Dear Editor,

We would like to cordially thank the Editor and the Reviewers for their valuable suggestions and critical highlights concerning our manuscript.

We carried out the revision according to the inputs from the peer review process, and believe that the manuscript has been improved significantly to be resubmitted for publication in BMC Infectious Diseases.

Please find the revised manuscript attached. We also attached a point-by-point response letter below, with our comments in bold.

Thank you for your kind reconsideration in advance.

Yours sincerely,
Eszter Ostorhazi, M.D. PhD (corresponding author)

Balint Gergely Szabo, M.D. (first author)

Reviewer 1: This is a good retrospective paper with the old definition of sepsis. There are plenty of data and perhaps too many table. The interesting feature is that patients with community-acquired sepsis were included and the old definition was used.

General comments:

the paper is well written and it represents a good perspective

Line 126 "rande" is probably "range" – Corrected.

Line 193 "S. Enteritidis" is "S. eneteriditis" – According to the current taxonomy given by the Leibniz Institute DSMZ–German Collection of Microorganisms (www.dsmz.de/bacterial-diversity/prokaryotic-nomenclature-up-to-date), S. Enteritidis is the correct name form, while the capital "E" indicates that the microorganism is not an individual species, but rather a common serovariant of a subspecies (www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=149539).

Severe sepsis was associated with steroid usage. Is there a calculation of the relative contribution to mortality of these immunocompromised patients? – Unfortunately, the low percent of patients with chronic corticosteroid usage (7.9%) in the cohort complicates the exact calculation of a relative risk to mortality by this exposure. However, we note that there is a statistically non-significant +2.4% difference in the univariate analysis between surviving and dead patients, with an OR of 1.35 and a wide 95%CI, which might be suggestive of a negative effect of chronic corticosteroid usage on sepsis survival. We think that this additional risk could be validated further in a prospective cohort study enrolling patients in higher numbers.

In conclusion, I would shorten somehow the tables. – Accordingly, laboratory and some other data were removed from Table 1. In addition, Table 3. and 4. were merged, and all tables were reformatted to occupy less space in the manuscript.

Reviewer 2: Szabo et al. performed a retrospective cohort study to describe the epidemiology of community-acquired sepsis. Emphasis was on bacterial etiology and outcomes. I have the following suggestions to improve the paper.

1) The definition of community-acquired sepsis needs some fine-tuning. As I read it seems like this is a set of patients with infectious complications occurring early post-admission, but in patients admitted for another reason. While I guess that this is just a cohort of patients with
community-acquired infection/sepsis, including patients admitted for this reason, as well as those in which sepsis occurs early in the course following hospital admission. – We fine-tuned the definition accordingly, so it focuses more on ID symptomatology. Indeed, all of the included patients had signs or symptoms consistent with ongoing infection, and none were admitted for another reason. Additionally, some cases already satisfied the definition of sepsis at admittance, while other patients were diagnosed with sepsis early post-admission, but within the 72-hour limit.

We have edited the sentences in lines 97-101: „Patients were included if they were admitted with signs and symptoms consistent with infection, their case satisfied SIRS based sepsis criteria (see "Definitions"), and if the time to sepsis onset or diagnosis was within ≤72 hours from admittance or transportation occurred from another healthcare facility or the community within this time frame to our center because of CAS.”

2) The definition of appropriate empiric antibiotic therapy does not include a timeframe in which the first dose had to be administered. The relationship between timing of appropriate antibiotic therapy and mortality has been repeatedly stressed (e.g. Kollef M. Drugs 2003). In addition, in severe community-acquired pneumonia processes of care reflecting prompt anticipation on admission of a patient with severe infection and as such preceding antibiotic therapy have been demonstrated to lead to earlier initiation of antibiotic therapy as well as improved survival (Blot S, et al. Crit Care Med 2007). It would strengthen the manuscript if the authors could provide data on timing of antibiotic therapy and/or other processes of care facilitating early antibiotic therapy. If not possible, this must be acknowledged in the limitations part of the Discussion. – We agree with Reviewer 2 that early administration of antimicrobials is crucial in the adequate management of sepsis and the reduction of associated mortality. At our centre, septic patients receive the first dose of antimicrobial within 1 hour of recognition. Also, a standardized institutional protocol, adhering to the Surviving Sepsis Campaign guidelines (Rhodes A et al., Crit Care Med 2017), facilitates appropriate and early management. These data were added to the manuscript as requested in lines 127-128 and in lines 133--135.

3) Statistics: please report continuous variables with median (1th - 3rd quartile) instead of mean and SD. The former just gives more information about the cohort. – Continuous variables were reported accordingly.
4) I need information about the estimated annual incidence. Is this on nation-scale? Can the authors be (reasonably) sure that most of the patients with ID pathology are admitted to this particular hospital? If they cannot give a reliable estimate it is better to avoid this statement.

– We are reasonably sure that most patients with ID pathology are admitted to our hospital on a nation-scale, since we are the only national institute for such diseases. As outlined in Lines 167–168, the incidence was calculated to our total referral area, as we both serve as a local hospital and a tertiary referral center (Lines 87–88). A similar method of calculation was used and reported earlier by Nygård ST et al., BMC Inf Dis 2014. Additionally, in Limitations (Line 373), we reported that some patients, although in scarce numbers, might have been transported to other hospitals, which may lower the estimated annual incidence. In summary, we think that our incidence estimate is grossly reliable and representative.

5) Microbiology: data are reported according to sepsis, severe sepsis or septic shock (albeit that severe sepsis is an old concept following the sepsis-3 definitions). The should think about reporting the data according to infection (without sepsis), sepsis and septic shock. Furthermore, they should consider reporting microbiology according to site of infection, although I do not know whether the cohort is large enough for meaningful conclusions. The idea is that microbiology might differ according to site of infection but not according to severity of disease expression (as reported now). – Our cohort did not include infected patients without sepsis, therefore data could not be reported in this fashion. We note that SEPSIS-3 definitions were published after our study was planned and initiated, and our clinicians widely used the SIRS based terminology, including severe sepsis, at that time. We also note that experts raised concerns about SEPSIS-3 (Sartelli M et al., World J Emerg Surg 2018), and some state that the use of SIRS based definitions could still be justified (Simpson SQ, Chest 2016 and Chest 2018). We strongly agree with Reviewer 2 that causative agents of sepsis differ according to infection sites, but unfortunately, as Reviewer 2 correctly predicted, an adequately robust table with meaningful conclusions featuring microbiology and corresponding sites could not be constructed, perhaps due to the high number of patients without known sources or identified causative organisms. To overcome this, we added more details to the Results section, highlighting the infected regions and their most common pathogens instead in lines 203-205.

6) I’m questioning the logistic regression model to assess risk factors for mortality (Table 5). In abstract sense only 3 independent variables can be included as only 30 patients died. I assume this is an investment in over-fitting. Also, how can male gender being an independent risk factor for death in multivariate analysis when it was only associated with mortality at a level of p=0.22 in univariate analysis (according to the Methods only variables with p<0.1 were included in the multivariate model). This needs to be reconsidered. – As the 1 in 10 rule is indeed a well known rule of thumb, its limitations were noted by some (van Smeden M et
al., BMC Med Res Method 2016 and Vittinghoff E et al., Am J Epidemiol 2007). During planning, we used another common, but more relaxed rule of thumb, which states that a minimum of 15-times as many total events and non-events is needed as there are parameters in the full regression model, e.g. our 6 candidates minimally needed 90 events and non-events total (Harell FE, Regression Modeling Strategies, www.biostat.mc.vanderbilt.edu/rms). However, due to the use of this rule of thumb, some over-fitting might have arisen, so we included this in the Limitations section. Lastly, in the Methods section (Line 170), we wrote that biologically plausible parameters (age, gender etc.) will also be entered into the multivariate analysis, irrespective of their univariate p values (Heinze G et al., Transpl Int 2017). Gender was included because a recent article, also mentioned in the Discussion section, proposed that gender might negatively impact outcomes of CAS (Park DK et al., J Korean Med Sci 2012).