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RESEARCH

Screening Potential Donors for Signs of Sepsis

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ABSTRACT

CONTEXT: The Eye Bank Association of America Medical Standards provide guidance to participating eye banks on safe tissue donation. According to D1.110: Contraindications, tissue from donors with active septicemia is potentially health-threatening for recipients, can compromise the success of the operation, and should not be offered for penetrating keratoplasty. The Food and Drug Administration's Guidance for Industry states that sepsis is often described by clinical evidence of infection and lists 10 signs to screen for in donors. However, this document notes that "these signs [should] be considered in light of other information obtained about the donor in making a donor eligibility determination."

PURPOSE: (1) To assess whether an increasing number of Food and Drug Administration criteria for sepsis met by donor candidates correlates with a higher incidence of donor ineligibility and (2) whether any signs correlate with a higher incidence of sepsis and thus donor ineligibility.

METHODS: The medical records of 75 potential donors from the North Carolina Eye Bank with signs of possible sepsis were reviewed by an infectious disease consultant.

RESULTS: The only sign independently associated with active septicemia was positive blood cultures (χ^2=27.5; df=9; P<.001). Sixty-five percent of donors whose charts were reviewed were cleared as appropriate cornea donors who did not have active sepsis or bacteremia at the time of death.

CONCLUSIONS: When considering signs of sepsis, there is no clear cutoff at which an increased number of signs correlate with a higher likelihood of septicemia. These signs largely represent the physiologic response known as shock (all types), not just septic shock.

KEYWORDS: corneal transplantations, eye banks, sepsis

With an aging U.S. population and an increase in access to technology internationally, the demand for corneal transplants undoubtedly will increase. The number of donations reported by members of the Eye Bank Association of America (EBAA) increased from 110,630 in 2010 to 114,348 in 2011, an increase of 3.4%. In 2011, 46,196 corneal transplants were performed in the United States alone, and 67,590 corneal grafts were supplied by U.S. eye banks.[1] Therefore, donor screening and eligibility are increasingly important.

In June 1980, after reports linking diseases such as rabies and Creutzfeldt-Jakob disease to corneal donation, the EBAA codified standards to enhance the safety of cornea recipients and establish contraindications for donation.[2] Several iterations have been released, the most recent in 2011.[3] The EBAA identified 27 exclusion criteria for penetrating keratoplasty, including active septicemia (i.e., bacteremia, fungemia, and viremia). They called on eye bank medical directors to identify criteria for active sepsis and determine donor eligibility.[3]

Two major concepts apply to selection of tissue for corneal transplant: suitability and eligibility. The EBAA's suitability standard (F1.400) defines quality criteria for tissue used in procedures such as penetrating keratoplasty, endothelial keratoplasty, anterior lamellar keratoplasty, and Descemet's stripping automated endothelial keratoplasty. The eligibility standard (D1.000) refers to the general medical condition

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of the potential donor.[3] Donors are considered eligible if they have no communicable diseases or medical or social history that would place the recipient at undue risk for contracting communicable disease from their transplants.[3] High-risk social behaviors preclude donation because many infectious diseases linked to such behaviors have latency periods during which infectious organisms are present but not yet serologically detectable. In addition to screening the donor's history, infectious disease testing is performed; only potential donors with nonreactive tests are eligible.[3] The Code of Federal Regulations (21CFR1271.75, Relevant Communicable Disease Agent or Disease) and Food and Drug Administration (FDA) Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products requires screening of donors for hepatitis B and C, HIV, syphilis, prion (Creutzfeldt-Jakob) disease, other emergent diseases such as West Nile virus infection and, finally, sepsis caused by any microbial source.[4,5]

The FDA has designated 10 signs of sepsis. These include (1) temperature >100.4°F (38°C); (2) heart rate >90 beats/min; (3) respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg; (4) white blood count >12,000 cells/mm^3 or >10% immature (band) forms; more severe signs of sepsis, including (5) unexplained hypoxemia; (6) elevated blood lactate level; (7) oliguria; (8) altered mental status; (9) hypotension; and (10) positive (premortem) blood cultures.[4]

As an initial step in screening donors for sepsis, designees of the eye bank medical director assess patient charts to determine if the donor had any of the FDA signs at death. If 2 or more of these signs are noted in a patient chart, eye bank medical directors or other responsible persons (infectious disease consultants) must review the entire medical chart to determine if sepsis was present at death or if any other medical or historical findings preclude donation.[3]

If predictive patterns of the signs of sepsis could be defined, ineligible donors might be identified more promptly, and the need for time-consuming chart review might be reduced. This would be highly desirable, given that recovery and transplant of corneal tissue are time-sensitive. In conducting this study, we asked two questions. First, does an increasing number of FDA criteria for sepsis met by donor candidates correlate with a higher incidence of donor ineligibility? Second, are there any signs that correlate with a higher incidence of sepsis and thus donor ineligibility?

METHODS

A total of 75 potential donors from the North Carolina Eye Bank in Winston-Salem, North Carolina, who had signs of sepsis were evaluated by an infectious disease consultant. The cases selected represent all potential donors reviewed at the eye bank from July 16, 2009, through Jan. 18, 2011. Each donor case review was prompted by the presence of 2 or more signs of sepsis or other infectious disease risk factors, such as previous incarceration or known contacts with infectious diseases, as outlined by the FDA. The donor's entire available medical record was provided for review. The clinical course was reviewed, the number of signs was documented and tissue was either rejected or accepted for transplant. Eligible donors were designated as "Go," ineligible donors as "No Go."

Diagnosis of active septicemia was made by the infectious disease consultant reviewing the donor cases. Active septicemia was defined as the presence of positive blood cultures (deemed not to be a contaminant) at death in the setting of systemic inflammatory response syndrome, which was defined as 2 or more of the first 4 signs enumerated by the FDA and listed previously. The association between a confirmed diagnosis of active septicemia and the 10 clinical signs of sepsis outlined by the FDA was evaluated using χ^2 analysis. Statistical analysis was performed using the software with *Primer of Biostatistics*, 4th Edition, by Stanton A. Glantz, McGraw-Hill Health Professions Division. The same statistical method was used to determine whether an increasing number of signs was associated with an increased likelihood of a diagnosis of septicemia and whether a donor would ultimately be deemed ineligible.

RESULTS

Of all 75 donor cases reviewed, 65% were ultimately deemed eligible for donation. When 0 to 7 signs were present, the rate of eligibility remained between 65% and 69%. Of the 6 patients with 7 or more signs, 83% of donors were deemed eligible. Three patients had 8 or 9 signs that prompted review; in all cases, the potential donors were deemed eligible. No potential donor cases reviewed had all 10 signs. Neither an increasing number of signs nor a threshold number of signs accurately predicted sepsis or donor ineligibility. Sixty-five percent of donors whose charts were reviewed

Table 1: Donor Eligibility vs. Individual Number of Signs and Percentage of Donor Cases Reviewed Resulting in Either Eligibility ('Go') vs. Ineligibility ('No Go') as a Threshold Number of Signs of Sepsis

Number of signs	Cases with AT LEAST that many signs	Cases with AT LEAST that many signs that are 'Go'	Cases with AT LEAST that many signs that are 'No Go'	'Go' (%)	'No Go' (%)
0	75	49	26	65	35
1	57	37	20	65	35
2	49	33	16	67	33
3	42	29	13	69	31
4	35	23	12	66	34
5	29	20	9	69	31
6	18	12	6	67	33
7	6	5	1	83	17
8	2	2	0	100	0
9	1	1	0	100	0
10	0	0	0	0	0

Fig 1. Percentage of Sepis Cases Evaluated as 'Go' vs. AT LEAST 'x' Number of Signs of Sepsis

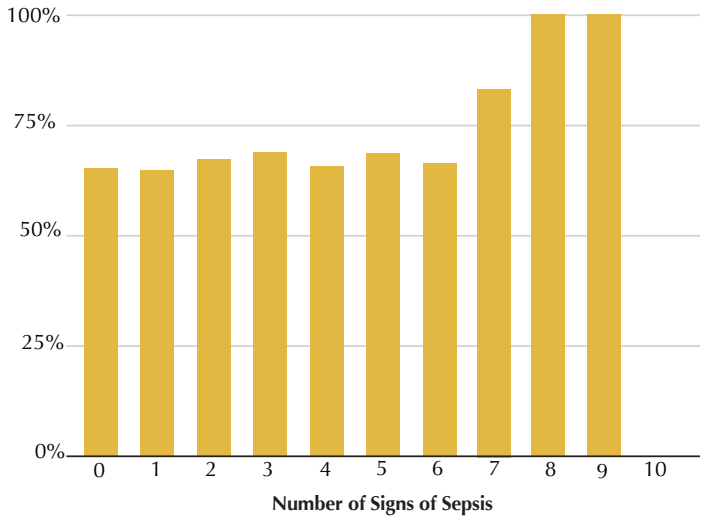

Fig. 1. Donor eligibility vs. threshold number of signs (graphical representation of data in Table 1) and percentage of eligible donors (percentage of cases marked "Go") vs. total number of signs. There is no threshold; in fact, it appears that, as more signs are found in the chart, the rate of eligibility stays the same or even increases.

were cleared as appropriate cornea donors who did not have active sepsis or bacteremia at death (Table 1 and Fig. 1). The only sign independently associated with active septicemia was positive blood cultures (after exclusion of contaminants). Four of 7 donors with positive blood cultures (57%) were ultimately shown to have sepsis ($\chi 2=27.5$; df=9; P<.001) (Table 2). No other sign showed a statistically significant relationship. Potential donors with elevated temperature, elevated heart rate, rapid respiratory rate, abnormal white counts, oliguria, and altered mentation were determined to have sepsis less than 20% of the time. Potential donors with elevated lactic acid levels were determined to have sepsis 25% of the time, while those with low blood pressure were determined to have sepsis 32% of the time (Table 2).

Table 2: Rate of Sepsis Development According to Individual Signs of Sepsis

	Elevated Temp.	Elevated Heart Rate	Rapid Respiratory Rate	Abnormal WBC	Hypoxemia	Elevated Lactic Acid	Oliguria	Altered Mentation	Low BP	Positive Blood Cultures
Signs leading to sepsis	3	3	0	7	1	7	3	1	7	4
Signs leading to not sepsis	13	28	23	34	24	21	13	29	15	3
Total cases with sign	16	31	23	41	25	28	16	30	22	7
Sepsis rate for sign (%)	19	10	0	17	4	25	19	3	32	57

DISCUSSION

Corneal transplantation uses live human tissue, which may be a vehicle for transmission of infectious diseases. Reducing the risk of transmission is especially important because transplantation often requires immunosuppression with either topical or systemic agents. The EBAA and FDA require chart review by an eye bank medical director or other responsible person if 2 or more signs of sepsis are present. After review, the clinical context is used to determine whether the donor is ultimately eligible for donation.

Most signs of sepsis outlined by the FDA can be attributed to non-septic forms of shock (i.e., hemorrhagic, cardiogenic, neurogenic, and anaphylactic). Our data suggest that the presence of 2 or more signs of possible sepsis does not absolutely indicate sepsis, and that potential donors with as many as 9 signs of sepsis (1 potential donor met this criteria) may still be eligible for donation. In fact, in our study, most corneal tissue donors who met 2 or more criteria for sepsis were determined to be eligible for donation, and only positive blood cultures predict sepsis at a relevant rate. The authors do not advocate revision of current review practices of donor eligibility based on this study, as our data set is small and limited to a single eye bank. Our goal is to prompt future research into the preliminary evaluation of donor eligibility to refine the screening procedures. Based on our literature search performed from April to June 2011 using the National Library of Medicine's PubMed database, no current research is being done on the correlation or predictive value of the signs of sepsis and ultimate corneal donor eligibility.

Because acquisition and storage of tissue are time-sensitive, finding a single sign or an increasing or threshold number of signs that correlate with a higher risk or rate of sepsis could be of considerable benefit. If such a pattern could be identified, the need for time-consuming chart review potentially could be reduced. Our data indicate that such a pattern is not clearly established with use of the FDA criteria. Currently, close scrutiny of patient history and thorough chart review are still necessary when signs of sepsis are present, because many donors are eligible for donation even when there are multiple signs of systemic inflammatory response syndrome or sepsis.

The major limitation of this study is its small sample size. Seventy-five potential donor cases from a single eye bank in North Carolina were reviewed. Increasing the number of cases reviewed and the number of sites contributing cases would improve the power of the study. It is doubtful that regional factors would reveal variable predictive patterns for sepsis and eligibility. Furthermore, this study is limited to quantitative evaluation of signs of sepsis in a patient at determination of donor eligibility. It would be interesting to determine if a unique pattern of signs were predictive of an ultimate designation of ineligibility for donation.

We found no clear cutoff at which an increased number of signs correlated with a higher likelihood of septicemia in cornea donors. These signs largely represent the physiologic response known as shock (all types), not just septic shock. However, until such a cutoff or pattern of signs is identified, thorough chart review will continue to be needed when signs of sepsis are present so that eligible donors are not needlessly eliminated.

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