Transfer Factor Revisited: Treatment of Candida Prosthetic Valve Endocarditis

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**ABSTRACT**

Candida prosthetic valve endocarditis (CPVE) is most commonly seen in persons who inject drugs intravenously or have indwelling catheters, pacemakers, or prosthetic joints that can serve as a nidus for candida suprainfection and seed the valve. Current treatment guidelines for CPVE include valve replacement and long-term antifungal therapy with intravenously administered Amphotericin B and parenteral or oral therapy with 5-fluorocytosine. Despite treatment, CPVE is characterized by a high recurrence rate (up to 36%) and a 5-year survival of less than 50%.

I review my past experience in treating recalcitrant CPVE with transfer factor (TF) immunotherapy and conclude that TF can be a valuable adjuvant in the treatment of CPVE that does not respond to conventional interventions.

**Keywords:** Transfer factor, dialyzable leukocyte extract, DLE, candida, prosthetic valve endocarditis, migration inhibition factor, MIF, monocytes, immunotherapy, immune exhaustion

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**Introduction**

Candida prosthetic valve endocarditis (CPVE) is most commonly seen in persons who inject drugs intravenously or have indwelling catheters, pacemakers, or prosthetic joints that can serve as a nidus for candida suprainfection and seed the valve. Current treatment guidelines for CPVE include valve replacement and long-term antifungal therapy with intravenously administered Amphotericin B and parenteral or oral therapy with 5-fluorocytosine. Despite treatment, CPVE is characterized by a high recurrence rate (up to 36%) and a 5-year survival of less than 50% (1).

This report reviews my past experience in treating CPVE with dialyzed extracts of leukocytes (DLE) obtained from candida skin test positive donors. DLE, also referred to as transfer factor (TF), contains more than 200 highly polarized, hydrophilic, low molecular weight peptides, and is capable of transferring both specific and non-specific immunity to healthy recipients (2). TF has previously been shown to be effective in the treatment of chronic mucocutaneous candidiasis in humans (3) and candida sepsis in mice (4).

**Case presentation**

A 25-year-old man with a two-year history of *Candida krusei* aortic valve endocarditis complicating intravenous heroin usage underwent an immune assessment in anticipation of transfer factor therapy. He had failed to respond to two aortic valve replacements and multiple courses of Amphotericin B and 5-fluorocytosine. Further surgery was technically impossible, the organism had become highly resistant to 5-fluorocytosine, and the presence of severe renal insufficiency precluded further trials of Amphotericin B. On no therapy, he was toxic and losing weight. His temperature spiked daily to 40°C, his body was covered with multiple petechiae, and he lapsed into a semi-coma. Multiple blood cultures and cultures of his urine and bone marrow grew *Candida krusei*.

Evaluation prior to immunotherapy revealed the presence of serum IgG anti-candida precipitins in a dilution of 1:256. He showed no response to skin testing with candida, trichophyton and mumps antigens and his white blood cell count ranged between 1,600 and 2,000 cells per cumm with 0% monocytes. There was a polyclonal elevation in serum IgG and IgA and serum levels...
of IgM, IgD, C3 and ABO isoagglutinins were normal. An assay for migration inhibition factor (MIF) production in response to candida antigen was negative.

In the absence of any other form of therapy, the patient received a single subcutaneous dose of 2.48 x 10^9 leukocyte equivalent units of TF. Three days after treatment he became afebrile, nontoxic, and his sensorium cleared. He began to gain weight and the petechiae resolved. His white blood cell count rose to 5,000 to 6,000 cells per cumm with 12-15% monocytes and blood cultures showed no growth. The MIF assay and cutaneous reactivity to candida antigen became positive (figure 1).

Ten days after the administration of TF the patient was able to leave the hospital on a four-day pass. Upon returning he suddenly expired. At post-mortem, the cause of death was not apparent. There was a thick fibrin deposit around the prosthetic aortic valve but no vegetations were seen and hematoxylin and eosin and Gomori’s silver methenamine stains of the valve were negative (figure 2). Candida was not seen on gross or microscopic examination of his other organs.

Three months after culturing, a few colonies of *Candida krusei* were isolated from the aortic prosthesis on Sabouraud’s glucose agar. All other fungal cultures remained negative.

**Figure 2. Prosthetic valve culture and fungal stain.**

**DISCUSSION:**

I subsequently treated two other cases of CPVE with TF. Both were anergic and had low blood levels of monocytes, and had failed to respond to a 3-week course of Amphotericin B and 5-fluorocytosine. They had persistent fever, toxicity and septic emboli, and were poor candidates for surgical intervention. Both men became afebrile and nontoxic beginning 48 to 72 hours after TF administration.

The first case was treated with a total of 2 grams of Amphotericin B and 6.88 x 10^9 LEU of TF (given in 2 doses) and was clinically well and culturally negative 5 months after treatment. However, he was readmitted 2 months later with recrudescence of his CPVE from which he expired.

The second case was treated with 3 grams of amphotericin B and 20 x 10^9 LEU of TF and was clinically well and culture negative until he was readmitted 2 months later with staphylococcal prosthetic valve endocarditis which required a second valve replacement. Cultures of the replaced prosthetic valve were negative for candida. The patient developed progressive aortic insufficiency and eventually died of a reinfection of the prosthetic valve with *Serratia marcesens.*
It is likely that the presented cases failed to control their infection because of immune exhaustion (5). They failed to replenish circulating levels of immune cells, particularly blood monocytes, and their cell-mediated immunity was severely impaired as evidenced by the absence of delayed cutaneous reactivity to a panel of antigens and by the absence of MIF production in response to candida antigen. MIF is an proinflammatory cytokine which is constitutionally expressed by immune cells, the hypothalamic, pituitary and adrenal glands, and by epithelial cells of the skin, lung, and GI tract. Microbial products and proinflammatory cytokines induce the release of MIF, which functions as an important regulator of both the innate and adaptive immune response (6).

In the presented cases, administration of a single dose of DLE prepared from candida skin test positive donors promptly reversed the immune deficits and rendered the patients culture negative in the immediate post-treatment period. One patient relapsed with CPVE 5 months after treatment and one patient’s prosthetic valve eventually grew several colonies of candida, indicating that additional treatments with DLE, whose immunological effects on monocyte mobilization last about 70 days (3), was indicated.

I conclude from these cases that TF can be a valuable adjunct to the treatment of CPVE and that further investigation on the ability of TF to mitigate immune exhaustion in chronic viral and fungal infections using modern day immunological technologies is warranted.

Side Bar
Preparation of dialyzable leukocyte extract (transfer factor):

TF was prepared by the method of Lawrence (2). For each batch of TF, 500 mL of whole blood taken from a candida skin test positive donor was collected in a heparinized polyethylene bag and transferred into a sterile glass container. Six percent dextran in saline (25% of final volume) was added, and the red blood cells allowed to sediment at room temperature for 90 minutes. The top layer (white blood cells and plasma) was removed and centrifuged at 4°C for 20 minutes at 367 g. The supernatant was decanted, and the cell layer suspended in ~ 6 mL lots of sterile distilled water. The suspended cells were then lysed by alternate freezing and thawing in dry ice and 37°C water. Lysates were pooled and dialyzed against 800 mL of sterile distilled water at 4°C for ~ 12 hours, using membranes that permitted egress of molecules of <10,000 molecular weight*. The dialysate was lyophilized in ~150 mL lots, and the lyophilized extracts concentrated by adding 5 mL of sterile distilled water to each lot, pooling the solutions, and re-lyophilizing overnight.

The concentrated dialysate was stored at -70°C until use. Dialysate reconstitution was done by adding 3 mL of sterile distilled water and passing the solution through a Millipore filter. The solutions were checked for endotoxin by the limulus amoebocyte lysate test. Sterile precautions were taken during the entire procedure.

*Cytokines are too large to pass through this filter

This study was approved by the Institutional Review Board of Northshore University Hospital, Long Island, New York, an affiliate of Cornell University Medical College, New York, New York at the time of the study.

References
