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The Inoculum Size Influences Illness Severity: A Review on Experimental Studies and Clues for Tackling the COVID-19 and other Infectious Diseases

Sérgio Britto Garcia*

*Department of Pathology and Legal Medicine, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil.

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ABSTRACT

The prognostic estimation for the human infectious diseases is frequently impracticable albeit important for both the patients and the health system management. Here we discuss the experimental available data showing a robust association between the inoculum size and the severity of diseases caused by protozoan, bacteria and virus. This association may have important repercussions on the understanding of the clinical evolution of patients as well as on the preventive strategies against infectious diseases.

Keywords: Infectious diseases, Inoculum, Load, Mortality, Protozoan, Bacteria, Virus, COVID-19

INTRODUCTION

The prognostic estimation for the human infectious diseases is complex and frequently impracticable albeit important for both the patients and the health system management. This has become even more evident during the current pandemic of COVID-19, in which the unpredictability of which patients will develop the severe forms of the disease jeopardizes the decision making about the provision of appropriate intensive care for all of them. Apart from the known risk factors (such as advanced age, obesity and coexisting diseases), there is a general lack of understanding on the causes for the high variability of the clinical evolution among the patients with infectious diseases.

It is axiomatic that the prognosis of a given infectious disease depends on the balance between the host susceptibility and the aggressor infectivity. This, in turn, is known to depend on its inoculum, virulence and resistance against treatments. Among these variables, the size and route of the inoculum seem to be the less known factors in terms of their relevance for the clinical evolution because data collection on the patients during acute infection is difficult.

Regarding the COVID-19, it has been observed, as in other viral diseases, that there is an independent relationship between high viral load and mortality [1]. Viral load is a measure of the number of viral particles present in an individual. However, it is only an indirect indication of the inoculum size because the variable time elapsed since the infection and the host immunity can both influence the viral load that is detected at a specific moment.

In fact, the actual role played by the inoculum characteristics is poorly known in its clinical aspects. On the other hand, there is robust evidence brought from experimental studies where the inoculum dose is known. In fact, apart from some few contradictory findings, most of the animal models for infections clearly correlated the characteristics of the inoculum with the clinical outcomes, including survivability. Theoretically even well functioning host defense mechanisms can become insufficient if an overwhelming load of infectious aggressors overcomes the immune defenses, causing massive tissue damage before the specific immunity has time to combat it. Another possibility is that a high initial load of an infectious agent may trigger uncontrolled defense responses due to the failure of the mechanisms that modulate the inflammatory reaction, also causing severe tissue damage. So, in both cases, the load of infectious agents that initially infects the host may influence the clinical outcome, either by a direct extensive initial damage and/or by the induction of excessive immune response.

Studies on the repercussions of the inoculum size have been performed in a variety of infectious agents. In general, there is a similar pattern for different infectious agents (protozoa, bacteria and virus). Various studies show that the lower

Corresponding author: Sérgio Britto Garcia, Faculty of Medicine of Ribeirão Preto/CEMEL, Department of Pathology and Legal Medicine, University of São Paulo, Brazil, Code 14061-140, Tel: 55-16-3315-3180; E-mail: sbgarcia@fmrp.usp.br

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inoculum produced lower tissue damages, while the higher inoculum produced high levels of tissue damages, as well as inflammatory infiltrates and cytokines production. In sequence, some selected studies relating the inoculum with the clinical outcomes are presented and briefly discussed. They were chosen considering their quality and clear description of methodology.

PROTOZOAN INFECTIONS

In general, there are few studies detailing the relationship between the inoculum characteristics with the evolution of diseases caused by *protozoa*. *The* colonic alterations experimentally caused by *Toxoplasma gondii* are more significant when the infection is induced by larger inocula [2]. In experimental infection with the protozoa *Trypanosoma cruzi* it has become clear that the higher the number of parasites in the inoculum, the lower were the survival rates. Furthermore, the size of the parasite inoculum determined the cytokine interplay, the inflammatory infiltrate and the tissue damage [3]. In relation to malaria the literature is not unanimous. A systematic review has shown that the dose was inversely related to prepatent and incubation period, while some studies suggested a relation between dose and severity of the disease, but others did not [4]. Recently it has been reported that the malaria infection likelihood correlates with mosquito sporozoite load [5], but the relationship between this load and the clinical outcomes remains unclear. Perhaps the remarkable rate of parasites proliferation inside the mammal organisms may minimize the role of the inoculum size on the severity of malaria.

BACTERIAL INFECTIONS

Regarding bacterial infections there are more reports in the literature relating the severity of the diseases with the initial load of microorganisms. For example, in rabbits inoculated with pneumococci, the inoculum size was observed as to be the most important single variable affecting outcome [6]. Also, a direct relation between the inoculum dose and the development of pneumonia was observed in rabbits end bronchially inoculated with increasing doses of *Streptococcus pneumoniae* [7]. Recently the ability of the rabbit immunity to control pulmonary *Mycobacterium tuberculosis* infection has been found to be directly dependent on the infectious inoculum [8]. The Induction of sepsis arthritis by streptococcus was directly dependent on the number microorganisms inoculated in mice [9]. Experimental infections by the Methicillin-Resistant *Staphylococcus aureus* has been recently reported to have had the clinical outcome (hemodynamic changes, lymphopenia, macrocytic anemia and thrombocytopenia) greatly influenced by the dose of inoculum and route of infection, as the orally infected animals showed the most severe presentation [10].

VIRAL INFECTIONS

A number of articles reported the relationship between the load of virus infections and disease outcome [11]. Mice infected in their eyes with herpes simplex virus type 1 had increased disease incidence with the increasing of the inoculum [12]. Furthermore, mice readily recovered following infection with an infectious dose of influenza A virus that was fatal when inoculated in higher volumes [13]. It has been observed that the size of the inoculum contributes to the outcome of hepatitis B virus infection by altering the balance between the kinetics and magnitude of infection versus the kinetics and magnitude of the immune response [14]. More recently, it has been reported that the inoculating volume of influenza virus is critical for the lungs of mice to be damaged [15]. In cats infected with feline immunodeficiency virus the infectious dose determines the disease onset [16] and the early kinetics of viremia and initial CD8+ T-cell activation [17]. A recent article shows that hamsters with surgical masks had milder manifestations of infections by SARS-CoV-2 [18].

Finally, it has been observed that not only the size of the virus load, but the route of its inoculum has also been related to the disease outcome: the aerosol exposure resulted in more efficient influenza replication in the respiratory tracts than the oral inoculation in chickens [19]. This sheds light on the importance of maintaining air quality in indoor spaces for avoiding more severe contaminations.

FINAL REMARKS

From the above discussion, it seems clear that the inoculum characteristics (size and route) do influence the clinical evolution and the severity of infectious diseases in experimental settings. Consequently, it is a crucial factor for the prognostic establishment at an individual level. These observations cannot be directly applied to humans, but they are strong indicators that the initial infectious load should be viewed more carefully in medical terms. This is supported by an epidemiological retrospective study regarding the 1918 influenza pandemic which showed the increase on the proportion of infectious persons as a proxy for the increase of the infectious dose and severity of the disease to which a susceptible person is exposed [20]. A recent opinion article also shares the point of view that the severity of the COVID-19 could be related to the initial load of exposure and the health care workers are particularly vulnerable since they "can be exposed more often to the virus due to numerous infected individual exposures" [21].

Whether the inoculum is accepted as a relevant player in clinical terms, it brings, as an unfoldment, its importance at a public health perspective as well. In practical terms, it is not only a question of getting or not infected, but a strategy for "reducing-the-size-of-inoculum-as-much-as-possible" should be taken into consideration. This point of view is corroborated by a recent publication that defends a hypothesis that the universal use of masks "reduces the inoculum of the COVID-19 virus for the mask wearer,

leading to more mild and asymptomatic infection manifestations" [22].

In summary, the preventive approach against infectious diseases should not only be directed towards avoiding any contagion of an infectious agent. It must also aim to reduce the infectious load as much as possible, as a mitigation damage approach. As a beneficial consequence, such approach could also favour the morale and motivation of the public in general, which is a major factor contributing to the overall success of any preventive strategy. From a practical point of view, it is intuitive the implicit difficulty to achieve an absolute prevention (a zero rate of contagion) in daily life, as it is sought in a surgical center, for example. This perception sometimes discourages part of the population to engage in the efforts to reduce the infectious spread, such as enduring social isolation and individual hygiene procedures. Some people may become discouraged when they think it is not worth the effort to avoid a contagion, since they believe that sooner or later it will be inevitable. But, considering that there would be major advantages if the inoculum could be as small as possible, there would be more motivation in general to keep the preventive efforts.

The acceptance of the importance of the initial infectious load as a relevant player in disease outcomes would also demand from the public health authorities a clearer strategy to reducing it. For example, the planning and implementation of more efficient air cleaning systems in crowded indoor spaces would become urgent.

As a final comment it may be interesting to mention that the reasoning about the size of the inoculum influencing the severity of an individual infectious disease shares resemblances with the evolution of one disease in a population. That is, a high initial load of the aggressor agent may overcome the individual immune defenses, similarly as a high spread rate of the agent in the population may overcome the health system due to the lack of available time for it to adapt to the situation. In consequence the risk of death will be increased in both cases, at individual or population levels.

In conclusion, even if the relationship between the initial infectious load and the clinical outcomes cannot be definitively established in humans at this moment, the strong possibility that it does exist justifies further studies on this issue. Moreover, it also justifies that more efforts to reduce it as much as possible should be done, as a precautionary attitude towards increasing the chances of survival for everyone, with emphasis on the current pandemic of COVID-19.

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