Received: 25 July 2022 | Accepted: 9 January 2023

DOI: 10.1111/1467-9566.13619

SOCIOLOGY OF HEALTH & ILLNESS

ORIGINAL ARTICLE

Exploring valuation practices in diagnosis-as-category: The rising dominance of clinical practice in the categorisation of Sepsis, 1991–2016

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Abstract

This article contributes to the sociology of diagnosis by exploring how an acute medical condition, sepsis, was categorised over a 25-year period. We focus on publications reporting the outcomes of three consensus conferences that were convened to stabilise definitions of sepsis and on the failure of a controversial drug. We also focus on the category of *severe sepsis* by exploring why it was considered useful when introduced in 1991 but redundant by 2016. Drawing on insights from the sociology of valuation, our analysis of pivotal events within this period involving actors from clinical practice, biomedical science, regulation and industry identifies numerous and often contesting evaluative frameworks that came to bear on the categorisation of sepsis. Our analysis further reveals that the evaluative framework of clinical practice, mobilised by the professional specialty of intensive and critical care, became dominant in this categorisation, and that this did not reflect a dominance of biomedicine despite concerning an acute medical condition. Our contributions are to posit the ontological purpose of diagnostic categories

and the role of valuation practices and strategic agency in diagnosis-as-category.

KEYWORDS
Biomedicine, Clinical trials, Intensive care, Medical practice, Regulation

INTRODUCTION

Sepsis and septic shock are related conditions characterised by extreme dysfunctional organ responses to infection (Angus & van der Poll, 2013). Until 2016, an important category within this family of conditions was *severe sepsis*. The purpose of this article is to discuss why this category became important from 1991 but 'redundant' or 'superfluous' and discontinued from 2016 (Singer et al., 2016). As noted by Jutel (2009, p. 291ff), there are several 'engines' of diagnosis and our intention is to identify these and the means through which they came to bear on the categorisation of sepsis. The contribution of our article to the sociology of diagnosis is to show how the *processes of diagnostic categorisation*, intended to encourage the unproblematic indication of appropriate treatment, are themselves turbulent, in part because of the heterogeneous and contesting needs, perspectives and values of different actors in the field. In our case study of the categorisation of sepsis, the *work* required to define, maintain and redefine categories of sepsis was considerable, and our case study reveals the competitive dimension of diagnostic categorisation by exploring how some actors failed to influence the construction of sepsis as a set of diagnostic categories while others succeeded.

Understanding how the categorisation of sepsis (particularly regarding the category of severe sepsis) has changed is useful for the sociology of diagnosis because the changes involved reveal much about the relative power and interrelations of medical and other actors. These changes were significantly affected, we argue, by the evaluative frameworks of different domains: biomedical science; clinical research and regulation; the pharmaceutical industry; and clinical practice as represented by the professional specialty of intensive and critical care.[1] Our study's importance for the sociology of diagnosis thus lies in exploring these evaluative frameworks, how actors mobilised them to achieve impact or failed to do so and how they ultimately came to bear on the categorisation of this acute biomedical condition.

Following a brief description of the methods of our study, we provide the theoretical context for analysis, which draws on developments in the emerging fields of the sociology of diagnosis and the sociology of valuation. We then present key changes in the categorisation of sepsis and the pivotal events surrounding them between 1991 and 2016. In the following section, we analyse these changes and events to identify the different evaluative frameworks that came to bear on the categorisation of sepsis and the heterogeneous network of actors involved. In the discussion, we elaborate on how these actors, including clinicians, regulators and a pharmaceutical company (incorporating both biomedical scientists and marketers), mobilised their evaluative frameworks in attempts to shape the categorisation of sepsis. At the outset, we note that these evaluative frameworks are neither monolithic nor uniform, but for interpretative purposes we discuss four, which we term *Clinical Practice*, *Clinical Research*, *Biomedical Science* and *Commercial*. We conclude by considering the implications of our case study for the sociology of diagnosis and medical sociology more generally, particularly

regarding recent sociological debates about medicalisation, biomedicalisation and pharmaceuticalisation (Busfield, 2017a, 2017b; Williams et al., 2017). Finally, following reflexive examination of our own analytical, valuation and categorisation processes, we suggest specific ways in which sociological analysis can contribute to debates about the appropriateness of health-care interventions.

METHODS

Our awareness of this case of disease categorisation originated from the first author's continual research on intensive care, including three extensive projects (an organisational ethnography, an evaluation of an organisational innovation and an interview-based study). While reflecting on the findings from the third study in particular (Carmel, 2023), we were intrigued that the categorisation of sepsis had changed several times over a 25-year period. The present project was then undertaken from January to June 2022 to identify and examine the forces driving these changes. Our research began by identifying the consensus conferences convened to (re)define sepsis and we carefully read the publications that presented their decisions, namely Bone et al. (1992), Levy et al. (2003) and Singer et al. (2016). We then followed up citations of these articles in major medical journals (most notably the *New England Journal of Medicine, Journal of the American Medical Association, Critical Care Medicine* and *Intensive Care Medicine*), which presented carefully crafted points of view representative of various medical opinions at the time and provided explanations, research findings and recommendations for medical practice. We thus treated the consensus conferences' categorisations of sepsis like focal objects that we followed through the literature.

As a process of analysis, we first created a chronological timeline of events, including the consensus conferences as well as the clinical trials, empirical studies and publications that informed and discussed each conference. We then identified the key actors and their actions in the emerging narrative. We developed preliminary themes around the actors' motivations for convening each conference, the categorisations reported and the actors' reasonings for either supporting or critiquing these categorisations. Debates and differences of opinion within the literature enabled us to develop and confirm our interpretations regarding the different actors' influences on the categorisation of sepsis. We developed our analytical lens regarding valuation practices accordingly. Quotations from the literature were then selected to illustrate the valuation practices of these actors. We adopt a philosophical position of *practical constructivism* (Kjellberg & Helgesson, 2006)—that is, ontological relativism and epistemological realism—to examine this case. From a practical constructivist point of view, a diagnosis of sepsis can be not only construed in several ontologically distinct ways (cf. Mol, 2002), but also constructed using different logics, practices and evaluative frameworks. In fact, we suggest that the current categorisation of sepsis (Sepsis-3, Singer et al., 2016) is also premised on a philosophical position similar to *practical constructivism* and we return to this matter in the Conclusion.

DIAGNOSIS-AS-CATEGORY

Diagnosis consists of categorising disease states. While Blaxter (1978) observed that diagnosis can be conceived as category or as process, she also noted that diagnosis-as-process must be

dependent on diagnosis-as-category. She also concluded that diagnosis is overwhelmingly a prescriptive activity, following Linder (1965):

> the diagnostician's task is not to describe, nor to predict, nor to explain; rather, the diagnostician is more usefully conceived as one who prescribes solutions to problems. A diagnosis ***is*** a prescription no matter how phrased or how conceptualized.
> (Linder, 1965, p. 1084)

Thus, while the analytical distinctions between process and category and between diagnosis and treatment might be helpful, the distinctions should not obscure the fundamental connections. Diagnosis is a salient juncture between disease (illness) and treatment with, in many cases, putative treatments themselves contributing to the construction of disease categories (Jutel, 2009). As Rosenberg (2002, p. 240) puts it, 'diagnosis labels, defines, and predicts and, in doing so, helps constitute and legitimate the reality that it discerns'.

Such a formulation invites us to ask who and what powers are constructing diagnostic reality (Brown, 1995). Our view is that while the sociology of diagnosis has a rich history in the sociological analysis of the medicalisation of social, lifestyle and psychiatric conditions (i.e., the social construction of illness), there is some way to go in developing a comparable corpus of sociological knowledge regarding the construction of biomedical diagnoses. Notable exceptions here are Linder's (1965) account of the diagnosis of tuberculosis and Bloor's (1976) discussion of adenotonsillectomy disposals, both of which are especially helpful in reminding us that in clinical practice the connection between diagnosis and treatment is extremely pertinent. Furthermore, while some sociological studies had presumed a biological, mind-independent and objective ontology of disease, Mol's (2002) path-breaking description of the 'ontologies' of atherosclerosis continued to break down the distinction between disease as objective reality and illness as socially constructed by documenting how distinct medical practices enact multiple ontologies of a single disease, giving rise to an ontology of emergent social practice. We build on Mol's work, but also aim to address two issues concerning her analysis identified by Weinberg (2021). First, we explore the contested status of sepsis as an empirically identifiable medical phenomenon by demonstrating empirically the practices through which various actors attempt to render the reality of sepsis (albeit multiple) a matter of medical consensus. Second, we make explicit our own ontological claim regarding the categorisation of sepsis and highlight how this claim aligns with the enactment of sepsis by the actors in our study.

We therefore note that clinical practice has its own sophisticated understanding of disease ontology and the epistemological warrants for its measurement. What we call *clinical epistemology* is not a presumed form of normative, empiricist epistemology, but instead a form of interpretative science, dictated by the pressing need of clinical action (albeit with scientific and other knowledge bases in the background).[2] In fact, since medical practice is fundamentally a practice with people as its core focus, clinical work may bear similarities to sociology as much as to science per se. As Weinberg recently argued, a 'softer epistemological break' between sociological knowledge and that of our research participants may benefit sociology as a whole. This would require:

> a more porous sociology wherein we might sometimes treat our research subjects' practices and perceptions, including their discursive testimony, not only as *topics* for

> reductive sociological explanation [...] but as provisionally epistemologically legitimate, or provisionally valid, theoretical *resources* in their own right.
>
> (Weinberg, 2021, p. 381)

In our analysis, we thus follow Weinberg's (2021: 385) argument that 'both epistemological and ontological questions are raised and addressed for local reasons with local theoretical repertoires and in accord with local standards of value'. We therefore extend Blaxter's (1978) conceptualisation of diagnosis-as-category by exploring the multiple standards of value and practices of valuation present in the medical world that have stabilised and contested the categories of sepsis. Here, we draw on the sociology of valuation that studies how things are made commensurate, compared, categorised and clarified; and ultimately how some things are judged to count more than others (Kornberger, 2017).

Values are neither 'in' objects nor are they simply a matter of subjective preference or utility; rather, Kornberger (2017) argues to understand the values of objects we need to study the valuation practices that constitute these objects as valuable in the first place. In studying valuation, 'the appropriate unit of analysis shifts from individual behaviour (preferences) and social macro-structures (norms) to the material and discursive practices through which valuations are accomplished, and, as their corollary, values are constituted' (Kornberger, 2017, p. 1762). Here, categorisation is understood to be a key mechanism in valuation since categorisation involves practices of purification, qualification and legitimation (Ariztia, 2015; Callon, et al., 2002; Lamont, 2012) used to determine which elements to include and which to exclude in any given category. Through these practices, categories can then function as collective evaluative schemata that structure and frame the encounters between actors as they use these schemata to 'sort things out' (Bowker & Star, 1999).

However, as Stark (2009, p. 12) points out building on the work of Boltanski and Thévenot (2006), the orders of worth mobilised in categorisation often contain distinct and incommensurable principles of equivalence as each one 'defines the good, the just, and the fair—but according to different criteria of judgement'. Each order of worth thus qualifies objects according to distinct grammars or logics of evaluation that entail discrete metrics, measuring instruments and proofs of worth that are objectified in artefacts in the material world (Stark, 2009). Therefore, while categorisation can enable collective action through the creation of collective evaluative schemata that mediate and structure encounters between distinct actors, categories can also be contested as actors struggle over competing claims regarding the legitimacy of various valuation practices, devices and criteria mobilised during categorisation (Kornberger, 2017). We therefore understand categories, including those of diseases, to be constructed through continuous negotiation, and we do not uncritically assume that the processes of disease categorisation take 'the form of universal and value-free scientific procedures [...] immune to the explanatory repertoire of sociology' (Weinberg, 2021, p. 368).

We thus follow Kornberger (2017) to explore how disease categories are deconstructed to make them comparable (commensuration) and then reassembled into new orders of worth (categorisation), as well as the externally imposed criteria that these processes of re-organisation are based on. We therefore ask: first, who is involved in the valuation of sepsis; second, how are sepsis categories deconstructed (commensuration); third, how are sepsis categories reassembled (categorisation); and fourth, how are sepsis categories visualised and made mobile and impactful? Furthermore, following Stark (2009), we explore the multiple evaluative frameworks that exist in the medical nexus around Sepsis. In short, evaluative frameworks tell us what about a category is valued. For example, different actors in the field may not only interpret scientific results

differently; they may view clinical trials as fundamentally less valuable than clinical examination. As our case study shows, clinical practitioners, biomedical scientists, regulators and pharmaceutical marketers all mobilise categories of sepsis that are informed by their own evaluative frameworks. Ultimately, our argument is that, in the categorisation of sepsis, the perspective of clinical practice has come to count over and above that of biomedical science, clinical research and industry, and we reiterate the pre-eminence of clinical practice in disease categorisation.

THE CONSTRUCTION AND OBSOLESCENCE OF SEVERE SEPSIS, 1991–2016

Contemporary pathophysiological understanding posits sepsis and related conditions as dysregulated host (i.e., patient) response to infection leading to organ dysfunction (Angus & van der Poll, 2013; Arina & Singer, 2021), normally requiring intensive care. Up until the early 1990s, several overlapping terms were in use: bacteraemia, septicaemia (blood poisoning), sepsis, septic syndrome and septic shock (Bone et al., 1992). One of the ambitions of the first consensus conference, convened in 1991, was to agree common terminology. This conference specified, for the first time, the category *severe sepsis*, which was still regarded as 'useful' by a second conference in 2001 but 'superfluous' or 'redundant' by the time of a third conference in 2014–2015. Taking these conferences and other pivotal events as punctuation points, in this section, we describe how severe sepsis was conceptualised by three intersecting sets of actors: academic clinicians who wrote the definitions; drug company scientists, marketers and their medical advisors; and regulatory agencies and their medical advisors. In the following section, we infer the evaluative frameworks that first stabilised sepsis into three categories, then destabilised the central category of severe sepsis and finally re-stabilised sepsis by discarding this central category.

August 1991: Inception of severe sepsis

The first consensus conference, a joint effort between the American College of Chest Physicians (ACCP) and the (North American) Society of Critical Care Medicine (SCCM), proposed initial definitions based on the view that sepsis resulted from a 'systemic inflammatory response' to infection. They defined systemic inflammatory response syndrome (SIRS) as two or more of four measurements (temperature, heart rate, respiratory rate and white blood cell count) being outside a normal range, thus giving a physiological foundation to the definition. The conference proposed three categories:

- *Sepsis*: 'when SIRS is the result of a *confirmed infectious process*, it is termed sepsis' [our emphasis].
- *Severe sepsis:* sepsis complicated by organ dysfunction.
- *Septic shock:* 'sepsis-induced hypotension persisting despite adequate fluid resuscitation'; that is, sharing the characteristics of severe sepsis but additionally a patient exhibits abnormally low blood pressure, which is not responding to treatment.

It is notable that around a quarter of the conference publication (Bone et al., 1992) is devoted to 'evaluating innovative therapies in severe sepsis', guidance made necessary by burgeoning clinical research studies. In clinical research, patient eligibility must be precisely specified, and we

infer that the degrees of sepsis specified by the conference, including the necessity for infection to be 'confirmed', are a necessity for well-designed clinical trials. The perception of the conference had been that the existing varied terminology was hampering the establishment of a cumulative knowledge base. In other words, the first consensus conference appeared to be motivated by developing research agendas as much as clinical practice.

There was some debate in the intensive care literature about these definitions, with the most comprehensive critique coming in the form of a pithily titled article, 'Dear SIRS, I'm sorry to say that I don't like you' (Vincent, 1997). Stemming from the observation that 'As far as the ICU physician is concerned, SIRS is so common that its use has no clinical implications' (Vincent, 1997, p. 373), the article mentioned that SIRS was too sensitive to be useful for enrolling patients in clinical trials; that it says little about pathophysiology; and that it does not help in clinical practice. It was suggested, therefore, that using SIRS as a basis for defining sepsis was not helpful for three domains of interest to clinician-researchers: clinical trials, pathophysiology and clinical practice. Nevertheless, despite such critique, clinical trials in intensive care continued space, with the enrolment of patients into large randomised controlled trials for therapeutic agents and devices for severe sepsis (Warren et al., 2002).

1998–2002: Scientific evaluation of rhAPC

A conspicuous set of clinical trials during this period was evaluating the efficacy and safety of a novel therapeutic agent, recombinant human Activated Protein C (rhAPC). The pivotal trial, published in early 2001 (Bernard et al., 2001), used slightly modified entry criteria for severe sepsis, with the main differences being that infection can be known *or suspected* and that three (rather than two) of the four 'SIRS criteria' must be met. This trial showed a strong beneficial effect of the drug, with an absolute reduction in mortality of almost 20%, widely regarded at the time as very encouraging (in fact, the trial was stopped early because of the strong beneficial effect). However, the trial data also raised safety concerns due to an increased risk of bleeding, and in consequence of these concerns, the regulatory approval process was not straightforward. The Advisory Panel for the US Food and Drug Administration (FDA), meeting in November 2001, was evenly split on whether approval should be granted (10 members voting in favour, and 10 against). Those against immediate approval suggested that a second confirmatory trial was needed (Sweeney et al., 2008, p. 1274). Both the FDA and the European Medicines [Evaluation] Agency (EMEA) took the unusual step of approving the drug only for the sickest patients, and imposed conditions such as annual (rather than five-yearly) safety monitoring. This regulatory ambivalence spilled over into scientific discussion regarding rhAPC.

The drug company scientists, in a presentation to the regulators, described the pathophysiology of severe sepsis as one in which 'infection, inflammation and coagulation activation are tightly linked' (Drug Company Presentation, 2001). While they acknowledged that 'the specific mechanism by which [rhAPC] exerts its clinical effect is not known' (Sepsis—a background guide, n.d.), their conception of severe sepsis facilitated an emphasis on the anti-inflammatory and anti-coagulation (specifically pro-fibrinolytic) properties of rhAPC. Thus, although there were several complex mechanisms whereby rhAPC could improve outcomes in severe sepsis (as per the pivotal trial), they came to be described in more general terms as 'anti-inflammatory and anti-coagulant'. The regulators largely followed the drug company scientists in this conception of the pathophysiology of severe sepsis. For example, the EMEA referred to severe sepsis as resulting from a 'generalised inflammatory and procoagulant response to infection' (2004, p. 1) and

members of the FDA panel later referred to the drug's trial as testing 'the hypothesis that part of the pathophysiology of sepsis is caused by unrestricted or inappropriate coagulation in the microcirculation' (Warren et al., 2002). This condensed version of the pathophysiology of severe sepsis formed the basis of ensuing scientific controversy about the balance between efficacy and safety for rhAPC (Carmel, 2023).

In summary, during this period of scientific evaluation, regulation and early marketing of rhAPC, severe sepsis was being discussed in terms of a 'problematic inflammatory and procoagulant response to infection', rather than in terms of the consensus definition, which had specified organ dysfunction (Bone et al., 1992). At around this time, a second consensus conference was convened.

December 2001: Second consensus conference

The second consensus conference was jointly organised by five medical societies,[3] two of which represented intensive care. The stated reason for a new consensus conference was that there had 'been an impetus from experts in the field to modify these definitions to reflect our current understanding of the pathophysiology of these syndromes' (Levy et al., 2003, p. 531). Evidently, however, the 'current understanding of pathophysiology' was not compelling, as the conference concluded that 'current concepts of sepsis, severe sepsis, and septic shock remain useful to clinicians and researchers' (Levy et al., 2003, p. 536). We have, then, a moment of uncertainty: a consensus about a perceived need for change but little shared clarity about precisely what that change should be.

While the conference did not change the 'current concepts', they did suggest changes to the measurements used. They recommended discontinuing the use of the SIRS criteria by replacing the four physiological criteria with an expanded list, suggesting that sepsis could be identified by 'some' of 26 parameters. As the authors explained:

> The use of the word "some" [parameters] reflects the clinical reality at the bedside rather than an arbitrary list invented for the purpose of clinical trial entry criteria.
>
> (Levy et al., 2003, p. 533)

Another change was downgrading the necessity of evidence of infection to diagnose sepsis: infection needed to be 'documented *or suspected*' (our emphasis), with the comment that frequently 'infection is strongly suspected without being microbiologically confirmed' (Levy et al., 2003, p. 533). Finally, in a marked departure from the 1991 conference's emphasis on standardisation for research protocols, the 2001 conference explicitly stated the priority of clinical practice:

> It was the opinion of the group that facilitating bedside diagnosis should have primacy over research entry criteria.
>
> (Levy et al., 2003, p. 534)

2002–2012: Controversy on scientific evaluation of rhAPC

From the point of view of the drug company manufacturing and marketing rhAPC, it made sense to portray severe sepsis as 'problematic inflammatory and procoagulant response to infection',

since this characterisation binds rhAPC as a treatment to the diagnosis. The incidence of bleeding reported in the trial needed to be explained as only a potential occurrence, which could be alleviated with close monitoring (as would be possible in intensive care). However, there remains a notable dilemma in emphasising a mechanism of anti-coagulation where there is a recorded risk of serious bleeding. While this pathophysiology of severe sepsis enabled rhAPC's anti-coagulation properties to be marketed (as helping prevent disease pathways such as the inflammatory cascade), there would be lingering doubts as to rhAPC's safety. An intensive care professor explained:

> When they launched it, they didn't really have an idea of how it worked, and because it was an anticoagulant they pushed 'oh it worked as an anticoagulant, stopping blood clots being formed in the circulation and therefore that's its mechanism of action' [...] But the trouble is [...] they emphasised that it worked through an anticoagulant action, and as the side effect of the drug was bleeding [...] that scared [intensive care practitioners], especially after a surgical operation [...] where your risk of bleeding is higher.
>
> (Interview, May 2011; see also Carmel, 2023)

In other words, while the balance of efficacy and safety had in principle favoured efficacy in the pivotal trial (Bernard et al., 2001), the marketing of the proposed mechanism of action continually reminded practitioners of the risks, which were reiterated in articles and blogs (e.g., Eichacker & Natanson, 2007; Hopley & van Schalkwyk, 2006; MacKenzie, 2005).

The controversy about rhAPC abated only once a second, confirmatory trial, mandated by the EMEA, had been agreed. In contrast to the earlier trial, the drug did not show improved outcomes over standard care (Ranieri et al., 2012) and it was withdrawn from all markets in October 2011. This negative trial result, along with others at about the same time, was described as a 'major disappointment' (Angus, 2011), prompting reflection on the direction of research and the therapeutic approach to sepsis, as well as its definitions (Vincent et al., 2013). Clearly, the field was ready for such reflection, as within a few years a third consensus conference had been organised, starting in January 2014.

2014–2015: Consensus conference—Sepsis-3

The third consensus conference was facilitated by co-chairs appointed by the two main intensive care professional societies,[4] who organised a series of meetings and communications of selected experts with the aim of re-examining the definitions of sepsis. There are three salient and inter-linked aspects of the resulting publication (Singer et al., 2016). The first is the now explicit distinction between the definition of sepsis (called a 'clinical concept') and the clinical criteria for its operationalisation (i.e., measurable manifestations). Second, rather than three categories of sepsis, the new definitions proposed just two. Third, there is an explicit focus on and prioritisation of clinical practice, both within and outside the ICU.

Sepsis was now defined as 'life-threatening organ dysfunction caused by a dysregulated host response to infection' (Singer et al., 2016, p. 801). Thus, what is retained from the earlier definitions is the causal presence of infection (which does not need to be confirmed) leading to a 'dysregulated host response'. The dysregulated host response is no longer assumed to be an inflammatory one, which reflects changes in the understanding of pathophysiology to the effect

that sepsis may have 'both pro-inflammatory and anti-inflammatory mechanisms' (Angus & van der Poll, 2013, p. 843).

Rather than three categories (sepsis, severe sepsis and septic shock), the new definitions proposed just two (sepsis and septic shock). We note that the new category of sepsis, which includes 'life threatening organ dysfunction', is markedly similar to the earlier definition of severe sepsis. However, whereas between 1991 and 2015, the category sepsis had been considered physiological derangement (e.g., SIRS, or 'some of' 26 parameters) caused by infection, the category sepsis is now organ dysfunction caused by infection. The former category is based on criteria which by themselves may not necessarily warrant intensive care, whereas the latter category is based on criteria which are likely to warrant intensive care. This simplification process has rendered the category severe sepsis redundant, but when applied to clinical (hospital) practice, it has brought all categories of sepsis under the purview of intensive care.

Operationalising the 'clinical concept' consisted of specifying physiological criteria for Sepsis-3. It was suggested, based on multivariable logistic regression of a large clinical database, that just three criteria could have predictive value: respiratory rate, altered mentation and low systolic blood pressure.[5] This was explicitly intended to overcome the difficulties of diagnosing sepsis ('even for experienced clinicians'), recognising that health-care practitioners require improved clinical prompts and diagnostic approaches to facilitate earlier identification. The criterion of infection is specified as 'clinically suspected' rather than laboratory confirmed—again reflecting a priority of urgent clinical practice where it is more important to commence treatments than wait for laboratory results. In summary, Sepsis-3 defines sepsis as life-threatening, and in its conceptualisation and clinical operationalisation prioritise the prompt identification of the condition 'at the bedside'.

TRACING THE ONTOLOGY OF SEPSIS AS DIAGNOSTIC CATEGORY, 1991–2016

Stabilisation, approximately 1991–2001

As a specialty that evolved contemporaneously with the evidence-based medicine movement, the field of intensive care has placed significant value on 'high-quality large-scale clinical trials' (Finfer & Vincent, 2013, p. 370)—the importance placed on clinical research reflecting its connection to clinical practice. The design of high-quality large-scale trials involves the enrolment of certain groups of patients, who must meet clearly and narrowly specified criteria to be selected from the heterogeneous population of intensive care patients, and this gives impetus to the categorisation of disease states (diagnoses).

In the case of sepsis, the impetus for effective categorisation reached a peak in 1991. As previously noted, up until then, a broad array of overlapping terms had been in use. The fact that this was not considered conducive to the precise specification of patient eligibility for clinical trials played a significant role in the organisation of the first consensus conference and its emphasis on the evaluation of innovative therapies. Importantly, what was thus at stake at this conference was not just the categorisation of sepsis, but the ontological role of diagnostic categories. From the outset, it was clear that the conference sought consensus on a category intended to be performative (see Jacobi et al., 2015)—that is, a category that would not merely describe the reality of sepsis but that would help bring into existence a particular reality. In this instance, the reality to be brought into existence is one in which the nature of sepsis as it exists within an individual's

body in intensive care is inextricably linked with effective treatment acting within the body. The success of the conference's categorisation thus depended on its usefulness for clinical trials, and consequently the evaluative framework of clinical research significantly shaped how the conference categorised sepsis.

Biomedical science of course played a central role in the conference's valuation of sepsis; however, this was largely confined to the deconstruction (commensuration) of the disease into observable physiological markers as well as the presence of infection and organ dysfunction. The conference's decision to then reassemble these into three categories reflects the perceived need for performative categorisation. First, the delineation in severity from (1) SIRS resulting from infection to (2) additional organ dysfunction to (3) additional unresponsiveness to treatment, represents the world of clinical practice; in particular, severe sepsis specifies the point at which a patient receives intensive care. Second, the decision to include a *confirmed* infectious process as a prerequisite for diagnosis represents the world of clinical research; a specification that the conference considered useful in the enrolment of patients for clinical trials to evaluate treatments.

The conference was successful in disseminating its categorisation, which despite some criticisms that mainly concerned the performativity of the category SIRS became sufficiently stabilised to form the basis for clinical trials in the decade to follow. However, as noted above, the value of this categorisation, and thus its continued stability, hinged upon its performative power to enable clinical research to identify effective treatments.

Destabilisation, approximately 2001–2013

Destabilisation of the first consensus conference's categorisation of sepsis began in 2001 when both the FDA and the EMEA granted only limited approval to rhAPC as a treatment for severe sepsis due to trial data showing an increased risk of bleeding. Since the trial data had initially been considered extremely encouraging, close attention was paid to the regulatory approval process by the scientific and medical research communities. In an attempt to receive full approval, the drug company behind rhAPC reconfigured the category of severe sepsis by linking infection, inflammation and coagulation activation. Notably, the drug company acknowledged that it did not know the specific mechanism underlying rhAPC's effect, revealing that its goal was not to produce a category describing the precise nature of severe sepsis but, like the consensus conference definitions, was a performative one—in this case, aimed at positioning rhAPC as a safe and effective treatment by emphasising its anti-inflammatory and anti-coagulation properties. Thus, the drug company looked to mobilise the evaluative framework of biomedical science, hoping that it could sway regulators and practitioners by claiming a sufficiently strong link between rhAPC and the pathophysiology of severe sepsis.

While the drug company would eventually fail to sway regulators to fully approve rhAPC, its categorisation of severe sepsis became sufficiently stabilised and compelling for it to be largely adopted by regulators and for enough intensive care experts to call for the first conference's categorisation of sepsis to be revised to warrant the organisation of another consensus conference. This second conference, ultimately, concluded that the categories of sepsis, severe sepsis and septic shock originally developed remained useful for clinicians and researchers but that some changes should be made, including using an expanded list of physiological parameters and downgrading the necessity that infection be confirmed (Levy et al., 2003). Thus, on the one hand, the drug company's pathophysiological conception of severe sepsis did not prove sufficiently compelling to completely destabilise the first conference's categorisation of sepsis,

which could have given rise to a new categorisation clearly prioritising biomedical science over clinical research. However, on the other hand, the changes proposed by the conference reflect a significant shift away from the categorisation's initial goal to impact clinical research towards the explicitly stated new goal to impact clinical practice (Levy et al., 2003). The regulatory ambivalence over rhAPC and the scientific arguments this fuelled clearly seem to have thrown into question the value of clinical research as a central evaluative framework for the construction of severe sepsis as a diagnostic category.

The controversy surrounding the regulatory approval process of rhAPC centred on the findings that rhAPC was an effective but also risky treatment. In an attempt to receive full approval, the drug company appeared to promote efficacy over safety. Its emphasis on rhAPC's anti-coagulant properties configured not only a clear pathway between rhAPC and the company's biomedical categorisation of severe sepsis, but also between rhAPC and an increased risk of bleeding. Many intensive care practitioners meanwhile prioritised safety over efficacy, specifically because the potential for serious bleeding tends to be a critical factor in intensive care. In the ensuing controversy, the evaluative framework of biomedical science was thus mobilised by the drug company to qualify rhAPC as effective while the evaluative framework of clinical practice was mobilised by some intensive care authors to qualify it as unsafe. The regulatory ambivalence at the time then represents a failure of clinical research in this case to mediate between the two by establishing an efficacy-to-risk ratio accepted by both. Over the course of the following decade, the drug company marketed rhAPC directly to intensive care practitioners but was unsuccessful in establishing its clinical value and in compelling practitioners to include the drug widely in treatment plans, making rhAPC a commercial failure.

Destabilisation of the first consensus conference's categorisation of sepsis then reached a pivotal moment in 2011 when, following a decade of controversy, a second confirmatory trial of rhAPC concluded that the drug did not show improved outcomes over standard care (Ranieri et al., 2012), leading to its withdrawal from all markets. Thus, while clinical research had ended the controversy surrounding rhAPC, it had still not helped find an effective treatment for sepsis, two decades after the first conference. The drug company had ultimately been unsuccessful in shaping the reality of sepsis by developing an effective treatment which would also integrate its commercial values.

However, the drug company's attempt to shape the categorisation of sepsis had significant consequences. At that time, after more than two decades of clinical research on severe sepsis, this confirmatory trial was for 'the only approved drug specifically indicated for the treatment of severe sepsis' (Angus, 2011, p. 2614). Hence, countless other trials on severe sepsis had not identified a single therapeutic agent. By the time the final rhAPC trial concluded, the chains of association between rhAPC, the drug company's pathophysiological category of severe sepsis and the broader pathophysiological categorisation of sepsis had become so strong that the revelation that rhAPC could not actually be linked to the reality of sepsis brought into question the very understandings of sepsis (and severe sepsis) that had been developed over the previous 20 years. Furthermore, since the diagnostic category of severe sepsis had been constructed specifically to improve enrolment in clinical trials to help find a treatment, the 'failure' of these trials to discover a treatment for severe sepsis also implied the failure of the diagnostic category of severe sepsis. This complete destabilisation of severe sepsis as a diagnostic category—with the central purpose of linking disease and treatment—created the need for intensive care practitioners to reflect not only on the definitions of sepsis, but also on the evaluative frameworks shaping its categorisation. A third consensus conference was thus organised to discuss the categorisation of sepsis as well as the direction of research and therapeutic approach to be taken.

Re-stabilisation, approximately 2014–2016 (and onwards)

The third consensus conference, which took place from 2014 to 2015, introduced significant changes, all of which reflect a continued rise in the dominance of clinical practice in the categorisation of sepsis. The conference created the categorisation Sepsis-3, with sepsis and septic shock as subcategories. Notably, the subcategory severe sepsis was removed. In line with the controversy around rhAPC (as well as, presumably, other biomedical research which led to changes in the pathophysiological understanding of sepsis), dysregulated host response to infection was no longer assumed to be uniformly pro-inflammatory. Additionally, organ dysfunction became part of the definition of sepsis, when previously it had only been part of the severe sepsis and septic shock subcategories. This change is significant because it moves the treatment of sepsis entirely into the clinical domain of intensive care.

Furthermore, in line with what had been decided at the second conference, infection was a central element of the definition of sepsis, but only needed to be suspected, not confirmed, for diagnosis. Operationalising the 'clinical concept' of sepsis consisted of specifying just three physiological criteria. As noted in the previous section, this was explicitly done to facilitate diagnosis 'at the bedside' and prompt treatment, representing a prioritisation of urgent clinical care practices over laboratory testing. The third consensus conference thus maintained that the diagnostic category of sepsis needed to be performative. However, now its primary performative value was no longer deemed to be its impact on clinical research and the development of effective treatment, but instead its impact on clinical practice and a reduction in mortality via less complex diagnostic procedures and faster treatment. The link between disease and treatment embedded in the diagnostic categories of Sepsis-3 is thus not only one of biomedical intervention, but also one of prompt clinical response understood as a central component of treatment in its own right. Lastly, it is noteworthy that the conference decided to term its categorisation 'Sepsis-3' showing that it understands the ontology of sepsis as a diagnostic category to be stabilised, not stable, with Sepsis-4 representing a potential future categorisation.

CONCLUSION

The ontological purpose of diagnostic categories—Performativity, stabilisation, evaluative frameworks

Our first contribution is to posit the ontological purpose of diagnostic categories as both we and the actors in our study understand it. Our analysis has shown that actors involved in diagnosis-as-category take the value of diagnostic categories to lie in their performative potential (see Jacobi et al., 2015). These categories are established not merely to accurately describe the nature of diseases, but to actively reconfigure disease-states via the development, evaluation and administration of effective treatments. To ensure this performative capacity, actors further consider diagnosis-as-category to be an ongoing process of re-evaluating categories in light of advances in medical knowledge and technology. In doing so, the actors in our study explicitly described the diagnostic category of sepsis as stabilised, not stable. This is captured well in the final recommendation of the article summarising the third consensus conference's decisions:

> These updated definitions and clinical criteria should clarify long-used descriptors and facilitate earlier recognition and more timely management of patients with

> sepsis or at risk of developing it. This process, however, remains a work in progress. As is done with software and other coding updates, [...] the task force recommends that the new definition be designated Sepsis-3, with the 1991 and 2001 iterations being recognized as Sepsis-1 and Sepsis-2, respectively, to emphasize the need for future iterations.
>
> (Singer et al., 2016, p. 809)

Our second contribution is to posit the role of evaluative frameworks in shaping diagnostic categories. Our analysis highlights four interrelated and at times contesting evaluative frameworks that became mobilised to shape the diagnostic category of sepsis, which we broadly term commercial, biomedical science, clinical research and clinical practice. First, the drug company's commercial evaluative framework sought to categorise sepsis as a disease treatable by the pharmacological agent it had developed. To achieve this, the drug company mobilised the evaluative framework of biomedical science to establish a pathophysiological pathway between its drug and a conception of severe sepsis that it aimed to make compelling through various marketing activities. However, the valuation practices of clinical research (large-scale clinical trials) ultimately showed that no pathway could be proven between the company's drug and sepsis. Here, we do not mean to critique biomedical science, but rather want to highlight how the mobilisation of the evaluative framework of biomedical science does not necessarily lead to better diagnostic categories. Finally, the evaluative framework of clinical practice replaced that of clinical research as the dominant way of determining the performative value of the diagnostic category of sepsis. By the time of Sepsis-3, the need for precision for clinical trial enrolment was demonstrably subservient to the need for immediate identification of patients facing pressing need of intensive care.

Our analysis thus documents the ontological nexus of sepsis wherein chains of association are created between: the observable condition of patients in intensive care; reported diagnoses for patient enrolment in clinical research; statistical reports of clinical trials; biomedical understandings concerning pathophysiology; and potential treatments developed by drug companies. However, our analysis also shows that these chains of association are not equal in strength or durability. For example, in the case of rhAPC, the chain of association between septic patients and their increased risk of bleeding in intensive care undermined the pathophysiological chain of association between rhAPC and sepsis; eventually, the latter was entirely broken by the 'failure' of clinical research to substantiate it. Thus, while we consider all diagnostic categories to be constructed, we do not consider them all to have the same ontological status. For some diagnostic categories, the chains of association with the condition that they claim to diagnose will be stronger than for others.

Strategic agency—The rising influence of intensive care

Our third contribution is to posit the role of strategic agency (see Kornberger, 2017) in diagnosis-as-category, which can be mobilised by actors to influence the values shaping diagnostic categories. In the case of sepsis, intensive care practitioners became particularly successful at categorising sepsis according to their evaluative framework. This success reflects growing dominance in line with the specialisation's increasing status and influence within medicine since its origins in the 1950s, and especially over the last 20–30 years. This is exemplified not only by its central prominence during the COVID-19 pandemic, but also by both the increasing proportion of critical care beds and organisational innovations in acute hospital care (Durand et al., 2010; Finfer & Vincent, 2013). Furthermore, the specialty itself has become more established within

the institutions of medicine alongside other acute specialties. To take the UK as an example of developments in many countries, institutional work from 1992 onwards led to the establishment in 2010 of the Faculty of Intensive Care Medicine, now the statutory body responsible for standards, education and training in intensive care (Bion, 2010).

Especially in the case of sepsis, it is noticeable that the organisation of conferences aimed at reaching consensus over the definition of sepsis and their publication outlets indicate an increasingly self-confident specialty. The first consensus conference (1991) was organised jointly with the American College of Chest Physicians and published in the journal *Chest*. The second consensus conference (2001) was jointly organised with five medical societies and published simultaneously in *Critical Care Medicine* and *Intensive Care Medicine*—the emerging specialty thus both led the consensus process and published the final report in its own journals. For the third consensus conference (2014–2015), the two intensive care societies (SCCM and ESICM) completely led the process with minimal perceived need to involve other professional societies, who were only invited *after* the conference to endorse the definitions that had been developed. The final output was published as a special communication (clinical review and education) in the *Journal of the American Medical Association*, indicating a point of view that the field of intensive care had the capability to educate the broader medical profession. Thus, the field of intensive care was able to shape not only the categorisation of sepsis, but also the values that came to bear on this categorisation—values of clinical practice—which were embedded in and disseminated through the field's own growing societies, journals and conferences.

Reflections on philosophy, performativity and values

In light of the theories and perspectives used in this article, we feel it important to reflect on our study's own philosophical position, performative ambition and guiding values. The phenomenology of clinical practice was made explicit in Sepsis-3, which referred to 'the sepsis illness concept [...] as a constellation of clinical signs and symptoms' (Singer et al., 2016, p. 803). For Blaxter (1978, p. 10), the conflation of disease and symptom may occur in 'the most primitive stage of medicine'. There is, then, an irony that this definition of sepsis—a constellation of symptoms—is proposed by the technologically advanced and scientifically sophisticated field of intensive care. It suggests that progress in public health and clinical practice may be less closely coupled to progress in scientific knowledge than would be assumed if medicine were construed as a wholly scientific enterprise, and sociologists should be particularly cognisant of this. For example, the processes at work in this case study could be thought of as (attempted) forms of pharmaceuticalization or biomedicalisation. However, noting the strategic agency of intensive care discussed above, the better descriptive term is 'medicalisation' (Busfield, 2017a) since it is the point of view of *medical practice* that has predominated the categorisation of sepsis (at least for the time being).

The shift to a clinical perspective in the categorisation of sepsis leads us to reflect on clinical epistemology, by which we mean the evidence and reasoning that warrants clinical interpretation and action. As Carmel (2013) notes, there is a wide range of types of knowledge that is mobilised in intensive care. Here, normative epistemology (such as the provenance of data) is not immediately relevant since clinical phenomenology is shaped predominantly 'at the bedside' with patients requiring immediate treatment. The multiple domains of knowledge coming to bear on clinical practice, from pathophysiology to health policy, are ever-changing; hence, our adoption of *practical constructivism* as a philosophical approach, which we see reflected in the practices of this study's actors, especially regarding the last consensus conference and its explicit

acknowledgement that the categorisation of sepsis is protean and will inevitably need future iterations as knowledge in pertinent domains advances.

By documenting the heterogeneous and protean character of the categorisation of sepsis, we also highlight the constructed and provisional nature of diagnostic categories generally. While this construction is acknowledged by the field, this of course does not mean that intensive care practitioners are *social* constructivists—indeed, the Sepsis-3 article is predicated on 'considerable advances' in the understanding of the pathophysiology of sepsis—but there are indications that clinical epistemology, even in a highly technological and acute specialism, is as much oriented to the social realm as the biological. What does all this say about the sociology of diagnosis? Medical sociologists have long argued that diagnostic categories are imprecise. This imprecision can serve interpretative flexibility in treatment selection (Bloor, 1976). But in the categorisation of sepsis, we see a move towards precision, simplification and consensus. Diagnosis as nosology is of much less consequence than diagnosis as indication for treatment (Linder, 1965). Our analysis has shown this vital importance of treatment on the categorisation of a diagnosis: in essence, the category severe sepsis was abandoned when it failed to realise its performative potential to specify an effective treatment.

Furthermore, while we highlight the heterogeneous character of the categorisation of sepsis, we do not consider sepsis to be ontologically multiple (cf. Mol, 2002). Although there are multiple sites that enact sepsis in different ways—patients in intensive care, samples in laboratories, statistics in clinical trials—each site enacts a single ontology of sepsis. Specifically, by exploring the contested path towards consensus, we find that the actors in our study enact the ontology of sepsis as a single chain of associations connecting these diverse sites with the goal of finding better treatment. Thus, while this chain encompasses these diverse sites and multiple enactments, the ontological reality of sepsis results from the single chain, which currently is constructed by the field of intensive care, anchored in clinical practice and shaped by clinical epistemology.

We acknowledge that in the process of analysis we, like the actors in our study, have categorised and made some aspects more or less visible in line with our own evaluative framework. We too aim for our work to be performative: to encourage practitioners, policymakers and patient groups to reflect critically on how diagnostic categories and consequently health care become shaped. For the case of sepsis, the importance of the clinician's voice in the development of diagnostic categories can be clearly articulated; for other areas of medicine, there will doubtless be other stakeholders (e.g., patient advocacy groups, health-care funding agencies) whose values impact diagnosis-as-category. As a service to public health, a central challenge for sociological analysis is to explicate faithfully and reflexively the evaluative frameworks and strategic agency of these diverse stakeholders and thereby facilitate broad consensus about the most appropriate high-quality and cost-effective health care.

AUTHOR CONTRIBUTIONS

Simon Carmel: Conceptualisation (equal); Investigation (equal); Project administration (lead); Writing—original draft (equal); Writing—review & editing (equal). **Erik Jacobi**: Conceptualisation (equal); Investigation (equal); Writing—original draft (equal); Writing—review & editing (equal).

ACKNOWLEDGEMENTS

We are grateful for the encouragement of the special issue editors and the two peer reviewers, whose comments were very helpful in thinking about the wider implications and presentation of our argument.

DATA AVAILABILITY STATEMENT

No new data were generated in this research.

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ENDNOTES

[1] For brevity, henceforth we refer simply to intensive care.

[2] That medical reasoning is not strictly scientific has been long noted by sociologists (e.g., Freidson, 1970) and physicians (e.g., Fleck, 1986[1927]).

[3] SCCM, European Society of Intensive Care Medicine (ESICM), ACCP, American Thoracic Society, Surgical Infection Society.

[4] SCCM and ESICM.

[5] The latest guidelines for treatment of sepsis (Evans et al., 2021) recommend *against* using only these physiological measures for screening. They suggest, instead, selecting from several other screening tools. However, this does not affect the 'clinical concept' of sepsis nor the principles of its operationalisation, which is suspected infection plus a small number of straightforward measures of physiological derangement.

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How to cite this article: Carmel, S., & Jacobi, E. (2023). Exploring valuation practices in diagnosis-as-category: The rising dominance of clinical practice in the categorisation of Sepsis, 1991–2016. *Sociology of Health & Illness*, 1–19. https://doi.org/10.1111/1467-9566.13619