus pneumoniae and Haemophilus influenzae are the major bacteria associated in simultaneous co-infection with influenza virus [2]. In vitro studies have shown that S. pneumoniae enhances influenza replication by producing a neuraminidase [3]. It has been suggested that it is difficult to evaluate the importance of viral/bacterial co-infection in the early years of an influenza pandemic due to low immunity. Therefore, only after immunity against influenza is built up, or after drifts have accumulated and symptoms are milder, can the effects of co-infection be better observed [2].

Other viruses, such as enterovirus, have also been associated in co-infection. A study of infants below 90 days of age experiencing fever without a known source reported that 17.7% of cases had bacterial co-infection during enterovirus infection of the central nervous system[4]. In addition, a recent surveillance report by Lindsay et al.[5] indicated that about 30% of 2478 patients hospitalized for severe diarrhea were co-infected with rotavirus and Vibrio cholerae. Another recent report by Grimmer et al.[6], on severe diarrhea cases associated with rotavirus infections, reported co-infection with several bacterial pathogens, including Escherichia coli (45%), Shigella flexneri (3.2-8.0%), Giardia (1.7-8.6%), and Campylobacter (1.0 – 3.2%). In addition, co-infections with two different enteric viruses, e.g., astroviruses and rota viruses, have also been noted in cases of severe diarrhea, indicating that viruses can co-evolve with each other to cause clinical manifestations. Another study identified co-infection of enteric adenovirus subtypes (40/41), enteric astroviruses, Salmonella, Campylobacter jejuni and Yersinia enterocolitica[7]. This evidence collectively demonstrates that co-infection by bacterial and viral pathogens play a critical role in disease progression.

Gastroenteritis caused by bacterial and viral pathogens is a major public health threat causing 35% of hospitalizations in the United States. Salmonella enterica and noroviruses cause the majority of gastroenteritis infections, with emergence of sporadic outbreaks and incidence of increased infection. Both noroviruses and Salmonella are major foodborne pathogens in seafood and poultry. Though infection mechanisms of these pathogens have been studied separately, little is known about the mechanisms regulating co-infection. Few efforts have been made to elucidate the molecular mechanisms governing co-infection of foodborne bacterial and viral pathogens.

Although healthy adults show clearance of norovirus and Salmonella infections in a few days, these infections could be life-threatening to immunocompromised individuals, young children and elderly populations. Studies have shown that norovirus is the most commonly associated pathogen (27% of cases) in acute gastroenteritis illness in hospitalized children under 5 years of age. Furthermore, 20% of norovirus infections also have Salmonella-co-infection [8]. We recently evaluated the in vitro interaction between murine norovirus and Salmonella enterica as a model for human norovirus infection. We demonstrated that infection of RAW 264.7 cells with S. enterica reduces the replication of murine norovirus, in part by blocking virus entry early in the virus life cycle and inducing antiviral cytokines later in the infection cycle. In particular, bacterial infection prior to or during murine norovirus infection affected virus entry, whereas murine norovirus entry remained unaltered when the virus infection preceded bacterial invasion. This block...
in virus entry resulted in reduced virus replication, with the highest impact on replication observed during conditions of coinfection. In contrast, bacterial replication showed a threefold increase in murine norovirus-infected cells, despite the presence of antibiotic in the medium. Most importantly, we presented evidence that the infection of murine norovirus-infected macrophages by *S. enterica* blocked murine norovirus-induced apoptosis despite allowing virus replication. Apoptosis blockade was evidenced by reduction in DNA fragmentation and absence of poly-ADP ribose polymerase (PARP), caspase 9 and caspase 3 cleavage events. Our study suggests a novel mechanism of pathogenesis whereby initial coinfection with these pathogens could result in prolonged infection, by either of these pathogens or both together, by delaying cell death [9].

Human norovirus induces acute infection lasting 1 to 3 days. However, studies have shown that prolonged infection (20 to 180 days) occurs in immunocompromised patients. Nevertheless, non-immunocompromised individuals have also been reported to be chronically infected with norovirus [10]. It is possible that other external factors may contribute for the chronic infection of healthy individuals, such as the composition of the gut microbiome or coinfection with other gastrointestinal pathogens. Most important is the recognition that we may be misjudging the importance of co-infections by attributing the whole clinical picture to one agent and underestimating the other, thereby failing to administer the right treatment and/or support necessary to overcome the illness.

**Disclaimer**

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the US FDA.

**References**


