

Ideas for Educating Clinicians

Ideas for Future Clinical Trials

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Goals of this Talk

- Suggest some ways that clinicians have been informed about Angiostrongyliasis in the past and ways we might improve their knowledge in the future.
- Suggest ideas for future clinical trials.
- These are merely ideas to stimulate discussion.

Recent Review Articles

- Lv, et al. Section 12.2 in *Adv Parasitol* 72:355-63, 2010.
- Graeff-Teixeira, da Silva, et al. *Clin Microbiol Rev* 22:322-48, 2009.
- Ramirez-Avila, et al. *Clin Infect Dis* 48:322-7, 2009
- Eamsobhana, Yong. *Int J Infect Dis* 13:425-31, 2009 (Immunologic Diagnosis)
- Sawanyawisuth². *Trans R Soc Trop Med Hyg* 102:990-6, 2008 (Treatment)
- Wang, et al. *Lancet Infect Dis* 8:621-30, 2008.
- Lo Re, Gluckman. *Am J Med* 114:217-23, 2003.
- Mentz, Graeff-Teixeira. *Rev Inst Med Trop Sao Paulo* 45:179-84, 2003. (Drug Trials)

Case Reports +/- Reviews

- Tsai, et al *Intern Med* 50:771-4, 2011 (Frogs in wine)
- Ali, et al. *Travel Med Infect Dis* 6:41-4, 2008 (Belgium)
- Li, et al. *Am J Trop Med Hyg* 79:568-70, 2008. (Severe)
- Kirsch, et al. *J Neurol* 255:1102-3, 2008. (Germany)
- Leone, et al. *J Travel Med* 14:407-10, 2007 (Santo Domingo)
- Lai, et al. *Am J Trop Med Hyg* 76:399-402, 2007. (Frogs)
- Hidelaratchi, et al. *Ceylon Med J* 50:84-6, 2005 (Lizard)
- Lim, et al *J Travel Med* 11:388-90, 2004
- Hughes, et al. *Mil Med* 168:817-21, 2003 (Hawaii)

Publication of Proceedings of this Workshop

- Dr. Cowie suggested that a formal Volume be published by Univ. of Hawai'i.
 - Each presenter may submit a formal paper for this volume if they like.
- Supplement to Clinical Infectious Disease
 - A publication of IDSA
- Supplement to AJTMH
 - A publication of ASTMH
- Sponsors to pay costs of publication?
 - Grant?

Article in EID or MMWR

- Dr. Park suggested a White Paper in Emerging Infectious Diseases
 - Each talk summarized in about 1 paragraph.
 - Dr. Cowie to be first author and coordinator.
- Summary of public health implications.
 - Summarize US states & territories data.
 - Give recommendations
- MMWR article could be picked up by JAMA which would give it wide circulation.

Web Sites

- *Up To Date*: There is already a nice article on Eosinophilic Meningitis by Dr. Peter Weller here.
- *MedScape* reports on news from medical conferences.
- *WebMD* has nothing on EM or A.c.
- JABSOM reports on newsworthy events involving faculty.
- Wikipedia: the article is very limited and says almost nothing about treatment.

Press Release

- Could do a short press release on this workshop targeted at JAMA, Infectious Disease News, NEJM, American Family Physician, Websites, etc.
- These journals and websites may put a paragraph in their news sections.

Clinical Trials

- Need way to standardize severity of illness.
 - Perhaps a coma scale, APACHE score
 - Perhaps a point system, eg:
 - Altered sensorium = 1 pt.
 - Cranial Nerve abnormalities = 1 pt.
 - Motor weakness outside the head = 1 pt/
 - Ataxia = 1 pt.
 - Coma = 5 pts.
 - Point for each LP beyond fist one.

Clinical Trials

- Need way to positively identify causative organism in trials
 - Serology is limited in endemic areas due to prior exposure.
 - (Though often negative by 6 mos after infection)
 - PCR would be hard evidence of current or very recent infection.
 - (Once this has been formally validated)

Clinical Trials

- Need to see if antihelminthics given early enough would prevent or lesson severe disease.
 - Antihelminthic should probably only be used if steroids given simultaneously or prior, to block inflammatory responses.
 - But, antihelminthics may decrease migratrion that has caused deaths.
 - This may only be measurable in severe cases, such as seen with *Achatina fulica* ingestions.

Clinical trials

- Days after infection may influence response to therapy, so we need to stratify for this in data analysis.
 - First molt (L3-L4): d5-6 post infection (in rats)
 - Second molt (L4-L5): d 11-13 pi
 - Worms enter subarachnoid space: d 14-28
 - Death of young adult: d 28-60?

Clinical trials

- Perhaps multicenter trial could be set up for hospitals in Polynesia (Hawaii, Samoa, Tahiti), to look at EM caused by *A. fulica* ingestions.
 - These seem to be more severe, possibly due to higher worm burdens.
- Problem is: probably not enough numbers of cases for statistical power.

Clinical Trials

- Could Ivermectin be tested in place of albendazole?
 - Pros: rapidly effective against many helminths, including *Strongyloides*.
 - Cons:
 - poor CNS penetration
 - Significant CNS side effects
- Are there other anti-helminthic agents worthy of testing?
 - Lavamisole?

Clinical Trials

- Comparison of Prednisolone with and without Albendazole, **given early in disease.**
 - Days since ingestion $< x$. ($<14?$)
 - $N = > 55$
 - Score severity of illness.
 - Serial LPs: minimum of 3?

Pathophysiology

- We need to know the actual mechanisms of neurologic injury in humans.
 - Is it increased Intracranial pressure?
 - Is it inflammatory reaction; which cytokines?
 - Is it mechanical damage from worm migration?

Pathophysiology

- We need an animal model to replicate human CNS and parasitic responses.
- Do rats have behavioral changes associated with CNS infections?

Pathophysiology

- We need to know the influence of parasite inoculum on:
 - Incubation period.
 - Severity of illness.
- We need a way to estimate the parasite inoculum after the event, when the patient presents.
 - Average parasite loads of various intermediate and paratenic hosts important in human transmission should be quantified.

Pharmacology

- We need to know if albendazole kills L3, L4, L5 or all of these, and the LD50, LD90.
- We need to know the mechanism of action of prednisolone:
 - Is it reduction in ICP?
 - Is it blunted Eosinophils or IgE?

Conclusion

- Much remains to be done.
- These were discussed further in the work out sections.