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Bringing complexity into clinical practice: An internistic approach

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ABSTRACT

Modern medicine, still largely focused on single diseases, is unprepared for managing clinical complexity (CC), which is an emerging issue. Ageing of the general population has favoured the occurrence of chronic diseases, which generate multimorbidity that has been considered for many years the main feature of CC. However, more recent studies have shown that CC is something more and different and originates from the dynamic interaction among the patient's intrinsic factors (age, gender, multimorbidity, frailty) as well as contextual factors (socio-economic, behavioural, cultural, and environmental). The result of these interactions is non-linear and unpredictable behaviour, which is difficult to manage both in clinical practice and in the organisation of care. Up to now, the prevalent approach has consisted of breaking down and separately analysing each CC component. Consequently, only incomplete strategies to improve health outcomes have been developed, such as limited patient-centred algorithms, deprescription of therapies, and local clinical governance interventions. Medical education has a pivotal role in transmitting the knowledge of complexity, making it realistically understandable and manageable. Future research should aim at implementing our knowledge of CC, developing new tools for its quantitation, and finding new solutions to improve important health outcomes at a sustainable cost.

1. Introduction

Medicine is ever-changing and this conceptual and material dynamism of diseases should not be regarded merely as a bio-scientific process, but also involves a broad range of human and social experiences [1]. In the last decades, ageing of the general population has favoured the occurrence of chronic diseases, which tend to add up over time generating multimorbidity [2,3]. Multimorbidity has been considered for years the hallmark of clinical complexity (CC) [4], however more recent studies have shown that CC is something different and more, and originates from the interaction between the patient's own factors and other contextual factors [5–8].

Capturing complexity is one of the most challenging, yet largely unexplored, issues of modern medicine, since current health systems are still focused on single diseases or organ pathologies and are not equipped to handle CC [9]. We herein review in a narrative fashion the current tendencies regarding CC, ranging from its definition to how to measure it and how to implement its usefulness in clinical practice from an internal medicine point of view.

2. Materials and methods

2.1. Literature search strategy

In June 2018 we searched Medline by using the search terms “clinical complexity”, “complex systems”, “chronic diseases” matched with “elderly”, “ageing”, “frailty”, “multimorbidity”, “deprescribing”, “polypharmacy”, “medical education”, “healthcare utilisation” for all articles published within the last thirty years, but we did not exclude *a priori* highly regarded and highly cited older publications and landmark studies. More than one thousand papers were found with this search strategy, the majority of which were unrelated to the subject of this review and were not considered. We therefore selected only studies exploring the definition and the characterisation of complexity in clinical medicine, focusing on the general/internal medicine setting. We also searched the reference lists of pivotal articles on clinical complexity for additional papers we judged to be relevant to this review.

3. Complexity in medicine

Most physicians still use the term “complexity” in its colloquial

Abbreviations: CC, Clinical complexity; DRG, Diagnosis-Related Groups; NICE, National Institute for Health and Care Excellence

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Table 1
Features of complex systems.

Non-linearity	Every complex system has a non-linear course and small changes in a single part of the complex system may lead to huge changes in global outcomes.
Unpredictability	Complex systems are not governed by a simple cause/effect model.
Blurred boundaries	Agents can change and be members of several systems at the same time.
Adaptivity	Individual components can change and a complex system can adapt its behaviour over time.
Co-evolution	As complex systems are often embedded within other systems, the evolution of one system influences and is influenced by the other.
Context-sensitivity	Every issue is contextual, thus the solution to it cannot be transferred from one context to another.

connotation, which is “difficult to understand and/or to manage” [10]. However, this conceptualisation is incomplete and unsatisfactory, being dependent on the healthcare provider only, and it fails to delineate the multifaceted and multidimensional components of CC.

Currently, a universally accepted definition of complexity has yet to be agreed on. Experts of different fields have attempted to define it, including physicists, chemists, and biologists [11]. It is conceivable that medicine should be particularly complex, being a discipline that applies basic sciences to human beings. Human beings are complex systems in themselves, both at molecular and biological levels, and due to the social dimension of their nature.

A complex system may be provisionally defined as a network of individual factors from whose dynamic interaction new properties of the system itself emerge, and where the observable outcomes are different than the sum of its single parts [12]. Its main trait is therefore interconnectedness [10] and Table 1 summarises other essential features of complex systems [10,12]. Among them, non-linearity and, as a consequence, unpredictability, are ever-present features of a complex system. Co-evolution has an important role in medicine, and given that multiple embedded systems contribute to health-related outcomes, a multidimensional and holistic evaluation is the basis for analysing CC [13].

4. Biological determinants of clinical complexity

Though multimorbidity does not equate with CC [14–16], it represents the most studied of the factors related to the patient (Table 2). The incidence of multimorbidity has been growing over the last decades, probably because of longer life expectancy [17], the spread of unhealthy lifestyles [18], and the higher impact of non-fatal injuries [19]. In clinical practice, multimorbidity is burdened by duplication of diagnostic tests and healthcare utilisation [20], incongruous prescription of drugs [21], higher risk of non-adherence and adverse reactions [22], longer hospital stays and repeated hospital admissions [23,24], higher healthcare costs [23–25], worse prognosis and higher mortality rates [26].

Ageing generates multimorbidity and the prevalence of multimorbidity increases with age [27,28]. However, if we look at this phenomenon in terms of absolute numbers, we notice that more than half of patients with two or more diseases are actually younger than 65 years old [17,28]. Hence, geriatric medicine is not the sole specialty to deal with multimorbidity. Disappointingly, despite geriatric medicine has relevantly contributed to the definition of important goals in the care of elderly patients suffering from multiple chronic disorders [29], the concept of multimorbidity seems to be overlooked in younger adult patients. In fact, the occurrence of multiple diseases within the same patient are not only caused by independent events that mechanistically favour accumulation of morbidities over time [30]. Disease-associated proteins stochastically tend to cluster, forming disease modules that, overlapping with others through the elevated co-expression of gene products, may explain the molecular origins of multimorbidity [31].

Multimorbidity impact certainly depends on the severity of the single disease, but what makes it particularly threatening is the co-occurrence of frailty (Table 2) [32,33]. Frailty can be described as a state of decreased resistance to deterioration and capacity for recovery; in other words, frail patients are less resilient [34], that is, less able to bounce back to stationarity following a physical or social stressor. This lower capacity for recovery is partially explained by a progressive declining of multiple functions, both physical and cognitive. Frailty *per se* is associated with short-term mortality even in individuals without multimorbidity [35]. In fact, frailty can exacerbate and amplify minor stressors, causing disproportionate damage to patients' health [36]. Given its definition, it would be tempting to identify CC as frailty or multimorbidity, or at least to consider all these patients as having a relevant CC. However, other biological and non-biological determinants could still play a major role in determining global CC, with or without frailty and multimorbidity [37].

Finally, cognitive impairment, dementia, and psychiatric illnesses constitute a great burden for both patients and their caregivers. People suffering from severe mental illnesses are more likely to develop multimorbidity [38], and patients with cognitive impairment find it more difficult to adhere to medications, especially in case of complex regimens [39].

Patients' determinants of CC are summarised in Table 2, but in addition to these, a series of studies started at the beginning of this century, have shown that contextual, non-biological determinants toxically combine with these components [27,40] and should be fully integrated in the conceptualisation of CC [5–8,41].

5. Non-biological determinants of clinical complexity

Non-biological determinants of health encompass a number of contextual variables that may contribute to health status, namely socioeconomic, cultural, environmental, and behavioural factors (Table 3), and that interfere with biological factors in determining CC, as proposed by many authors [7,42,43]. This point of view was confirmed by a study conducted in an academic primary healthcare setting, in which patients were labelled as complex depending on the free, and empirically subjective, assessment of their treating physician [5]. Social

Table 2
Biological determinants of clinical complexity.

Multimorbidity	The coexistence of two or more chronic conditions, without an established index disease; different diseases tend to cluster together depending on direct causation, common environmental or genetic factors, or by chance over time.
Comorbidity	The occurrence of disease(s) additional to an index disease.
Ageing	A progressive process that affects all living organisms, caused by the accumulation of cellular and tissue damage.
Disease severity	The extent of the impact of the disease on biological functions, but also on social life and the healthcare system.
Frailty	A vulnerable state due to the reduced functional reserve of homeostatic systems.
Mental health impairment	Cognitive impairment and psychiatric illnesses pose a peculiar challenge for the management of concurrent diseases (*e.g.* communication barrier, lack of adherence to prescribed medications, need for a caregiver).
Resilience	The patient's capacity to recover quickly or to remain well following a physical or a social stressor.

Table 3
Non-biological determinants of clinical complexity.

Socioeconomic factors	Unemployment or precarious work, low income, lack of health insurance or of exemptions from healthcare costs, disabled family member, need for a caregiver, living alone, arduous or hazardous jobs.
Cultural factors	Low education level, language barrier, perceived discrimination, poor access to information, ethnic or religious minority, non-adherence to health screening programs.
Environmental factors	Difficult access to healthcare, home architectural barriers, lack of access to the closest hospital, pollution, occupational exposure to toxins.
Behavioural factors	Non-adherence to medications, alcohol abuse, drug abuse, active smoking, lack of physical activity, unhealthy diet.

and behavioural factors turned out to be among the most important independent predictors of this categorisation that correlated well with a worse clinical outcome, whereas multimorbidity indices demonstrated very modest agreement with the outcome. The same group, in a 4-year longitudinal study, subsequently confirmed the superiority of subjective evaluation -which included the relevance attributed to non-biological determinants- compared to classical multimorbidity indices, in predicting health status and the use of healthcare services [14]. These studies confirm that CC is multidimensional, not limited to the mere association of multiple diseases, and that non-biological components should be considered in the stratification of clinical risk and in the distribution of resources.

It stands to reason that socioeconomic inequalities cause health inequality [44] for different reasons. For example, in the US low socioeconomic indicators, including low education level and low family income, have been associated with worse health outcomes, such as low life expectancy, higher infant mortality, presence of an activity-limiting chronic disease, and poor health status [45]. Similarly, other health inequalities were found in people with low socioeconomic status in other European countries [44]. A high poverty rate is associated with higher utilisation of healthcare services in patients with multimorbidity [46] and it is worth noting that an inverse relationship between socioeconomic status and unhealthy behaviours (tobacco, alcohol, and drug dependence, physical inactivity, poor diet) has been described [47]. Finally, the growing migration flows increase the detrimental effects of language barriers, cultural differences, and low health literacy on the quality of care [48]. Therefore, the absence of social support may represent a challenging obstacle in the management of the patients and could be the major determinant of CC.

6. Assessment of clinical complexity

At present, there is no validated conceptualisation that considers all CC components, since the models proposed so far have either proven to be unable to grasp its various constituents or are characterised by difficulties in clinical transferability.

In the past, when multimorbidity and complexity were considered as synonymous, the Charlson Index was the most used method on account of its simplicity and repeatability, and, as expected, it correlated with mortality and utilisation of health resources [49]. Later, another instrument named INTERMED was introduced, which was able to identify characteristics that act as a barrier in clinical practice. INTERMED is a model that considers both psychological and clinical factors in a grid divided into 4 domains (biological, psychological, social, and health care), based on a thorough medical history in the context of time (past, current state, and prognosis) [50]. Despite the fact that this instrument is fairly complete, it fails to describe the dynamic interaction among variables and appears static and largely dependent on medical history. A “Complexity Framework”, encompassing five different health dimensions and adding a unifying approach to the past descriptions of CC, was proposed but has not yet been brought into practice, nor translated into a clinical tool [8]. The multidimensional approach for the study of elderly, frail patients has been proposed and promoted by geriatricians through the use of the Comprehensive Geriatric Assessment (CGA). CGA is a multidimensional and multidisciplinary diagnostic and therapeutic tool that has the aim of determining and addressing the medical (including mental) and functional problems in order to develop a coordinated and integrated plan for frail, elderly patients [51]. A more recent Cochrane review has shown that elderly patients who received CGA were more likely to be alive at follow-up, after hospital discharge [52]. This result is encouraging, but more studies are needed in order to evaluate the impact of CGA on other important outcomes, such as the length of stay, improvement of cognitive functions, and long-term cost-effectiveness [52]. Moreover, this tool has been specifically developed for elderly patients who are frail and admitted to hospital, and more evidence is needed in other clinical settings, in particular non-hospital medical care and in younger adult individuals who are commonly affected by multimorbidity [28]. A further comprehensive mathematical vector model of CC has been proposed by Safford et al. [7]. Five vectors, expression of the various domains of CC (Tables 2 and 3), intersect at a central point that represents the patient, thus highlighting the concept of an interconnectedness among the different domains. The model is able to determine the contribution of each domain, to evaluate the impact of one domain on another, and to add one domain to another so to get a global CC index. The limits that has made its use unfeasible in clinical practice so far consist of the lack of a clear definition of the variables that grade each domain and in not having hierarchised the weight of the various vectors [53]. To overcome these limits, a multi-professional consensus meeting has been set up to identify, prioritise, and parametrise five variables for each of the five domains that globally represent CC [54]. It has been suggested that this modified vectorial model, summarising multiple measures in a visual representation, may help healthcare professionals to better delineate the current needs of the individual patient and their clinical trajectories over time and across settings [55]. A prospective study with the aim of validating this model is currently ongoing (ClinicalTrials.gov identification number NCT03439410).

7. Management of clinical complexity

Rather disappointingly, although it is evident that CC is a clinical priority, medical care has moved instead towards increasing reductionism. In fact, the prevalent attitude towards CC still consists of breaking down into pieces and separately analysing its components, thus preventing an understanding of those interactions that represent its most relevant feature [56]. This is evident in the interplay between biological and non-biological factors, but also within the biological factors themselves.

Regarding biological components, above all multimorbidity, evidence-based medicine has focused more on the individual disease rather than on the individual patient, since complex patients with multiple diseases have been systematically excluded from randomised clinical trials [57]. By consequence, we have no validated guidelines for them and the current ones may even be harmful due to the high risk of over-prescription, drug interaction, and adverse events, if applied to the single components of multimorbidity [58,59]. The National Institute for Health and Care Excellence (NICE) in the UK has recently drafted recommendations on how to deal with multimorbidity through a holistic, patient-tailored approach [60]. Disappointingly, how to apply these recommendations in clinical practice has not yet been clearly defined. Moreover, a recent campaign on deprescribing has focused on the withdrawal or dose reduction of either useless or potentially dangerous

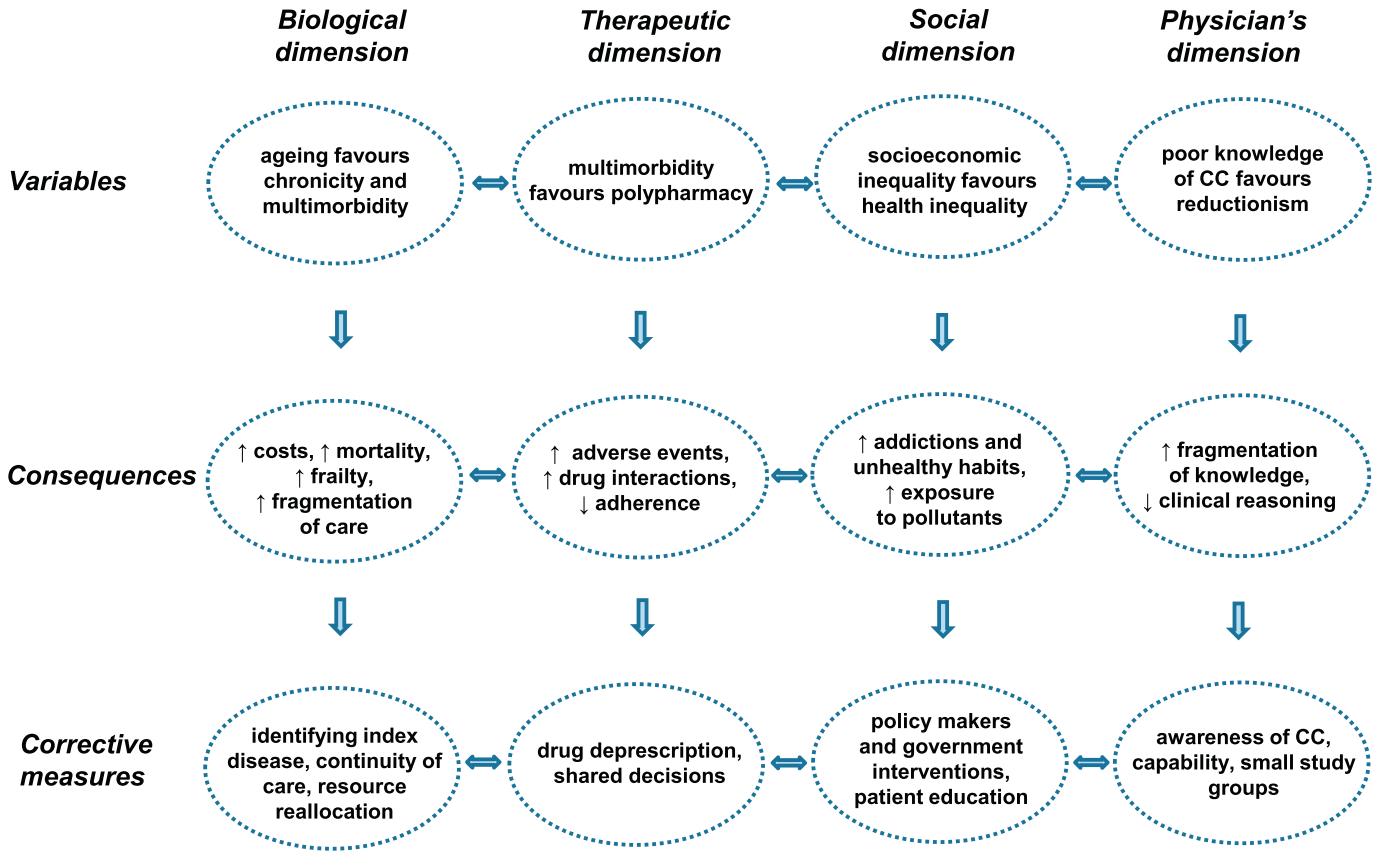

Fig. 1. Schematic representation of some important variables characterizing clinical complexity (first row), their main consequences (second row), and some possible corrective measures (third row), along with the pertaining dimensions (columns). Each of the variables mentioned encompasses in turn many other interconnected variables, thus forming a complex system network. It is not possible to alter a variable without influencing all the others. Further details can be found in the text. Abbreviation: clinical complexity, CC.

medications [61], but once again, only a few interventional studies have assessed this strategy, which proved ineffective in reducing important outcomes, such as mortality [62,63] and hospital admissions [63]. An alternative paradigm is to discuss the therapeutic options with the patient, taking into account personal preferences and priorities [64,65]. This could be a feasible option, considering that patients often perceive the maintenance of an acceptable quality of life as the primary outcome, rather than just prolonging life expectancy *per se* [66]. However, the recent results of a large three-dimensional interventional trial in a primary care setting -addressing health, depression, and drugs- using a patient-centred care model, showed that such approach was not able to improve the quality of life [67]. Hence, besides the challenges of multimorbidity and polytherapy, we should not forget that non-biological determinants of CC could be reduced with targeted structural and individual preventive measures [44]. "Upstream" structural measures include economic, legislative, and social interventions, whereas "downstream" individual measures comprise pedagogical, psychological, and educational interventions [44,68]. In this respect, it is very hard to define detailed and universally accepted interventional measures because of the structural and legislative heterogeneities among healthcare systems of different countries, and doing so would go beyond the aim of this review.

8. Teaching complexity

Being aware of the complexity in medicine is the first step in dealing with CC. Medical complexity can be initially taught through formal teaching by raising awareness on the matter and by making it understandable for students. The "sense of coherence", which includes understandability, manageability, and meaningfulness, should subsequently unify and connect the different aspects studied, despite the infinite complexity of biological and social life [69]. This way of teaching medicine would prepare physicians to manage CC through the application of medical knowledge and the progressive cumulation of experience. From this point of view, the mere knowledge of medicine and the acquisition of specific skills, though essential pre-requisites, are not enough to deal with CC. Consequently, "holistic care" can be learnt through practice, understanding interconnectedness of variables, and tailoring the intervention on a patient-centred basis [70]. In other words, the key factor in dealing with CC is being able to adapt to change, avoiding strict and non-crucial goals, but supporting the transition from individual competence to personal capability, in which existing competencies are adapted and tuned to always new circumstances [71].

If it is true that "complexity of medicine now exceeds the capacity of the human mind" [72], on the other hand we feel that machine learning and big data analysis are not the proper tools to deal with CC. Certainly, machine learning and algorithm-based treatments would aid physicians, however, such a system would not be devoid of mistakes, given that CC behaves non-linearly and unpredictably, and clinical reasoning would still be necessary to contextualise any treatment or intervention. Further, with the rise of data involved in CC, the signal-to-noise ratio would dramatically increase, making it virtually impossible to detect meaningful signal patterns [73]. To expand experience, the modern educator should therefore teach how to master knowledge. This can also be practiced in small study groups, with simulations, role-play, and case-based discussion [70,71].

9. Future perspectives

It is evident that CC is a rising topic that will have a significant impact on the global organisation of health systems, and we envisage further investigation of CC and development of new tools that can be used in clinical practice, considering its biological and non-biological determinants. We acknowledge that it is not easy for the clinician, who has always been focused on the diagnosis-treatment-healing axiom, to eventually recognise the clinical value of a series of external factors that, *vice versa*, consistently burden his/her daily clinical practice. Fig. 1 shows possible consequences and corrective measures coping with the essential dimensions of CC.

It is conceivable that in the near future the clinical management of CC will gradually shift towards general internal medicine. The hallmark of internal medicine is "expertise in caring for adult patients, especially those with complex and chronic illnesses" [74], where we would embrace the term "complex" in its non-colloquial connotation. The needed expertise encompasses adaptability, leadership, and professionalism, and may fill the gap left by an excessive number of consultations. To define the internist as the physician of complexity might be felt as an overstatement, but there is no doubt that complexity is an intrinsic characteristic of the discipline. At another level, healthcare providers and policy makers should plan pragmatic interventions, aimed at avoiding wasteful and duplicative examinations or treatments, reducing the gap between community- and hospital-based care, and better harmonizing generalist and specialist care. Much has been said about the ever-growing expenses for patients with multimorbidity [4]; however, little effort has been made to increase funding for these patients. Considering Diagnosis-Related Groups (DRG) has not proved to be a fair reimbursement strategy. The reimbursement for surgical major joint replacement costs roughly twice as much as care for patients with multiple chronic diseases or complications [75].

Lessons learnt from geriatricians have been very useful to pave the way for a more comprehensive patient assessment and care [76]. However, discontinuity of services, uncoordinated assistance, and the lack of planning of long-term care are common limitations in the management of complex patients [77,78]. The key to addressing these issues may hinge on the analysis of pragmatic, real-world studies. There are many different sources of real-world data, including administrative data that, albeit at times characterised by confounding factors and missing information, can be advantageously used in order to tailor *ad hoc* interventions for planning more equal reimbursement strategies and fair resource allocation [79].

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Competing interest statement

The authors declare no competing interests.

Declarations of interest

None.

Author contributions

All authors participated in the drafting of the manuscript or critical revision of the manuscript for important intellectual content, and provided approval of the final submitted version. Individual contributions are as follows: GRC, MVL, and PF equally contributed to designing the review, collecting data, writing the manuscript, and reviewing the paper; GRC made the final critical revision for important intellectual content. All authors approved the final version of the paper.

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