Journal of Infectious Diseases & Research
JIDR, 1(1): 12-19
www.scitcentral.com

Original Review Article: Open Access

Coinfection: Notes for Reflection on the Approach in General Medicine

Jose Luis Turabian*

*Health Center Santa Maria de Benquerencia, Regional Health Service of Castilla la Mancha (SESCAM), Toledo, Spain.

Received July 09, 2018; Accepted July 25, 2018; Published November 25, 2018

ABSTRACT

Comorbidity or multimorbidity, that is, the presence of two or more diseases, is a generalized phenomenon that affects the health of populations throughout the world, with the greatest burden among individuals or disadvantaged subpopulations, becoming a serious public health problem. Co-infection is an infection with two or more infectious organisms at the same time. Co-infections are common in the community, such as coinfection of respiratory viruses, Influenza A and B, viral and bacterial co-infection with influenza virus, pulmonary tuberculosis and HIV, HCV and HIV, HBV and HCV, coinfection of sexual transmission diseases, HIV and parasites, parasitic coinfections and tropical diseases such as chickungunya and dengue infections, co-infection with influenza and dengue viruses, malaria and cutaneous leishmaniasis, etc. And all these multi-infections go through the general medicine practice and frequently affect patients with other diseases such as hypertension or diabetes mellitus, COPD, depression, etc. Thus, coinfections must be understood within the broader concept of comorbidity or multimorbidity. However, many gaps remain in our understanding of their frequency and importance. Multiple infections can complicate immunity and treatment, although they can also provide an unexpected benefit for the patient. In this scenario, this article intends to initiate some notes for the reflection and systematization of the concepts of coinfection at the level of general medicine, which is a task that has not yet begun. For the general practitioner, some important aspects of coinfection are: the taking of the clinical history and the clues in the recent history of a patient who can provide evidence of coinfection, the risk factors of coinfections, the influence of coinfection on the accepted symptoms of each infection, the frequency of local coinfections, the main and most relevant coinfections, the impact of coinfection on the course of evolution and prognosis, the possible effect of drugs in the treatment of coinfections and the possible problem polypharmacy and its repercussions on the patient, including adherence to treatment.

Keywords: Coinfection, Comorbidity, Epidemiology, General practice

INTRODUCTION

It is common situation in general practice that patients say things like “This cold is lasting twice as much as others” or “I got better from the flu, but I have relapsed again...” Is it possible to catch two colds at the same time? Yes; the phenomenon is technically known as coinfection, an infection with two or more infectious organisms at the same time. Multiple infections can complicate treatment, although they can also provide an unexpected benefit to the patient, such as, for example, one organism suppresses the growth of another.

In nature, organisms are commonly coinfected by two or more strains of pathogens and have been shown to influence the virulence of the disease. Co-infections can be especially important for the ecology and evolution of opportunistic pathogens that are often able to persist and transmit from the environment. Opportunists, with a wide range of hosts, are more likely to find potential hosts than pathogens specialized. Since the probability of coinfections due to opportunistic pathogens transmitted by the environment is high, the genetic composition of the co-infecting population can lead to variable results of the infection. In addition, coinfections can select the most virulent pathogen strains [1].

On the other hand, coinfections modify the immune mechanisms of the host, but how the systemic and local processes at the site of infection interact is still unclear [2]. The majorities of studies on coinfections concentrate on one of the infecting species, an immune function or group of

Corresponding author: Jose Luis Turabian, Health Center Santa Maria de Benquerencia Toledo, Spain, E-mail: jturabianf@hotmail.com

Citation: Turabian JL. (2018) Coinfection: Notes for Reflection on the Approach in General Medicine. J Infect Dis Res, 1(1): 8-15.

cells and often focus on the initial phase of the infection [3]. Many people have multiple infections at the same time, but the combined contribution of those infections to disease-related mortality is unknown [4] as well as the effects of co-infections on the outcome of the disease in the community are poorly understood.

The multimorbilidad, that is to say, the presence of two or more illnesses, is a generalized phenomenon that affects the health of the populations in the whole world [5]. Generally, when talking about multimorbidity or comorbidity, one tends to think about the superposition of mental, cardiovascular, diabetes, cancer and respiratory diseases. But, infectious diseases are not usually included. However, all the elements that apply to the conceptualization of multimorbidity or comorbidity can be applied to co-infection. In fact, co-infection should be understood, from general medicine as comorbidity. There is a broad international consensus that multimorbidity is best addressed in primary care settings. These same principles should be applied, as a general rule, to coinfections.

In this scenario, this article intends, based on experience and a brief narrative review, to initiate some notes for the reflection and systematization of the concepts of co-infection in general medicine level, which is a task that has not yet been started and it supposes forgetfulness and a dramatic void in the health care and in the theoretical concepts accepted of morbidity.

DISCUSSION

The family doctor occupies an important place in the care of the health of the population, its role as guardian of health implies an action directed mainly to observe and act on any phenomenon or event that threatens the welfare of the community. The person is the centre of interest for the family doctor. The three key elements of general medicine, which are the clinical interview, continuity of care and attention to context, have fundamental implications in relation to individual health care and community medicine [6,7].

Family medicine is a major source of information about health problems and their variation. For most illnesses the general practitioner is the first point of contact in the health care system and he looks after a population whose age and sex composition is known. So, family medicine has important epidemiological connotations, presenting for example, a unique opportunity to study the natural history of a disease and to know the rates of diseases in small geographic bases that would facilitate planning and the adequate use of resources [6,8].

Infectious disease dynamics offer a wide variety of intriguing and unexplained phenomena. There is a gap in how diverse studies which encompassing immunology, mathematics, epidemiology and virology are able to combine to form a complete picture of this phenomenon. Among these specialties, to study infectious disease dynamics, family medicine should be included [9].

For the general practitioner, some important aspects about co-infection are: 1) taking of the clinical history, by a patient-centred approach and clues in the recent history of a patient that can provide evidence of co-infection; 2) the risk factors of co-infections; 3) the influence of coinfection on the symptoms accepted of each infection; 4) frequency of coinfections; 5) the main and the most relevant coinfections; 6) the repercussion of coinfection on the evolutionary course and the prognosis; and 7) the possible effect of the drugs in the treatment of coinfections and the problematic of the possible polypharmacy and its repercussions on the patient, including adherence to treatment. **Table 1** systematizes and conceptualizes these elements from the point of view of general medicine/family medicine.

Table 1: Some concepts of coinfection from the point of view of general medicine.

CONCEPT	COMMENTS
Taking of the clinical history, by a patient-centred approach and clues in the recent history of a patient that can provide evidence of coinfection	A general practitioner may suspect a coinfection on the basis of symptoms or risk factors, or the results of direct tests that demonstrate the presence of multiple organisms in the patient. Doctors need as much information as possible to decide what kind of tests are needed, how to intervene with the treatment. Patients should make sure that their doctors get a complete medical history. It is important to keep in mind that hiding evidence of coinfection due to shyness or concerns about censorship could result in getting the wrong treatment. Some clues in a patient's recent history may provide evidence of coinfection and could be useful for the doctor. Viruses, bacteria, protozoa, worms and other organisms can all be present simultaneously in a patient. Environmental, spatial, temporal or

	demographic factors affect the frequency of co-exposure to parasites.
Frequency of coinfections, the risk factors of coinfections	Two very common coinfections throughout the world are HIV and HCV, as well as HIV and TB. The risk factors for the three diseases are very similar and patients who have one can also lead to another. HIV and HCV, for example, are transmitted through blood contact, as seen among injecting drug users. Appropriate testing and identification for both HBV/HCV are important. Screening for viral hepatitis is important in individuals diagnosed as HIV positive. Co-infection between different sexually transmitted infections (STIs) is very frequent. Therefore, anyone who presents one of them should rule out the presence of others, particularly HIV infection and chlamydia infection; the latter is the most common STI in Europe and is frequently asymptomatic. Co-infection of community-acquired respiratory viruses was more often in patients <30 years of age. But, Infections by more than one respiratory virus were most often found in children and in individuals aged over 65. In critically ill patients with influenza, age and immunosuppression are risk factors for co-infection. Bacterial co-infection is frequent in influenza A H1N1 pneumonia, with COPD and increased platelet count as the main predictors. There are infections, as for example, those of chickungunya and dengue that coincide in space (tropical and subtropical regions) and usually coincide, also, in time. Patients can also host multiple bacterial infections as a result of untreated water or poor food hygiene. Infection with a parasite increases the susceptibility to infection by a second parasite. Malaria and Cutaneous Leishmaniasis are co-endemic throughout large regions in tropical countries and co-infection may impact the evolution of host-parasite interactions. *Borrelia burgdorferi*, *Anaplasma phagocytophilum* and *Babesia microti* are transmitted by the same vector, blacklegged ticks (Ixodes scapularis) and are carried by many of the same reservoir hosts. Medical practitioners should be aware, especially of the elevated risk of *B. microti*/*B. burgdorferi* co-infection. Co-infections may be common in children with diarrhoea who tested positive for *Clostridium difficile* infection. Given a lack of CDI case definitions, especially in young children under the age of 5 years, a broad panel of pathogens should be tested for to exclude other microbiological causes.
Influence of coinfection on the symptoms of each infection	The organisms involved in a coinfection typically interact with each other within the patient. Sometimes they amplify each other and worsen the symptoms. The symptoms can also be confusing to the general practitioner, since it may initially go unnoticed the fact that the patient's symptoms are the result of multiple diseases, not just one. Many infections produce very similar symptoms, such as

	respiratory symptoms, chikungunya and the acute phase of dengue, etc., which causes them to become indistinguishable diseases with the consequences that this entails in the diagnosis, treatment, control and prevention of both diseases.
Repercussion of coinfection on the evolutionary course and prognosis	Multiple infections can complicate treatment, although they can also provide an unexpected benefit to the patient, as sometimes one organism suppresses the growth of another. The organisms involved in a coinfection typically interact with each other within the patient. Sometimes they amplify each other and worsen the symptoms. Other organisms can act against each other. Bacteria, for example, are often quite aggressive around other bacteria to protect their territory and a coinfection can suppress the growth of an organism. In hepatitis B virus (HBV) and HIV co-infection the course of chronic HBV infection is accelerated. HIV/HBV co-infected patients had significantly higher serum bilirubin, ALT, alkaline phosphatase and lower platelet count. HBeAg positive co-infected patients had higher HIV RNA and HBV DNA compared to HBeAg negative co-infected patients. The consequences of poliparasitism are very little known, and may become very important, especially in vulnerable groups such as children and pregnant women in tropical and subtropical areas.
Effect of treatment	The general practitioner should consider co-infection in the process of developing a treatment plan. Medications can behave unexpectedly when there are multiple organisms involved. The drug could suppress one organism and promote the growth of another or allow a latent infection to flourish by killing the secondary infection it kept under control. Prior to initiation of antiretroviral treatment (ART) all patients HIV should be screened for HBsAg to initiate appropriate ART regimen. Effective management for viral hepatitis should be integrated into HIV treatment programmes. Some co-infection cases with HBV/HCV may be prevented through HBV vaccination and harm reduction activities for those with or at risk for HCV. Treatment against a parasite may not restore the patient's health if the competing parasite responds to compensate for the absence of the treaty. Therefore, the possible exacerbation of certain parasitic diseases should be taken into account when eliminating their competitors. Quantifying the importance of the interactions between infections and their hosts could better adjust the corresponding treatments. Empiric antibiotics with staphylococcal activity should be strongly considered in all patients with severe influenza A infection. Treatments with multiple drugs are often necessary and it can be difficult for patients to comply with treatment when numerous medications are involved, especially if side effects are unpleasant or medications are expensive.

Human immunodeficiency virus, hepatitis C virus, Hepatitis B virus and tuberculosis

The best data on coinfection come from studies of these viruses - HIV and HCV. Studies show that co-infection can worsen, improve or have no impact on the course of a disease. The result depends on the viruses involved. Progressive immune dysfunction and the acquired immunodeficiency syndrome (AIDS) develop in most persons with untreated infection with human immunodeficiency virus type 1 (HIV-1) but in only approximately 20 to 30% of persons infected with HIV type 2 (HIV-2); among persons infected with both types, the natural history of disease progression is poorly understood, but It seems that coinfection with the two main types, HIV-1 and HIV-2, is really beneficial and decreases the progression of the disease. Results suggest that HIV-1 disease progression is inhibited by concomitant HIV-2 infection and that dual infection is associated with slower disease progression. The slower rate of disease progression was most evident in participants with dual infection in whom HIV-2 infection preceded HIV-1 infection. These findings could have implications for the development of HIV-1 vaccines and therapeutics [10,11].

Clinical studies have provided compelling evidence that people coinfected with human immunodeficiency virus (HIV) and Mycobacterium tuberculosis have a 20-30-fold higher risk of developing active tuberculosis as compared to individuals with *M. tuberculosis* monoinfection. Studies have shown that rates of liver disease are higher in persons who are coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) than they are in persons with HCV alone, but estimates of risk vary widely and are based on data for dissimilar patient populations. There is a significantly elevated RR of severe liver disease in persons who are coinfected with HIV and HCV. This has important implications for timely diagnosis and consideration of treatment in coinfected persons [12].

Hepatitis B virus (HBV) and HIV co-infection has variable prevalence worldwide. In comparison to HBV mono-infection, the course of chronic HBV infection is accelerated in HIV/HBV co-infected patients. HIV/HBV co-infected patients had significantly higher serum bilirubin, ALT, alkaline phosphatase and lower platelet count. HBeAg positive co-infected patients had higher HIV RNA and HBV DNA compared to HBeAg negative co-infected patients. Prior to initiation of antiretroviral treatment (ART) all patients should be screened for HBsAg to initiate appropriate ART regimen [13].

HBV/HCV co-infection identification rates can have declined since the late 1990s, but appropriate testing and identification for both viruses are important. Some co-infection cases may be prevented through HBV vaccination and harm reduction activities for those with or at risk for HCV [14].

Respiratory infections

It can be affirmed that respiratory infections represent the most important percentage of infections in family medicine For Fry, in his classic publication, the most prevalent diseases in general medicine are respiratory infections with 25% [15]. Co-infection of community-acquired respiratory viruses among patients was communicated to be of 15%. The most common co-infections were influenza A and respiratory syncytial virus B and influenza A and enterovirus/rhinovirus [16].

Influenza virus infection remains a major cause of morbidity and mortality during winter seasons. Bacterial and virus co-infection is a commonly described situation in these patients. However, coinfection with influenza A and B, two main types of influenza virus, seems to occur in less than 2% of cases, but does not appear to affect the overall outcome. It has been described that Co-infection by influenza A and B viruses was significantly associated with nosocomial acquisition. Co-infection was not associated with worse outcome, previous underlying condition, or vaccination status [17].

Infection by human rhinovirus (HRV) is a major cause of upper and lower respiratory tract disease worldwide and displays considerable phenotypic variation. More than 100 viruses can cause the common cold, so it is not unusual to be exposed to two at the same time. And, since one virus does not generally confer immunity against the other, it is not unusual to be infected by two viruses at the same time. Coinfection in the common cold has been difficult to study in the past due to the large number of viruses that can cause a cold. In recent years, however, advances in molecular genetics have allowed scientists to know HRV, the most common cause of the common cold. All the genetic material of the known strains of rhinovirus has been sequenced and it has been reported that coinfection with multiple strains is a common occurrence [18].

It has also been reported that coinfection provides viruses with the opportunity to mutate into new strains. Diagnostic tests for many of the viruses that cause common colds are now commercially available. It has been reported that in children, almost half of them were infected with more than one virus when they became ill, but respiratory viral coinfection did not increase severity in all outcomes assessed. That is, children infected with multiple viruses did not appear to be sicker than those infected with a single virus, although they stayed sick for longer [19,20].

With influenza viruses, which cause respiratory infections similar to those of the common cold, coinfection could be uncommon. Epidemiological studies, as well as experimental models, suggest that clinical pictures of viral respiratory infections are often complicated by secondary bacterial infections. The control of primary viral and secondary bacterial infection depends on a multifactorial

balance between cell, bacteria and virus, which is seriously disturbed by coinfection. In this review we analyze the changes in the host cell caused by respiratory viruses and bacteria that favor coinfection [21]. The coinfection with influenza virus varies seasonally according to the beginning more or less early of the influenza season, when other respiratory viruses are less prevalent [22,23].

This co-infection can occur not only in immunocompromised individuals, but also in immunocompetent patients. Although co-infection appears to be a rare event, it may still play a role in the epidemiology, pathogenicity and evolution of influenza viruses [24]. Co-infection of different influenza A viruses is known to occur but how viruses interact within co-infection remains unknown. Simultaneous presence of the two influenza viruses increases the infectivity and the transmissibility of A/H1N1 virus but whether it changes the infectivity of A/H3N2 is unclear. In conclusion is suggested that influenza A viruses within co-infected patients can interact in some ways rather than transmit independently and this can enhance the spread of influenza A virus infection [25].

Bacterial co-infections in severe influenza infection were common, resulted in delay of antiviral therapy and were associated with increased resource allocation and higher mortality [26]. Bacterial co-infection was frequent in influenza A H1N1 pneumonia, with COPD and increased platelet count as the main predictors. Although associated with higher severe scales at admission, bacterial co-infection did not influence mortality of these patients [27].

Chickungunya and dengue infections and co-infection of the mosquito *Aedes aegypti*

Dengue-chikungunya coinfections can occur if the person is bitten by two mosquitoes infected with the different viruses or if a mosquito is infected by both viruses. Since there is neither a vaccine nor a specific treatment, the treatment focuses on the control of the symptoms, but despite this, the non-differentiation of both diseases can cause serious consequences. During outbreaks of dengue, or in countries that historically suffer from dengue epidemics, doctors tend not to confirm their diagnosis in the laboratory and it is usually assumed that it is a dengue infection. The *Aedes aegypti* mosquito spreads both dengue and chikungunya and is endemic in 174 countries and the *Aedes albopictus* mosquito, which also spreads both viruses, is adaptable to less extreme climates. The vector species that spread these pathogens and also the Zika virus - are the same; however, the number of countries that have reported cases of dengue is considerably higher than the countries that have reported Chikungunya, which can be caused for the widespread misdiagnosis of chikungunya with dengue [28,29].

Co-infection of the mosquito *Aedes aegypti* with two microsporidian parasites (*Vavraia culicis* and *Edhazardia aedis*) at two levels of larval food availability affects parasite transmission directly and indirectly through effects on host traits. Co-infections may modify parasite transmission opportunities directly as a consequence of interactions in the within-host environment, but also indirectly through changes in host life history. Furthermore, host and parasite traits are sensitive to the abiotic environment with variable consequences for parasite transmission in co-infections. Co-infection can negatively affect parasite transmission opportunities, both directly as well as indirectly via effects on host life history [30].

Sexually transmitted infections

Co-infection between different sexually transmitted infections (STIs) is very frequent. Therefore, anyone who presents one of them should rule out the presence of others, particularly HIV infection and chlamydia infection [31].

Parasitic co-infections

They are common in nature and the interactions between different species of parasites are similar. So far, very few studies have been carried out on the interactions that occur during these coinfections, despite their undoubted influence on the dynamics of parasitic diseases and their consequences.

It is assumed that the different species of parasites that colonize a given host usually do not interact because they often parasitize different tissues and the use of different resources limits competition. In mixed infections, treatment against a parasite may not restore the patient's health if the competing parasite responds to compensate for the absence of the treaty. Therefore, the possible exacerbation of certain parasitic diseases should be taken into account when eliminating their competitors [32].

Individuals living in areas endemic for helminths are commonly infected with multiple species. Variability in risk of *N. americanus* and *S. mansoni* co-infection between households cannot be entirely explained by exposure-related risk factors, emphasizing the possible role of other household factors in the heterogeneous distribution of helminth co-infection. Untangling the relative contribution of intrinsic host factors from household and environmental determinants therefore remains critical to our understanding of helminth epidemiology [33].

CONCLUSION

Co-infection is an infection with two or more infectious organisms at the same time. It is admitted that coinfections are frequent in the community, such as coinfection of respiratory viruses, Influenza A and B, viral and bacterial co-infection with influenza virus, TB and HIV, HCV and HIV, HBV and HCV, co-infection between different sexually transmitted infections, HIV and parasites, parasitic coinfections and tropical diseases such as chickungunya and dengue infections, influenza and dengue virus co-infection,

malaria and Cutaneous Leishmaniasis, etc. And all these multi-infections go through the consultation of general medicine and frequently they occur in patients with other diseases such as arterial hypertension or diabetes mellitas, COPD, depression, etc. Thus, coinfections must be understood within the broader concept of comorbidity or multimorbidity. However, gaps remain in our understanding of their frequency and important and so, clinical significance of co-infections is yet to be determined and it is a matter of discussion whether or not they confer greater severity. Multiple infections can complicate treatment, although they can also provide an unexpected benefit to the patient. For the general practitioner, some important aspects of coinfection are: the taking of the clinical history and the clues in the recent history of a patient who can provide evidence of coinfection, the risk factors of coinfections, the influence of coinfection on the accepted symptoms of each infection, the local frequency of coinfections, the main and most relevant coinfections, the impact of coinfection on the course of evolution and prognosis, the possible effect of drugs in the treatment of coinfections and the possible problem and its repercussions on the patient, including adherence to treatment.

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