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The ten "diseases" that are not true diseases

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Introduction

Intensive care medicine is a young medical speciality. As tremendous advances in life-supporting therapies have allowed patients to be kept alive for a prolonged time despite essential organs or biological systems failing [1], we have entered new medical territory with its own pathologies and disorders. Our way to chart this unknown domain recapitulates how we have developed medicine in general. First of all, we try to add some order to the

complexities of biological phenomena with the use of concepts such as diseases and syndromes (Fig. 1). Identifying causes may lead to prevention or etiological therapy, and unravelling courses may lead to strategies for reversal or mitigation. However, reality is often much more complex and unpredictable than our concepts. As such, some diseases may be rather mental constructs or oversimplifications, and syndromes may be ragbags: in both cases, they are poor or even misleading guides for therapy.

1. ARDS

Despite recent refinement and stratification of the ARDS definition [2], a clinical diagnosis of ARDS is poorly correlated with the histopathological substrate. Diagnosing ARDS is important in selecting patients for interventions that limit iatrogenic pulmonary damage such as muscle relaxation or prone ventilation, but lacks accuracy in predicting a response to pharmacological treatment of the disease process. Indeed, a diverse spectrum of pathologies may hide under the moniker of 'nonresolving ARDS' [3]: some of these can be characterized by specific histological patterns (such as bronchiolitis obliterans organizing pneumonia or forms of subacute hypersensitivity pneumonitis) and are likely to respond to corticosteroid therapy, while others, especially those with predominant fibrosis, are much more refractory to corticosteroids.

2. VAP and VAT

In the absence of a gold standard diagnosis, defining ventilator-associated pneumonia (VAP) remains elusive [4]. A clinical/radiological diagnosis of VAP is **Fig. 1** What makes a disease a true disease? Framework for a causal, clinical, biologic, and pathologic definition of diseases



inaccurate, includes many non-infectious conditions, and leads to antibiotic overtreatment; requiring more stringent microbiological criteria for diagnosis increases specificity at the cost of reduced sensitivity and missed opportunities for timely antibiotic therapy. Rather than considering VAP as a clear-cut disease, it should be approached as the more relative concept of a probability tool guiding antibiotic decisions. The inaccuracy of VAP diagnosis and the continuum between colonization and tissue invasion by pathogens inevitably lead to intermediate clinical pictures. Ventilator-associated tracheobronchitis (VAT) is VAP minus the presence of new infiltrates on chest X-ray. Given the suboptimal sensitivity of portable X-ray and the interobserver variability for alveolar infiltrates, it is likely that VAT has a significant overlap with VAP. Currently we are not sure how to approach VAT. The impact of early systemic or aerosolized antibiotic therapy on the outcome of VAT remains unclear [5] and a recent study using a preemptive approach in a cardiovascular surgery population reduced the incidence of VAP and VAT but did not change major clinical outcomes and had the potential to induce antimicrobial resistance [6].

3. VAE

Using VAP rates as a marker of quality of ICU care is hampered by subjectivity of various components of the diagnosis and by variability of VAP rates using different diagnostic criteria [7]. The concept of ventilator-associated event (VAE) has been proposed as a more objective and thus more solid tool for benchmarking. However, VAE is a very heterogeneous condition, capturing VAP only partially and including many non-infectious complications [8]. Before embarking on widespread and/or compulsory VAE monitoring and reporting, it should be made more clear to what extent VAE reflects quality of care and whether it is preventable.

4. Sick euthyroid illness

In the absence of true understanding of how critical illness profoundly affects or alters homeostasis, we project definitions and concepts from non-critically ill to critically ill patients. This results in the introduction of diagnoses that are essentially defined by numbers and not by actual pathophysiological derangements. Aiming to correct the below normal hormone levels in patients diagnosed with sick euthyroid illness has no consistent <u>effect</u> and may be associated with increased harm [9].

5. Relative adrenal insufficiency

While there is no doubt that adrenocortical function may be impaired by critical illness and that corticoid substitution may help to overcome the adverse metabolic and hemodynamic effects of cortisol deficiency, the syndrome of relative adrenal insufficiency (RAI) continues to be an area of great uncertainty. There exists no uniformly accepted diagnostic test for RAI, the relationships between plasma cortisol levels and patient outcome are complex, and cortisol substitution has not consistently been shown to improve outcome in RAI [10].

6. Delirium

From what initially was perceived as 'confusion', 'ICU psychosis', 'withdrawal state', or was overlooked altogether, we have recognized a syndrome called delirium, and started to gain knowledge of its epidemiology, risk factors, and impact on outcomes. ICU delirium has been identified as an independent predictor of poor outcome, yet it seems likely that ICU delirium is largely a manifestation of underlying 'vulnerability' [11]. The incidence of ICU delirium varies widely across different studies, which is attributable to differences in terminology, sedation practices, and patient case-mix [12–14]. While data are accumulating about strategies and interventions to prevent delirium in the ICU, we are still unsure about how aggressively we should treat it when it is present [15].

7. Acute renal failure/acute kidney injury

Studies on the epidemiology, impact, and treatment of acute renal failure (ARF) have been plagued by confusion through the lack of consensus about its practical definition. In addition, the concept of ARF as a principal disease or syndrome of the kidney is probably flawed. On the one hand, minor changes in serum creatinine of little immediate clinical importance have a major impact on overall outcome. On the other hand, mortality remains excessively high in ICU patients requiring renal replacement therapy, despite its efficacy in eliminating nitrogenous waste products, restoring fluid balances, and normalizing electrolyte levels. Different modalities, intensity, and timing of renal replacement therapy have not resulted in better outcomes (e.g., [16]). The concept of ARF has been superseded by that of acute renal injury, which encompasses a much wider spectrum of abnormalities and appreciates the heterogeneous character of the concept.

8. Catheter-associated urinary tract infection

In patients with indwelling urinary catheters, it is recommended to take into account clinical signs and symptoms to distinguish catheter-associated urinary tract infection (CAUTI) from asymptomatic bacteriuria not requiring treatment with antibiotics. However, in critically ill patients, symptoms such as dysuria, urge, and abdominal pain often cannot be reliably assessed, are often absent in CAUTI, or may be elicited by the catheter itself. Bacteremia associated with CAUTI is rare [17]. Despite the lack of any reliable diagnosis of CAUTI in the ICU and <u>no</u> clear <u>benefit</u> associated with the <u>use of antibiotics</u> [18], a clinical suspicion of CAUTI remains one of the main drivers of antibiotic consumption in the ICU.

9. Malnutrition

Energy depletion, nutrient deficiencies, and protein catabolism are common in critically ill patients and have been associated with increased morbidity and mortality. How to define the nutritional needs of critically ill patients and how to meet them are less clear. Studies that compared different nutritional strategies have produced conflicting or inconclusive results, and better achievement of predefined nutritional goals has not necessarily translated in better outcome [19]. Whereas in the general population several diseases have been linked to malnutrition and nutrient deficiencies and may be prevented or reversed by adequate substitution, malnutrition in the ICU still behaves as a moving target that escapes our one-menufits-all approach [20].

10. SIRS and sepsis

Although widely embraced by the critical care community as a condition with undisputable clinical and epidemiologic relevance, perhaps the Achilles heel of sepsis is related to its definition. Since it was first defined in 1992 along with the systemic inflammatory response syndrome (SIRS) criteria, the definitions have evolved in an attempt to capture the growing knowledge of pathophysiology as well as the mechanisms and features of organ dysfunctions. The broad definitions, while important for epidemiologic purposes, have failed to provide adequate groups of patients with homogeneous etiologies, presentations, and outcomes. This fact is often ascribed as one of the causes for the failure of several randomized controlled trials (RCTs) that tested the efficacy of adjuvant sepsis therapies. A good example of how better clinical phenotyping may help guide therapy comes from the 1980s when patients with **Pneumocystis jiroveci** pneumonia and acquired immunodeficiency syndrome (AIDS) were stratified to receive steroids according to a clinical profiling approach. Then, patients with a specific immunologic profile (T cell type immunodeficiency), with a single pathogen (P. jiroveci), presenting with a well-defined organ dysfunction (severe hypoxemia and respiratory failure) were considered eligible to receive adjunctive corticosteroids [21].

For these reasons and also as a result of recent challenges to the SIRS definition in light of new epidemiologic data [22], new definitions are being developed and should be available in 2015 [23].

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Conflicts of interest None.

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