A novel murine model of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) induced by immunization with a spermine binding protein (p25) peptide

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CHRONIC PROSTATITIS/CHRONIC pelvic pain syndrome (CP/CPPS), category III prostatitis, is the most common form of prostatitis, comprising more than 90% of all cases (10, 22, 31) and affects 10–14% of men of all ages and ethnic origins (39). The CPPS phenotype includes chronic genitourinary or pelvic pain, with or without voiding symptoms, in the absence of bacterial infection or other identifiable causes, such as malignancy. Men with CP/CPPS often have a poor quality of life (28).

The etiology of CP/CPPS remains unclear. Immunological, neurological, endocrine, and psychological factors have been implicated. An autoimmune basis for CP/CPPS is one prominent theory. T cells, B cells, granulocytes, and macrophages were found in prostatic massage fluid of patients with CP/CPPS without infections (27). Self-antigen-specific IgG were found in sera from patients with CP/CPPS (9, 14, 34). Autoantibodies and immunoreactivity to seminal plasma have also been reported (9, 14, 34). These data suggest that CP/CPPS may, in part, have autoimmune etiopathogenic features, involving immunity against prostate-specific antigens.

Several CP/CPPS animal models exist (15, 33, 38, 44). Most of these models were created with prostate insults (e.g., inflammation) and result in low incidence rates (30%) (44). Although all of these models mimic characteristics of human chronic prostatitis, few demonstrated chronic pelvic pain. One study using male prostate homogenate showed chronic pelvic pain in mice but did not mimic other symptoms of CP/CPPS (38). Further, immunization with homogenate may induce a systemic inflammation beyond prostatitis due to inclusion of both prostate-specific and nonspecific antigens. Thus, there is a need for a CP/CPPS model that combines all the phenotypical features, including frequency, urgency, and pelvic pain with prostate specificity and high incidence rate.

Our strategy involves mobilizing a sensitized T-cell response capable of proliferating and differentiating in response to organ-specific proteins (2, 4, 19, 20). In particular, peptides containing a tetrapeptide sequence motif, in which arginine or lysine is separated from serine, threonine, or cysteine by two amino acids, are often immunogenic and capable of inducing several CD4+ T-cell-mediated autoimmune diseases in SWXJ(H-2b) mice (41). Using this strategy, we have successfully developed multiple autoimmune models of disease (2, 4, 18).

In this study, we sought to isolate and use peptides derived from prostate-specific proteins: spermine binding protein (p25), six transmembrane epithelial antigen of the prostate (STEAP), and probasin (PB) (11, 16, 30). The prostate specificity and tissue expression levels of p25, STEAP, and PB render them potentially good markers of prostate-specific disease, as well as good targets for prostate-specific autoimmune-
nity. Herein, we describe a novel form of experimental autoimmune prostatitis (EAP) induced by CD4+ T cells targeted against the prostate-specific p25 99–118 peptide. Furthermore, we characterized the phenotype of this new model in regard to pelvic pain and lower urinary tract function.

**MATERIALS AND METHODS**

**Peptide.** To identify immunogenic peptides, we located the -K/R-X-X-S/T/C- tetrapeptide sequence motif, associated with IAα- and IAβ-restricted CD4+ immunogenicity, in the sequences of the mouse prostate-specific proteins p25 99–118, STEAP 311–330, p25 109–128, and PB 64–83. Twenty-mer peptides containing this motif were synthesized and purified at the Molecular Biotechnology Core Facility of the Lerner Research Institute (Table 1).

**Mice and immunization.** Eight-week-old male SWXJ (H-2q,s) mice (n = 140; Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously in the abdominal flank with 200 μl of an emulsion consisting of equal amounts of water and complete Freund’s adjuvant (CFA) with (EAP mice) or without (control mice) 200 μg peptide and 400 μg of *Mycobacteria tuberculosis* H37RA (Difco, Detroit, MI), as described previously (2, 4, 18). Control mice were immunized with CFA alone, and naive mice were also included as controls. Mice were killed by asphyxiation with CO2 followed by cervical dislocation. All protocols were submitted to, approved by, and conducted under the guidance of the Institutional Animal Care and Use Committee of Case Western Reserve University in compliance with the Public Health Service policy on humane care and use of laboratory animals and the Declaration of Helsinki.

**Cell culture and proliferation assays.** Cell culturing and proliferation assays to determine immunogenicity were performed as described previously (4). Briefly, 10 days after immunization with each peptide, lymph node cells (LNC; 10-day primed) were removed from mice and cultured in 96-well plates, as described previously, with serial 10-fold dilutions of immunizing peptide added to triplicate wells (4). Inhibin-α 215–234 (FLVAHTRAPSAGERRSS) was used as an irrelevant antigen specificity control (4). In some experiments, CD4+ and CD8+ T cells were purified from 10-day primed LNC by positive selection using anti-CD4- and anti-CD8-coated magnetic beads and double passed through a MACS LS column using a MidiMACS cell separator (Miltenyi, Auburn, CA). The purified T cells were cultured with 5×10^5 γ-irradiated (2,000 rad) syngeneic splenocyte feeders and activated with 20 or 100 μg/ml peptide. To measure recall responses to immunogens, spleens were removed 9 wk after immunization, and mononuclear splenocytes were cultured with serial dilutions of peptide, as described previously (3). Inhibin-α was used as a control antigen.

**Cytokine ELISAs.** Purified capture/detection antibody pairs and recombinant cytokines were obtained commercially (BD Biosciences, San Jose, CA) and included anti-mouse IFN-γ (R4–6A2 and biotin XMG12), anti-mouse IL-2 (JES6–1A12 and biotin JES6–5H4), anti-mouse IL-4 (11B11 and biotin BV6D–24G2), anti-mouse IL-5 (TRFK5 and biotin TRFK4), and anti-mouse IL-10 (JES5–2A5 and biotin SXC-1). Absorbance was measured at 405 nm using a model 550 ELISA microplate reader (Bio-Rad, Hercules, CA) and converted to nanograms per milliliter using individual cytokine standards.

**Antibody isotyping.** Isotype-specific antibody titers to p25 99–118 were determined in serum samples obtained from mice 9 wk after immunization with p25 99–118 or CFA (negative control). Microtest wells coated with p25 99–118 antigen were blocked with BSA and incubated with 1/500 dilutions of the serum samples. Mouse MonoAb ID/SP ELISA (Zymed, Invitrogen, Carlsbad, CA) were used according to the manufacturer’s instructions, and biotinylated antibodies specific to each mouse IgG isotype were added, followed by detection with streptavidin-HRP and 2,2'-azino bis (3-ethylbenzothiazoline-6-sulfonic acid) substrate, and measurement of absorbance at 405 nm.

**Immunocytochemistry.** Immunostaining was performed as described previously (4, 19). Briefly, unmasked and blocked, formalin-fixed, paraffin-embedded 5-μm tissue sections were treated with a 1:250 dilution of rat anti-mouse CD3 antibody (Novacwastra, Newcastle Upon Tyne, UK) followed by a 1:100 dilution of mouse-adsorbed biotinylated goat anti-rat IgG (BD Biosciences). Slides were developed conventionally using streptavidin-HRP (Vectastain ABC kit, Vector Laboratories, Burlingame, CA) with 3,3'-diaminobenzidine chromogen and hydrogen peroxide substrate solution (BioGenex, San Ramon, CA) and examined by light microscopy (Olympus DP70 digital microscope).

**Real-time quantitative RT-PCR.** The levels of mRNAs for inflammatory cytokines IFN-γ, TNF-α, IL-17A, and IL-1β were determined by real-time (RT)-PCR. Prostate and bladder tissues were harvested from mice 9 wk after immunization with UPK3A 65–84 or CFA alone, and from naive mice, taking care to exclude the pelvic ganglia. Total RNA was isolated from the tissues using TRIzol reagent (Invitrogen, Carlsbad, CA), and cDNA was synthesized from the RNA using Super Script III cDNA synthesis kit with random hexamer primers (Invitrogen). PCR was performed from the cDNA using the primers listed in Table 2 and a SYBR Green PCR Master kit with an ABI Prism 7500 Sequence Detection System (Applied Biosystems, Foster City, CA). Cytokine gene expression levels normalized to expression of the housekeeping gene β-actin and relative to the average level in naive mice for each tissue were calculated with the comparative cycle threshold (Ct) method (26), after confirming that the mean levels of β-actin mRNA did not differ significantly between the EAP and CFA mice.

**Measurement of C-reactive protein, nitrate/nitrite, and antioxidant serum capacity.** Serum levels of C-reactive protein (CRP) (6), nitrate/nitrite (13), and total antioxidant enzymes (5) were assessed as nonspecific markers of inflammation and oxidative stress. CRP was measured with murine-specific enzyme immunoassay kits (ALPCO Diagnostics, Salem, NH). Mouse serum nitrate/nitrite levels and antioxidant capacity were measured using a colorimetric assay kit and an antioxidant assay kit, respectively (Cayman Chemical, Ann Arbor, MI), according to the manufacturer’s instructions.

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Sequence with -K/R-X-X-S/T/C- Motif</th>
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<tbody>
<tr>
<td>p25 99–118</td>
<td>LTFFTNKORVATPGVRGRKY</td>
</tr>
<tr>
<td>p25 109–128</td>
<td>ATPQVRRGRYTFSGOTSGSDKH</td>
</tr>
<tr>
<td>STEAP 311–330</td>
<td>PCKRLKIKITRCGRGVDVSKY</td>
</tr>
<tr>
<td>PB 64–83</td>
<td>QVYLYFPGKGGTPQGQVKVYI</td>
</tr>
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Underlined letters refer to the -KXXS- motif on the synthesized peptides.
Micturition habits by urinary frequency-volume chart analysis. Twenty four hours prior to initiating frequency-volume chart (FVC) analysis, solid food was removed from the cages and replaced with lactose-free milk (Lactaid 100 whole milk; McNeil Nutritional, Fort Washington, PA), as described previously (1, 25). For measurements, each mouse was placed individually in a metabolic cage (MED-CYT-M; Med-Associates, St. Albans, VT), and urine was collected in a plastic tray located on an analytical balance (VI-3 mg; Acculab, Huntingdon Valley, PA) placed directly under each cage. Balances were connected to a data acquisition software program designed by the vendor for measuring the weight (mg) of urine collected, which was recorded continuously over a 24-h period. Mice were provided with free access to lactose-free milk and water throughout the assessment period. This strategy substantially reduces the frequency and weight of feces generated during testing, ensuring that any feces droppings are represented by minor peaks in the chart that are easily distinguished from voided urine (1, 25). In addition, mice were observed continuously by a veterinary care assistant over the initial portion of the 24-h FVC period, long enough to ensure that only actual urine voids were recorded. The testing room was maintained on the usual 12–12-h light-dark cycle.

Fig. 1. Characterization of the immune response to the prostate-specific p25 99 –118 peptide. A and B: relatively higher recall response was observed with p25 99 –118, compared with STEAP 311–330, p25 109–128, and PB 64 –83 peptides. Ten day-primed lymph node cells (LNC) were cultured with serial dilutions of the immunizing peptide and were pulsed with [3H]thymidine. Results are expressed as the means ± SD of four mice per group expressed as the stimulation index (A) or radioactivity in counts per minute (B). C: recall proliferative responses were observed in p25 99 –118 peptide, but not in the irrelevant immunogenic inhibin-α 215–234 peptide, by splenocytes obtained 9 wk after immunization with p25 99 –118 (n = 5 mice per group; values are means ± SD). D: ELISA analysis of cytokines from the 48-h supernatant of cultured 10-day primed LNCs demonstrated the response to p25 99 –118 was predominantly a type-1 proinflammatory response characterized by high production of IFN-γ and IL-2 and nominal production of IL-5 and IL-10 (n = 5 per group; *P = 0.001). E: magnetic bead separation of cultured 10-day-primed LNC demonstrated that recall proliferative responses to p25 99 –118 were elicited from purified (≥90%) CD4+ T cells, but not from CD8 + T cells (n = 5 per group). F: ELISA analysis of serum at 1/500 dilution taken 9 wk after immunization with p25 99 –118 involved both a type-1 response with high production of IgG2a and IgG3 and a type-2 response with high production of IgG1 (n = 4 per group; *P < 0.0001). All values in D–F are expressed as means ± SD.
Prostate weight assessment. Dorsolateral and ventral lobes of prostate glands were removed by cutting the ducts at the urethral connection, as described previously (43). All tissues were weighed immediately after removal.

Pain assessment. Nine weeks after immunization, mice were tested for tactile allodynia and referred hyperalgesia by von Frey filaments to the pelvic region (23, 38). Mice were tested in individual chambers with a stainless-steel wire grid bottom. Eight forces from 0.008 to 4 g were applied with different sizes of von Frey filaments. Behaviors considered a positive response were sharp retraction of the abdomen, instant licking and scratching, and jumping. Withdrawal response frequency was determined for each filament as the percentage of positive responses of 10 stimuli, each applied for 3-s with 5-s intervals between stimuli. Data are expressed as the mean percentage of response frequency for each filament.

Statistical analysis. Means and standard deviations for each group were calculated. The unpaired, two-tailed Student’s t-test was used to analyze differences between the p25 99–118 group and each control.
group (CFA-immunized or naïve) individually in each experiment of qRT-PCR, micturition frequency, mean urine output/micturition, 24-h fluid intake, CRP, nitrate/nitrite, antioxidant capacity of serum, and individual prostate lobes weight-to-body weight ratios. For analysis of pain assessment data, the 50% response threshold, i.e., the filament force in grams that caused a response in 50% of the applications, was estimated for each mouse by performing linear regression on the linear portion of the graph of response frequency vs. log of the filament force. The 50% thresholds of the p25 99–118-immunized and CFA control group were then compared by the unpaired, two-tailed Student’s t-test. Welch’s correction was used in cases of unequal variances.

RESULTS

Only p25 99–118 elicited a substantial recall proliferative response from 10-day-primed-LNC (Fig. 1). Therefore, p25 99–118 was used for all additional experiments. Splenocyte recall responses 9 wk after immunization with p25 99–118 showed specificity for the immunogen because proliferative responses were not elicited by the control peptide inhibin-α 215–234. LNC responding to p25 99–118 showed a proinflammatory type-1 cytokine response characterized by enhanced expression of IFN-γ and IL-2 and low production of IL-5 and IL-10. Specific responses to p25 99–118 were elicited from purified (>90%) CD4+ T cells, but not from purified T cells CD8+. High titer serum antibody responses were observed after immunization and consisted of a type-1 antibody response involving elevated production of IgG2a and IgG3 and elevated type-2 IgG1 antibodies.

T-cell infiltration was only observed in prostates from p25 99–118-immunized mice, not in CFA-immunized mice (Fig. 2). Specifically, periglandular and stromal infiltration was done predominantly by CD3+ T cells (Fig. 2A). qRT-PCR analysis showed significantly elevated gene expression levels of the inflammatory cytokines, TNF-α, IL-17A, IFN-γ, and IL-1β, in prostate tissue of mice immunized with p25 99–118 compared with prostates from either naïve or CFA-immunized mice (Fig. 2B).

Serum CRP levels were increased 9 wk after p25 99–118 immunization compared with CFA-immunized mice (68.37 ± 3.87 vs. 51.07 ± 5.17; P < 0.0001). Markers of oxidative stress, including antioxidants (0.55 ± 0.15 vs. 0.13 ± 0.03; P < 0.0001) and nitrate/nitrite (2.61 ± 0.30 vs. 1.01 ± 0.24; P = 0.039) levels were significantly higher in p25 99–118-immunized mice compared with CFA-immunized mice (Fig. 3).

Functional analysis demonstrated significantly increased urinary frequencies (65.6 ± 9.44 vs. 44.4 ± 6.97; P = 0.004) and significantly decreased mean urine outputs per void (0.48 ± 0.047 vs. 0.61 ± 0.0032 g; P = 0.001) 9 wk after immunization with p25 99–118 compared with CFA (Fig. 4). Total 24-h urine output determined from the FVC traces was slightly, but not significantly, higher among p25 99–118-immunized mice compared with CFA control mice (31.1 ± 3.06 vs. 26.9 ± 3.10 g). Similarly, no difference in 24-h intake of fluids (water and milk) was detected between the groups (29.0 ± 1.01 vs. 28.6 ± 1.14 g in p25 99–118 vs. CFA mice, respectively; Fig. 4A, right). Dorsolateral and ventral prostate weight (mg)-to-body weight (g) ratios were also significantly increased in p25 99–118- vs. CFA-immunized mice (2.18 ± 0.18 vs. 1.58 ± 0.24, P < 0.0001; and 0.52 ± 0.054 vs. 0.39 ± 0.035, P < 0.0001; for dorsolateral and ventral prostate, respectively). Finally, mice with p25 99–118-induced EAP demonstrated significantly elevated responses to forces of von Frey filaments applied to the pelvic region (i.e., decreased evoked pain response threshold) compared with CFA controls 9 wk after immunization (Fig. 5). Similar micturition and pain response results were obtained from p25 99–118-immunized and CFA control mice 5 wk after immunization (data not shown). Overall, we have performed functional assays on more than 50 mice after immunization with p25 99–118, and 100% of the mice exhibited increased micturition frequency, decreased urine output per void, and increased pelvic pain responses.

DISCUSSION

Herein, we report a CP/CPPS phenotype in mice immunized with a 20-mer peptide from p25 99–118 that is highly immunogenic and specifically induces CD4+ T cells with a Th1 response, with a 100% incidence rate of EAP. CP/CPPS was characterized by increased urinary frequency, decreased volume per void, and increased pelvic region tactile hyperalgesia, compared with control mice. Furthermore, we demonstrated a CD4+-mediated autoimmune, prostate-specific inflammatory response indicated by the presence of T-cell clusters in the prostate, high expression of proinflammatory cytokines, and increased prostate-to-body weight ratio.

Currently, multiple animal models (24, 33, 35, 36, 38) of autoimmunity or antigen-independent prostatitis suggest that some determinants of normal prostatic proteins are not tolerated by the immune system. In contrast, cytotoxic T-cell markers were identified in expressed prostatic secretion of men.
with CP/CPPS, consistent with autoimmune inflammation or secondary remodeling of injured tissue (40). The significantly increased IFN-γ levels observed in the supernatants from prostate p25 peptide-stimulated cells further suggest a prostate-specific response. In our model, IgG antibody isotype and cytokine profile expression were consistent with a type-1 immune response in CP/CPPS.

IFN-γ-secreting lymphocytes specific to prostate antigens were detected in 34% of patients with chronic noninfectious prostatitis (9). In addition, seminal plasma of CP/CPPS patients show higher levels of proinflammatory cytokines (IL-1β and TNF-α) and chemokines (IL-8) compared with controls. Those data confirm the importance of the enhanced expression of these inflammatory mediators in prostatic tissue. In our model, we found T-cell invasion of prostate interstitium and epithelium associated with a significant increase in IFN-γ, TNF-α, IL-17A, and IL-1β. In particular, IL-17A augments other members of the proinflammatory cytokine family (42).

Consistent with the phenotype of our model, persistent pain/genital pain with or without urinary symptoms in the absence of infection is the hallmark of type III prostatitis (22). CPPS has been used as an inclusive term of both interstitial cystitis/painful bladder syndrome and CP (8). Past studies revealed the role of mast cells in the induction of cystitis pain (37). Enhanced nerve fiber expression with differential innervation on dorsal and lateral prostate was a proposed mechanism of pelvic pain in a previous model of EAP (38). Although we did not explore the role of mast cells in our study, the overexpression of TNF-α in immunized mice was striking. The basis of pelvic pain could be local neuroinflammation induced by local cytokine production and autoimmune/inflammatory processes. The role of TNF-α in neuroinflammation, peripheral sensitization, and afferent hypersensitivity is well established. An exaggerated “sterile” inflammatory response, including a persistently elevated proinflammatory cytokine profile, delayed resolution of the inflammatory cascade, and depressed anti-inflammatory cytokine expression, may contribute to the onset and maintenance of pelvic pain in CPPS. As a pluripotent cytokine, TNF-α activates an inflammatory cytokine cascade and the release of proinflammatory cytokines IL-1β, IL-6, and IL-8 (7, 32, 45). Additionally, TNF-α is involved in hypernociception during antigen-induced inflammation (7) and induces

**Fig. 4.** Micturition abnormalities in male SWXJ mice immunized with p25 99–118. A: 24-h micturition frequencies were significantly higher 9 wk after immunization of male SWXJ mice with p25 99–118 compared with control mice immunized with CFA (left; *P* = 0.004). Inversely, mean urine output/micturition was significantly lower in p25 99–118-immunized mice compared with control mice (middle; *P* = 0.001). Twenty-four hour fluid ingestion (water + milk) did not differ significantly between groups (right) (*n* = 5 per group). All values are presented as means ± SD. B: representative frequency volume chart traces of individual mice 9 wk after immunization with p25 99–118 peptide (left) or CFA (right). Each vertical line represents a micturition event, and the height of each vertical line indicates the micturition output in grams.

**Fig. 5.** Pelvic pain assessment. Referred hyperalgesia and tactile allodynia were examined with von Frey filaments applied to the pelvic region. Mice immunized with p25 99–118 developed chronic pelvic pain, as indicated by a decreased threshold of pain response to stimulus on the pelvic region, as the meaning of referred pain of the prostate organ, compared with CFA-treated mice. Values in the graph are presented as means ± SD. Estimated 50% response thresholds ± SD for p25 99–118-immunized, CFA-injected, and naïve mice were 0.086 ± 0.065, 1.21 ± 0.88, and 1.81 ± 0.94 g of force, respectively. Comparisons of 50% thresholds by unpaired *t*-test yielded *P* = 0.0030 for p25 99–118-immunized vs. CFA mice, using Welch’s correction; no significant difference between CFA-treated and naïve mice was found. ANOVA of the 50% thresholds with the Tukey multiple-comparison test also revealed significant differences between p25 99–118 mice and either CFA-treated or naïve mice, but not between CFA and naïve mice.
hyperalgesia (17, 32). Increased TNF-α levels may also lead to upregulation of voltage-gated sodium channels (Nav1.3 and Nav1.8) in uninjured dorsal root ganglion neurons following neuronal injury and neuroinflammation; implicating injured and uninjured neurons in neuropathic pain (12). Prolonged production of TNF-α may mediate persistent “sterile” secondary inflammation. Clinical studies involving anti-inflammatory treatments, such as infliximab for CPPS, could be a new treatment pathway.

Voiding symptoms associated with prostatitis could be a reflection of prostatic urethral afferent hypersensitivity or bladder outlet obstruction. The former is suggested by our finding that the bladder was completely devoid of any type-1 or -2 inflammatory changes. However, confirmation will require additional studies, such as simultaneous cystometry and electromyography of the bladder outlet.

The role of inflammation in the sterile environment of the prostate in CPPS is not clear. Recent data, however, indicate that androgen-modulated disruption of the tight junction architecture of prostatic epithelial cells may contribute to development of inflammation and/or autoantigen exposure (29). The inciting event for an eventual self-sustaining mechanism could include prostatic inflammation, sexually transmitted disease, voiding dysfunction and reflex, trauma, and/or hormonal imbalance. Self-sustained immune reactions directed toward prostatic autoantigen (27) or nonprostatic antigens, such as spermatozoa (34), could also be mechanisms. Spermine-binding protein, the source of p25 99–118, is a highly androgen-dependent protein expressed in ventral lateral prostate. Prostate injury from any of the described insults could expose prostatic antigen to immune recognition and sustained immune activity. Genetic background also plays a significant role (21).

To our knowledge, this is the first report to show close resemblance to the human CP/CPPS clinical phenotype in an animal model by inducing an autoimmune response to a prostate-specific peptide or protein. This novel animal model provides a tool for studying both pathogenesis and new therapeutic agents in CP/CPPS and gives credence to the autoimmune theory of chronic prostatitis and to the possibility that the target antigen of the autoimmune response could be of prostatic origin.

Our findings show that a clinically powerful autoimmune response occurs in mice immunized with p25 99–118 that is specific to prostate tissue. The resultant autoimmunity is characterized by urinary frequency, decreased urine output per void, and pelvic pain-recognized phenotypes of CP/CPPS. Further characterization of our autoimmune prostatitis model of CP/CPPS should include characterization of the mechanisms of pelvic pain and further assessment of prostate epithelium damage.

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REFERENCES


DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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