24 MAY 2016

MEMORANDUM FOR TRS
ATTN: MAJ KATHERINE S TILLE

FROM: 59 MDW/SGVU

SUBJECT: Professional Presentation Approval

1. Your paper, entitled **Difficult Stinging Insect Immunization** presented at/published to **World Allergy Organization-Online Interactive Difficult Case Study** with MDWI 41-108, and has been assigned local file #16220.

2. Pertinent biographic information (name of author(s), title, etc.) has been entered into our computer file. Please advise us (by phone or mail) that your presentation was given. At that time, we will need the date (month, day and year) along with the location of your presentation. It is important to update this information so that we can provide quality support for you, your department, and the Medical Center commander. This information is used to document the scholarly activities of our professional staff and students, which is an essential component of Wilford Hall Ambulatory Surgical Center (WHASC) internship and residency programs.

3. Please know that if you are a Graduate Health Sciences Education student and your department has told you they cannot fund your publication, the 59th Clinical Research Division may pay for your basic journal publishing charges (to include costs for tables and black and white photos). We cannot pay for reprints. If you are 59 MDW staff member, we can forward your request for funds to the designated wing POC.

4. Congratulations, and thank you for your efforts and time. Your contributions are vital to the medical mission. We look forward to assisting you in your future publication/presentation efforts.

[Signature]

LINDA STEEL-GOODWIN, Col, USAF, BSC
Director, Clinical Investigations & Research Support

*Warrior Medics – Mission Ready – Patient Focused*
INSTRUCTIONS
USE ONLY THE MOST CURRENT 59 MDW FORM 3039 LOCATED ON AF E-PUBLISHING

1. The author must complete page two of this form:
   a. In Section 2, add the funding source for your study [e.g., 59 MDW CRD Graduate Health Sciences Education (GHSE) (SGS O&M), SG5 R&D, Tri-Service Nursing Research Program (TSNRP), Defense Medical Research & Development Program (DMRDP); NIH; Congressionally Directed Medical Research Program (CDMRP); Grants; etc.]
   b. In Section 2, there may be funding available for journal costs, if your department is not paying for figures, tables or photographs for your publication. Please state "YES" or "NO" in Section 2 of the form, if you need publication funding support.

2. Print your name, rank/grade, sign and date the form in the author's signature block or use an electronic signature.

3. Attach a copy of the 59 MDW IRB or IACUC approval letter for the research related study. If this is a technical publication/presentation, state the type (e.g. case report, QA/QI study, program evaluation study, informational report/briefing, etc.) in the "Protocol Title" box.

4. Attach a copy of your abstract, paper, poster, and other supporting documentation.

5. Save and forward, via email, the processing form and all supporting documentation to your unit commander, program director or immediate supervisor for review/approval.

6. On page 2, have either your unit commander, program director or immediate supervisor:
   a. Print their name, rank/grade, title; sign and date the form in the approving authority's signature block or use an electronic signature.

7. Submit your completed form and all supporting documentation to the CRD for processing (59crdpubsres@us.af.mil). If you have any questions or concerns, please contact the 59 CRD/ Publications and Presentations Section at 292-7141 for assistance.

8. The 59 CRD/Publications and Presentations Section will route the request form to clinical investigations, 502 ISG/JAC (Ethics Review) and Public Affairs (59 MDW/PA) for review and then forward you a final letter of approval or disapproval.

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10. If your manuscript is accepted for scientific publication, please contact the 59 CRD/Publications and Presentations Section at 292-7141. This information is reported to the 59 MDW/CC. All medical research or technical information publications/presentations must be reported to the Defense Technical Information Center (DTIC). See 59 MDW 41-108, Presentation and Publication of Medical and Technical Papers, for additional information.

NOTE: All abstracts, papers, posters, etc., should contain the following disclaimer statement:
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NOTE: All abstracts, papers, posters, etc., should contain the following disclaimer statement for research involving humans:
"The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and DODI 3216.02_AFI 40-402."

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"The experiments reported herein were conducted according to the principles set forth in the National Institute of Health Publication No. 80-23, Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966, as amended."
PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

1. TO: CLINICAL RESEARCH

2. FROM: (Author's Name, Rank, Grade, Office Symbol)
   Katherine S Tille, Maj, O-4, 59 TRS

3. GME/GHSE STUDENT: ☐ YES ☐ NO
   N/A

4. PROTOCOL NUMBER:

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6. TITLE OF MATERIAL TO BE PUBLISHED OR PRESENTED:
   Difficult Stinging Insect Immunization

7. FUNDING RECEIVED FOR THIS STUDY? ☐ YES ☑ NO
   FUNDING SOURCE:

8. DO YOU NEED FUNDING SUPPORT FOR PUBLICATION PURPOSES? ☐ YES ☑ NO

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       World Allergy Organization - online interactive difficult case study"

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    **NOTE:** All publications/presentations are required to be placed in the Defense Technical Information Center (DTIC).

   DATE
   July 01, 2016

13. 59 MDW PRIMARY POINT OF CONTACT (Last Name, First Name, M.I., email)
    Tille, Katherine S.  katherine.tille@us.af.mil

14. DUTY PHONE/PAGER NUMBER
    210-292-4278

15. AUTHORSHIP AND CO-AUTHOR(S) List in the order they will appear in the manuscript.

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I CERTIFY ANY HUMAN OR ANIMAL RESEARCH RELATED STUDIES WERE APPROVED AND PERFORMED IN STRICT ACCORDANCE WITH 32 CFR 219, AFMAN 40-401_IP, AND 59 MDW 41-108. I HAVE READ THE FINAL VERSION OF THE ATTACHED MATERIAL AND CERTIFY THAT IT IS AN ACCURATE MANUSCRIPT FOR PUBLICATION AND/OR PRESENTATION.

16. AUTHOR'S PRINTED NAME, RANK, GRADE
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17. AUTHOR'S SIGNATURE
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18. DATE
    17 May 2016

19. APPROVING AUTHORITY'S PRINTED NAME, RANK, TITLE
    Tonya S. Rans, 0-5, Program Director, Allergy/Immunology

20. APPROVING AUTHORITY'S SIGNATURE
    Rans, Tonya S. 10812603031

21. DATE
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<tr>
<td>Rocky Calcote, PhD, Clinical Research Administrator</td>
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<td>Christopher Carwile, TSgt/E-6, NCOIC, PA</td>
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Difficult Stinging Insect Immunization

- TM Freeman
- KS Tille, AL Parker

- Edited by Bob Lanier MD
  - University of North Texas
The patient is a 25-year-old woman with a prior history of allergic asthma.

She has had at least five episodes of anaphylaxis (involving immediate onset urticaria, globus, rhinitis, asthma) while living in the United States.

She reports for allergy evaluation and has skin test positivity to pollens, dog, dust mite, and fire ant. The fire in sensitivity is positive at 1:20,000 ID wheal/flare 5/30

A decision was made to initiate allergy immunotherapy with whole body extract against fire ants.

The course was a stormy one.
Choices in complicated insect immunotherapy

- Discontinue her immunotherapy
- Obtain a baseline serum tryptase
- Reduce the dose of IFA/WBE
- Reduce the dose of AIT
- Initiate a pre-treatment regimen
Here we go....

- 20 minutes after the dose of allergy immunotherapy 0.25 ml (1:1000 volumes/volume) and WBE of .25 ml (1:200,000 weight/volume) to develop significant symptoms including ocular pruritus and injection, urticaria, globus, and drop in pulmonary function of 12% FEV1.
- WAO severity grade 3
- she had an immediate response to epinephrine, all symptoms were resolved within an hour.

- So what would you do now?
That's possible– Sometimes prudent

• However, when living in endemic area exposure is virtually certain. Each patient and the doctor will ascertain the risk of continuing, but education and early management of any anaphylaxis is absolutely crucial. In addition because of the rapid onset of this problem, a convenient source of epinephrine should be kept with this patient at all times.

• Most allergist will keep on trying:
• **Choices in complicated insect immunotherapy**
Tryptase in insect sensitivity

You should absolutely get tryptase level


- **OBJECTIVE:** Our aim was to evaluate the association of baseline serum tryptase concentrations and other variables routinely recorded during patient evaluation with the frequency of past severe anaphylaxis after a field sting.

- **METHODS:** In this observational multicenter study, we enrolled 962 patients with established bee or vespid venom allergy who had a systemic reaction after a field sting. Data were collected on tryptase concentration, age, sex, culprit insect, cardiovascular medication, and the number of preceding minor systemic reactions before the index field sting. A severe reaction was defined as anaphylactic shock, loss of consciousness, or cardiopulmonary arrest. The index sting was defined as the hitherto first, most severe systemic field-sting reaction. Relative rates were calculated with generalized additive models.

- **RESULTS:** Two hundred six (21.4%) patients had a severe anaphylactic reaction after a field sting. The frequency of this event increased significantly with higher tryptase concentrations (nonlinear association). Other factors significantly associated with severe reactions after a field sting were vespid venom allergy, older age, male sex, angiotensin-converting enzyme inhibitor medication, and 1 or more preceding field stings with a less severe systemic reaction.

- **CONCLUSION:** In patients with honeybee or vespid venom allergy, baseline serum tryptase concentrations are associated with the risk for severe anaphylactic reactions. Preventive measures should include substitution of angiotensin-converting enzyme inhibitors

Her tryptase level 4ng/l (normal)  IgE 69kU/l
You could do that

- But it might take a long time to reach dose that's capable of inducing protection.
- What about pre-treatment?
  - Venom-specific immunotherapy (VIT) is considered for the treatment of patients with IgE-mediated systemic allergic reactions (SARs) after developing a Hymenoptera venom allergy. Tolerance is achieved in a majority of patients after only a few days or even hours of rush immunotherapy. After VIT discontinuation, the allergy returns in up to 15% of patients. During VIT, the majority of patients have local reactions at the site of venom injections. SARs to VIT are much more frequent in honeybee-treated patients than in wasp-treated patients. Increased baseline serum tryptase and increased allergen-specific sensitivity of basophils are other factors that might be associated with systemic reactions (SRs) during VIT. Severe SRs occur mainly during the build-up phase but can also occur in the maintenance phase of the VIT, even in patients with a well-tolerated dose-increase phase. Pre-treatment with humanized anti-IgE antibodies (omalizumab) is effective in patients with repeated SARs; however, this use of omalizumab is off-label. In highly exposed patients with a history of very severe reactions, there are virtually no absolute contraindications for VIT.
Okay, we pretreat with Omalizumab

- Omalizumab is used 150 mg SQ monthly for two months. We know the free IgE drops very quickly.
- **However,**
- 30 minutes after .15 ml WBE 1:2,000,000 weight/volume, she developed ocular pruritus, rhinorrhea, chest tightness, tingling, and a 9% drop in pulmonary functions
- WHO grade 2
- immediate response to epinephrine, symptoms gone within an hour
You have a very sensitive patient be careful

- This patient was admitted to the ICU.
- 3 day Pre medications
- included cetirizine 10 mg twice a day, ranitidine 150 mg TID
- prednisone 30 mg Q d
- What are the chances of an easy course?
  - 75%
  - 10%
Careful, careful

- Day one – ocular pruritus and injection after 1: 200,000 weight/volume responded to antihistamines

- Day 2 – ocular antihistamine drops added prior to injection

- Subjective symptoms of ocular and pharyngeal pruritus, nasal congestion and sinus pressure self resolved
- Reached 0.3 ML of 1 to 200 weight by volume
- maintenance dose given two weeks later

- but there's more to the story.....
She became pregnant later

- Omalizumab—pregnancy category B — WBE IT continued throughout pregnancy.
- Delivered healthy male term
- no reactions to IFA after 15 months of therapy
- Read the whole story here

[Imported fire ant rush desensitization using omalizumab and a premedication regimen. Tille KS, Parker AL. Ann Allergy Asthma Immunol. 2014 Nov;113(5):574-6]
Thanks to Dr. Freeman Dr. Tille, and Dr. Parker

"The views expressed are those of the authors and do not reflect the official views or policy of the US Department of Defense or its Components".