International Journal of Medical Science and Clinical Invention 7(8): 4925-4930, 2020
DOI:10.18535/ijmsci/v7i08.06 ICV: 77.2
e-ISSN:2348-991X, p-ISSN: 2454-9576

Research Article

Pathogen Infection Recovery Probability (PIRP) Versus Proinflammatory Anti-Pathogen Species (PIAPS) Levels: Modelling and Therapeutic Strategies

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Abstract:

CoVID-19 pandemic due to SARS-CoV-2 virus has been spreading rapidly worldwide since late 2019, and it may become one of the largest pandemic events in modern human history if out of control. It appears most of the CoVID-19 infection resulted deaths are mainly due to severe hypoxia from dysfunction of the lung, and that could be attributed to host's immunodysfunctions particularly hyperinflammatory type disorders or allergic reaction. In this brief review and study, a mathematical model is proposed to correlate the Pathogen Infection Recovery Probability (PIRP) versus Proinflammatory Anti-Pathogen Species (PIAPS) levels, where a maximum PIRP is expected when the PIAPS levels are equal to or around PIAPS equilibrium levels at the pathogen elimination or clearance onset. Based on this model, rational or effective therapeutic strategies at right stages or timing, with right type of agents (immuno-stimulators or immuno-suppressors), and right dosages, could be designed and implemented that are expected to effectively achieve maximum PIRP or reduce the mortality.

Key words: COVID-19, SARS-cov-2, pathogen, proinflammatory anti-pathogen species (PIAPS), optimal PIAPS level, immunodysfunctions, hyperinflammatory disorders, modelling, pathogen infection recovery probability (PIRP), maximum PIRP.

Introduction:

COVID-19 pandemic due to SARS-cov-2 viruses has been spreading around the globe since late 2019 and has resulted in over seven hundred thousand human deaths with over twenty million confirmed infections worldwide[1-2]. In addition to loss of human life, social and economic losses or effects can be very significant. A number of notable global pandemics occurred in human history can be attributed to pathogen infections[3]. Though there are differences among different pathogen induced infections, there were certain similarities among all pathogen infections. The pathogens here mainly include but may not be limited to, bacteria, viruses (such as the new SARS-cov-2 virus causing the covid-19 pandemic), or certain other species that can trigger or initiate a host immune system responses resulting in the production (clonal expansion) of anti-pathogen species (APS), particularly a series of proinflammatory anti-pathogen species (PIAPS). PIAPS here mainly refer to "double-edged sword" species such as certain white blood cells (wbcs) or their generated/related species, such as oxidative radical species and antibodies[4-6], cytokines[7-12, 18-20], *etc*. "Double-edged sword" refers to certain PIAPS that not only attack the pathogens but also attack host normal cells and tissues[4-12, 18-20].

Analysis and Modeling:

Pathogen infection modeling could be very useful for understanding the infection mechanisms and processes, and for preventive or therapeutic strategies. However, most of the existing modeling works are mainly focusing on multiple host infection and transmittance statistics over time

domain[13-17], very few modeling work provide insights on pathogen infection recovery probability (PIRP) over anti-pathogens species (APS), particularly over proinflammatory anti-pathogen species (PIAPS) which is the focus of this study. A pathogen infection in a host may result in pathogen un-controlled growth if the host immune system is too weak, deficient, or dysregulated (including immunoparalysis and a series of immune deficiency syndromes) that could result in sepsis or septic shocks[20]. In a host with normal immune response system, as illustrated in Figure 1, a pathogen infection at time t_0 (end of incubation period) typically trigger a normal and efficient growth (clonal expansion) of immune system generated anti-pathogen species (APS, including PIAPS at an initial level x_0 and time t_0) and ideally shall result in pathogen being eliminated/cleared at t_e[13]. Once the pathogen is eliminated by the APS or PIAPS at t_e, the APS or PIAPS growth are supposed to cease and either remain at their equilibrium levels x_e or decrease (shown by blue solid lines). Certain APS (such as certain pathogen specific antibodies) are expected to remain at their equilibrium levels for certain period of time so the same pathogen infection can be prevented (principle of vaccination), but APS/PIAPS level decrease are normal or expected[13-17].

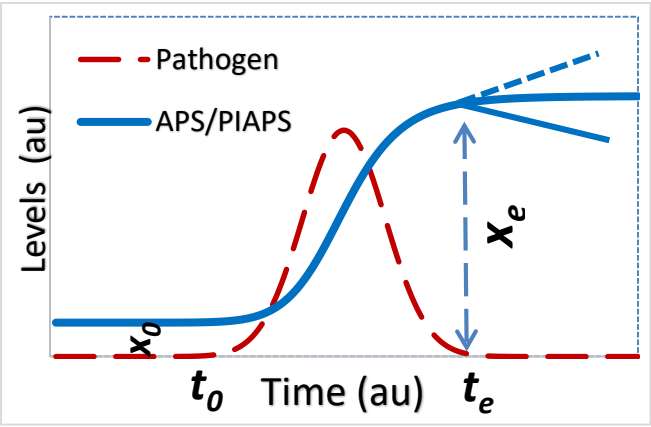

Figure 1. Schematic levels of pathogen (dashed red curve) and host immune system generated anti-pathogen species (APS), including proinflammatory anti-pathogen species (PIAPS), for normal (solid blue curve/line) and abnormal (dashed blue line, reflecting hyperinflammatory disorder) immune response reactions over time.

However, in certain immunodysfunction disorders, particularly certain hyperinflammatory disorders, such as in cytokine release syndromes (CRS) or cytokine storm (CS)[4-12], macrophage activation syndromes (MAS) or macrophage-cytokine self-amplifying loop (MCSAL)[11], WBS proliferative disorders[4], certain PIAPS (*e.g.*, Interleukin-6 or IL-6) can grow out of control or not being efficiently dampened (blue dashed line in Fig. 1) by the host anti-inflammatory species (*e.g.*, IL-10) even after t_e where the pathogen level may be very low or have been cleared. It has been known that a number of PIAPS attack or damage normal cells resulting in tissue death (gangrene) and multiple organ dysfunctions or failures[2, 4-12, 18-20]. Based on these and for potential and practical therapeutic strategies, a normal distribution function Y has been proposed to model the Pathogen Infection Recovery Probability (PIRP, or the survivability, counter to the mortality) versus the PIAPS levels x (shown in Figure 2) and is exhibited with equation (1)[21]:

$$Y = \beta\, exp[-(x-x_e)^2/\alpha] \qquad (1)$$

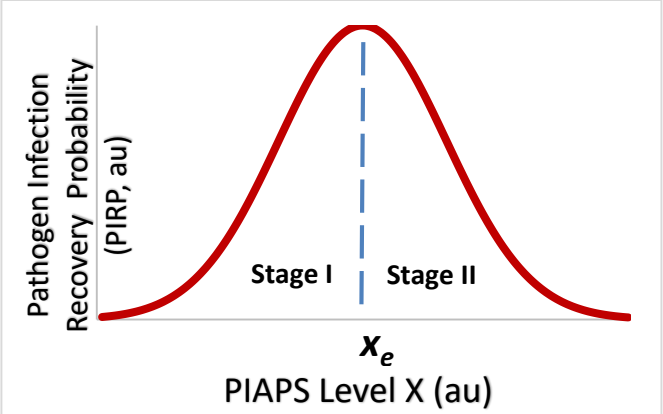

Figure 2. Scheme of Pathogen Infection Recovery Probability (PIRP) versus certain Proinflammatory Anti-Pathogen Species (PIAPS) levels based on equation 1.

Where α parameter is proportional to the PIRP distribution peak full width at half maximum (FWHM) that affects the PIAPS level range width around PIRP maximum**.** During this range, PIAPS levels can significantly elevate PIRP as compared to other PIAPS range where PIRP remains relatively low. B parameter represents a coupling factor of PIRP versus PIAPS levels, reflecting how significant or effective PIAPS level affects PIRP.

Based on this math model, the PIRP-PIAPS distribution function curve are divided into two stages: 1) Stage I or the PIRP rising stage corresponds to pathogen/APS evolution time period between t_0 to t_e as shown in Figure 1: The PIRP of the pathogen infected host starts to rise as the host normal immune response generated APS (including PIAPS) are growing from initial levels of x_0 (x_0 can be zero for pathogen specific APS) and eventually approaching at their equilibrium levels x_e (blue solid line) where the pathogens are being eliminated or

cleared. 2) Stage II or the PIRP descending stage: The PIAPS level may further grow beyond their equilibrium levels x_e as represented by the dashed blue line (representing immunodysregulation such as hyperinflammatory disorders)[2, 4-12, 18-20], the PIRP descends presumably due to excessive PIAPS start to damage the normal or healthy tissues or organs. Eventually the PIRP descend to a very low level due to heavy damages of cells and tissues that can result in multiple key organ failures[2, 7-12, 18-20].

Results and Discussions:

Based on this model, the general therapeutic strategies for minimizing mortality is to achieve and/or to sustain maximum PIRP via a two-stage protocol as following: 1) In stage I or the PIRP rising stage between t_0 and t_e, if the host has a normal immune response to the pathogen infection, the host's APS/PIAPS should grow efficiently toward their equilibrium levels x_e where the pathogens are being eliminated or cleared. In this situation and stage, viral elimination focused therapies maybe unnecessary except supportive therapies are needed for the following situations: a) If the host exhibits breath difficulty (dyspnea) or low blood oxygen level due to the immune reaction generated liquids/mucous in the upper respiratory tubes or lungs (lung infections), then mechanical respiration ventilators and/or oxygen therapy may be utilized to prevent potential oxygen deficiency syndromes and related complications (hypoxemia and hypoxia); b) If the pathogen growth is out of control (such as in the cases where the host has any immune deficiency syndromes), than either pathogen inhibitors/suppressors (if available) or APS boosters/enhancers (immuno-stimulators, such as certain WBC therapies, antibody/immunoglobin therapies, interferon therapies, or therapies utilizing plasma and antibodies from the convalescent patients) may be administered to reduce potential viral damage resulted complications, but the immuno-stimulators must be administered at the right time (in stage I before t_e), right type (APS/PIAPS boosters/enhancers instead of inhibitors/suppressors), and at the right dosages (*i.e.*, APS/PIAPS levels should be carefully monitored and controlled to be equal or close to their equilibrium levels x_e). 2) In stage II or the PIRP descending stage after t_e, when the PIAPS levels are excessive or their growth are out of control (dysregulated), the most critical or essential therapeutic task in the post t_e period or stage II shall be to promptly terminate or suppress the further growth of the PIAPS levels (also called immuno-suppressing or dampening, and a variety of known anti-inflammatory therapies may be utilized with care) at or nearby their equilibrium levels x_e, while pathogen inhibitors/suppressors may not be necessary at this time if the pathogens have been eliminated. In case where the coupling of the host generated APS to the pathogen is very poor, *i.e.*, hyper-inflammation or cytokine storm has occurred but the pathogen level is still high, pathogen suppressors/inhibitors (if available), anti-inflammatory or non-inflammatory APS, as well as PIAPS suppressors may all be administered for this situation and in this stage but with carefully controlled dosages. Certain host immune system self generated anti-inflammatory species (AIS, such as IL-10) may slowly grow to counter the inflammation, but such anti-inflammatory response could be too slow and may eventually reduce the host PIAPS levels well below the equilibrium levels that may result in immunoparalysis[20]. A number of therapeutic PIAPS control (immunomodulation) efforts have been reported in recent years[4-12], however, the timing, type, and dosages of PIAPS suppressors/antagonists must be carefully monitored and controlled and this appears has not yet been systematically investigated, as PIAPS over-suppression or at wrong stage could result in delayed or incomplete pathogen elimination as well as vulnerability of host re-infection or secondary infections and related complications[20]. Finally, since the host's mental/psychological status or modes (fear such as claustrophobia, anxiety, distress, depression, *etc.*) could also enhance host's catecholamine/adrenaline level which in turn could boost APS/PIAPS levels, macrophage-cytokine self-amplifying loop MCSAL[11], and inflammations[22], and may result in mode-inflammation self-amplifying loop (MISAL), psychological counselling to the host thus also appear very important to improve host's PIRP. Precise, fast, convenient, and reliable protocols of measuring and monitoring pathogen and key "Double-edged sword" PIAPS levels are essential not only to validate this model, but to utilize this model and its generated protocols for safe and effective therapeutic treatments of the infected hosts. Both pathogen and key PIAPS (*e.g.*, IL-6) should be targeted as critical biomarkers ASAP.

As an example, in the case of COVID-19, while there appears lack of evidences of organ damages

directly due to SARS-cov-2 virus[23], excess levels or presences of certain PIAPS such as macrophages, neutrophils, or inflammatory cytokines (such as IL-6) were observed in multiple damaged organs in the autopsies and biopsies of the SARS-cov-2 virus infected hosts[18, 24], *i.e.*, the evidences imply the death of covid-19 infected hosts appears to be mainly due to immune-mediated rather than pathogen mediated organ injuries[24]. Additionally, the fact that the average viral levels of intensive care unit ICU (*i.e.*, critically ill) patients were surprisingly lower than those non-ICU patients also seem to confirm that many ICU patients may have been already in stage II[25]. Though APS/PIAPS boosters (such as interferon INF-alpha, gamma immunoglobulin, convalescent plasma containing SARS-cov-2 antibodies collected from COVID-19 recovered patients) were recommended for COVID-19 treatments[18], based on this proposed model, such treatments should be used only for those hosts with deficient or very weak immune responses and should be administered in stage I. PIAPS suppression via a series of inflammation antagonists, or cytokine elimination via blood purification[18] appear useful for controlling CRS but they should be done after t_e in the stage II, *i.e.*, the PIAPS level control are extremely critical for COVID-19 therapy. Most importantly, the levels (vital loads) of SARS-cov-2 and key PIAPS levels (particularly IL-6, macrophages, neutrophils, or certain immune system generated radicals) at appropriate time intervals need to be measured and monitored precisely and closely in order to monitor and determine the virus growth, virus elimination onset time t_e and the corresponding PIAPS equilibrium levels x_e. For COVID-19 infection, it appears many host's antibody IgG equilibrium level x_e is about four times of its initial level x_0[18]. An approach on controlling dysregulated interferon INF-I production in COVID-19 infection[19] appears potentially useful for validating or utilizing this model, again the interferon INF-I level surpression should be done after t_e and the level should not be over suppressed well below x_e. Another example where this two-stage model might be applicable is the application of certain anti-oxidants (assuming Vitamin-C and Vitamins-E have such functions), where the anti-oxidant or radical scavengers appear necessary only during stage II, this is because pathogen supressing oxidative radicals may be needed in stage I. Finally, multiple host units can be utilized to obtain average values of all six parameters of this model (t_0, x_0, t_e, x_e, α, β) for a particular host group, and the average values could be useful for therapeutic treatments of an individual host that is the same or similar to the members of the group.

Summary:

In summary, a normal distribution function containing two stages is proposed to model the Pathogen Infection Recovery Probability (PIRP) versus Proinflammatory Anti-pathogen Species (PIAPS) levels in a pathogen infected host. Based on this model, therapeutic strategies should be based on two stages: In the first stage, medical treatments may not be necessary for most hosts with normal immune responses as PIRP are expected to grow and remain at the maximum due to APS/PIAPS growing to and remaining at the equilibrium levels x_e for certain periods, except supportive treatments are needed for oxygen deficiency syndromes. Hosts with weak or deficient anti-pathogen immune responses may need either pathogen suppressors or immuno-stimulators, however, timing, type, and dosages of both pathogen suppressors and immuno-stimulators are critical. In the second or the PIRP descending stage II due to PIAPS excessive or abnormal growth or levels, it is essential to control the PIAPS around their equilibrium levels x_e via immuno-suppressors or inflammation antagonists. If pathogen levels are still high in stage II, then non-inflammatory immuno-stimulators may be applied. Again, timing, types, and dosages of therapeutic treatments are extremely critical depending on the PIRP stages and on pathogen/PIAPS levels. Precise and timely monitoring and controls of both pathogen and PIAPS levels are essential in order to fully utilize this model to reduce mortality. Increased survivability or reduced mortality could be potential key outcomes if this model is fully developed, well characterized, and implemented after innovative and carefully designed and controlled clinical trials. For instance, for current COVID-19 infections, immunomodulation via timely and precise monitoring and level controls of key biomarkers (including the virus, IL-6, macrophages and/or neutrophils, oxidative radical species, IL-10, *etc*) appear essential for clinical therapeutic strategies.

Acknowledgement:

The author wishes to thank allergy specialist Dr. Kelly Maples for helpful discussions on cytokines/chemokines related hyper-inflammations

in pathogen and food allergies, and to thank his colleague biochemistry professor Dr. Joseph Hall for helpful discussions on pathogen/anti-pathogens. The author also wishes to acknowledge his brother Mr. Honggang Sun on insightful discussions about "Happy Medium" doctrine of the Confucius philosophy that was established in China for thousands of years. The author particularly wishes to acknowledge and thank Dr. Donald Soles (MD, family medical practitioner) who has been busy taking care of many patients (including COVID-19 patients) and also graciously spent time to review and discuss with author on this article. The author wishes to express his deep appreciation and admiration to all medical staff (medical doctors, nurses, *etc*) worldwide who are risking their own lives trying to save lives of others in the current global humanity's battle against covid-19!

Conflict of Interest:

The authors declare no any conflict of interest for publishing this article.

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