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Pilot Study Report on Sepsis Criteria

AATB Physicians Council Sepsis Working Group

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Background

According to FDA regulations, tissue establishments recovering and processing tissues for the purpose of transplantation are required to have “appropriate screening measures that have been developed for detection of sepsis, such as the medical history interview, and clinical and physical evidence.” In accordance with 21 CFR § 1271.75: “Persons who are deceased and have a documented medical diagnosis of sepsis or have documented clinical evidence consistent with a diagnosis of sepsis that is not explained by other clinical conditions at the time of death” should be excluded. The guidance also advises that deceased donors may still be eligible if they had an initial diagnosis of sepsis which has been ruled out.¹

Sepsis is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection” with life threatening physiologic derangement.² A diagnosis of sepsis in the hospital and emergency room setting has become exceedingly common in the United States and worldwide in the past decade, most likely due at least in part to the Surviving Sepsis Campaign (SSC). SSC is a global initiative to develop and increase awareness of the scope of sepsis syndrome. The goal of this campaign has been to provide successful quality improvement techniques through published guidelines for the treatment of sepsis in addition to guideline implementation, behavior change, and data collection. The SSC has significantly influenced the screening and management of sepsis in the United States and worldwide, with ongoing revisions and updates most recently in the Sepsis 3 recommendations.² The sepsis syndrome can be promptly identified at the bedside with quick Sepsis-related Organ Failure Assessment (qSOFA), which includes two of the following three components: an alteration in mental status, systolic blood pressure ≤ 100 mm Hg, or respiratory rate ≥ 22 /min.² With these tools for early recognition of sepsis and ease of diagnosis, the syndrome is currently estimated to be among the top single most common diagnoses in US hospitals.³⁻⁷ Other causes for the increased reported incidence of sepsis could include aging populations with more comorbidities and the use of reimbursement-favorable coding.^{8,9}

While electronic medical records (EMR) have greatly streamlined the various aspects of health care flow and reduced some time-consuming aspects of documentation and charting, they have also produced exceedingly long, occasionally inaccurate notes with redundancy, inconsistency, and outdated information. The use of copy and paste and copy forward functions used by an overwhelming number of clinicians/health care workers can inadvertently result in the passive repetition of patient problem lists, even when some of the patient problems may have been completely resolved. Active documentation is required to remove or update a patient problem in the EMR. This documentation is often

completely skipped, resulting in long problem and discharge diagnoses lists which are not updated.¹⁰

To avoid unnecessary donor deferrals, tissue banks who recognized these redundant issues with EMR documentation have developed various strategies to comb through the records in order to screen donors who may be eligible to donate because of evidence of resolution of sepsis or evidence that sepsis was ruled out. Many of the tissue banks have multiple medical reviewer policies and regular medical director meetings to discuss complex donor cases.

Recently, viable tissue products were produced from two donors who were later found to have tuberculosis. There was significant morbidity and mortality caused by outbreaks of tuberculosis after using these viable cell products. Understandably, both the AATB and FDA were very concerned after these events. It is predicted that in the aftermath, the FDA will further restrict acceptance of donors who may not have had systemic transmissible infection at time of death by further tightening the sepsis criteria. It is the hope of this AATB Physicians Council Sepsis Working Group, along with several major volunteering tissue banks, that this prospective chart review study would quantify the number of donors who had sepsis documented in their charts, the number of donors considered to be truly septic, and finally, the number of donors who would be excluded if FDA requires more stringent criteria for sepsis-related donor eligibility.

Frequency of sepsis diagnosis among individuals with in-hospital deaths

Sepsis is a growing worldwide healthcare challenge associated with significant morbidity and mortality. In 2017 there were an estimated 49 million cases of sepsis recorded worldwide with 11 million sepsis-related deaths. This accounted for 19.7% of all global deaths.¹¹ In 2018, sepsis/septicemia was the most common non-maternal/neonatal primary diagnosis in the United States accounting for 2,218,755 or 8% of all hospital admissions.⁸ The number of sepsis admissions increased to 2,446,047 by 2021.¹²

Sepsis is not only the most common primary diagnosis among hospitalizations but also a common secondary diagnosis. The number of hospital discharges associated with a diagnosis of sepsis noted during the admission has steadily increased from 2.74 million to 3.2 million from 2017-2021.⁸ (Fig. 1) Although the rate of in-hospital deaths related to sepsis had been declining prior to 2019, sepsis related deaths spiked to 12.5% in 2021, likely related to the COVID19 pandemic.⁸ (Fig. 2) Furthermore, sepsis disproportionately

impacts older patients. The diagnosis of sepsis among adults aged 65 and older has increased by 7% since 2016 accounting for 1.4 million or 56% of all inpatient sepsis-related stays by 2021.³

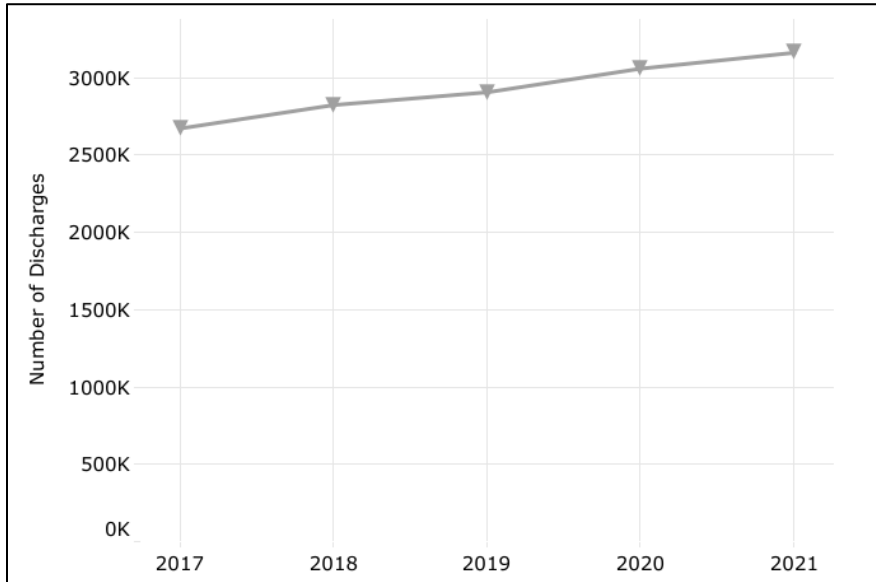


Figure 1. Number of hospital discharges in the U.S. with a listed diagnosis of sepsis/septicemia during admission, 2017-2021.³

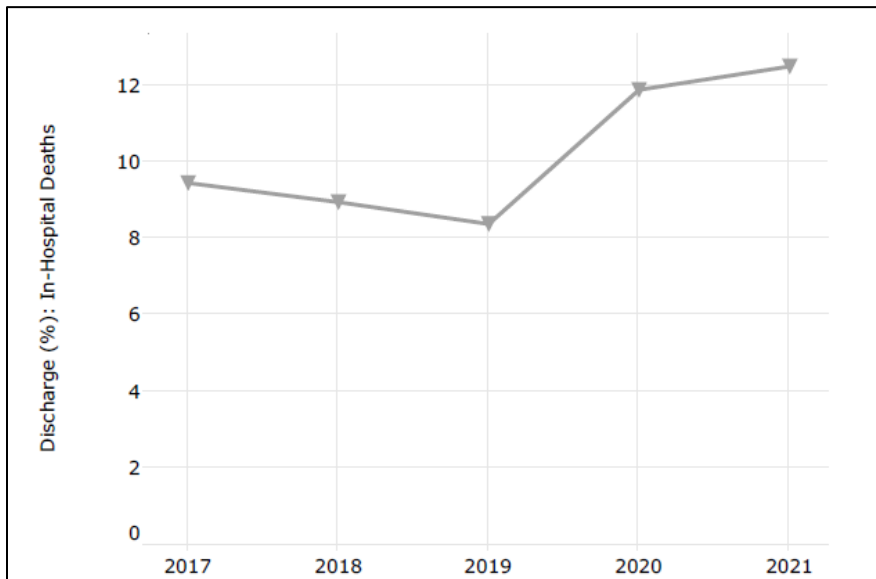


Figure 2. Percentage of U.S. in-hospital deaths with a primary diagnosis of sepsis/septicemia, 2017-2021.³

It is important to note that most data reported on sepsis rates include all hospital patients, the majority of whom survived their admission. However, the pool of potential cadaveric HCT/P donors is comprised exclusively of individuals who die. Therefore, rates of sepsis among hospital deaths provide data more relevant to tissue donation. A 2014 retrospective analysis using the Sepsis-3 criteria of 2.9 million adult admissions in 409 hospitals showed an overall hospital sepsis incidence of 6% and that sepsis was present in 35% of all hospitalizations culminating in death.¹³ Also in 2014, Liu reported on hospital deaths in patients with sepsis from two independent patient cohorts from the Kaiser Permanente Northern California (KPNC) healthcare system (N=482,828 admissions/14,206 deaths) and the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS) (N=6.5 million admissions/143,312 deaths). The authors identified patients with either an explicit ICD-9 diagnosis code of sepsis, severe sepsis, septic shock, or septicemia or an implicit diagnosis which included the addition of patients with evidence of both an infection and acute organ failure. The KPNC cohort showed an 11% explicit and 17% implicit overall rate of sepsis. The NIS cohort had an overall 4% explicit and 11% implicit rate of sepsis diagnosis. Among the KPNC deaths, 37% had an explicit diagnosis of sepsis and 56% had an implicit septic diagnosis. The NIS deaths showed a 35% explicit and 52% implicit rate of sepsis diagnosis.¹⁴ A 2018 retrospective cohort study of 568 adults from 6 US hospitals who either died in the hospital or were discharged to hospice showed that sepsis (possible, probable, or definite) was present during hospitalization in 300 (53%) patients and was the immediate cause of death in 198 cases (35%).¹⁵

In summary, these data indicate that a diagnosis of sepsis impacts approximately 35% of the potential in-hospital cadaveric HCT/P donor pool. More significantly, when clinical criteria such as infection coupled with organ dysfunction is added, over 50% of potential in-hospital cadaveric donors are impacted.

Pilot Study Methods

Pilot Study Data Collection Methods:

This prospective pilot study aimed to primarily evaluate the incidence of sepsis diagnosis, satisfaction of sepsis diagnostic criteria, and medical director suspicion of true transmissible infection via tissue donor chart review. A structured survey tool was designed to collect the appropriate data, and accompanying instructions were provided. Participants were medical directors from the AATB Sepsis Working Group who volunteered to independently complete the survey tool and included those from several large tissue banks with diverse areas of medical expertise.

Between 7/15-8/05/2024 medical directors filled out the data collection tool concurrently with donor chart review for every donor record participating medical directors reviewed during that time. Medical directors representing seven tissue establishments participated in this prospective data collection effort. Charts were de-identified to maintain confidentiality.

The data collection tool (Appendix 1) and instructions for the pilot study are provided (Appendix 2).

Data Collected during Pilot:

- A. Chart number
- B. Chart Review Date
- C. Donor ID (de-identified/not provided)
- D. Sepsis Diagnosed During Hospital Stay (in problem list or discharge diagnosis) [corresponds to first part of sepsis screening criteria in current DE guidance]
- E. SIRS (or SOFA) + Suspicion of Infection criteria met? [corresponds to second part of sepsis screening criteria in current DE guidance]
- F. If yes, was sepsis later “ruled out” by treating MD?
- G. Sepsis is not diagnosed in the chart, but medical director believes there is potential for transmissible infection
- H. Transmissible/ suspected infection treated appropriately and not a concern at TOD
- I. Medical director believes true risk of transmissible infection present?
- J. Cause of Death?
- K. Notes

Experiences with using the data collection tool and the results from the pilot data were reviewed as a working group after the pilot completion. The instructions and data collection tool were refined for clarity in preparation for a larger effort (if appropriate), and the date of recovery was added to the data collection tool for future use.

Results

Simple descriptive statistics of the dataset are provided. Raw data are provided. (Appendix 3)

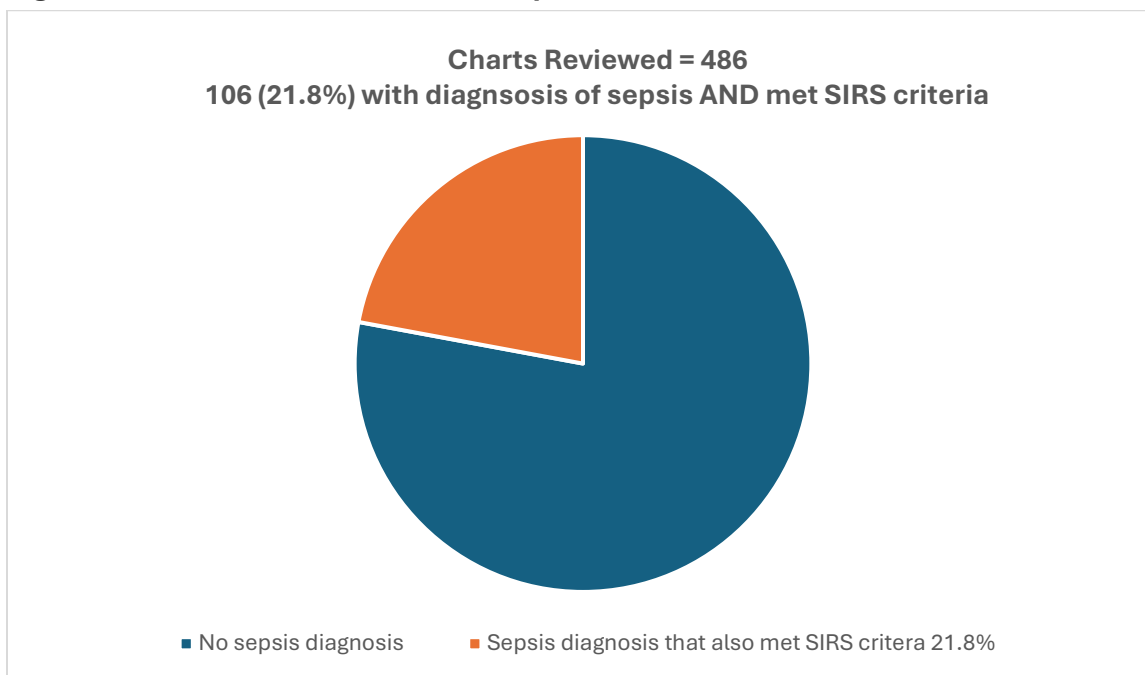
Total number of donor charts reviewed were 486 (n=486).

Total Number of charts with Sepsis diagnosis were 112, as a percentage of the total number of charts reviewed (112/486) 23.0%.

Six charts had diagnosis of sepsis but did not meet SIRS criteria.

Total Number of charts with Sepsis that ALSO met SIRS Criteria were 106, showing that 95% of donors diagnosed with sepsis (112) also met SIRS criteria (106/112=95%) and as percentage of total chart reviewed were 21.8%. (Fig. 3)

Fig 3. Total Number of charts with Sepsis that ALSO met SIRS Criteria



Total number of charts meeting SIRS criteria + suspicion of infection but NOT diagnosed with Sepsis were 73, or 15 % of the total number of charts reviewed (73/486).

Total number of charts with sepsis diagnosed where sepsis was later “ruled out” by the treating provider and documented in the medical records were 13.

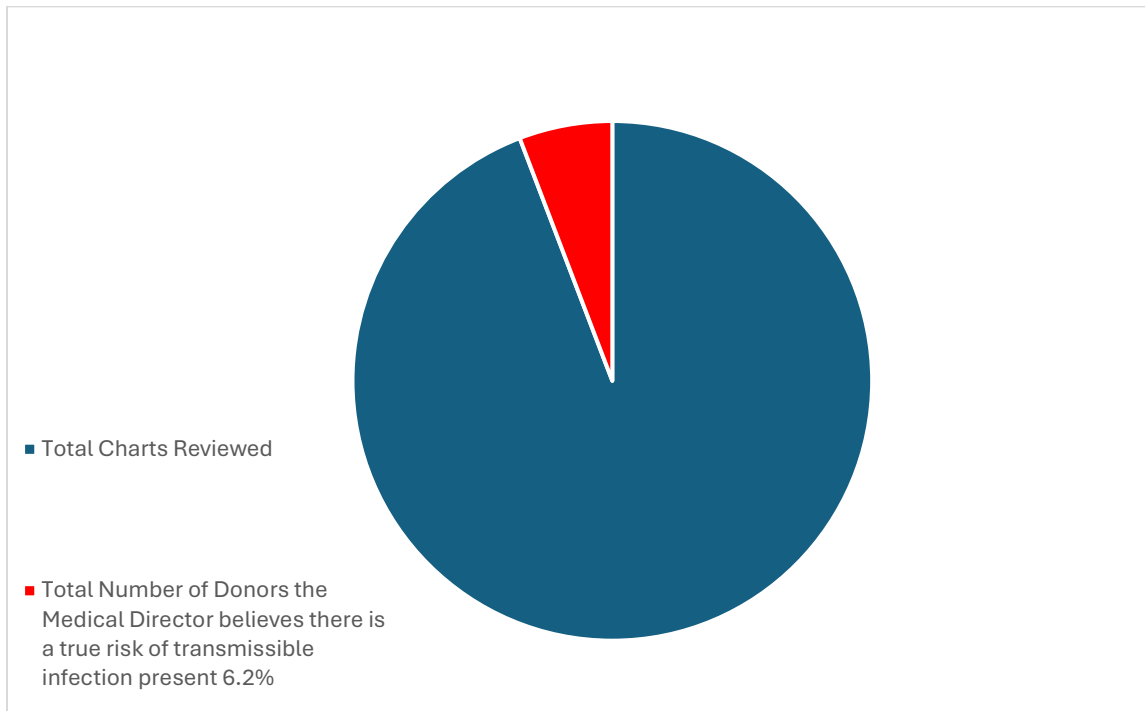
Total Number of Donors diagnosed with Sepsis for which the Medical Director believes the suspected infection was treated appropriately and therefore is not a concern at the time of death were 64 donors.

- As a percentage of charts with diagnosis of Sepsis (64/112) = 57%

- As a percentage of donor charts meeting Sepsis + SIRS (64/106) = 60%
- As a percentage of all donor charts reviewed (64/486) = 13%

The total Number of Donors for which the Medical Director believed a true risk of transmissible infection is present was 30 or 6.2% of the total number of charts reviewed (30/486). (Fig. 4)

Fig 4: Total Number of Donors the Medical Director believed there is a true risk of transmissible infection present (30/486)



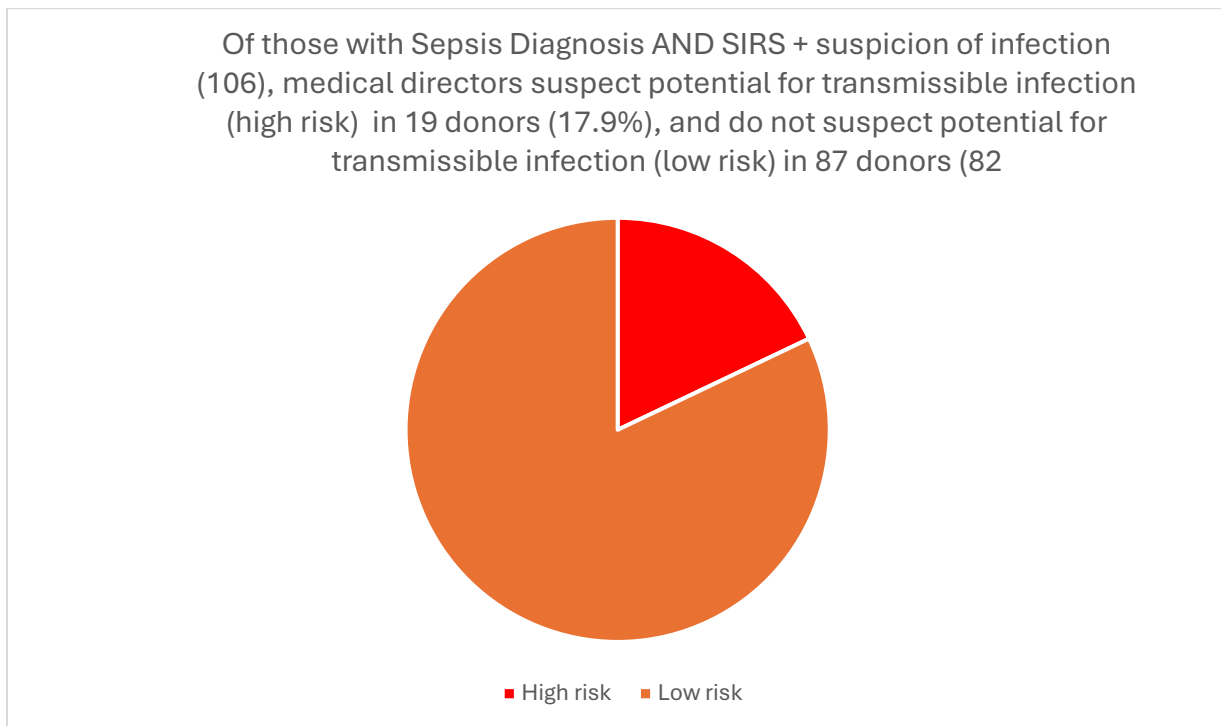
This group also enumerated **the total Number of Donors for which the Medical Director believed there is a true risk of transmissible infection present** (Table 1):

- As a percentage of the total charts meeting Sepsis Diagnosed AND met SIRS Criteria AND had suspicion of infection, 17.9% (19/106 charts). (Fig. 5)
- As a percentage of charts meeting SIRS + suspicion of infection only with no sepsis diagnosis in chart, 11% (8/73 charts).
- As a percentage of charts with sepsis later documented as ruled out by the provider, 5% (2/40 charts).
- As a percentage of charts with donors deemed to have their suspected infection treated appropriately, 3.8% (3/78 charts).

Table 1. Donor charts where transmissible infection is suspected by medical director, in relation to various criteria

Criterion (total number of donor charts with the listed criterion):	Number (and %) with Transmissible Infection suspected
Sepsis Diagnosis AND SIRS + suspected infection (106)	19 (17.9%)
SIRS + Suspected infection but no explicit sepsis diagnosis documentation (73)	8 (10.95%)
Sepsis later ruled out (40)	2 (5%)
Infection treated appropriately (78)	3 (3.8%)
Total Charts (486)	30 (6.2%)

Fig 5: Total number of charts meeting Sepsis Diagnosis AND met SIRS Criteria + medical director suspects potential for transmissible infection (19/106 = 17.9%)



Discussion

Our data indicate that a sepsis diagnosis is present in 23% of donor charts reviewed, whereas a diagnosis of sepsis that *also* meet SIRS criteria plus suspicion of infection was found in 22% of donor charts. This indicates that when a sepsis diagnosis is present in the donor chart, there is a high likelihood that donor will also have met SIRS criteria.

The study did not evaluate those donors who were excluded by pre-screeners due to infection/sepsis concerns, due to those charts never making it to review by medical directors, suggesting that the percentage of sepsis diagnosis in overall deceased donors is at least larger than 23%. Literature review indicated that a diagnosis of sepsis impacts approximately 35% (at least one third of donors) of the potential in-hospital cadaveric HCT/P donor pool (see details above).

The study shows that among Tissue Bank Medical Directors evaluating donor charts for potential of transmissible infections, the diagnosis of sepsis is considered concerning for transmissible infectious risk in only 17.9% of charts meeting both “Sepsis Diagnosed” AND “SIRS Criteria + suspicion of infection” (19/106). This indicates that the majority (82%) of such donors were considered with no or low risk for infection transmission. This conclusion is usually reached because infection transmissibility by tissue is evaluated by taking into consideration multiple aspects of the donor and the tissue intended for transplant, and not solely based on finding sepsis documentation in the chart. Sepsis, being neither specific nor diagnostic of transmissible infections by tissues, is taken into consideration as one item among many and is not the sole determinant of eligibility. Other factors evaluated include the medical, social and behavioral history of the donor which determines epidemiologic exposures, immune status, susceptibility to infections and potential of harboring certain transmissible infections. The physical exam findings, laboratory, microbiological and imaging data are also evaluated. Occasionally donors may also have autopsy, biopsies with histologic exams, or known outcomes of organ transplant, further contributing to the risk assessment process.

Sepsis is a crucial diagnosis to be made early in course of admission to improve outcomes in patients with significant physiologic derangements and hence clinicians tend to document and act on it, regardless of whether there is any evidence of infection or if there is another clear diagnosis that explains the physiologic derangements. Even with abundant evidence of absence of infection, documentation of “sepsis resolved” or “sepsis ruled out” is infrequent; our study showed such documentation was made in only about 5% (2/40) of charts with a sepsis diagnosis. This is due to several reasons, some of which were highlighted in the background section above. Our data collection notes section (see Appendix 1, Column J) shows cause of death of the donors with sepsis documentation, other than infection, included conditions like myocardial infarction, stroke, COPD, metabolic, brain anoxia due to drug overdose, and trauma which can produce physiologic derangements that meet criteria of systemic inflammation plus or minus organ dysfunction, which is used to make a diagnosis of sepsis at the bed side. It is understood that “culture/ work up negative infectious work up” may not exclude certain infections with organisms that are difficult to detect, such as mycobacteria, mycoplasma, certain viruses

and fungi. However it is also understood that these types of infections are not the most common causes of sepsis in US hospitals and moreover more frequently infect certain populations with certain risk factors, already being screened for by other parts of donor screening such as, IVDU and other high risk behavior, alcohol use disorder, homelessness, travel and other exposures and epidemiologic factors, medical history that assesses donor immune function, and hence vulnerability to certain difficult-to-detect organisms.^{16,17}

The pilot study shows that the total percentage of donors who had *either* a sepsis diagnosis or met SIRS criteria constituted about 38% of charts reviewed. If we were to adopt an even more general and hence more restrictive and exclusionary sepsis criteria for donor eligibility, donor loss could increase to 38% (more than one third) of donors, even *after* various methods of pre-screening for undoubtedly ineligible donors. Of note, requiring both Sepsis diagnosis + SIRS criteria for donor exclusion rather than solely requiring a Sepsis diagnosis alone appears to have a minimal impact on improving tissue availability. (Table 2)

Table 2: Percentage of Donor Charts that would be found ineligible if exclusionary criteria during the hospital stay immediately preceding death include:

Sepsis Diagnosis Present During	Sepsis AND SIRS Criteria Met	SIRS Criteria Met	Sepsis OR SIRS Criteria Met
23%	21.8%	36.8%	38%

- Data shown in table 2 are likely to be an underestimate of those that would be ineligible if the criteria were Sepsis Dx + SIRS criteria alone (without suspicion of infection explicitly noted), given that Column E in the data collection tool was not consistently interpreted to mean “SIRS Criteria Alone” met, but was designed to include SIRS + suspicion of infection or sepsis (see data limitations below).
- Had Column E solely asked “Were SIRS criteria met?”, we predict the number marked “Yes” would have been much higher.

Data Strengths:

- This prospective study collected real-time data from seven large tissue establishments by experienced medical directors who are very familiar with reviewing medical records of deceased donors.
- A large number of charts were reviewed to produce the data set (486).
- Data collection criteria provided a mix of objective and subjective data collection, same as the real-life process of donor eligibility determination.

- The data collected includes data from multiple medical directors and multiple processors.

Data Limitations:

- Convenience sample of donor charts reviewed by medical director members of the Sepsis Working Group over the given period of time:
 - Unable to design a statistically representative sample without knowledge of the total number of donor charts reviewed each year (i.e., no available denominator data)
 - Geographic location of donors is not evaluated/considered
 - The participating tissue establishments represent some of the larger US processors, but this is not considered a representative sample of the types of processors seen across the tissue banking industry, e.g., mid- to small-size establishments are not well-represented
- The donor charts reviewed by medical directors is not representative of all *potential* donors evaluated by tissue establishments
 - Each establishment has different pre-screening criteria for what donor charts make are provided to the medical director for review
 - While the pre-screening criteria varies amongst tissue establishments, no establishment provides all potential donors for medical director review – there is some culling of charts so that some clearly ineligible donors are not included for medical director review
 - While we cannot estimate the extent, the percentage of donor charts with sepsis included as a consideration (either diagnosed with sepsis, or meets suspicion of infection + SIRS/SOFA) in this data set is almost certainly an under-estimate
- There may be variation by season, given the seasonality of many infections:
 - This would be anticipated to be mitigated somewhat by the fact that donor charts are reviewed at varying timeframes after tissue collection (e.g., range of weeks to about a year)
 - If more data are collected, we would include the recovery date in the data set
- During the pilot review, we noted some inconsistencies in the interpretation of how to report for Column E. The instructions (see Appendix 2) were as follows:
 - " SIRS (or SOFA) + Suspicion of Infection criteria met? - (Drop down Yes, No, N/A) The SIRS or SOFA criteria PLUS any suspicion of infection."
 - "For purposes of this data collection, we will use the Sepsis-2 and/or Sepsis-3 definitions, which essentially are either SIRS or SOFA (or qSOFA) criteria being met PLUS any suspected infection. *If SIRS alone and no*

documentation in record of diagnosis or suspicion of infection or sepsis, please do not mark YES"

- Yet, in review the column E header was noted to have been interpreted in various ways. Some marked "Yes" if SIRS alone was met, some only marked "Yes" if SIRS+ suspicion of Infection met, and some marked N/A if Sepsis was not diagnosed in column D. Thus, we are unable to determine with high certainty the true incidence of charts that met *SIRS alone without Sepsis diagnosis, vs SIRS+ some suspicion of infection with or without Sepsis diagnosis. If further data were to be collected, Column E would be modified for clarity.*
- Another limitation to be noted is that the participants of the study are mostly from larger-sized processors who are known to have more selective criteria for what potential donors they would consider reviewing. In other words, it is highly unlikely that the mix of available donor charts amongst non-participants of this pilot study would have a lower sepsis diagnosis rate; in fact it is the consensus of this working group is that the percentage is likely to be much higher than 23% showed in this study.

Conclusions

- The AATB Physicians Council Sepsis Working Group (PC Sepsis WG) believes the donor screening criteria for “sepsis” would best be aligned with the presence of a true systemic infection transmissible by tissues given that is what produces the actual risk to recipients, not the physiologic response to an infection (i.e., with sepsis being a dysregulated physiologic response to a suspected infection, which is in itself is not transmissible). The diagnosis of sepsis is a clinical *tool* used to *prevent* morbidity and mortality from an inflammatory response in living patients and is not an accurate predictor of transmissible infection involving transplantable tissue from deceased donors.
- Furthermore, there needs to be greater focus on objective data points such as blood cultures and processing cultures.
- Currently, the donor eligibility guidance permits medical directors to accept donors meeting SIRS/ SOFA criteria if they believe the symptoms are explained by an alternative diagnosis.
 - Sepsis criteria changes that do not allow the medical director to interpret the available data and clinical course of donors meeting SIRS/ SOFA criteria will likely have a significant impact on tissue availability.

- Currently, medical directors feel comfortable accepting donors where there was a clinical diagnosis of sepsis during the hospital stay when a source of infection was identified that was adequately treated prior to death.
 - Sepsis criteria changes that do not permit accepting donors with a diagnosis of sepsis where the infection was adequately treated will likely have a significant impact on tissue availability.
- Currently, medical directors feel comfortable accepting donors where the clinical record indicates that sepsis is resolved (albeit that does not occur frequently).
 - Sepsis criteria changes that do not permit accepting donors with a diagnosis of sepsis where the clinical records formally indicate “sepsis resolved” prior to death will likely also impact tissue availability.
- Potential donors with a diagnosis of sepsis without a clear cause of the physiologic response to a possible infection is the most challenging category to assess, as the lack of finding a causative agent for the sepsis response could represent either a difficult to detect infectious agent (e.g., mycobacteria, mycoplasma, viruses, or certain fungi) or a lack of infectious cause – but there are no available data to reliably discern between these possibilities.
 - In such cases it is imperative to risk stratify all donor aspects including medical, social history, immune status, exposures in addition to all available chart data. It is imperative to also consider the type of tissue to be used, understanding that viable products are considered most at risk to transmit donor related microbes, and act accordingly.
- The AATB Physicians Council Sepsis WG believes that prevention of tuberculosis transmission is best done from the standpoint of improved epidemiologic and risk factor screening and stratification, which has since been implemented through the updated DRAI and eligibility Standards.^{18,19} As tuberculosis lesions can “hide” in tissues without causing Sepsis syndrome, a more robust and specific analysis tool was needed and created.
- The AATB PC Sepsis WG is working to formulate criteria for screening for tissue transmissible systemic infections, and plan to then develop algorithm/flow chart to aid in making the donor eligibility determination.
- We can foresee that consideration of having stricter sepsis criteria for donors of tissues containing viable cells than donors of highly processed tissues (like AATB developed for MTB donor screening) could be very helpful in balancing safety and availability.

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