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Review

Why do We Look at Asthma through the Keyhole?☆

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ABSTRACT

As happens with the rest of pathology, the study of asthma has been traditionally conducted from postulates set by reductionist science. That model still provides answers to theoretical and practical questions that establish diseases, but does not offer us a complete view of their complexity and multidimensionality. To overcome this limitation has emerged medicine directed towards systems based on the application of biological systems concepts and tools. Biological systems is a cross-disciplinary strategy which, from the data generated by the "-omic" sciences, helps to relate the elements of an organism or biological system, to understand the properties arising from the same and to generate mathematical models capable of predicting their dynamic behaviour. The application of biological systems to asthma starts is starting to make ground. The main challenge today is to understand the need to change focus. The starting point is to abandon the idea that asthma is exclusively an airways disease and considering that the whole lung is involved and, even more, the possibility that it is, at least in part, a systemic process. In view of our current limitations, to understand asthma and design personalised treatment strategies for each patient, requires thinking of systems medicine.

¿Por qué miramos el asma a través del ojo de la cerradura?

Palabras clave:
Asma
Medicina orientada hacia sistemas
Biología de sistemas
Ciencias ómicas

RESUMEN

Al igual que sucede con el resto de la patología, el estudio del asma se ha venido realizando tradicionalmente desde los postulados marcados por la ciencia reduccionista. Ese modelo sigue aportando respuestas a las preguntas teóricas y prácticas que las enfermedades plantean pero no nos ofrece una visión completa de su complejidad y multidimensionalidad. Para superar esta limitación surge la medicina orientada hacia sistemas basada en la aplicación de los conceptos y herramientas de la biología de sistemas. La biología de sistemas es una estrategia analítica transdisciplinar que, a partir de los datos generados por las ciencias ómicas, permite relacionar los elementos de un organismo o sistema biológico, comprender las propiedades emergentes del mismo y generar modelos matemáticos capaces de predecir su comportamiento dinámico. La aplicación de la biología de sistemas al asma comienza a dar ya los primeros pasos. Hoy el reto principal es comprender la necesidad del cambio de enfoque. El punto de partida pasa por abandonar la idea del asma como enfermedad exclusiva de la vía aérea considerando que en su patogenia participa todo el pulmón y, aún más, que posiblemente se trate, al menos en parte, de un proceso sistémico. Vistas nuestras limitaciones actuales, entender el asma y diseñar estrategias terapéuticas personalizadas para cada paciente exige pensar en medicina de sistemas.

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Introduction

Beyond its inflammatory nature, if something stands out in the field of asthma as an unquestionable truth, it is its complexity and multidimensionality. This plural behaviour is revealed at different levels. It is a polygenic disease with an inheritance pattern that does not follow simple Mendelian models,[1-3] and which involves a number of cells and mediators that vary in importance during its natural history.[4-6] Likewise, its clinical expression can take on different phenotypes, not always static and therefore always changing over time.[7-9] It is common to find the coexistence of comorbidities that alter or affect the course, therapeutic response and prognosis in the short, medium or long term.[10,11] What's more: several studies have shown how, in this condition, the concomitance of inflammatory stimuli aggregates, pulmonary or extrapulmonary, worsens the evolution of respiratory symptoms.[12,13]

Faced with all this, and according to the method used by science since the seventeenth century, the traditional orientation of asthma has maintained a focused approach on causal linearity and settled on the reductionist assumption of fragmenting the object into simpler parts, hoping that segmentation will allows us to elucidate the functioning of the set.[14] Under these assumptions, we have no doubt been able to scrutinize and solve many of the theoretical and practical questions posed by the disease. The best proof is that its mortality rate or the number of hospital admissions have experienced significant reductions in recent decades.[15,16] However, despite the successes achieved, the idea that this orientation shows signs of exhaustion is growing, by failing to explain the occurrence of non-linear situations and that it does not provide a holistic vision of the topic.[14] Indeed, we have not cured asthma, nor have we always achieved adequate control of the disease, nor does it seem we are developing therapeutic alternatives with competitive advantages over those available,[14] a problem that is also present in many other fields of pathology.[17]

If we accept this reality, we should agree that perhaps it's time for new strategies capable of integrating all known information about the elements that make up the reality called asthma, thus offering a detailed mapping of its complexity. This approach is known under the generic name of *systems-oriented medicine* and the applicable methodology tool, *systems biology.*[18-21]

Systems-Oriented Medicine

In contrast to conventional reductionist approach of 'divide and conquer', medicine oriented systems seeks to identify not just the constituent parts of the problem, but also, above all, the nature, direction and characteristics of the relationships that exist between them.[20,22] The underlying principle is that only in this way we will likely capture the emergent qualities of the set (property not justified by the simple addition of the parts) and ultimately understand the global dynamic behaviour.[22] Life itself represents its own clear, emerging pattern. It arises not from DNA, RNA, proteins, carbohydrates or lipids. Life springs from their actions and interactions.

This shift (from top to bottom, from general to particular) seeks to overcome errors generated when trying to understand phenomena at higher scales based on lower scales, forgetting that in the complex, the whole is greater than the sum of the parts or, perhaps better, that the whole is different from the sum of its parts ("We can't see the forest for the trees").[19,22,23] In the words of Denis Noble, essential innovation requires discarding as erroneous the prevailing model for a one-way chain of cause and effect (from genes to the body) and complementing it with downward causation, assuming, among others, certain well proven core principles in biological systems, where: a) functionality is multilevel; b) information is not produced unidirectionally, c) the transmission of heredity rests not only in DNA, and d) there are no privileged levels of causality.[24]

Systems oriented medicine symbolises the translation and application of the theory of complex, non-linear systems that interact with the environment to the field of medicine. Such systems, ubiquitous in our environment (from autocatalytic chemical reactions to social and cultural processes), are basically characterised by the following:

In the first place, the mix of variables that compose them (here genes, molecules, cells...) display a heterogeneous connectivity pattern (free of scale), with few highly bound links (*hubs*) and many with few links.[25,26] From a certain level of abstraction, these components can be translated into a series of nodes or vertices connected together by links or along edges. The nodes and connections form a network, or in more formal mathematical language-a graph (figs. 1 and 2).[26] Complex biological systems often assume a modular design upon grouping the vertices into very interconnected sets with common functions.[25,26]

Given that there is a dynamic of fluid interactions between its components, this type of system can potentially exist in many different states. However, and through a process of "self-organization", the system incorporate a reduced number of "stable" configurations that allow it to maintain its essential "emerging order" function structure.[27]

Secondly, as we move forward, the group tends to have a high degree of strength against disturbances, so that temporary or permanent failure of some components often have little or no impact on the overall operation.[28-30] By definition, strength divers from stability or homeostasis in one major detail: its objective is to conserve the activity of the system rather than the state of the system.[30,31] By definition, too, strength, homeostasis and stability are equivalent concepts when the function per se remains to preserve the state of the system.[30] We should also remember that the strength of a subsystem often leads to homeostasis of the system at a superior level.[30]

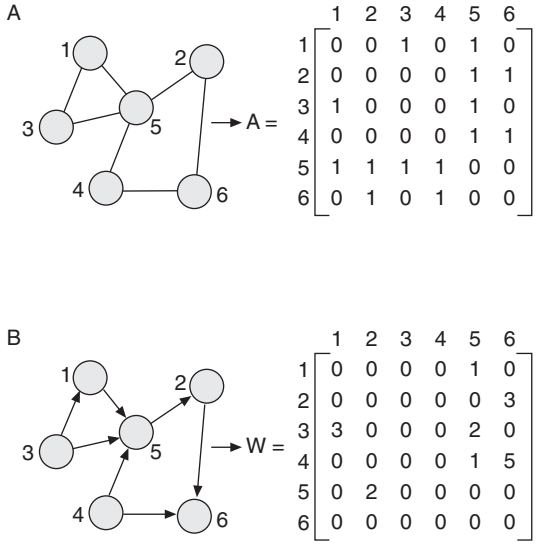

Figure 1. Representation of a network as a graph. A graph G is a pair G (V, E) where V is a finite set of points called vertices or nodes and E is a set of edges or links connecting the nodes within a group. The links can be undirected (simple) or directed (the connections between nodes have a sense). Any graph can be represented by an array and the contents of this array depend on the associated links. There are 2 types of matrices: the adjacent matrix (A) and the weight matrix (W). Each element of the matrix A expresses the presence (1) or absence (0) of a connection between nodes in an undirected network (fig. 2A); note also that while node 5 has four connections to the rest of network elements, the number of links to other vertices is only 2. The matrix W summarises the strength of each connection in a directed network, for example, the link directed from the 2-6 (W26 = 3) is weaker than the existing one from the 4-6 (W46 = 5) (fig. 2B).

In biology, the strength is due not so much to the presence of copies of a given element with the ability to compensate for their failure (redundancy), but instead, above all, to the implementation of the same task from different structural elements (degeneracy), modularity, the activation of feedback mechanisms and the presence of hubs.[29-31] The preservation of the stability of the internal parameters is not always an advantage to the organism, and cancer cells are a good example.

Thirdly, complex nonlinear systems exhibit sensitive dependence on initial conditions: faced with certain stimuli, tiny differences in the baseline system itself give rise to different responses.[27,32] In other words, although the triggers have the same magnitude, they do not necessarily cause the same magnitude of event and often there is no proportionality between cause and effect: small causes can generate enormous effects and vice versa. Failing the principle of proportionality, initial behaviour is unpredictable beyond a certain time horizon. However, the final product, far from being random and erratic, contains an internal order governed by strict laws underlying dynamic evolution and that is measurable using nonlinear differential equations.[27,32] The estimation of the future state of the system will always be based on probability.

Assuming that biological behaviour emerges from the orchestrated activity of many components interacting with each other should lead us to admit that the disease condition arises when enough of a disruption occurs within the system to change the interactions that occur and partially or completely compromise functions and set properties (failure in the strength of the system and loss of plasticity).[20,27] As noted above, what really matters is not to identify which pieces of the puzzle are not working, but rather the links between these parts and the altered underlying dynamics without forgetting time, space and context factors (fig. 3).

Ahn et al, have summarized in an excellent way what are, in medicine, main differences between reductionist ontology and ontology of systems, reminding us that the disadvantage of the conventional reductionist approach does not lie in its use. It lies in thinking that it is always the only solution (table 1).[19,22] Paraphrasing Thomas Lemberger, the application of systems biology to medical research, both basic and clinical, opens a path to: a) increase understanding of the genotype phenotype relationship; b) provide relevant information on the impact of interactions between environmental conditions and phenotype, c) explore new mechanistic functional approaches based on global approximations without preconceived ideas, and d) develop predictive models that capture the intricacy of the physiological (and pathological) states.[20]

Systems Biology

Systems biology is a field of research that is concerned with the comprehensive study of biological processes, analysing the way in which all components interact functionally over time.[18,21,33] From recent academic institutionalisation, systems biology is born in the "post-genomic era" thanks to the coincidence of two circumstances: a) the development of automated high-performance technologies that allow obtaining highly accurate quantitative data, and b) designing software to properly handle and interpret the information generated.[34,35] Systems biology constitutes, in short, a transdisciplinary field of knowledge (the prefix *trans* simultaneously indicates *between*, *through* and *beyond* disciplinary boundaries), where scientists with disparate theoretical training converge (biologists, physiologists, biochemists, mathematicians, physicists,

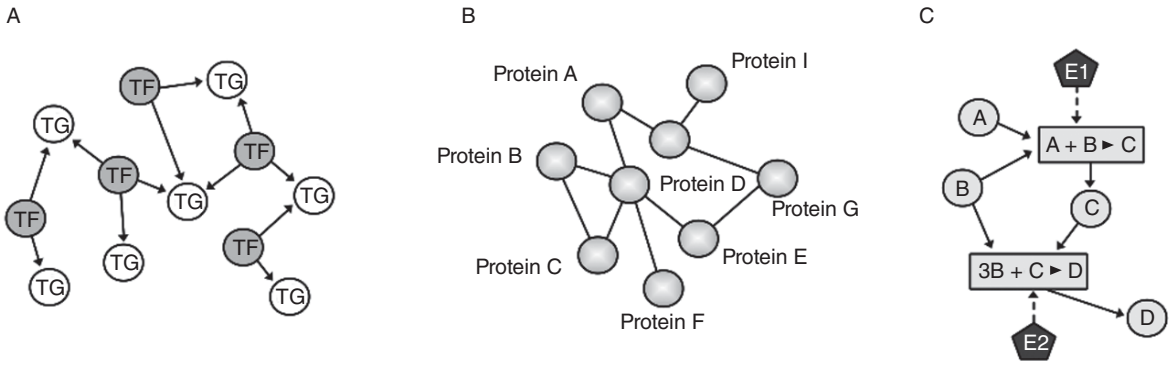

Figure 2. Scheme of 3 types of biological networks: A) a transcriptional regulatory network with two components (transcription factor and target genes), B) a protein protein interaction network (two proteins are connected if there is a coupling between them), and C) a metabolic network constructed considering the reactants, chemical reactions and enzymes. TF transcription factor; TG; target gene; E1 and E2: enzymes 1 and 2.

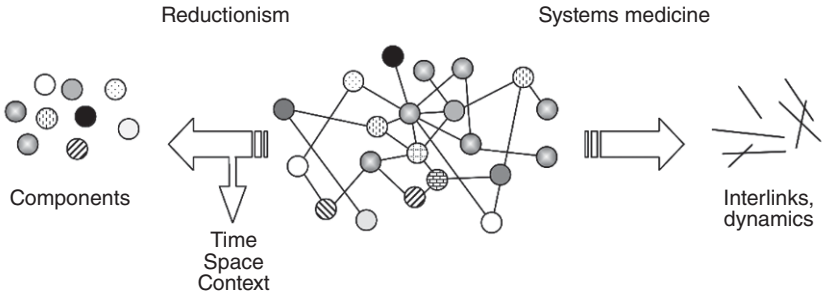

Figure 3. Reductionism vs. systems medicine. In reductionist medicine, the focus of attention remains centered mainly on the components of the problem at hand, and misses information about time, space, and context. In systems-oriented medicine, not only the individual elements are attempted to be identified, but also their interactions and evolution.

Table 1
Reductionist medicine and systems-oriented medicine: essential differences (based on references 19 and 22)

Characteristics	Reductionist	Systems-oriented
Principle	The behaviour of the biological system can be explained by the properties of its components	Biological systems present emerging properties that are not explained by the simple summation of its components
Approximation	One or a few factors are considered in order to interpret the phenomenon under study	Many factors are taking into account at the same time to evaluate the dynamic of the system
Characteristics of the model	Linear, predictable, frequently determinist	Non-linear, sensitive to initial conditions, probabilistic, chaotic
Prototype of disease to apply	Simple, acute diseases	Complex, chronic diseases
Examples of diseases	Urinary infection, appendicitis	Asthma, COPD, diabetes, heart disease
Theoretical limitations	Reduces importance of component-component interactions and their dynamic	Increased costs and time consumption

Table 2
Some of the main "omics" principles: object of study and definition

Discipline	Object of study	Definition
Genomics	Genome	Genome study of DNA molecular organisation and physical mapping to predict the function of genes by taking their sequence as a starting point
Transcriptomics	Transcriptions	Identification of all RNA messengers transcribed starting from a genome
Proteomics	Proteome	Scientific discipline responsible for developing the technology to analyse global patterns of expression of proteins of an organism
Peptidomics	Peptides	Analysis of all peptides belonging to a cell or organism; refers both to the peptides encoded in the genome as well as derivatives of proteases
Metabolomics	Metabolism	The study of all low molecular weight molecules present in a cell, comprises both primary and secondary metabolites
Cytomics	Cytome	Analysis and definition of the apparent molecular phenotype of a cell that results from the interaction between their genotype and exposure to external and internal factors

Table 3
Description of some of the analyses and experimental techniques used in systems biology

Analysis	Techniques
Analysis of the genetic sequence: sequencing the genome of the organism, description of the genes that regulate or are part of a network of interactions, genetic variation responsible for the differential expression of proteins (polymorphisms)	DNA sequencing
	Genotyping
	Indentification of genetic deletions
	RNAi *Knockouts*
Analysis of genetic expression: description of positively and negatively regulated genes in response to genetic or environmental disturbances; identification of the genes expressed as a function of tissues and conditions	DNA microarrays
	DNA marking
Analysis of DNA-protein interactions: description of the genes regulated by determined transcription factors in defined conditions	Chromatin immunoprecipitation
	Biochips (location of binding sites, Chips-chips)
Analysis of protein-protein interactions: description of proteins in enzyme complexes, nuclear pores, cytoskeletons, identification of proteins that modify other proteins during signalling cascades	Two-hybrid system
	Affinity purification
	Mass spectometry
	Quantitative proteomics
Analysis of subcellular protein location: localisation and destination of protein synthesis inside the cell	*Call by cell* sorting
	Molecular marking using tracers or antibodies

computers...) with an ultimate goal: integrating laboratory experiments, called "wet", with those in silico, known as "dry".[35]

The "wet" involves the collection and accumulation of data from the scientific study of genes, their initial (RNA transcripts) and final (protein) products, and participating products or derivatives (metabolites) of metabolic processes in which proteins are involved ("-omics" science).[36,37] Tables 2 and 3 show, respectively, the materials of interest from leading "-omics" and a brief description of some of the analysis and techniques used in them.

On the other hand, the "dry" or *in silico* experiments (an expression meaning "done by computer or via computer simulation") require software that, starting with the information from the "-omics", establish predictive models of biological systems.[38,39] The tools used are based on the development of computer algorithms, the application of mathematical models (statistical, kinetic, neural networks, Markov models...) and reproduction and computer simulation of the behaviour of the whole set.[35,40]

Systems biology uses a circular strategy in which, according to Kitano, one can distinguish four consecutive stages: a) the definition of the components, structure and interactions of the system, b) analysis of their response to external stimuli (disturbances) to build the initial model, c) updating and refinement of the model

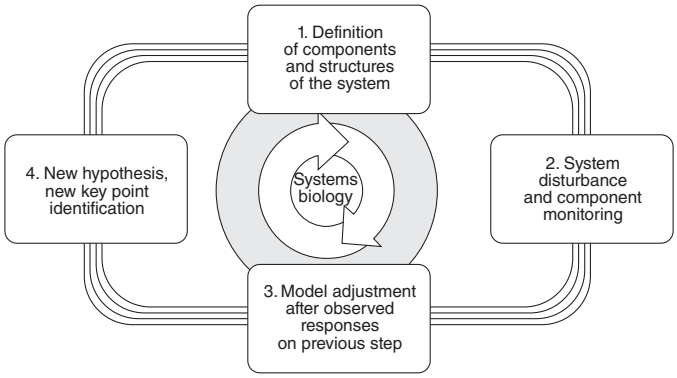

Figure 4. Diagram of the process of systems biology (see text).

from the responses observed in the previous step, and d) the formulation of new hypotheses and identification of new key points (fig. 4).[18]

In this field of knowledge, the road ahead is still a long way. However, the achievements so far allow us to speculate that this method of approaching problems will provide solutions of great interest in terms of unravelling the complexity of biological networks, deciphering the pathogenesis of diseases, identifying powerful biomarkers, designing different therapeutic solutions and moving towards personalised medicine.[17,19,21,35]

Systems Medicine in Asthma. Principles for a Change in Strategy

The logic and instruments of systems biology have begun to be applied in various fields of pathology. Evidence can be found in the published literature on this issue on multiple organ dysfunction,[27] metabolic disorders,[41] cancer,[42] pulmonary fibrosis,[43] inflammation,[44] tuberculosis,[45] autism,[46] Alzheimer,[47] chronic obstructive pulmonary disease,[48] congestive heart disease,[49] or immune response.[50] In the field of asthma we are also witnessing the emergence of the first studies[51-54] with which we are making progress in the understanding of asthma and unravelling a part of the puzzle not suspected previously.

Nevertheless, in my opinion, regardless of the (r)evolution initiated by basic researchers, the problem here is that the translation to the clinical world of new relational data that become available will be much more difficult unless doctors understand the need for a change of model/approach. The starting point would abandon the concept of asthma as a disease unique to the airway and to consider that its pathogenesis is involved the entire lung or even more- it has to do, at least in part, with a systemic pathology. The idea is not new.[13,14,55] The turnabout lies in accepting that if we want an elegant, unifying, and real vision of asthma (where the real is relational), we must stop looking at the asthma through the keyhole, discard its conceptual fragmentation and agree that, while complex thinking per se does not solve complex problems, it helps to design strategies to solve them.

These are precisely the lines of the opinion article, signed by Voelkel and Spiegel, entitled: *Why is effective treatment of asthma so difficult? An integrated systems biology hypothesis of asthma.*[56] From their point of view, the explanation of the pathogenesis of asthma will always be incomplete while selectively focusing on actions on the respiratory tract of eosinophils, mast cells and leukotrienes (and I quote only some of the traditional paradigms). The core resides in integrating that asthma is, in the light of current information, a more general process where systemic inflammatory mediators act as parts responsible for: a) the perpetuation and expansion of the alterations in the lungs, b) the occurrence extrapulmonary effects, and c) the local and general "dialogue" and interaction between the two phenomena.[56] The bone marrow and nervous system participate in the propagation and dissemination of the necessary signals.[14,56,57,58] The role of bone marrow has received special attention in recent years when it was found that lung inflammation induced by various stimuli (including allergens) leads to the synthesis of mediators capable of causing bone marrow production of haematopoietic and mesenchymal progenitor cells involved in the regulating pulmonary inflammation and perhaps also in its expansion to other territories.[14] Togian already pointed out this alternative, focusing on the "general" effects of the "local" allergic processes.[58] Based on his comments, Figure 5 summarises the various routes by which asthmatic inflammation may cause a distant inflammatory response (extrapulmonary).

But even if the system was an epiphenomenon, what cannot be forgotten is the inherent complexity of the altered pulmonary dysfunction inflammation itself in this disease and its changes over time. In asthma more than 50 cytokines acting through more than 20 types of receptors are involved.[56] Do we really believe that their pathogenesis will be discovered by only studying one of these elements?

Systems medicine is still in its infancy and there is still a long road until its research methodology, systems biology, gives us the solutions we have been seeking for so long. Asthma, and we noted in the introduction, is a complex illness and to understand complex problems requires the application of study tools that overcome the limitations of mechanistic science. Now we have the technology. What we need is its generalisation and, above all, to understand the change in paradigm that has been produced in the study of biological phenomena. The perspectives of simplicity were born of the analytical focus that reduces the world to the unit and that concieves diversity as a mere combination of units. From this point of view at the most we can begin to think in terms of complications. However, complexity is something very different from mere complication. It implies building a completely different framework that allows us to concieve

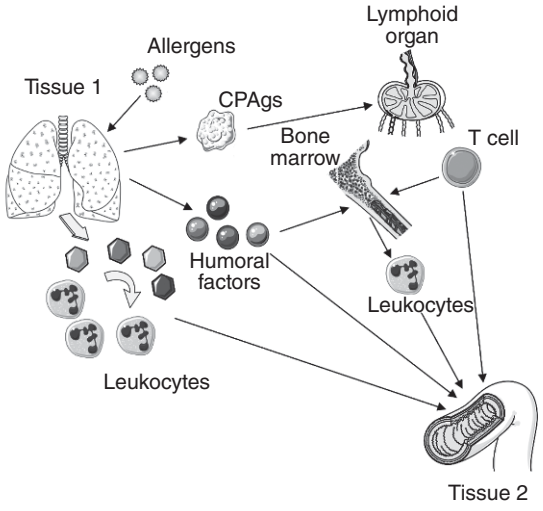

Figure 5. Possible pathways involved in the development of distant inflammation (tissue 2) after the initiation of an inflammatory response, in the example by allergens, located in tissue 1 (lung). As a result of allergic reaction in a tissue 1, an increased expression of adhesion molecules on postcapillary venules would take place. This circumstance would determine the activation of circulating leukocytes that reach other tissues (tissue 2). In addition, humoural factors derived from the original reaction migrate through the bloodstream to tissue 2. Simultaneously, antigen presenting cells (CPAgs) would transport allergens to lymphoid organs where they will be exposed to T cells. Once activated, T cells enter the bloodstream and go to the original reaction site (tissue 1) or other areas (tissue 2). Lastly, the precursor cells existing in bone marrow leukocytes can be activated (by the action of humoral factors or cytokines released from lymphocytes) and begin to circulate.

of multidimentional systems born of a relational dynamic. Seeing our current limitations, understanding asthma and designing useful therapeutic strategies for each patient, demands thinking in terms of systems medicine.

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