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LETTER

Sepsis hysteria: facts versus fiction

Konrad Reinhart[1,2,3*], R. D. Daniels[4], D. Schwarzkopf[3] and N. Kissoon[5]

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Dear Editor,

"Sepsis hysteria: excess hype and unrealistic expectations" was the title of a recent correspondence to The Lancet by Singer et al. [1]. Their opinion piece comprises claims which are at odds with the available scientific evidence on the burden of sepsis and the effectiveness of efforts to improve the quality of sepsis care. Contrary to the fact that sepsis-related deaths account for 19.7% of global deaths (80% of which occur in low and middle income countries (LIMCs)) [2], the authors state "Sepsis …only develops in a tiny minority of patients".

Additionally, recent studies from high-income countries (HICs) suggest considerable underreporting, with only between 15 and 50% of clinically suspected sepsis cases being coded in the International Classification System of Diseases (ICD) [3, 4]. Singer et al. postulate that HICs overestimate incidence, blaming financial incentives and "pressure groups" in countries like the USA and UK for annual relative increases of between 5 and 15%.

Indeed, Rhee et al. [3] found a 10% relative annual increase in US (ICD 9-based) sepsis incidence between 2009 and 2014 from 1.4 to 2.5%, but showed electronic health record data analysis-based incidence to be stable at around 6% of hospitalizations, or 517 episodes per 100,000 population. Sweden has until very recently seen neither performance incentives nor public awareness initiatives, yet a recent health record study suggests population sepsis incidence at around 700 per 100,000 [4].

The authors claim that most sepsis deaths occur among frail elderly patients. They state that in England "approximately 150 sepsis-related deaths occur annually in children aged 0–18 years: a hospital mortality of 0.075%". This differs substantially from the hospital mortality rates among children under 5 years reported for New York State (11.8%) [5] and Germany (17.2%) [6]. Every year, 2 million neonates and children under 5 die with sepsis worldwide [7], with mortality at 19% in HICs and 32% in LMICs [8, 9]. Indeed, the Institute for Health Metrics and Evaluation estimated that 25 million children developed sepsis in 2017 [2]. In the UK alone, NHS Digital Hospital Episodes Statistics indicated 350,000 episodes of sepsis in 2017–2018, of which 38,000 were in children under 5 [10].

Are media and patient advocacy groups "creating a distorted picture of sepsis epidemiology and unrealistic expectations of outcomes"? No, but we accept that we don't truly understand the burden of this prevalent condition, and urgently call on governments to create surveillance systems to improve our understanding.

> *The high incidence of frailty and severe comorbidities makes most sepsis-related deaths neither attributable to sepsis, nor preventable.*

The authors cite a US study which showed that only 12% of sepsis-related deaths were preventable, examining the deaths of just 300 patients of whom a surprisingly high 40.3% had hospice-qualifying conditions [11]. This patient population is not representative of hospital-treated patients with sepsis in HICs, and even less so for sepsis patients in LMICs. According to the national ICU registry in England, which is not prone to billing incentives or coding changes, hospital mortality for sepsis decreased between 2000 and 2012 from 45.5 to 32.1% [12]. Over a ten-year period, although the age of patients with sepsis admitted to European ICUs increased by 2 years, the odds of ICU mortality decreased [13]. This increase in survival observed in other countries perhaps most markedly Australia, brings into question whether we need to accept death from infection or sepsis as inevitable.

*Correspondence: konrad.reinhart@charite.de
[1] Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany
Full author information is available at the end of the article

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The evidence base [behind Quality Improvement (QI) and timely antibiotic administration] is underwhelming and openly challenged.

The survival benefit of QI has been demonstrated by a meta-analysis of 48 trials [14], and by prospective trials in many countries. Indeed, state-mandated protocolized sepsis care in New York resulted in decreased mortality compared to control states [15]. As depicted in Tab. 1, the evidence certainly supports time-dependent survival with early antimicrobials, both in secondary analysis of routine data [16–18] and large prospective studies [19, 20]. Early antimicrobials appear to matter in patients with or without septic shock [20], and delays appear to increase transition from sepsis to septic shock (OR = 1.08 per hour) [18]. The rapid administration of antimicrobials should not be limited to "the rare cases of severe infection (e.g. in patients with shock)", but to any patients with infection and signs of acute organ dysfunction.

Despite concerns, there are no published data demonstrating harm with early antibiotics in patients with or without sepsis. Early recognition and prompt antibiotic administration remain the mainstay of care in adults and children. Improved awareness and earlier recognition, tempered by judicious application of diagnostic criteria, save lives. Late presentations to non-resilient healthcare systems are rife in resource-limited settings, but also occur in some disadvantaged populations in HICs.

As has been pointed out [21] the same data source on which Singer based the assertion that sepsis incentives have doubled antimicrobial consumption in Emergency Departments show total hospital consumption of antibiotics to have remained static. We're unable to find evidence linking sepsis improvement programs to antimicrobial resistance. In 2015, Ireland implemented its National Clinical Guideline and commenced annual publication of National Sepsis Outcome Reports [22]. Antimicrobial usage has not increased, and no adverse impact on multi-drug resistant organism incidence has been observed, while mortality has decreased by 4.7%.

Nevertheless, antimicrobial resistance (AMR) remains a major problem. There is an increasing body of evidence that the use of biomarkers may help prevent inappropriate use of antimicrobials and may improve survival [23, 24]. Furthermore, it is likely that biomarkers and molecular diagnostic techniques will help develop a better understanding of individuals' immune status and prognosis related to both host and pathogen. This may not only contribute to the development of novel immunomodulatory therapies, but also to prevent futile therapy.

Of course "a balanced strategy must be delivered in policy, public messaging, and frontline care". However, the current evidence in published literature overwhelmingly supports treating sepsis as an emergency without any unnecessary delay. Also a report by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) on the process of care received by patients with sepsis in UK concluded that "Sepsis is a major cause of avoidable mortality and morbidity", because, in a significant number of patients, outcome was affected by delays in antimicrobial and source control [25]. Any discussion about sepsis initiatives that ignores the issue of AMR is counterproductive. Both in concert with other infection prevention strategies should be the foundation of public health strategies. Vulnerable patients with sepsis require concerted global efforts between academics, clinicians, commissioners and policy makers to obtain robust data around the burden of sepsis through analysis of clinical data and point prevalence studies. The huge burden of

Table 1 Effects of time of beginning of antimicrobial therapy on mortality in patients with severe sepsis including septic shock

Study	Type of data	Patients	Starting point for measuring time to AT	*N*	Effect on mortality[a] per hour delay of AT
Liu et al. [16]	Medical record data	ED treated	ED registration	35,000	0.3% (CI 0.01–0.6%)
Seymour et al. [17]	Secondary analysis of mandated sepsis reporting	ED treated	Initiation of 3 h-bundle	49,331	OR = 1.04 (1.03–1.06); ~ 0.8% increase[c]
		ED treated	ED registration	49,331	OR = 1.04 (1.02–1.05)
Whiles et al. [18]	Medical record data	ED treated	ED triage	3929	OR = 1.05 (1.03–1.07)
Ferrer et al. [20]	Secondary analysis of prospective trial data	ICU treated	First presentation of symptoms of organ dysfunction	17,990	~ 1.4% increase[b]
Bloos et al. [19]	Secondary analysis of prospective trial data	ICU treated	First presentation of symptoms of organ dysfunction	3870	OR = 1.02 (CI 1.01, 1.03)

AT antimicrobial therapy, *ICU* intensive care unit, *ED* emergency department

[a] Effects on 28-day mortality (Bloos et al.) or hospital mortality (all other studies)

[b] Mean increase per hour obtained from Fig. 2 in Ferrer et al.

[c] Mean increase per hour obtained from Fig. 3B in Seymour et al.

sepsis demands that, from a humanitarian and scientific perspective, there is no alternative but to harness our resources and work responsibly and collaboratively.

The actions undertaken in the USA and England have become examples of sound public health policy. The benefits goes beyond improvement of care but serves to encourage other countries to integrate sepsis in national health strategies—most recently, the Ministries of Health in France, Sweden and Australia.

Addressing the burden of sepsis and showing improving trends by increasing awareness and quality improvement initiatives by high profile and esteemed sepsis experts provides a counterbalance for all those who are still ignoring this global health priority.

We believe that our patients deserve more from us than this unfortunate level of polarization. Today, tens of thousands of patients will die or be disabled by sepsis globally. This is not hype, this is a tragedy.

Author details
[1] Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany. [2] Berlin Institute of Health, Campus Virchow-Klinikum, Berlin, Germany. [3] Institute of Infectious Diseases and Infection Control, Jena University Hospital, Jena, Germany. [4] University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK. [5] Department of Pediatrics, Emergency Medicine and Critical Care, University of British Columbia, Vancouver, Canada.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflict of interest.

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