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Missouri Medicine

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About *Missouri Medicine*

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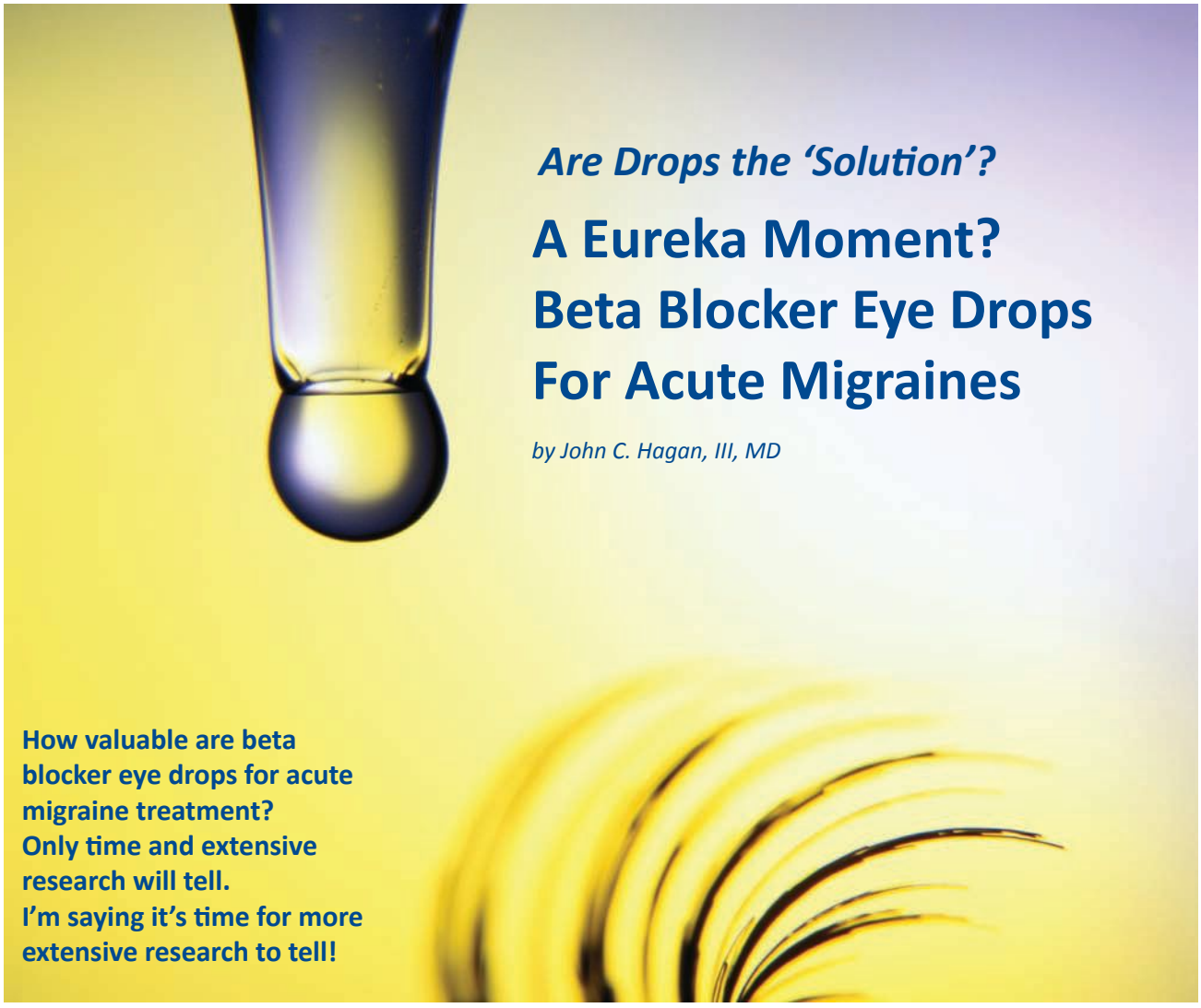
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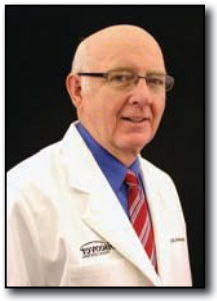


Are Drops the 'Solution'?

A Eureka Moment? Beta Blocker Eye Drops For Acute Migraines

by John C. Hagan, III, MD

How valuable are beta blocker eye drops for acute migraine treatment? Only time and extensive research will tell. I'm saying it's time for more extensive research to tell!



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This issue of *Missouri Medicine* features a novel therapy for acute migraines using inexpensive generic (e.g. $4 for 5 ml. at Walmart), widely-available, relatively safe beta blocker eye drops. The authors are Carl V. Migliazzo, MD, and myself. (See page 283). This is the largest number of successful cases to date; we summarize the previous reports and meager literature.

The first published beta blocker eye drop treatment of headache was in 1980. The author was enthusiastic and called for additional research. So have subsequent papers. Thirty-four years later the promising research has still not been conducted.

Is our enthusiasm warranted? Do beta blocker eye drops deserve to be intensively studied for acute migraine? So far the answer is an enthusiastic "yes." For chronic migraine? Possibly. As editor/co-author I chose to make peer review of our article exceptionally rigorous. The initial reviewers were a clinical neuro-ophthalmologist, an academic professor of neurology, and an academic professor of pharmacology, the latter with masked authorship. All made helpful suggestions and recommended publication. To accompany this expedited manuscript, a second set of experts were given the final version of the paper, copies of referenced

material and asked to write independent editorial critiques. Included are two professors of neurology at the University of Missouri (See page 289); a neuro-ophthalmologist from Saint Louis University (See page 294) and two nationally known headache-migraine specialists from Springfield (See page 292). Please read our article and the three editorial critiques carefully. In this editorial let me flesh out the back story of how our paper initiated and developed.

Our Eureka Moment at Iron Horse

According to popular lore Archimedes jumped out of his bath and shouted, "I have found it!" (Greek = Eureka) after he suddenly conceived of a method of detecting if Hiero II, the King of Syracuse's new gold crown, had been debased by devious goldsmiths. Other select "Eureka Moments" include: special theory of relativity (Einstein), alternating current (Tesla), television (Farnsworth), coordinate geometry (Descartes), Velcro (de Mestral) and Post-Its (Fry).

Eureka came to us this year while playing golf at our favorite course - the Iron Horse Golf Club in Leawood, Kansas. For over a decade Carl Migliazzo, MD, myself, and Chuck Lederer, MD, have pursued our golfing muse over various courses in Kansas and Missouri. Midway through a typically less than stellar round, I happened to mention that both my daughters had developed migraines in their late 30s. Carl helpfully suggested they try beta blocker eye drops as quickly as possible when a migraine started. He said he had treated a number of his patients with migraine this way including several scrub nurses and other hospital staff that learned of the novel treatment by word of mouth.

This stopped me in my tracks. "Carl, this is new knowledge; we have to write this up."

Carl and Chuck are glaucoma specialists and I have a large glaucoma segment in my adult/geriatric ophthalmology practice. Collectively the number of patients we've treated with beta blocker eye drops in the last three decades is in the tens of thousands. We knew that systemic absorption occurs and the same contraindications and side effects for beta blocker medication by mouth exist for their eye drop form. We have had many patients, because of their beta blocker eye drops, develop wheezing, chronic cough, profound fatigue, and troublesome bradycardia. We knew that chronic migraines were often treated with oral beta blockers but that they were not used successfully for acute migraine. How could we explain the success of beta blocker eye drops in acute migraine?

At this point the lure of more bad golf intervened. I offered to do a literature search and we would pick the discussion up later. The literature was scant and mostly single case reports dating back to 1980. The neurology-migraine literature confirmed prospective, controlled studies had shown oral beta blockers ineffective against acute migraine. Once again how to reconcile the success of beta blocker eye drops on some acute migraine patients?

Getting the Drop on Acute Migraines

Scores of emails, more discussion interwoven with more bad golf, hours of pondering and speculation led us to what now seems obvious. As ophthalmologists we wanted to get beta blockers into the eye to lower intra-ocular pressure but not in the blood where it might cause unwanted side effects. Research (referenced in our study) had shown that beta blocker eye drops reached therapeutic blood levels within several minutes of installation on the eye. For glaucoma patients this was considered a bad thing. For migraine patients this might be a good thing.

To minimize systemic absorption in glaucoma patients, ophthalmologists instruct patients after instilling their drops to shut their eyelids and not blink for a couple of minutes, dab excess drops away, use finger compression of the lower tear ducts, and sometimes we used drops once a day rather than the standard every 12 hours. The glaucoma pharmaceutical industry developed once daily drops, slow release gel forming drops, select beta blocker and non-beta blocker types of eye drops that had fewer side effects and/or were more effective. Presently laser trabeculoplasty treatment is ideal primary and adjunct therapy. Consequently beta blocker eye drops are used much less now than during previous decades.

Anecdotally, and not reported in our paper, when beta blocker eye drops were approved in 1978 they became the first line glaucoma treatment. Some glaucoma-migraine patients reported fewer migraines. When latanaprost (Xalatan®) was released in 2002 some patients were taken off beta blocker eye drops. Some glaucoma-migraine patients had an increase or re-occurrence of their migraines. This is also described in some of the literature we cite.

So here is where the serendipity starts. One of Dr. Migliazzo's glaucoma patients told him she found if she put in a drop of her beta blocker at the start of her acute migraine it stopped her migraine cascade in its tracks. He tried the beta blocker eye drops on other carefully selected and informed acute migraine patients. For many it worked.

"Eureka! Eureka! Eureka!" *- Archimedes*

"Chance favors the prepared mind." *- Louis Pasteur*

"Carl, this is new knowledge; we have to write this up." *- John C. Hagan, III*

Drops Reach Therapeutic Blood Levels Quickly- Pills Not so Much

So this is the hypothesis we propose: applied to the eye, beta blocker eye drops, passing through the tear ducts, reach therapeutic levels for acute migraine treatment within minutes. This is mainly via trans-nasal mucosal absorption. Theoretically, a beta blocker nasal spray might also be developed and tested. Sublingual use worked for some migrainers.

Oral beta blocker medication takes hours to achieve therapeutic blood levels and is too slow to stop the acute migraine cascade but does work when taken regularly for chronic migraine prevention. Or so it seems.

Beta Blocker Eye Drops For Other Indications

So what about using beta blocker eye drops to try and achieve rapid, therapeutic beta blockade? Attention neurologists and cardiologists.

Involuntary Stress Tremor

It is well known in ophthalmology that beta blocker eye drops instilled on the eye or taken sublingually shortly before ophthalmic microsurgery can dampen the surgeon's involuntary stress tremor. The practice allegedly is *de rigueur* in some ophthalmology training programs. Of course the usual beta blocker contra-indications exist and one well know eye surgeon told me "It works but I was almost too tired to finish my cases so I can't use them."

For non-medical use it is accepted that beta blockers in the blood will dampen stress-related tremor. Beta blockers are routinely tested for in some Olympic sports. At the last Olympics a North Korean pistol competitor was disqualified when found to have beta blockers on board to calm his shooting hand.

Essential Tremor

Oral beta blockers are a mainstay in treating essential tremor. How about testing beta blocker eye drops for intermittent treatment or for patients that were helped by oral beta blockers but developed side effects?

This is more than theoretical. I have an elderly essential tremor patient who was well controlled on oral beta blockers. She developed side effects that necessitated discontinuing her medication. I told her about our migraine paper. She asked if she might try eye drops on "bridge day" and when her grandchildren were coming to see her because her shaky hands embarrassed her. At press time her family physician is planning to do a therapeutic trial of beta blocker eye drops during an office visit.

Cardiovascular Indications

What about testing using beta blocker eye drops for conditions where rapid therapeutic levels are needed but intra-venous access not available or possible. Examples: in medical settings where IV cannot be established, first responder use, in patients that cannot swallow, in ambulances. What about having high risk heart patients keep an inexpensive bottle of beta blocker eye drops at home for emergency use with possible myocardia infarct, (chew an aspirin, take beta blocker eye drops and call 911), angina, arrhythmia? What about testing beta blockers by eye drop, nasal spray or sublingual as standard therapy for acute or chronic administration of this class of medications?

It's Time for Prospective Studies

Actually, it's long overdue for prospective, masked, controlled, randomized, adequately statistically powered studies to prove or disprove whether beta blocker eye drops are useful for treating acute, even chronic migraines. It is unlikely that the pharmaceutical industry will invest much money or resources in a generic, inexpensive eye drop. However, the NIH is offering major multi-year funding and soliciting grant proposals for novel treatment of migraine. See http://grants.nih.gov/grants/guide/pa-files/PA-14-069.html. It's also likely that thoughtful applications to foundations or funding sources with interest in migraine might finance research. There may be commercial value in some of the other proposed applications or delivery methods.

Conclusion

How valuable are beta blocker eye drops for acute migraine treatment? Only time and more extensive research will tell. I'm saying it's time for more extensive research to tell! **MM**

CASE PRESENTATIONS AND REVIEW

Beta Blocker Eye Drops For Treatment of Acute Migraine

by Carl V. Migliazzo, MD & John C. Hagan, III, MD

We report seven cases which describe the successful use of beta blocker eye drops to abort or attenuate acute migraine symptoms. If beta blocker eye drops are effective against acute migraine symptoms, this would be a welcome addition to migraine therapy.



Carl V. Migliazzo, MD, (left) is a Kansas City ophthalmologist specializing in glaucoma treatment. John C. Hagan, III, MD, MSMA member since 1977, is a Kansas City ophthalmologist.
Contact: carl@migliazzo.com and jhagan@bizkc.rr.com

Abstract

We report seven cases of successful treatment of acute migraine symptoms using beta blocker eye drops. The literature on beta blockers for acute migraine is reviewed. Oral beta blocker medication is not effective for acute migraine treatment. This is likely due to a relatively slow rate of achieving therapeutic plasma levels when taken orally. Topical beta blocker eye drops achieve therapeutic plasma levels within minutes of ocular administration which may explain their apparent effectiveness in relief of acute migraine symptoms.

Introduction

Sporadic case reports have suggested that beta blocker eye drops are effective for acute migraine treatment and chronic prevention of migraine attacks[1-5] (See Table 1 and Figure 1). Although widely prescribed for glaucoma therapy, beta blocker eye drops are rarely used for acute or chronic migraine treatment. Recent comprehensive reviews on migraine therapy do not mention the potential therapeutic value of beta-blocker eye drops.[6, 7, 8, 9]

Oral beta blocker medications are commonly and successfully used for chronic migraine prophylaxis.[7, 8,9] However, beta blocker medications taken orally are not effective in treating acute migraine.[10, 11] Topically applied beta blocker eye drops are systemically absorbed by the nasal mucosa and therapeutic plasma levels are achieved within minutes.[4, 12, 13]

In this paper we report seven cases which describe the successful use of beta blocker eye drops to abort or attenuate acute migraine symptoms. The scant published literature on using beta blocker eye drops to treat migraine is reviewed.[1-5] We present an explanation of why beta blocker medication by topical eye drop, but not by oral administration, may be effective for acute migraine treatment.

Case Presentations

Case 1

CH is a 61-year-old female who has suffered from migraines for approximately 30 years. Her typical migraine is a throbbing, right-sided pain that radiates to her neck and shoulders, occasionally associated with nausea, and a preceding visual aura. Her headache will last one to two days if not treated. Previous trials of oral medications, the names of

which she does not remember, did not give her sufficient relief, so she stopped using them. Approximately 15 years ago she began using at onset of acute migraine levobunolol 0.5% ophthalmic solution one drop in each eye along with ibuprofen 600 to 800 mg orally. She rates her headache relief as a 10 on a scale of 1 (no relief) to 10 (complete relief) since she started using topical beta blocker eye drops. She has had no side effects from the drops and only uses them for acute attacks.



Figure 1
Beta blocker eye drops are inexpensive, available worldwide, and have rapid trans-mucosal systemic absorption when taken topically. Sporadic case reports and the literature collectively [1-12] suggest that the success of beta blocker eye drops in treating acute migraine may be due to the rapidity of eye drops in achieving effective blood levels when instilled shortly after symptom onset.

Case 2

MM is a 66-year-old female who describes the onset of her migraines as throbbing, one-sided, pain sometimes lasting for up to three days. Nausea and sensitivity to light, sounds and smells are often associated with her headaches. Her symptoms began 32 years ago and for the past eight years she has used prophylactic topiramate 50 mg bid and nadolol 40 mg at bedtime. Approximately one year ago she began using topical timolol 0.5% ophthalmic solution one drop in each eye at the onset of her attack. Within 15 to 30 minutes she gets complete relief (10 on a scale of 1-10) of her symptoms. Occasionally, she will take Fioricet® with codeine along with her eye drops; most of the time does not. She has experienced no side effects from the drops and only uses them for an acute attack. She feels that the management of her migraines has been greatly improved with the addition of topical beta blocker eye drops.

Case 3

DW is 38-year-old female who first noticed the onset of her migraines about 25 years ago. She describes an acute attack as a constant pain that begins in her right temple and then radiates to a throbbing vein in her left temple. Associated symptoms include nausea, vomiting, blurred vision, light and noise sensitivity, diaphoresis, and confused mentation. Duration of attacks without treatment is 24 hours or more. She has tried several different oral drugs for the past 14 years and they would take several hours before she had any relief of symptoms. Most of the time she tries to fall asleep. Two years ago she began using topical timolol 0.25% ophthalmic solution one drop in each eye at the onset of a migraine. She noticed some slight shortness of breath and now only uses one drop in one eye and has no side effects. Symptom relief begins in about 10 to 20 minutes and she rates her relief as an 8 on a scale of 1 – 10. Although her symptoms are not completely relieved with one drop, she is at least able to function. If a migraine is particularly severe, she will take oral analgesic medications after instilling an eye drop.

Case 4

EM is a 61-year-old female who describes the onset of her migraines as a visual aura with a classic fortification scotoma that begins with blurred central vision then expands towards the periphery until her central vision clears. This is followed by a one-sided, constant headache associated with nausea, light and sound sensitivity, and pain behind her eyes. Untreated duration of these attacks is 24 hours or more. Prior to using eye drops, oral ibuprofen would give partial relief in about 30 to 60 minutes. Often, she would go to bed and try to fall asleep. About five years ago she began using topical timolol 0.5% ophthalmic solution one drop in each eye at the first onset of a visual aura. Within two minutes she rates her relief of symptoms as 9.5 on a scale of 1 – 10. If she does not instill the drops at the very first visual symptom, relief may take longer, but usually within 10 to 20 minutes. She continues to take ibuprofen along with her topical beta blocker eye drops and has had no systemic or ocular symptoms from the eye drops. She only uses the drops for an acute attack and does not use them prophylactically.

Case 5

JW is a 63-year-old female who had the onset of migraines 27 years ago. She describes a sudden, left-sided, pounding and throbbing temple pain that radiates into her left ear and jaw. Associated nausea, vomiting, and sound sensitivity will occasionally occur. She had previously tried many different oral medications and alternative treatments for her migraines including acupuncture, chiropractic manipulation, various diets, and a nasal-palatine block. Oral medications would take

Table 1

Topical Beta-blockers Commonly Used for Glaucoma Treatment

Generic Name	Trade Name	Receptors	Concentration	Dose	Clinical Pearl
Timolol	Timoptic®	Beta 1 and 2	0.25%, 0.50%	BID	Former gold standard
Timolol	Timpotic XE®	Beta 1 and 2	0.25%, 0.50%	QD	XE is gel form
Timolol	Betimol®	Beta 1 and 2	0.25%, 0.50%	BID	Hemihydrate
Betaxolol	Betoptic®	Beta 1	0.50%	BID	Betaxon (newer)
Betaxolol	Betoptic S®	Beta 1	0.25% (susp)	BID	More selective
Levobunolol	Betagan®	Beta 1 and 2	0.25%, 0.50%	BID or QD	Longest half-life
Meti-pranolol	Optipranolol®	Beta 1 and 2	0.30%	BID	Rare uveitis risk
Carteolol	Ocupress®	Beta 1 and 2	1.0%	BID	Intrinsic sympathomimetic activity

up to 60 minutes to obtain partial or complete relief of symptoms. She is currently taking duloxetine and topiramate for migraine prophylaxis which has reduced the frequency of her attacks. Approximately six years ago she began using topical levobunolol 0.5% ophthalmic solution two drops in each eye at the first onset of symptoms. She will repeat the drops in 15 minutes if she doesn't get meaningful relief after the first set. She gets complete relief of symptoms in about 70 – 80 % of acute migraine attacks with levobunolol eye drops alone. If she obtained no relief, she would use oral medication. She tried using daily, topical levobunolol prophylactically, but it did not eliminate her attacks, so daily use was discontinued. No systemic or ocular side effects have been noted with topical beta blocker use.

Case 6

VB is a 57-year-old female with onset of frequent migraines at age five. She describes sparkling light aura lasting 10-20 minutes followed by severe right-sided pain above the eye, radiating into the temple and head. She had photophobia, nausea and difficulty with thinking clearly. The migraine would often last four to six hours followed by a "migraine hang-over" lasting a day or two. She treated these with Excedrin and lying quietly in a dark room. In her mid 30s she began using timolol 0.5% ophthalmic solution one or two drops sublingually at the first onset of her aura. She experienced improvement of her symptoms in about 10 minutes with complete relief in 30 to 45 minutes. Although she has asthma, she experienced no breathing problems or other side effects. She used the beta blocker eye drops till her mid to late 40s when she ceased to have further migraines.

Case 7

SW is a 76-year-old female whose migraines began in high school. Her typical attack begins with a visual aura of a "broken glass/mirror" followed by a left temporal pain that increases in intensity and radiates to both sides of her head. Nausea, vomiting, garbled speech, and post-migraine fatigue are often associated with her headaches. Symptoms would typically last from 24 to 72 hours. She began using topical timolol 0.5%, one drop in each eye, approximately five years ago. If she instills the drops within a few minutes from the onset of an aura, her symptom relief is immediate and complete. If there is a delay in eye drop instillation, she rates her relief as an 8 on a scale of 1 – 10. She does not take any oral medications along with her drops and she has not had any side effects.

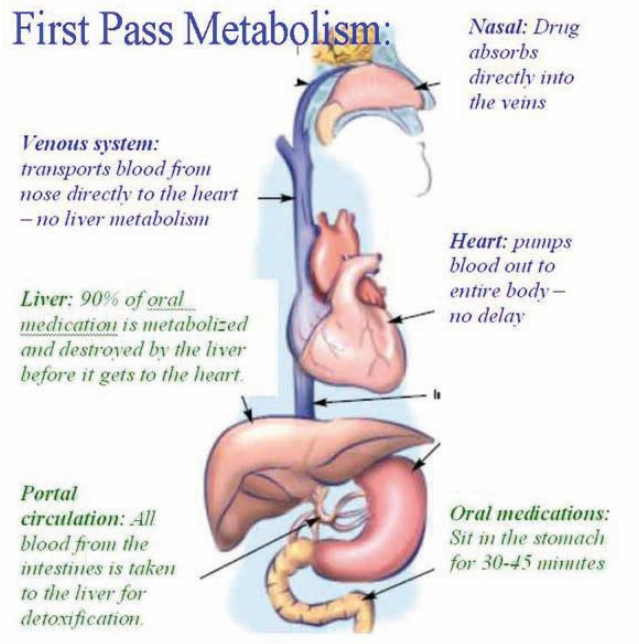
Discussion

The literature on using beta blocker eye drops to treat migraine is sparse. A 1980 report stated that topical timolol 0.5% relieved symptoms of Horton cluster headaches compared with placebo in four patients.[1] In 1999, a 59-year-old female with migraine and glaucoma had no improvement in migraine over 10 years on timolol drops although it controlled her glaucoma. She had a dramatic improvement of her migraines when carteolol beta blocker eye drops were substituted for timolol for better glaucoma control.[2] In 2000, a 4-year-old girl with ophthalmoplegic migraine was treated successfully with 0.25% timolol maleate bid.[3] A 64-year-old woman with classic migraine resistant to standard oral therapy was started on timolol maleate 0.5% eye drops to both eyes. She had been migraine free for 18 years when the case

was reported in 2004.[4] Lastly, a 52-year-old male with "normal tension glaucoma" and migraines had relief from his headaches when placed on Timoptol-LA once per day for glaucoma therapy.[5]

Physicians often consider migraine prophylaxis when three or more attacks occur per month. Other indications include intolerable migrainous side effects that may constitute a danger to the patient or unsuccessful acute migraine therapy.[6, 7] Two of the four FDA approved oral drugs for migraine prophylaxis are beta blockers (timolol and propranolol).[7] The non-beta blockers are topiramate and divalproex.[7] Three other beta blockers are often used 'off label' (atenolol, metroprolol and nadalol) for chronic migraine prevention. Neurologists and general practitioners preferentially used oral beta blockers for migraine prophylaxis in a European study.[8] However, two double-blind, and placebo controlled studies have shown that oral propranolol has no significant effect in aborting acute attacks of migraine when compared with placebo.[10, 11]

Figure 2



The success of beta blocker eye drops in treating acute migraine may be due to the rapidity of eye drops in achieving effective blood levels. Eye drops pass directly into circulation. Therapeutic blood levels occur in 4-10 minutes. Oral beta blocker medication is subject to first pass metabolism and takes several hours to reach therapeutic blood levels.
Source: http://intranasal.net

Timolol ophthalmic solution was the first topical beta blocker approved by the FDA for the treatment of glaucoma in 1978.[9] It is a highly effective glaucoma medication with few ocular side effects and was for years the first line treatment for glaucoma world-wide. Several other ophthalmic beta blocking eye drops were subsequently approved. All of them have been used extensively (See Table 1). Beta blocker eye drops achieve pharmacologically active concentrations in the plasma.[4] Ophthalmic beta blocker solutions applied topically to the eye are rapidly absorbed into the systemic circulation primarily by lacrimal duct transit into nasopharyngeal mucosa and, to a lesser extent, the conjunctival epithelium and the gastro-intestinal tract.[12] Pharmacokinetic analysis has shown that one drop of timolol ophthalmic solution 0.5% in each eye will reach a plasma concentration of 2 ng/ml within 10-15 minutes.[10] Beta 1 and beta 2 receptor blockade has been calculated to be approximately 80% with this plasma concentration.[10] Our case reports support these observations with acute migraine symptom relief within minutes of beta blocker eye drop instillation especially if the drops are instilled as soon as possible after symptom onset.

Our cases and the literature collectively[1-12] suggest that the success of beta blocker eye drops in treating acute migraine may be due to the rapidity of eye drops in achieving effective blood levels. Oral beta blocker medication is subject to the "one pass effect,"[16] i.e. inactivation of alimentary beta blocker by bacterial, gut and gut wall enzymes and hepatic metabolism (See Figure 2). In chronic migraine therapy, daily oral beta blocker medication attains effective blood levels for migraine prevention within hours to days. This would also explain the effectiveness of oral beta blockers on chronic migraine prevention.

Beta Blocker Eye Drops Therapy for Acute Migraine

A migraine patient reported to one of the authors (CVM) that instilling a drop of beta blocker eye drop at the earliest onset of her aura aborted the migraine attack. Subsequently other acute migraine patients have been successfully treated with beta blocker eye drops taken as early as possible at migraine symptom onset. Seven of them filled out a questionnaire which is used as the basis for these case reports. The others

Table 2
Case Summaries

Case	Typical Symptoms	Duration	Concurrent oral meds	Eye drops	Rated symptom relief with eye drops (1-10)	Side effects
61 y/o female	Visual aura, right sided pain, nausea	1 – 2 days	Ibuprofen	Levobunolol 0.5% both eyes	10	none
66 y/o female	Unilateral headache, light, sound, and smell sensitivity	1 – 3 days	Topiramate and nadolol daily	Timolol 0.5% both eyes	10	none
38 y/o female	Right-sided headache, nausea, vomiting, light and sound sensitivity, confused mentation	24 hrs or more	Occasional analgesics	Timolol 0.25% one eye	8	Shortness of breath if drops in both eyes
61 y/o female	Visual aura, unilateral headache, nausea, light and sound sensitivity	24 hrs or more	Ibuprofen	Timolol 0.5% both eyes	9.5	none
63 y/o female	Unilateral headache, nausea, vomiting, sound sensitivity	Unknown	Duloxetine, topiramate	Levobunolol 0.5% both eyes	8 - 10	none
57 y/o female	Visual aura, unilateral headache, nausea, photophobia, confused mentation	4 – 6 hrs or more	none	Timolol 0.5% one or two drops sublingual	10	none
76 yo female	Visual aura, unilateral radiating headache, nausea, vomiting, garbled speech	24 – 72 hrs	None	Timolol 0.5% both eyes	10	none

did not complete the form or could not be specifically identified. Table 2 summarizes our case reports described in detail above.

Patients undergo a medical history and ophthalmic examination prior to advising this method of treatment to ensure that they do not have contra-indications to beta blocker use.[14, 15] As in glaucoma patients, the potential pulmonary and cardiovascular side-effects are discussed especially slowing of the pulse, wheezing and/or difficulty breathing. Patients are told that the eye drops are typically used in glaucoma patients and have been helpful in some patients who suffer from

acute migraine attacks. They are advised to read the package insert and call if they have any questions or if symptoms develop. Treated patients have had an established, usually longstanding, diagnosis of migraine. Their physicians are informed of their acute migraine beta blocker eye drop use. New cases with symptoms suggestive of migraine are referred to their physicians for appropriate work-up to confirm the diagnosis.

Migraine patients typically put one drop of timolol ophthalmic solution 0.5% or a comparable beta blocker in each eye as early as possible in the aura or migraine evolution. Patients are advised to blink vigorously several times which encourages drop passage into the lacrimal drainage duct for enhanced systemic absorption. If no relief or partial relief of migraine symptoms occurs after 10 minutes, patients are instructed to instill another drop in each eye. If the drops do not work at this point, they are discontinued and other acute migraine medications previously prescribed by their physicians are utilized.

All of our reported cases had a complete eye examination by an ophthalmologist before therapy was started. Ideally before starting beta blocker eye drop therapy physicians should refer their patients to an ophthalmologist for a comprehensive eye examination. It is important to exclude glaucoma, lacrimal stenosis, punctal occlusion or external ocular disease.

Conclusion

Beta blocker eye drops (See Figure 1) are inexpensive, available worldwide, and have rapid trans-mucosal systemic absorption when taken topically. Used acutely at the start of a migraine, they would be expected to cause fewer side effects than oral beta blockers and other potent prescription migraine medication. If beta blocker eye drops are effective against acute migraine symptoms, this would be a welcome addition to migraine therapy.

As with this paper, all previous publications describing the beneficial effects of beta blocker eye drops for the treatment of migraine headaches are small case reports. No controlled, prospective or retrospective study has been done on acute migraine treatment by beta blocker eye drops; such a study was first called for in 1999.[2] A prospective, masked, placebo controlled study, perhaps with a cross-over design, is both feasible and warranted.

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Disclosure

None reported.

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EDITORIAL CRITIQUE: NEUROLOGY

Beta Blocking Eye Drops in Acute Migraine: A Novel Use of an Old Drug

by Brandi R. French, MD & Niranjan N. Singh, MD

The NIH has issued a call for research on migraine. Beta blocker eye drops and could pose an attractive and feasible area for study of a new use of an old medication.





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Migraine affects 29.5 million Americans and according to the American Migraine Prevalence and Prevention study (AMPP), the largest study of migraine sufferers, approximately 12% American have migraines with higher prevalence in woman than man, 17% vs. 6% respectively.[1] Migraine is usually characterized by one-sided pulsating pain with nausea, vomiting and sensitivity to light and noise. A minority of the migraine sufferers have aura, visual displays before or during attack. Estimates vary anywhere from 2-61 working days lost per patient per year due to migraine, depending on the population studied.[2] Numerous print and online resources are dedicated to those seeking permanent disability due to migraine. From these data, it is clear that both long term preventive and acute abortive therapy must continue to advance, and novel therapies must be sought.

In this issue of *Missouri Medicine*, Migliazzo and Hagan (See page 283) present a series of seven of their own patients who were treated with topical beta blocker eye drops for treatment of acute migraine attacks. All patients were long-standing migraine sufferers with well-established patterns of pain and response to standard acute abortive medications. There was rough equivalency of migraine patients with and without aura, with only one patient having additional neurologic deficits (garbled speech) associated with attacks. All patients were screened with a medical history and ophthalmological evaluation prior to instituting therapy, and were advised of the possibility of systemic side effects. Patients reported, via questionnaire, that there was relief of pain within minutes of instilling eye drops, with infrequent need for repeat drops though some used coincident NSAIDS. The authors correctly point out that this is a novel use of beta blocker eye drops with only sporadic reports in the literature of similar use. Of these, only one was a small series of four patients, the rest being case reports.[3, 4, 5]

It is noted in this paper that the use of oral beta blockers is useful in, and FDA approved for, migraine prophylaxis[6], though ineffective in acute abortive treatment.[7, 8] It is postulated that this differing usefulness of beta blockers in migraine treatment depending upon the route of administration is due to the speed by which the medication achieves a therapeutic blood level. It can take hours to days for oral administration though only minutes with the eyedrop route.[8, 9]

Current acute abortive therapy consists of conservative over-the-counter analgesics and NSAIDS, as well as newer caffeine-containing "for migraine" preparations combined with analgesics; these can be associated with unwelcome side-effects, particularly in those with GI illness. Prescription medications such as ergotamine and triptans have several limitations, most important being patients with coronary disease, stroke and peripheral vascular disease. This presents a unique challenge when treating older patients, or those with significant vascular disease, who suffer persistent migraine pain. The abuse potential of some of prescription remedies, or propensity for rebound phenomenon also poses unique challenges in the acute and chronic treatment of migraine. There is an ongoing search for an effective antimigraine treatment which works faster, can be used at home and is devoid of these unwanted side effects.[1, 10]

Off-label rapidly acting intravenous medications include valproate and verapamil. It is postulated that the rapid attainment of therapeutic levels of these medications is responsible for the rapid resolution of migraine pain. Small trials of intravenous valproate provide conflicting results regarding efficacy.[11,12] Case series of verapamil primarily address hemiplegic rather than common or classic migraine, though tend to be supportive.[13,14] We have located no reports thus far regarding the use of intravenous beta blocker agents for acute migraine control. However, the intravenous form of delivery is inconvenient, necessitating office, or more commonly emergency department visits, and by its very nature patients will have suffered hours prior to achieving any form of relief. A fast-acting alternate form of delivery could be ideal.

The authors of this paper emphasize the safety of beta blocker drops, and all patients were given a medical history interview and ophthalmological examination. The only reported side effect in the authors' population was shortness of breath with multiple drops. The literature indicates additional common side effects being generally mild hypotension and bradycardia, which occasionally can be dose-limiting.[9, 15]

There are several strengths of this paper. This is the largest case series review of patients treated with beta blocking eye drops for the indication of acute migraine, with no stronger study designs available in the literature. There is a clear demonstration of efficacy in a well-established migraine population, with documentation of the duration of migraine history and prior response, or importantly lack of response to traditional acute abortive therapies. Compelling argument is made for the efficacy of beta blockers possibly due to route of administration and lack of first pass effect[16], with coincident rapid escalation of plasma level of drug.[9] Further mechanism of action is unknown or unclear, and parallels the lack of clear known mechanism for other off label agents.

The weaknesses of this paper involve study design with it being a case series, with a small number of patients, and lack of an available control. The authors have described seven cases of migraine, five of them are more than 60 years of age. Timolol eye drops has been used in five of them while levobunolol in two patients. Five of seven patients have also used NSAIDs acutely. The frequency of use of the eye drops is not reported. Beta blockers are known to have prophylactic properties for migraine. Additionally, while there was no neurologist's documentation of the migraine diagnosis, the description of symptoms provided for each patient helps the reader draw the diagnostic conclusion of migraine with or without aura.

This therapy is attractive due to its possible efficacy as a novel agent for the acute treatment of migraine. The widespread use of beta blocking eye drops do indicate that it is safe across a broad spectrum of the population.[9, 15] The route of administration is both easy and convenient, with the added benefit of being inexpensive and widely available. Additionally and importantly, it may be more generalizable to the elderly or those with cerebrovascular or cardiovascular disease, a known contraindication to triptans or other sympathomimetics.[10] While migraine tends to wane in the elderly, a significant subset of older patients do continue to have migraine pain.

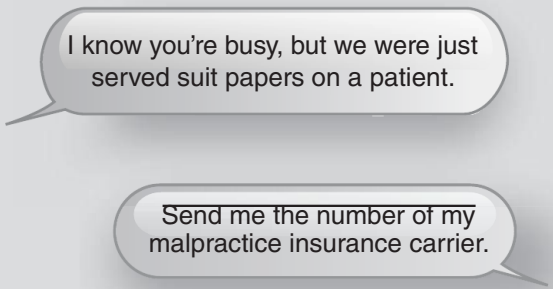
Given substantial prevalence, morbidity and disability, these results are compelling. However, to have more definitive answers, the beta blocker eye drops need to be tried against placebo without any supplemental nonsteroidal anti-inflammatory medications. Their use as a prophylactic agent should also be investigated. Further aspects of this treatment to explore include the possibility of rebound effect with multiple or frequent doses. Additionally, its sustained efficacy in large populations of patients will need to be verified, though the case reports provided by the authors provide preliminary support to efficacy over time. As called for in 1999 further studies are warranted.[4] The NIH has issued a call for research on migraine (http://grants.nih.gov/grants/guide/pa-files/PA-14-069.html) and this could pose an attractive and feasible area for study of a new

use of an old medication to address a pervasive problem throughout the population, particularly in the important subset of those with vascular disease in whom treatment options become more limited. We would anxiously await institution of trials to explore expanding our therapeutic repertoire.

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EDITORIAL CRITIQUE: HEADACHE MEDICINE

Ophthalmic Beta Blockers: Treatment for Acute Migraine?

by J. Kent Dexter, MD & Roger K. Cady, MD

Further large scale randomized placebo controlled studies of beta blocker eye drops for acute migraine are clearly warranted.



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Migraine is the most prevalent neurological disease in the world and a leading cause of medical disability worldwide.[1] While important advances in treating migraine have been made in the last 25 years, migraine continues to be significantly under-diagnosed and under-treated.[2] Unfortunately, available acute treatments for migraine are not always effective. Numerous studies suggest that oral triptans provide sustained pain free outcomes in less than 25% of attacks.[3] In addition nearly 80% of patients are willing to try new treatments, further suggesting the need for better more successful acute treatments for migraine.[4]

In this issue of *Missouri Medicine*, Carl V. Migliazzo, MD, and John C. Hagan, III, MD, present a series of seven case reports of patients successfully treating attacks of acute migraine with beta blocker eye drops. (See page 283). While this is a small case series and as such has numerous limitations, the authors' report is both well organized and compelling. If beta blockers ophthalmic drops are demonstrated to be effective in rigorous clinical trials, this novel approach to acute treatment would add much to the care of migraine patients.

The case reports provided by Migliazzo and Hagan have both strengths and weaknesses. Each of the seven cases discussed in their article provides enough information to confidently assume a correct diagnosis of migraine with or without aura. The outcome of six of the seven patients was provided through use of a questionnaire mailed to patients and measurement of efficacy while confined primarily to pain relief and functional restoration is clinically valuable. There is however, no acknowledgement of the number of unreturned questionnaires or if there were patients who did not respond to topical beta blockers that are not reported in their article. In addition most of the patients are in their 60s which may represent a unique subset of the migraine population which is most prevalent in the third and fourth decade of life. Another confounding factor is that several of the patients are reported to be using topical beta blocker eye drops in conjunction with another NSAID or analgesic. Finally, the number of cases reported is small making any generalization of these observations impossible.

That being said, there is significant positive potential for exploring the role of topical beta-blocker eye drops as acute

treatment for migraine. Inhibitory modulation of peripheral and central neuronal pathways provides the pharmacological basis for several common acute treatments for migraine. Most notable are triptans and ergotamines which are agonists of the inhibitory neurotransmitter serotonin (5-HT). 5-HT 1 b/d receptors are well documented as the principle mechanism by which triptans and ergotamines abort acute migraine.[5] Divalproex sodium is an FDA approved migraine prophylactic medication that has studies demonstrating efficacy for acute migraine when given as a rapid IV infusion.[6] Valproic acid is a GABA agonist and another important inhibitory neurotransmitter. Non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis and glial recruitment of neurons and are also widely used acute treatments.

Both timolol and propranolol are FDA approved for migraine prophylaxis and numerous other beta blockers are commonly employed in in this role. While the exact mechanism of action of beta blockers in migraine is not fully understood, they are known to rapidly inhibit adrenergic drive, block smooth muscle contraction and prevent arterial dilation and pain. Further, beta blockers inhibit catecholamine-induced platelet aggregation and adhesiveness as well as block catecholamine-induced lipolysis and prostaglandin production. Finally beta blockers inhibit forebrain postsynaptic serotonin receptors.[7] Many of these mechanisms could potentially have a positive benefit in acute treatment of migraine.

Other positive attributes of beta blockers are that they are well tolerated and have a high benefit to risk ratio in numerous therapeutic areas including migraine prophylaxis.[8] Given their use as daily prophylactics over extended periods of time, it is unlikely that beta blockers would lead to Medication Overuse Headache which is a common liability of currently used acute treatments. Topical beta blocker eye drops provide significant blood levels sufficient to provide beta-blockade within minutes of administration; an ideal pharmacokinetic feature of an acute migraine medication.

Given the efficacy reported in this small series of case reports, the mechanistic potential of beta-blockers to be effective as an acute treatment, and the tolerability and safety of this class of medication further large scale randomized placebo controlled studies are clearly warranted.

An interesting historical footnote might be that the use of propranolol as a migraine prophylactic was made by a physician noting improvement of migraine in a patient being treated for angina pectoris.[9] We commend the authors on their astute observations and bring this novel and potentially important concept to the attention of the medical community.

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EDITORIAL CRITIQUE: NEURO-OPHTHALMOLOGY

Can Topical Beta Blockers be Successful for Acute Migraine Management?

by Sophia M. Chung, MD

The authors successfully have contributed an additional seven cases to the literature supporting an alternate treatment for acute migraine.



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I appreciate the opportunity to review the article entitled, "Beta Blocker Eye Drops for Treatment of Acute Migraine: Case Presentations and Review." (See page 283.) The manuscript is a report of seven patients who suffered from migraine headaches but who successfully modify their pain with the instillation of topical beta blocker eye drops, traditionally used in the management of chronic open angle glaucoma. This is the only case series using topical ophthalmic beta-blockers to manage acute migraine published in the literature. The encouraging positive response of the acute migraine in these patients supports the need for a prospective, randomized and masked study of a topical beta-blocker.

Migraine is thought to result from cortical spread of depression (CSD), a well-defined wave of cortical neuronal excitation that spreads 2-6 mm/min. A whole host of neurochemical and physiologic changes occur and are beyond the scope of this review. But as a result of this CSD, there is an activation of the trigeminovascular system to stimulate nociceptive neurons on dural blood vessels that releases plasma proteins and a variety of pain-generating substances such as: calcitonin gene-related peptide, substance P, vasoactive intestinal peptide, and neurokinin A.

The resultant state of sterile inflammation is accompanied by further vasodilation exacerbating pain. Numerous pain centers in the thalamus, cortex, and potentially a "migraine center" in the brainstem are activated to contribute more inflammatory signals to cause vasodilation and additional pain. The changes in neuronal and vascular membranes and release of inflammatory cytokines should allow targeted pharmacotherapy to modulate the response and therefore reduce or hopefully stop migraine pain.

Beyond disease modifying changes in lifestyle, pharmacotherapy has traditionally been used for migraine and can be categorized into abortive therapy and prophylactic therapy. The goal of abortive therapy is to achieve resolution of pain within two hours with one therapeutic choice without significant adverse events. Non-steroidal anti-inflammatory agents such as aspirin, ibuprofen, naproxen, acetaminophen, and diclofenac sodium have been the mainstay of treatment. Triptans are the other most common acute treatment for migraines. There are seven triptan tablets, two fast-melt tablets, two nasal sprays, and three types of injection. While the oral treatments are most commonly used,

the nasal sprays and subcutaneous injections offer quicker onset for many patients bypassing the slow gastrointestinal absorption.[1]

When patients suffer more than two to three migraines/month, prophylactic therapy should be strongly considered. Four drugs are approved by the Federal Drug Administration (FDA) in the preventative management of migraines: timolol and propranolol, the only beta blockers and topiramate and divalproex sodium, both originally designed as anti-epileptics. But a whole host of medications are used off-label including a number of other beta-blockers, antidepressants (e.g., amitriptyline, nortriptyline), calcium channel blockers (e.g., verapamil and flunarizine), and commonly anticonvulsants (e.g., gabapentin and lamotrigine).[2]

Beta blockers were discovered to be beneficial in migraine by serendipitous happenstance. A patient enrolled in a study of propranolol to prevent angina reported improvement not only in his angina but also his migraines while on propranolol but recurrence after crossover to the placebo.[3] Since that report, beta-blockers have become first line prophylactic therapy for migraines. In addition to timolol and propranolol, a large meta-analysis showed acebutolol, atenolol, nadolol, and metoprolol were all better than placebo in the prophylactic management of migraine.[4]

Beta-blockers were initially thought to be effective solely by its vasodilation benefits. We now recognize multiple mechanisms including inhibition of Na+ release and tyrosine hydroxylase, reduction of neuronal firing rate of noradrenergic neurons of the locus coeruleus, modulation of the serotonin receptors, and action at the ventroposteromedial thalamic nucleus and inhibition of the cortical spread of depression.[5] Hence the successful benefit of beta-blockers in the newly accepted context of CSD as the cause of migraines. However, beta blockers are considered beneficial only as a prophylactic agent and not in the acute management.

Topical timolol was the first FDA approved beta-blocker to be used in glaucoma in 1978. It acts by reducing the formation of aqueous humor and therefore lowers the intraocular pressure. When applied to the eye, not only are there local ocular effects but it is also absorbed systemically via mucosal membranes primarily in the nasopharynx. As Migliazzo and Hagan have discussed, pharmacologically active levels in the blood are quickly achieved after topical administration,[6] but may cause side effects in the heart and lungs including bronchospasm, bradycardia, and hypotension. Therefore, reactive airway disease and bradycardia are considered relative contraindications in patients whom topical beta-blockers are being considered.

Conversely, potential systemic benefits could result from the same attained pharmacologically active concentrations of beta-blockers such as management of migraines. As detailed by the authors, there are several prior case reports of beneficial effect of using topical beta-blockers in the eye in the acute management of their recurrent migraine. Herein, the authors add an additional seven patients, the first case series of patients, to the literature. All of these cases are women who reported longstanding history of migraine (with the exception of case 4 whose duration is not recorded) three of whom had consistent visual aura preceding the headache and pain. Six of the seven women instilled topical levobunolol 0.5% or timolol 0.25-0.50% into one or both eyes while one woman used it sublingually within minutes of onset of migraine. Six of the seven patients achieved complete or near complete relief within 45 minutes. The seventh patient achieved complete relief in 70-80% of acute attacks. Five of the seven supplemented the topical beta-blocker with oral analgesics at least some of the events. One case tried using the topical beta-blocker daily as a preventative measure but she continued to have break-through-migraine attacks. One woman suffered some shortness of breath with two drops of beta-blocker ophthalmic solution but when she lowered her dose to only one drop, her side effects resolved. And finally, one patient with known asthma did not suffer exacerbation of bronchospasm with sublingual ophthalmic solution of beta-blocker.

The proposed mechanisms of beta-blockers are discussed above. As the authors have proposed, immediate instillation and rapidity of systemic absorption of topical ophthalmic solution through mucosal membranes may indeed explain the benefit in the acute management of migraine. Immediate access and treatment is important in nearly all migraine patients to attenuate the symptoms before CSD has advanced significantly. The dosing of topical beta-blockers remains uncertain; the fact that such a dilute solution and small quantity would be so effective is remarkable.

The report is certainly encouraging but there are weaknesses of the case presentations that may inadvertently favorably alter the patients' responses. As the authors have acknowledged, this paper reports the results of a retrospective, unmasked, questionnaire. We are not told the number of questionnaires nor to whom the questionnaires were distributed. Details about the patients' past medical history and medication lists are not provided. Concurrent diseases such as renal insufficiency or failure will alter drug availability. Systemic medications similarly

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may affect bioavailability of the topical agent. Parallel use of beta-blockers for systemic hypertension or nonsteroidals for arthritis may potentiate effects of topical agents. The average age of the patients reported in this study is 61 years of age, older than most studies report for migraine. Migraines typically peak between 35 and 45 years of age.[7] As a result, this group of older patients, all women and most are likely post-menopausal, may have different responses to medication than the typically younger patient. Finally, generalizations cannot be made from the observations of seven patients.

Nonetheless, I agree with Drs. Migliazzo and Hagan that the seven reported cases should stimulate us to consider a prospective, randomized, masked, and controlled study examining the role of topical beta-blockers in the treatment of acute migraine. The low cost, wide availability and relatively successful tolerance of this medication all favorably support its use. The immediacy of systemic absorption and therapeutic benefits seemingly outweigh the risks. The authors successfully have contributed an additional seven cases to the literature supporting an alternate treatment for acute migraine.

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Getting Comfortable With Death

Evolution of the Care of the Dying Patient

by Paul E. Tatum, III, MD, Kevin W. Craig, MD, Karla T. Washington, PhD & Debra Parker Oliver, PhD

To cure sometimes,
to relieve often,
to comfort always.
-Dr. Edward Trudeau






From top left: Paul E. Tatum, III, MD, MSPH, CMD, FAAHPM, Associate Professor Kevin W. Craig, MD, MSPH, Assistant Professor, Karla T. Washington, PhD, MSW, Assistant Professor, and Debra Parker Oliver, PhD, MSW, Professor, are in the Department of Family and Community Medicine at the University of Missouri School of Medicine in Columbia, Mo.
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Abstract

In this article, we provide an overview of the historical evolution and ongoing transformation of care for the dying patient. We examine the rise of hospice and palliative care and its eventual designation as a formal discipline and discuss growing recognition of the need for earlier palliative care for the seriously ill. Finally, we consider potential future challenges in the delivery of care to the dying patient as health care continues to change over time.

Introduction

There has been tremendous, rapid change in the way health systems provide care for the dying patient over the last few decades. In this article, we provide an overview of the historical evolution and ongoing transformation of care for the dying patient internationally, in the United States, and within the state of Missouri. We examine the rise of hospice and palliative care and its eventual designation as a formal discipline with specialty status and discuss growing recognition of the need for earlier palliative care for the seriously ill. Finally, we consider potential challenges in the delivery of care to the dying patient in the future as health care continues to change.

From the Art of Caring for the Dying to the Rise of Complicated Death

The following three quotations attributed to Hippocrates may sum up a philosophy of care that has guided medicine for centuries: "Life is short, art is long," "It is far more important to know what person the disease has than what disease the person has," and "To do nothing is also a good remedy." In short, caring for the ill has historically been regarded an art that needed to be person-centered and that should incorporate an acknowledgement that every

Table 1
Leading Causes of Death: 1910 and 2010

1910	2010
Heart disease	Heart disease
Pneumonia and influenza	Malignant neoplasm
Tuberculosis	Chronic lower respiratory disease
Diarrhea, enteritis, and ulceration of intestines	Cerebrovascular disease
Intracranial lesions of vascular origin	Accidents

Source: Centers for Disease Control and Prevention Leading Causes of Death 1900-1998 and National Vital Statistics Reports - Deaths: Final Data for 2010

potentially harmful treatment need not be applied. One could say the purpose of medicine has been best described by Dr. Edward Trudeau as "to cure sometimes, to relieve often, to comfort always." These values may have achieved their artistic apogee in Sir Luke Filde's *The Doctor*, which depicts a Victorian doctor attending to a dying child with compassion.

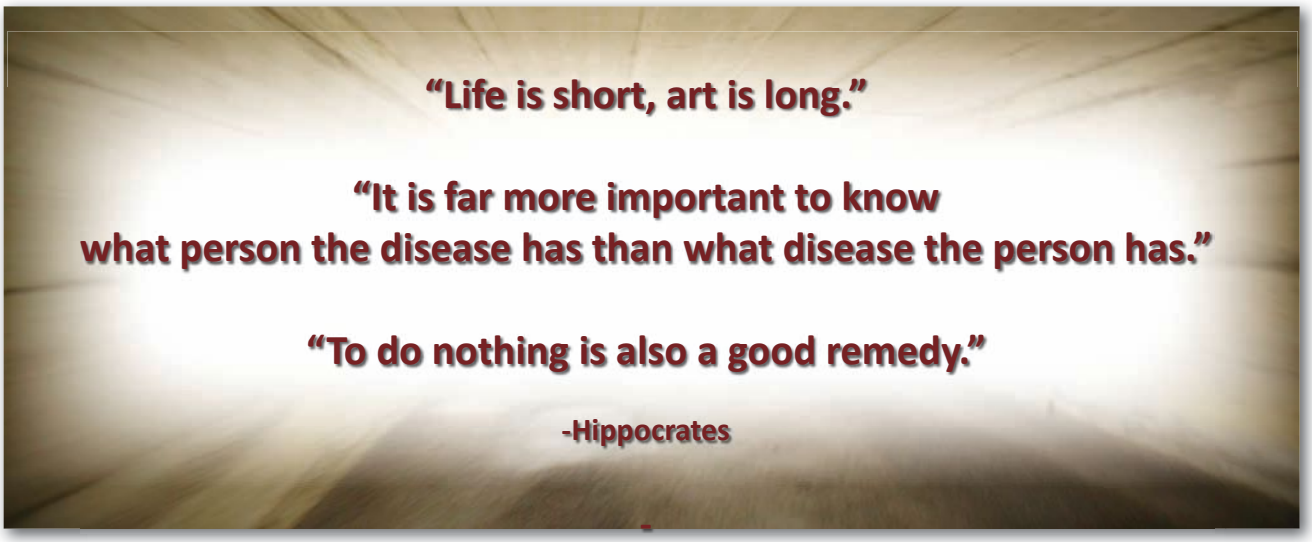
Historically, caring for the seriously ill was limited to easing the symptoms of the dying. In the pre-antibiotic era, death was often sudden and related to infectious disease.[1] The twentieth century changed how death was perceived through a combination of rapid technological change, ability to treat acute illnesses successfully, and changed societal expectations. As late as 1910, the top causes of death primarily remained infectious diseases;[1] death was typically sudden and the average life expectancy in the United States was 50 years.[2] By the end of the twentieth century, most people could reasonably expect to live well into their 70s and were more likely to die as the result of a chronic illness than an acute event.[3] Table 1 contains a list of causes of death, providing a contrast between 1910 and 2010.

The age of antibiotics would lead to cures to more infections. Even new epidemics like HIV/AIDS would rapidly be transformed from a death sentence to a survivable chronic illness. Early lessons from the battlefield, beginning with the Civil War and progressing with each subsequent war throughout the twentieth century, brought rapid technological advances in surgical technique and response to injury. Technological advances may have culminated with the development of dialysis and transplantation medicine, which would appear early on to defeat death. Pharmaceutical advances created cures for non-infectious scourges and transformed cancer from a solely terminal illness to an apparent chronic disease to be dealt with accordingly. While death remained inevitable, the prevailing optimistic mood was that a "War on Cancer" would bring a cure.

In addition to advances in treatment, the dying process changed as the culture of medicine changed. Medical education was transformed with the Flexner report.[4] Doctors were no longer trained in small rural apprenticeships with wide variability in quality but rather in standardized institutional settings of academia and increasingly with physicians who specialized in one area. Today, patient care is largely focused on chronic disease and is often fragmented. Rather than seeing one trusted physician, the typical Medicare beneficiary sees a median of seven different physicians in a year.[5] With increasing health care complexity, patients now spend more time in the intensive care unit (ICU) at the end of life. In 2000, 24.3% of decedents had an ICU stay in the last month of life; by 2009, that figure had increased to 29.2%.[6] In addition, patients often face multiple transitions to different care facilities in the time preceding death, with location of care transitions in the last three days of life rising a dramatic 40% between 2000 and 2009.[6]

Attitudes toward death, however, changed even before the Flexner report with the discovery and development of bacteria and bacteriology, aseptic techniques, and anesthesia. Society now witnessed people survive diseases and conditions not previously survivable. The attitude of denial of "death comes to us all" arrived. Patient and family expectations followed, and physicians responded with the attitude that "death is a failure." The centuries-old expectation that everyone would die at home surrounded by loved ones changed. Whether from the hope of families that medicine would "save" their loved one or expectations of physicians with the "God complex," people began dying in medical facilities, away from the care of loved ones.

While the location of end-of-life care has shifted away from the home and into institutions such as hospitals and nursing homes,[7] the majority of Americans - about 70% - prefer to die at home.[8] The same number, if given a 25% chance of survival, would choose a plan



of care that "would relieve them of their pain and shorten their life, rather than a plan of care that would extend their life but with more pain and discomfort."[7] Almost two-thirds (66%) worry about experiencing great physical pain before they die. The same number is concerned about how their family or loved ones will be cared for after their death.[7] These desires and concerns set the stage for our discussion of the rise of hospice and palliative care.

The Development of Modern Hospice Care

The word "hospice" is derived from hospitium, which is derived from the Latin root words hospes/hospit. Thus, hospice shares its word origins with both hospital and hospitality. In medieval times the word was used to refer to a place of shelter. During the Crusades hospices were used to provide care for ill travelers on long journeys. Hospices were often found in monasteries, but they did not only care for the dying but rather anyone in need: from the woman in labor, to the hungry, to the poor.

Hospice was first introduced in the modern health care context as a name for specialized care for dying patients by Dame Cicely Saunders. Dame Saunders was a nurse, social worker, and physician who worked with terminally ill patients in England. She went on to create the first modern hospice, St. Christopher's, in suburban London in 1967. Saunders studied the care given to the dying with rigorous scientific methods. From her work, she coined the term "total pain" to describe pain as having potentially physical, emotional, social, and spiritual origins which may interact to produce the sum total of pain that a patient experiences.

During a visit to Yale University, Saunders lectured about the concept of comprehensive holistic care of the dying with a hospice model. The lecture led Florence Wald, Dean of the Yale School of Nursing, to eventually take a sabbatical from Yale University to work at St. Christopher's. In 1974 Florence Wald founded Connecticut Hospice, the first hospice in the United States, in Branford, Connecticut.[9] The same year, Senators Frank Church and Frank Moss introduced the first legislation to provide federal funding for hospice programs; however, the legislation was not enacted. In 1978 a task force of the United States Department of Health, Education, and Welfare concluded that hospice was a viable concept and recommended federal support for hospice care. A year later, the Health Care Financing Administration (referred to today as the Centers for Medicare and Medicaid Services or CMS) began a demonstration project at 26 hospices across the country, eventually determining hospice care to be cost-effective. In 1982 Congress created the Medicare Hospice Benefit, which became permanent in 1986, at which time individual states were given the option of including hospice in their Medicaid programs.[10]

Hospice Care in Missouri

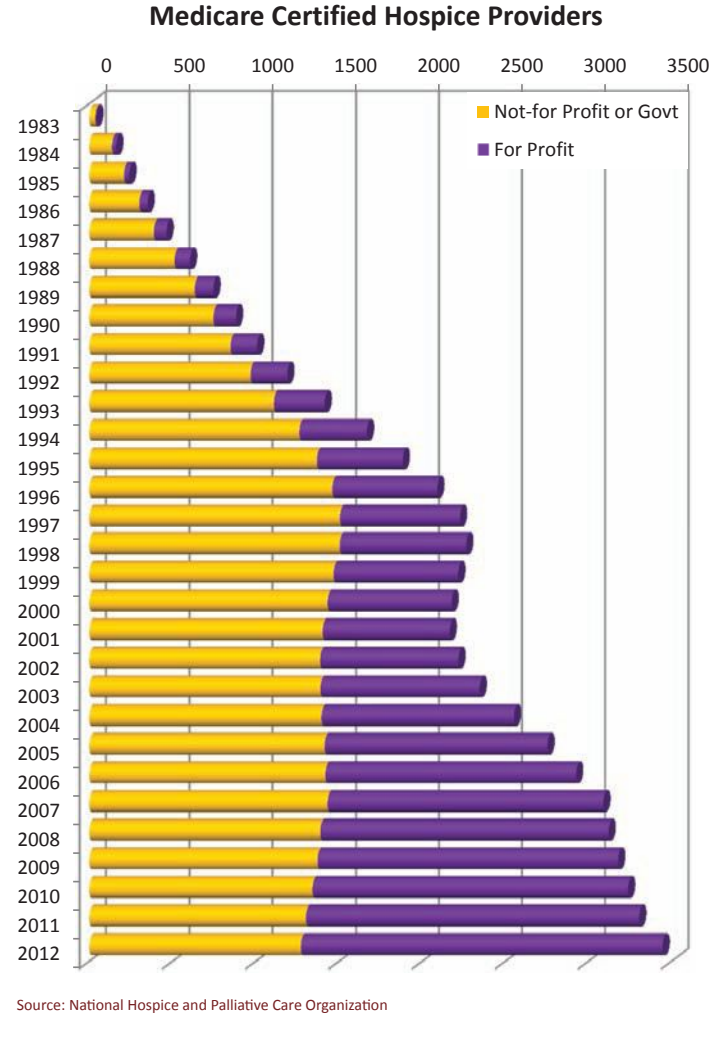
Hospice programs grew throughout Missouri in a specific pattern.[11] Diffusion was clustered around the early founding programs. The first three documented hospices in Missouri became Medicare certified in 1984. Hospice of Care (Houston, Missouri), Hospice of Southwest Missouri (Springfield, Missouri), and

Kansas City Hospice (Kansas City, Missouri) were the first hospices certified to receive Medicare in the state. Beginning as volunteer programs, these three appeared in the first annual hospice report from the Missouri Department of Health, Bureau of Home Health and Hospice Licensing. These programs provided hospice care to individuals residing in 23 counties. Two years later in 1986, the fourth program, Visiting Nurse Association (VNA) of St. Louis, became certified and increased access in Missouri to 30 counties. St. Luke's Hospice (Shawnee Mission), Hands of Hope Hospice (St. Joseph), and Citizens Memorial Hospice (Bolivar) became certified in 1987. By 1991 a total of 28 hospices were serving 73 counties, covering 70% of the state. It was not until 1996 that every county in Missouri had access to hospice care. The southern counties had earlier access then northern counties. As late as 1991 the northern part of the state had many counties without access to hospice, while every southern county had at least one and, in several instances, more than one hospice. The early hospices struggled financially, relying heavily on volunteer support and fundraising activities. Financial gain was not the motive of the early hospices, as the first for-profit hospice in the United States did not appear until 1993.[12] In Missouri, as in the rest of the U.S., social change, an alternative to the medical model, and a desire to return to the traditional community value of dying at home was the driving force behind the "hospice movement."

The Complementary Rise of Palliative Care Systems

In 1975 Dr. Balfour Mount established the first comprehensive palliative medicine program at the Royal Victoria Hospital in Montreal, Canada. A year later, the International Congress on Palliative Care held its first meeting, also in Montreal.[7] In 1987 Dr. Declan Walsh established the first academic hospital palliative care program in the United States at the Cleveland Clinic.[7] In the relatively short duration of its existence in the United States, the concept of palliative care has rapidly transformed. While originally focused on hospital systems, there has been increasing recognition that many patients outside of the hospital who do not meet hospice criteria would benefit from palliative care services. The Center to Advance Palliative Care (CAPC) released its definition of palliative care in 2011, indicating that "palliative care is specialized medical care for people with serious illnesses. This type of care is focused on providing patients with relief from the symptoms, pain, and stress of a serious illness - whatever the diagnosis. The goal [of palliative care] is to improve quality of life for both the patient and the family. Palliative care is provided by a team of doctors, nurses, and other specialists who work with a patient's other doctors to provide an extra layer of support. Palliative care is appropriate at any age

Figure 1



Source: National Hospice and Palliative Care Organization

and at any stage in a serious illness, and can be provided together with curative treatment."[13] This definition highlights two key points: 1) palliative care is not just for the dying, and 2) a key benefit of palliative care is that is adds a layer of support to patients and families.

Nationally, the number of palliative care teams within hospitals has increased approximately 138%, from about 600 in 2000 to more than 1,500 in 2009.[14] Within Missouri, there is significant variability. Missouri access to palliative care in communities with only one hospital provider is currently 41%. Approximately 75% of Missouri public hospitals with more than 50 beds have a palliative care program; however, the prevalence of palliative care programs in Missouri's for-profit hospitals with more than 50 beds is only 33%.[15]

Hospice and Palliative Care: Today and Tomorrow

The last 30 years of hospice and palliative care can be characterized as a time of rapid change, with tremendous growth in the number of programs, increased professionalism and opportunities for formal education and training, and a growth in research. Once envisioned as part of a countercultural movement, the provision of compassionate palliative care for the seriously ill and dying has been accepted into mainstream medicine. As depicted in Figure 1, in 2011, approximately 44.6% of all deaths in the United States were attended by hospice.[16] The previously described expansion of palliative care can be expected to continue as the evidence base for its benefit builds. The professionalization of hospice and palliative care is now well established and consists of formal education and certification. Organizations such as the Center to Advance Palliative Care, the American Academy of Hospice and Palliative Medicine, the Hospice and Palliative Nurses Association, and the Social Work Hospice and Palliative Care Network continue to grow in size and influence.

The future evolution of hospice and palliative medicine will likely involve better integration with health care systems and comprehensive use of early palliative care for serious illness. Hospice will continue to provide care for those in the last six months of life. Key issues in the evolution of hospice and palliative care in the near-future will include: 1) advancing palliative-specific research, 2) maintaining sufficient workforce, and 3) overcoming fiscal and regulatory constraints. The aging demographics will challenge hospice and palliative medicine to have adequate workforce to deliver care. The fiscal and regulatory constraints of healthcare delivery will offer both challenges and opportunities to hospice and palliative medicine.

Evidence supporting hospice and palliative care is building. For example, a 2010 study by Temel and colleagues[17] showed that patients with metastatic non-small-cell lung cancer who received early palliative care saw improvement in both quality of life and mood. Not only did quality of life improve, but patients receiving early palliative care actually lived longer than those who did not receive early palliative care. Research on hospice and palliative care is increasing with support from organizations such as the National Palliative Care Research Center, the National Institutes of Health, and the American Cancer Society. However, the size of these funding efforts pales in comparison to the amount of funding available for disease-directed treatment and technological advances aimed at prolonging life.[18]

For palliative care to truly integrate into health systems, there must be a sufficient workforce to deliver services. A study of the workforce need for palliative specialty care estimates that 4,487 hospice and 10,810 palliative care physicians practicing full time are needed to staff current programs at appropriate levels; between 6,000 and 18,000 additional physicians are anticipated to be needed in the future to meet predicted growth.[19] It is clear that specialists alone will never provide enough manpower to meet the need. All physicians (primary care physicians, cardiologists, oncologists, nephrologists, pulmonologists, intensivists, emergency room physicians, etc.) should consider themselves the primary palliative care physician with expert tertiary-level palliative care available if needed.[20] Yet, many physicians express discomfort about their ability to deliver high-quality palliative care.[21] Research has identified a need to expand training to physicians currently serving in hospice or palliative care-specific roles. A recent study of Missouri hospice medical directors found that none had palliative fellowship training, few had specific training in palliative care, and very few were board-certified in hospice and palliative care.[22] In fact, Missouri is the only state without a formal palliative medicine fellowship.[23] While several institutions are ready to begin a fellowship, the lack of Graduate Medical Education (GME) funding makes starting a new program difficult. The Palliative

Care Hospice and Education and Training Act is one potential way to expand palliative care services through creating regional training centers and training for already practicing providers.

Another key issue shaping end-of-life care in the US involves financial and regulatory policy issues. Currently hospices face tremendous regulatory changes with serious financial implications. While requirements for increased physician involvement in hospice with face-to-face visits have the potential to improve care, the recent elimination of "adult failure to thrive" and "debility" as eligible diagnoses for the complex older patient [24] is expected to decrease access to hospice services. In addition, targeted audits of hospices with substantial payment penalties have led to the closure of one of the country's most prestigious training programs (San Diego Hospice) and could potentially curtail hospices' willingness to certify patients until the last few weeks of life, given the challenges of accurately predicting prognosis. 2011 Missouri Medicaid data show that hospice care results in significant savings in both hospital costs (where patients typically do not want to die) and provider costs.[25] Issues related to cost-effectiveness will continue to emerge. Both hospice and palliative care will have to continue to justify their cost based on savings and value rather than just "doing the right thing."

End-of-life care, like all medical care, will continue to be challenged as our culture and our regulatory and financial resources change. Everyone dies and everyone faces the end of life, not only for themselves but also for their loved ones. How we choose to provide care to individuals and their families at their most vulnerable time, their time of greatest need, the very transition of life to death, is an important matter, regardless of changes in the health care system. We must hope that this significant event and the matter in which it is experienced continues to be of interest to the broader society in such a way that it unifies policy makers, regulators, administrators, and health care providers toward a common goal. As Dame Cicely Saunders eloquently advocated, "you matter because you are, and you matter to the end of your life. We will do all we can not only to help you die peacefully, but also to live until you die."

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Disclsoure

None reported. **MM**



The gift of life is greater than the sum of its parts, and, whatever consciousness is, survives death.



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It was a beautiful August day at Sleepy Hollow Lake in Athens, New York in 1994. The occasion was my in-laws celebrating their annual group birthday gathering. About twenty relatives and their siblings were in attendance. While the children ran amok screaming and playing, I prepared the party barbeque. We had gathered on the second floor of a lakeside pavilion. The ground level included picnic tables and barbeque pits. A payphone was attached to the wall on the side of the building.

As the thought occurred to me to call my mother and check on her, I remember seeing a few light sprinkles of rain. In the midst of the revelry and chaos, and unbeknownst to me, the beautiful sunny day had surrendered to powerful dark storm clouds moving swiftly in over the lake. I ambled around the building to the pay phone and dialed my mother's familiar number. I let the phone ring eight times, but there was no answer. With my left hand I pulled the phone hand piece away from my face to hang it up. When it was about a foot away from my face, I heard a deafening crack. Simultaneously I saw a brilliant flash of light exit the phone hand piece I was holding. A powerful bolt of lightning had struck the pavilion, traversed through the phone striking me in the face, as its massive electrical charge raced to ground.

My Near Death Experience & Out of Body Experience

The force of the lightning blast threw my body backwards like a rag doll. Despite the stunning physical trauma, I realized something strange and inexplicable was happening. As my body was blown backwards, I felt "me" move forward instead. Yet I seemed also to stand motionless and bewildered staring at the phone dangling in front of me. Nothing made sense.

At that moment, I heard my mother-in-law scream from the top of the stairs above me. She raced down the stairs towards me. I felt like a deer in the headlights. As she

approached I could see she was looking beyond me to my right and headed that in that direction. She was oblivious to me standing there. I turned to see where she was going. Suddenly, I realized what was going on. A motionless body was lying on the ground some ten feet behind me. To appearances the person was dead. To inspection the person resembled me. To my astonishment another look confirmed it was me!

I watched as a woman who had been waiting to use the phone dropped to her knees and began CPR. I spoke to the people around my body but they could not see or hear me; I could see and hear everything they did and said. It suddenly occurred to me that I was thinking normal thoughts, in the same mental vernacular I had always possessed. At that moment I suddenly had one simple, ineloquent and rude thought, "Holy shit, I'm dead."

This cosmic realization of consciousness meant that my self-awareness was no longer in the lifeless body on the ground. I, whatever I was now, was capable of thought and reason. Interestingly there was no strong emotion accompanying my apparent death. I was shocked, certainly, but otherwise I felt no reaction to what should have been the most emotional of life's events.

Seeing no point in staying with my body, my thoughts then moved to walking away. I turned and started to climb the stairs to where I knew my family still was. As I started to climb I looked down at the stairs like I would normally do. I saw that as I reached the third stair, my legs began to dissolve. I remember being disconcerted that, by the time I reached the top of the stairs, I had lost all form entirely and instead was just a ball of energy and thought. My mind was racing frantically trying to record and make sense of what was happening.

At the top of the first flight, the stairs went up and left into the second flight. Instead of bothering with the stairs, I passed through the wall into the room where everyone was. I went diagonally through the room, over my wife who was painting children's faces. She had one child in front of her, one behind that person and one to the left. I had a clear realization that my family would be fine. Dispassionately, I departed from the building.

Once outside the building, I was immersed in a bluish white light that had a shimmering appearance as if I were swimming underwater in a crystal clear stream. The sunlight was penetrating through it. The visual was accompanied by a feeling of absolute love and peace.

What does the term 'absolute love and peace' mean? For example, scientists use the term absolute zero to describe a temperature at which no molecular motion exists; a singular and pure state. That was what I felt; I had fallen into a pure positive flow of energy. I could see the flow of this energy. I could see it flow through the fabric of everything. I reasoned that this energy was quantifiable. It was something measurable and palpable. As I flowed in the current of this stream, which seemed to have both velocity and direction, I saw some of the high points and low points in my life pass by, but nothing in depth. I became ecstatic at the possibility of where I was going. I was aware of every moment of this experience, conscious of every millisecond, even though I could feel that time did not exist. I remember thinking, "This is the greatest thing that can ever happen to anyone."

Suddenly, I was back in my body. It was so painful. My mouth burned and my left foot felt like someone had stuck a red-hot poker through my ankle. I was still unconscious, but I could feel the woman who was doing CPR stop and kneel beside me. It seemed like minutes before I could open my eyes. I wanted to say to her, "Thank you for helping me." Nonsensically, all that came out was, "It's okay, I'm a doctor."

Shortly after I regained consciousness camp security arrived and requested that an ambulance be called, which, to their frustration, I promptly refused. Although I realized I probably made little sense, the truth about lightning strikes is that you are either dead or alive, and there is not much in between. In retrospect it is obvious I wasn't thinking clearly, but at the time, I was still reeling from what I had just experienced. My family drove me the two and a half hours home to Oneonta, NY, wobbly and confused. Once there, I saw my local cardiologist and neurologist who did all the appropriate tests and examinations. They told me how lucky I was to be alive.

I was able to resume work two weeks after the initial lightning strike when my brain seemed to function normally again. In the weeks and months after the lightning strike, however, I changed in many ways. The story of my developing musical ability and composition as a result of this event has been touched on in several books and documentaries. [1, 2,3,4,5] (See Sidebar page 308.)

Can Science Explain NDE/OBE?

I had experienced what Raymond Moody, MD, defined as an out-of-body experience (OBE).[6] I will refer to this phenomenon as a ND/OBE (near-death out-of-body) experience. For the purpose of this article, I am going to focus primarily on the experiential aspect of ND/OBEs and attempt to apply scientific reasoning to what may defy explanation with our current knowledge.

"God created souls as spirit entities whose goal is to merge with the divine ... able to be eternal, transmigrate, and reincarnate."

-Pythagoras

As a physician and scientist, I think it is extremely important to attempt a logical explanation of what happened and to examine what I experienced that fateful day. As an individual, however, I also think it is extremely important to appreciate the indescribable miracle that I experienced. I was presumed dead on the ground, yet I was later able to see and verify things that had been happening around me and that happened in another room where it was physically impossible for me to have seen. Both are imperative variables in arriving at a viable conclusion to this enigmatic event.

My friend and colleague the imminent neurologist and renowned author Oliver Sacks, MD, assures me that I was hallucinating ... but was I? Dr. Sacks has described hallucinations associated with "ecstatic" seizures in temporal lobe epilepsy that certainly sound like some descriptions by people who have had actual NDEs.[7] However, numerous reports have been presented and verified where experiencers of NDE/OBEs have been able to describe in incredible visual and auditory detail their NDE/OBEs. A case in point is that of Pam Reynolds, described in Michael Sabom, MD's book, *Light and Death*[8] and further studied by Holden[9] and Woerlee.[10] Reynolds was a patient who had a NDE/OBE during a neurosurgical procedure called "standstill" pioneered by Robert Spetzler, MD, at the Barrows Neurosurgical Institute. This procedure was used during a brain aneurysm resection where the patient had an induced cardiac arrest and the brain was monitored and was documented to be isoelectric and non-reactive. Just before the standstill procedure was begun, Reynolds was deeply anesthetized, with her eyes taped shut and a sheet over her head. Her brain activity was monitored in more than one way to confirm that her anesthesia was complete and yet she described "popping" out of her body - having a ND/OBE, whereupon she was able to describe sounds, "see" where people were standing, and describe the shape of surgical instruments used on her that she could not have seen physically. Dr. Gerald Woerlee[10] claims she may have had moments of light anesthesia, which certainly can happen in surgery, but that would allow only auditory, not visual recognition. She was able to mimic the sound of a brutish instrument called a Midas Rex that was used to cut through her skull. More importantly she was able to accurately describe what it looked like in lay terms.

An extensive number of cardiac arrest cases have been recorded with similar experience to the Reynolds case. Pim van Lommel, MD, a cardiologist in the Netherlands, did a prospective analysis of 509 successful resuscitations in 344 Dutch patients who suffered a cardiac arrest.[11, 12,13] Of those, 18% had a NDE/OBE. In other studies, the percentage varies for adult cardiac arrest victims who recall a NDE or OBE.[14] Morse[15] found 85% in children. An obvious question is why not all? Ring [16] found that blind people who had experienced ND/OBEs also reported veridical perception in which perceptions that were impossible from the vantage point of the physical body, and sometimes that totally contradicted their expectations at the time, were later verified to be accurate.

What Do the Skeptics Say?

Despite the strength of evidence in support of the reality of NDE/OBEs, many authorities still believe it is the work of a dying brain. Some of the controversy comes from studies that can simulate an experience that has some shared characteristics with actual NDEs. Those studies go back to Wilder Penfield's physical stimulation of the brain in patients.[17, 18] Olaf Blanke, et al.[19] was able to recreate a partial OBE in patients when electrodes were stimulated in the temporal lobe/amygdala region of the brain. Nelson, et al.[20, 21] ascribes the arousal/REM system as an integral part in the expression of NDEs and that hypoxia and cerebral ischemia are influential in the expression of the NDEs. Some new studies in rats by Jimo Borjigin et al.[22] and Chawla et al.[23] in humans suggest that within 30 seconds after

cardiac arrest there is a transient surge of synchronous high frequency gamma oscillations (a neuronal feature thought to underpin consciousness in humans) that precedes isoelectric EEG (flat line) or brain death. The authors make a giant leap to suggest this mechanism underlies NDEs. That hypothesis would negate cases of documented cardiac arrest and brain death where patients have returned to life after death and brought back information they would have no possible way of obtaining through mediation of the senses and the brain.[24, 25]

Other Theories and Notions

The notion of consciousness surviving death is not new. Plato's story of *Er in The Republic*[26] and Pythagoras,[27] who believed God created souls as spirit entities whose goal is to merge with the divine ... able to be eternal, transmigrate, and reincarnate, are but a couple of examples. There are many books detailing the science of NDE and a vast compendium of credible cases supporting the survival of consciousness.[28, 12] I think there is certainly something inherent in the temporal lobe/amygdala area that has a connection to what people experience as NDE, OBE, autoscopy (the experience in which an individual perceives the surrounding environment from a different perspective, from a position outside of his or her own body) or other unexplained phenomena.[29] There is experimental evidence to support that connection. But, there is obviously much missing. Real life changing NDE/OBEs, where people spiritually separate from their bodies and afterward can verify details they would not have any humanly way of gathering, are as yet unexplained and cannot be simply explained as a dying brain, anoxia, hallucinations, or sudden bursts of electrical activity.

What Do I Conclude?

In my case, being both a physician and scientist, I have approached what I experienced with some trepidation. What is clear to me is that my consciousness survived death and I was able to verify details of my near-death and out-of-body experience that I would have no conceivable way of knowing except through conscious travel of my spiritual self outside of my body. As Robin Kelly, MD, states, "Our brain may not be the seat of consciousness, but merely a vessel through which consciousness is realized."[30]

I can only hope that through further experimentation and study that meaningful data will be found to corroborate what many of us near death experiencers already know — that the gift of life is greater than the sum of its parts and, whatever consciousness is, survives death.

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Disclosure

None reported.

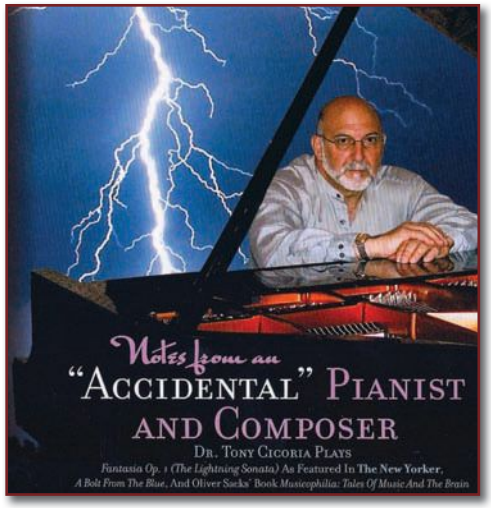
MM

The Electrifying Story of The Accidental Pianist & Composer

by Tony Cicoria, MD

About two weeks after being struck by lightning and my near-death experience/out-of-body experience, I began to have an insatiable desire to listen to classical piano music. This was a startling departure from previous musical interests. I was a child of the 60s and was raised on rock and roll. Even as an adult I was only interested in classic rock. When I was seven, my mother insisted I take piano lessons for a year. Dutifully and reluctantly I did. I had no interest in the piano and would much rather fish or play sports. I abandoned the piano rather quickly. Now, dare I say like a bolt out of the blue, I was obsessed by the need to hear classical piano music.

Living in rural New York, I had to drive 60 minutes to Albany to even find CDs of classical piano. When I walked into the music store, a CD of Vladimir Ashkenazy playing his favorite Chopin seemed to fly into my hands. I listened repeatedly throughout the day. Within two weeks I realized I had to learn how to play the music on the CD. Unfortunately, I did not have a piano and remembered nothing from my childhood lessons. Several days after that realization, our babysitter asked if she could store her old piano with us for a year. Now that I had a piano, I promptly went to the music store and purchased some beginner's books on learning to play the piano. I also ordered all the sheet music listed on the CD that I listened to daily.

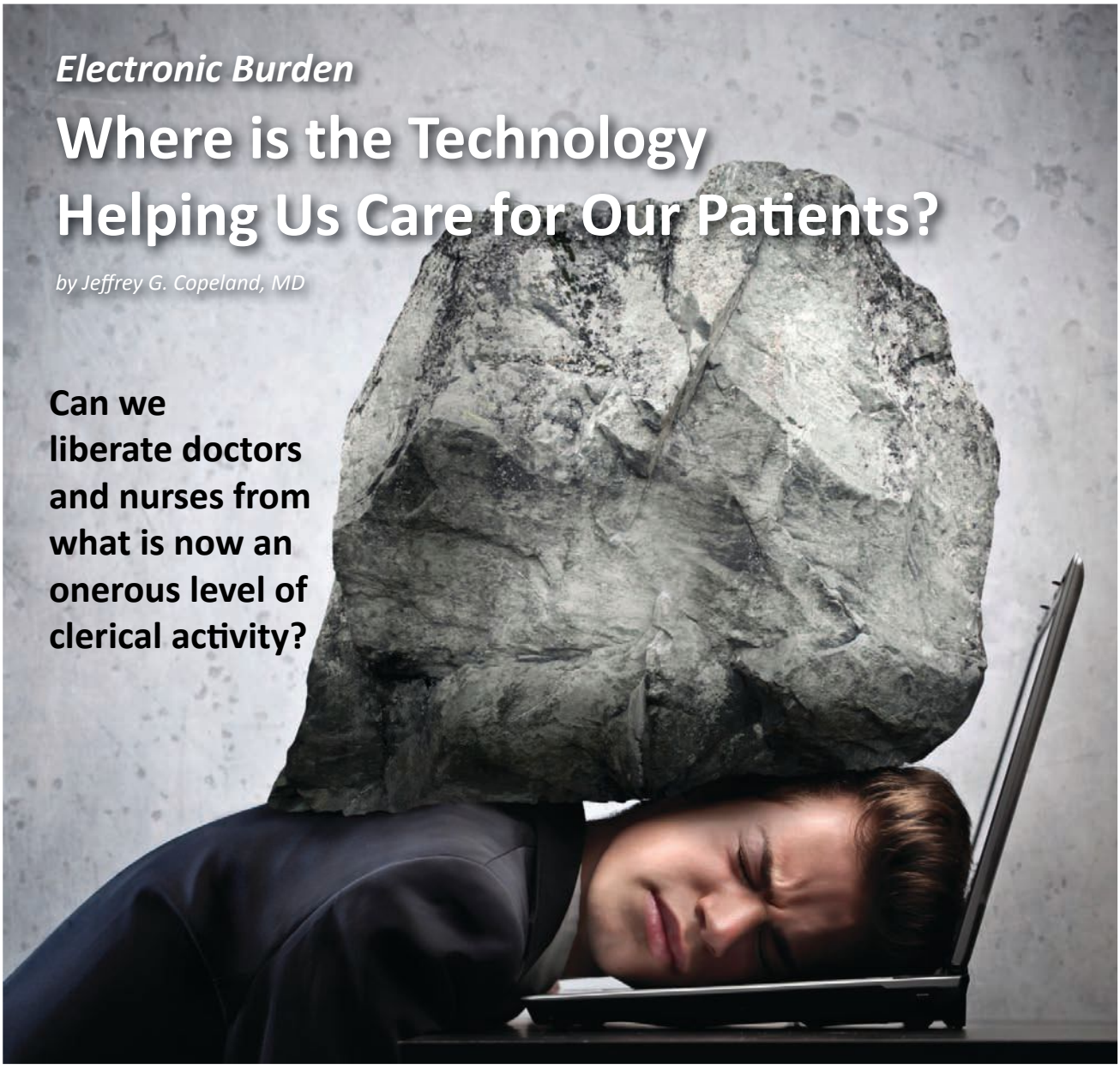


A few months after the piano came to live with us, I had a dream. This was not an ordinary dream, though — it was like an out-of-body experience. In the dream, I walked up behind myself and saw that I was sitting at the piano and was playing music in a concert hall. It was so real. I later drew a picture of the inside of the theater. I watched myself playing and suddenly realized that this was not someone else's music being played, it was my own! I listened to the music intently as it climaxed in a crescendo that woke me from a sound sleep. It was 3:15 a.m. I got up and went out to the piano to try to play some of what I heard despite having no idea how to write music, let alone play it. Frustrated, I went back to bed.

From that moment on, whenever I sat to play piano, the music would start to play in my head like a recording. If I tried to ignore it, it became more insistent. I became obsessed with the piano and came to believe the only reason I survived the lightning was because of the music. I practiced in the morning from 4:00 a.m. to 6:30 a.m. before work, worked 12 hours, gave our kids their baths and tucked them into bed with a goodnight song. Then I was back at the piano until my eyes could no longer focus. Everyday I would write down a few notes or measures of my music and throw them in a drawer for later use. It was shortly thereafter that I became aware of my own ineptitude for self-teaching and began piano lessons with Sandra Campbell McKane, a Julliard graduate and professor of music at Hartwick College. The year was 1998.

I continued along this difficult path of piano competency. Annually, I spent a week at Sonata Piano Camp in Bennington, Vermont. In 2006, I met Erica Van der Linde Feidner who knew Oliver Sacks, MD. Erica knew he was writing a book on music and the brain. Through a complex sequence of events, Dr. Sacks interviewed me in August of 2006. At the end of that day, as we shook hands in his doorway, he looked into my eyes as if looking through me and said, "The music from the dream went through an awful lot of trouble to get here, the least you can do is write it." I was so shaken by what he said, I went home and bought a Sibelius music writing program. I wrote bits and pieces of an original composition. I spent the next seven months writing frantically every day after work. Dr. Sack's book, *Musicophilia: Tales of Music and the Brain*, came out in 2007. I gave my first public concert in 2008 at the Goodyear Performing Arts Theater at State University College at Oneonta in New York. The music was recorded on CD and is available at CDBaby.com.

A You-Tube video of me at the Mozart House in Vienna, Austria playing "The Lightning Sonata", one of my original compositions, can be found at www.youtube.com/watch?v=tDtYkxSCV18. **MM**



Electronic Burden

Where is the Technology Helping Us Care for Our Patients?

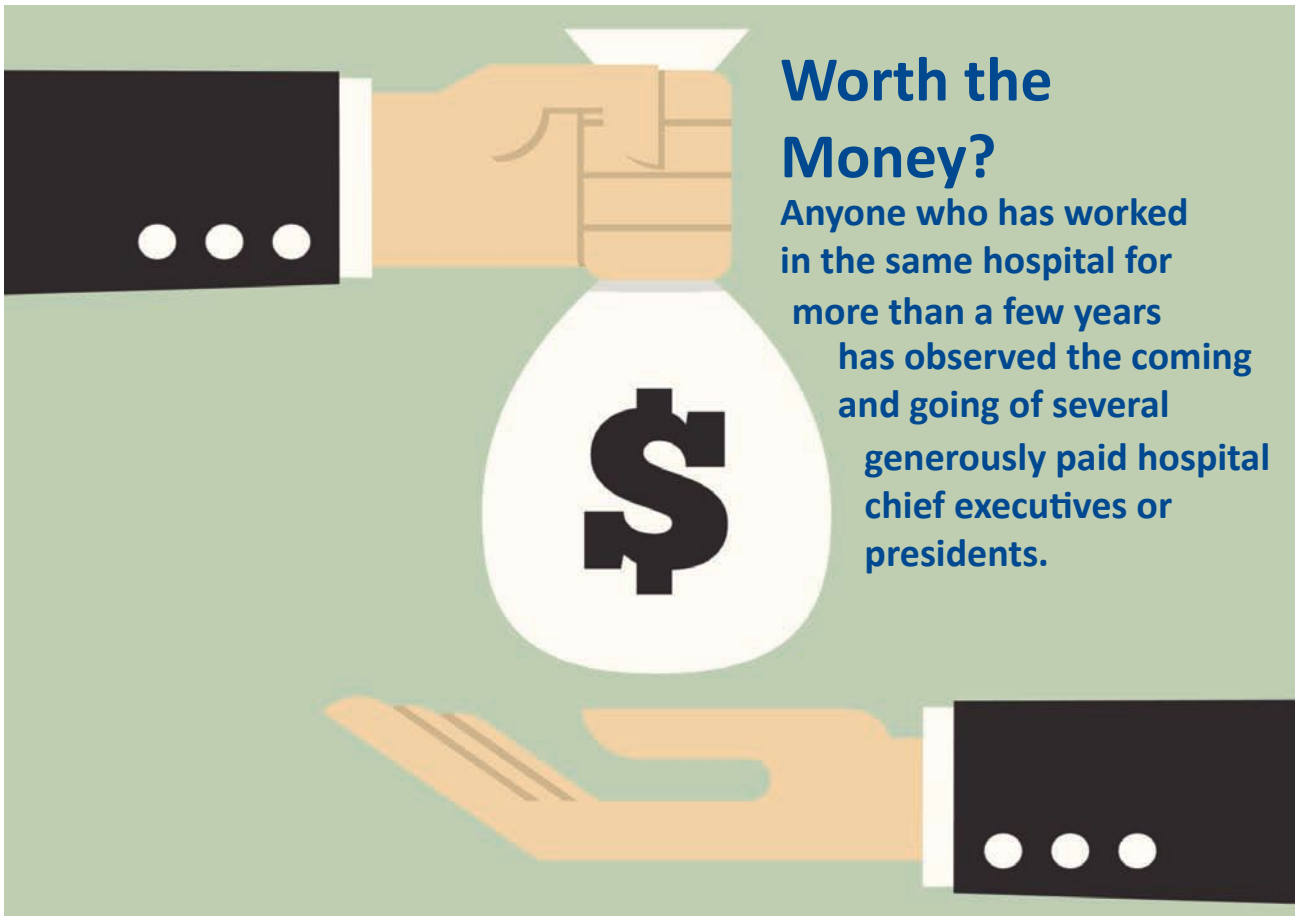
by Jeffrey G. Copeland, MD

Can we liberate doctors and nurses from what is now an onerous level of clerical activity?

With the advent of electronic media, it has become extremely easy to find and disseminate information about not only progress in medical knowledge, but also considerable information about the business of medicine. With growing digital capabilities, opportunities for increasingly complex levels of management have also appeared.

I'm reminded of the patient I had years ago who told me that he had witnessed the bombing of Pearl Harbor from a relative position of safety in Hawaii. He shared his written account of that day with me. That was interesting, but more interesting was what he told me about his work with the government. He worked in accounting for the Defense Department. He designed the first computerized bookkeeping system for the Pentagon. By his description, at that time the Pentagon was, from a budget standpoint, more segmented, and individual parts of it had their own silos of management and their own assets which were more or less invisible to other areas. He came along with his program that was able to keep track of all the financial information from all the areas at one time, thereby interfering with business as usual. His project was, of course, challenged, but he had taken the step of trying the system out away from the Pentagon, and had effectively worked the bugs out of it so that when it did go live, it worked well. Clever man.

Obviously, he created some problems for people who had sequestered monies for their area. It changed the style of management and truly introduced some transparency that was lacking. My patient's project was successful and not



inherently good or bad, but it did change things. From the standpoint of those whose responsibility was management of the money, it was progress. For those who had worked to make their area of defense activity as strong as it could be, it was intrusive. His system's value really depended upon which side of the fence one was on. Neither side had bad intentions, but some were better than others.

In medicine today, we have an analogous situation where health care system managers and business people can collect a lot of quantitative information about the "efficiency" of health care delivery. It only makes sense that their orientation is toward reducing costs and increasing profit. (Did I say profit? I must be confused). From my viewpoint as a private physician, this is not a direction that inherently produces improved health care or increases my ability to provide for my patients' needs or increases my efficiency or effectiveness.

In fact, in my sphere, it seems to have the opposite effect. It pushes physicians to see more patients and, increasingly, to become employed by health care systems which use their information, or the control of the collection of the information, to watch over the financial welfare of whatever entity they are. There are now myriad rules and requirements from the federal government that must be met to receive maximum reimbursements. Those requirements may occasionally have a positive impact on our patients' welfare I believe that does nothing to provide incentive to produce the kind of health care information systems that we could have if priorities were switched to making the physician-patient relationship as good as it can be.

I am also concerned about the current way that hospitals and systems are empowered to game the system. They can designate the offices of employed physicians as "outpatient clinics," deemed extensions of the hospital, and are then allowed to charge a "facility fee," on top of the professional fees normally charged for the service. This ostensibly helps the hospital cover its costs of doing business, like housekeeping, etc. Additionally, they can charge a higher professional fee for the same service because the billing is coming from an employed physician. A private, non-employed physician is allowed no facility fee, but carries those costs of maintaining the office with no offset and then can only charge the lower professional fee. If I were a health care system and this opportunity presented itself, I would accept it, but it really seems that the system is out of balance, especially when we are trying to conserve resources. How will that all play out when we are "value-based" instead of the current system? If the systems remain in the driver's seat, they will still have control over the division of reimbursement.

Employed physicians do get an umbrella of security over them, with less headache about day-to-day management, less worry about consistency of income and sometimes a better, more predictable schedule. I can understand the desirability of that. But, there is some unavoidable diminution of the relationship with the patient. The patients belong to the system now. This is clear if the physician leaves the system. Those records don't travel well.

I cannot resist repeating that the current tools for keeping electronic records are not as well designed as they could be. This came home to me again when I was speaking with a new mother who had a book of neonatal baby photos produced by a company which does that exclusively. She told me that the book, including photos and layout, was ready for her approximately 10 minutes after the photos were taken. It included different page layouts, meaningful phrases which were appropriate to the photos and good physical quality, almost immediately.

We have technology that can easily produce such result, or affordable 3D printers for personal use or video communication of good quality which my mother can use without having to understand a lot of technical information. We have reasonably good voice recognition software that is helping me prepare this message right now. To me, it seems clear that the focus of the technology has everything to do with how well it works, because the building blocks for building incredible things are right there. And, there is huge money as an incentive to the development of efficient, easy to use medical information technology.

So where is that technology which can help us care for our patients? Nowhere, right now, because the people who are funding it lack the appropriate focus to achieve what we physicians and our patients, who are the recipients of the health care we provide, would really like.

Maybe if that doctor-patient technology became available, patient care would "magically" improve because we could find the things we need when we need them and not spent a lot of time generating information that has little use. We might also liberate doctors and nurses from what is now an onerous level of clerical activity. We might be able to communicate between doctors and nurses without barriers so that issues like transition of care and continuity could be made much more seamless. Simply stated, our tools are not aligned with our goals.

Health Care Executive Reimbursement

On an unrelated topic, Medscape on July 2, 2014, referenced a report in the *New England Journal of Medicine-Internal Medicine*[1] The thoughtful author of this article, K.E. Joynt, MD, was discussing the reimbursement of health care executives. I have been aware for a long time that people in those positions are very well remunerated. Often, their income is shielded from curious eyes by various business maneuvers, but by all accounts, they make excellent incomes. It was pointed out that changes in the IRS form 990 which not for profit organizations are required to file yearly have now made discovery of some of those salaries easier. The usual series of reasons that those people are "worth the money" were referenced including significant responsibility, lack of a big supply of people with those capabilities and the perceived need to retain executives at that level. This last seems a little shaky to me because anyone who has worked in the same hospital for more than a few years has observed the coming and going of several hospital chief executives or presidents. Their lifespan in a given position tends to be short. Granted, occasionally a president will stay in their position for decades, but that seems to be the exception.

Additionally, it was pointed out that there does not appear to be a lot of relationship between the performance of the institution or system and the degree of reimbursement. The rest of us are now measured by our "quality" and if it does not meet certain rather questionable standards (including cost effectiveness) we may be "deselected." In the same setting, executives may enjoy substantial bonuses.

And that does not even touch the health insurance company CEOs. The top 11 companies' CEOs average income was $11.3 million. And top biotech company leaders average $18.3 million/year according to *Forbes* for 2012.

I think it is time for invocation of that magical word, "Transparency," in this realm. And a sense of proportion. That money could buy a lot of patient care.

Finally, a Couple of Requests

Please pay attention to the AMA's grassroots activities to strongly encourage Congress to get rid of the Sustainable Growth Rate and replace it with some rational alternative.

Talk to your local state politicians about Tort Reform in our own state. If we act now, we may be able to avoid the problems with expensive insurance and loss of physician workforce and patients' access to care.

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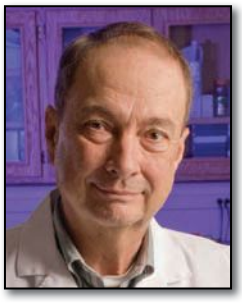
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Missouri Delegation Continues in Leadership Roles at AMA

by Charles Van Way, III, MD

The AMA adopted a policy urging Congress to fix the problems, and urging the President to allow veterans access to health care outside the VA system.



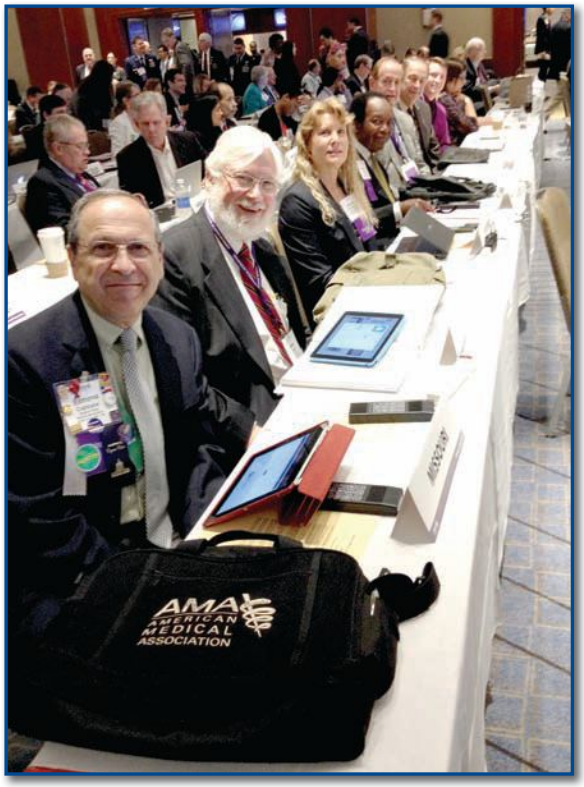
Charles W. Van Way, III, MD, FACS, FCCP, FCCM, MSMA member since 1989 is an Alternate Delegate in the Missouri Delegation to the American Medical Association and Missouri Medicine Contributing Editor. Content contributing by the MIssouri Delegation.
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Your Missouri Delegation continues to have an impact on the American Medical Association. The AMA House of Delegates held its annual meeting in Chicago, June 7-11, 2014. Especially prominent at the meeting were David Barbe, MD, Mountain Grove, who continued as Chair of the AMA Board of Trustees. Edmond Cabbabe, MD, of St. Louis, serves the AMA as President of the AMA Foundation. He also ser ves as Chair of the Heart of America Caucus, consisting of Missouri, Kansas, Oklahoma, and Arkansas. Like most other states, we join with other state delegations in our region to ensure that our voice is heard in all of the reference committees and deliberations. Rebecca Hierholzer, MD, of Kansas City, served as a member of Reference Committee D, which deals with public health issues.

The exposure of substandard care and long waiting times at the Veterans Affairs health care system was of particular concern to the House of Delegates. The AMA adopted a policy urging Congress to fix the problems, and urging the President to allow veterans access to health care outside the VA system. A letter was sent to President Obama on June 10, during the meeting, urging him to use the private health care system to alleviate the stress on veterans unable, because of geography or waiting time, to obtain timely care in the VA system.

This year, more than 1,000 MD and DO graduates from U.S .schools were unable to find residency positions after graduation. There simply aren't enough jobs to go around. This year's group adds to the growing pool of young physicians who cannot continue in their training. The AMA did pass several resolutions and one report. All supported the idea that someone should find alternate and novel methods of paying for additional residency positions. Other wise, the House of Delegates did its best to ignore the issue. As we all know, there is a new Missouri law which allows recent medical school graduates to practice as assistant physicians under the guidance of mentors in private practices. This came under harsh criticism. Resolution 324 was passed, setting the AMA in opposition to all such attempts to provide alternate pathways for those graduates unable to find residency slots. In view of the obvious appeal of such programs to other state legislatures around the country, the AMA's action would seem to be going against the tide.

Nonetheless, it is now AMA policy that new graduates cannot have privileges equal to those given to physician assistants and other paramedical personnel. We can only hope that wiser heads will prevail next year, and that the AMA will find ways to keep these young physicians in the profession. And the AMA needs to take the lead with specific proposals to increase the number of residency slots available, so that no graduate will go untrained.



Missouri physicians from left: Drs. Ed Cabbabe, James Conant, Rebecca Hierholzer, Nat Murdock, Bill Huffaker, Charles Van Way, MD, and Nathan Nolan, Medical Student, represented their colleagues at the AMA Annual Meeting in June and tackled issues such as quicker care for veterans, maintenance of certification, telemedicine, e-cigarettes, and better electronic data interchange.

Maintenance of certification, always a contentious issue, attracted considerable attention. The AMA is particularly opposed to linking maintenance of licensure with MOC. Beyond that, the AMA is now committed to working with the credentialing organizations to ease the burden of MOC on practicing physicians. There was much discussion at the meeting concerning this. Most physicians recognize the need for MOC, both to maintain competence, and to reassure the public that physicians are maintaining their skills. But there was general agreement that MOC has become overly burdensome. This seems to be especially true in the medical subspecialties, but is true to some degree across the profession. The AMA will continue to work in this area, to ease the burden on practicing physicians.

The failure by Congress to reform the Sustainable Growth Rate formula once again this year was addressed by Ardis Dee Hoven, MD, the outgoing AMA President. She felt that we were closer to the goal than ever before, with bipartisan support in both houses of Congress. The AMA will continue its efforts to achieve repeal of the SGR. However, we would be remiss if we did not refer to the editorial by Charles Van Way, MD, in the May/June issue of Missouri Medicine.[1] As he pointed out, Congress has a great deal of incentive to keep things just the way they are.

Dr. Hoven also commented on the one-year postponement of implementation of ICD-10. The AMA will continue to oppose the implementation of ICD-10, and to work to minimize its negative impact on medical practice. She also noted that the famous "data dump" of Medicare billing data was full of errors, and has been mined by newspapers to reach completely misleading conclusions. While this particular cat is roaming free of the bag, she promised the AMA will work with the Center for Medicaid and Medicare Services to improve data in the future. Despite her optimism, the "data dump" was a hostile action towards physicians by the Center for Medicare and Medicaid Services (CMS). It is somewhat unlikely that they will moderate their policies in the near future.

There was considerable attention to the recent report from the Rand Corporation. In 2012, the AMA commissioned the Rand Corporation to conduct a survey of factors affecting physician professional satisfaction. Given the many changes in the health care system, it was felt that such a study would help the AMA to promote physician well-being and professional satisfaction. The report is quite well done, and is too long to even summarize here. However, a major and unexpected negative factor came out of the survey: the electronic health record. To quote the report:

"The current state of EHR technology appears to significantly worsen professional satisfaction for many physicians, sometimes in ways that raise concerns about effects on patient care."2

It should be pointed out that the Rand Corporation has long been a major advocate for electronic health records. Their finding that EHR's are a major problem is certainly not a surprise to physicians. The AMA takes this issue very seriously, and proposes to work towards improving EHRs.

There was a great deal of other discussion on EHRs. One Board of Trustees report addressed the issue of "copy and paste," as well as a number of other usability issues. A second Board report addressed the costs of transitioning to electronic medical records. Several resolutions adopted by the House of Delegates called for improvements in the use, practicality, and functionality of existing EHRs. Many issues were raised by discussants. Physicians are strongly resisting becoming data entry clerks. Indeed, it is difficult to see how turning physicians and nurses into highly paid typists will significantly advance health care. The whole "copy and paste" issue is that physicians are trying to save time while still completing the required documentation. This practice

The new Missouri law which allows recent medical school graduates to practice as assistant physicians under the guidance of mentors in private practices came under harsh criticism at the AMA. Resolution 324 is new AMA policy that states new graduates cannot have privileges equal to those given to physician assistants and other paramedical personnel.

seems to offend those who designed the systems, most of whom are not, of course, physicians. Improvement of electronic records will become a recurrent theme at the AMA, and rightly so. There seems general agreement that most do not want to go back to paper and pen, but that EHRs are clearly not anywhere near their potential. Much improvement is needed.

Related to this was adoption of a policy to tr y to persuade the Center for Medicare and Medicaid Services to suspend the e-prescribing requirements for meaningful use. Discussion revealed that most pharmacies don't accept them. It is therefore unreasonable to require physicians to use them in a specified percentage of their prescriptions. Whether CMS will respond favorably on this issue remains to be determined. The second phase of meaningful use has been widely criticized as being unattainable for the practicing physician, but that may have been their purpose. In any case, the AMA will keep pushing on this issue.

Insurance coverage and payment for telemedicine services has been an ongoing issue for several years. Without payment for telemedicine, the potential advantages of such services will be lost. The House adopted a set of principles or guidelines for telemedicine services to abide by in order to receive adequate reimbursements from payers. These principles include descriptions of face-to-face encounters, recommendation of consultation and coordination with that patient's primary care provider, and a statement that such services must abide by state licensure laws.

Of particular interest to those of us in the nutrition field, the House approved a resolution endorsing the use of nutrition support teams in treating malnutrition in hospitals, as well as advocating payment mechanisms for the reimbursement of their services. It was pointed out in the resolution that while the Joint Commission mandates nutrition screening of hospitalized patients, malnutrition is still common in hospitalized patients. Treatment is often neglected. While nutrition support teams were relatively widespread in the 1980s and 90s, their use has dropped considerably. Many hospitals have no organized system for treating malnutrition. Recommendations by dietitians are routinely ignored. CMS has begun to treat this as a safety issue. Health care facilities have been inspected and sanctioned for neglecting the nutritional care of patients.

The Medical Student Section introduced this particular resolution, and a number of others. The MSS was very active in the reference committees and on the floor of the House, as well. It is encouraging to see the extent to which today's students are active in the AMA. It bodes well for the future of organized medicine and of our profession.

One of the more controversial topics at this year's annual meeting included a proposal for the AMA to conduct a national sur vey of US physicians, asking the question, "When considering the topic of health care reform, would you prefer to make improvements to the current public/private system, or a single payer system such as a 'Medicare for all' approach?" With a hefty price tag and the consensus that the AMA House of Delegates adequately represents state and specialty societies on such matters, the proposal met with defeat.

And then there is cheerleading. As anyone who follows high school and college athletics, "cheer" has become a highly structured, athletic sport, with many elements of gymnastics, and is a popular activity both for spectators and participants. But with the increasing complexity of the "stunts" done on the field comes a significant risk of injury. In fact, cheer is the most significant cause of injuries in young women athletes. A major reason for this is that, under National Collegiate Athletic Association rules, it isn't a sport. Therefore, most of the protections built into youth sports, such as use of trainers, coaching support, and so on, are lacking. After a great deal of largely positive debate on this issue, the AMA declared that cheerleading is a sport. This doesn't compel the NCAA to do anything, of course – nothing does, other than money – but it strengthens the hand of those responsible for the welfare of young athletes.

Why isn't cheer already a sport? Children start it in grade school. There are summer camps for cheer. It has all of the characteristics of a sport. The problem revolves around Title IX. This legislation has greatly increased opportunities in women's sports. But if cheer becomes a sport, then it would allow colleges to count cheerleaders as women athletes, with a possible adverse effect on the support for other women's athletic activities. Since nobody wants to upset the status quo, it remains a "non-curricular activity." And participants injure themselves, disproportionately to other sports. The House, after considering these arguments, decided that our concern should only be for the young athletes, and they will be best served by a declaration by the AMA that it is indeed a sport.

Brain damage to young athletes continues to be a matter of great public health concern. Three resolutions addressed concussions in young athletes, one concerning "heading" in soccer, and two more generally. These were all referred for consideration by the Council on Public Health, which will, it is hoped, recommend further action by the AMA.

So-called "vaping" was the subject of at least a half-dozen resolutions. E-cigarettes, in which a solution of nicotine is vaporized by a microprocessor-controlled heating element, were introduced only 10 years ago. But their use is spreading widely, both through internet sales and retail shops. Soon, major tobacco companies will begin to advertise and sell them. Disturbingly, they are often marketed to teens, and there is some concern that they may be a "gateway" to cigarette smoking. On the other hand, advocates feel they can be an aid to smoking cessation. Evidence for either position is scant. We don't really know the hazards of their use. The final position adopted by the House of Delegates is that they need to be regulated more strongly, especially as they may be used by children and teens, and that the FDA is the appropriate regulator. Marketing to children and teens should be strictly limited. With the FDA soon bringing out regulations on e-cigarettes, the AMA is prepared to support better regulation.

The important subject of physician ethics was the subject of an excellent Board of Trustees report. After a great deal of discussion, the report was referred back to the Board, rather than being adopted. Apparently, medical ethics are so complex that the House cannot agree on a unified approach. The Board will try again next year. Other Board of Trustee reports recommended improved availability of mental health services for school-aged children and easing barriers to permit transferring pediatric medical orders between states.

A number of issues related to the Affordable Care Act and the Center for Medicare and Medicaid Services. Resolution 707 addressed the issue created by the ACA whereby patients may have insurance provided by insurance exchanges that may not be in force due to lack of premium payment. Several resolutions identified areas where physicians are being asked to provide unreasonable documentation for patients to obtain CMS services. Documentation should be standardized, with reimbursement for their completion, or else eliminated. Unnecessarily complex authorizations create barriers for patients, and are unreasonably burdensome for physicians.

The AMA continues to advocate for physician leadership for medical team care. This includes team care in hospitals and outpatient settings, medical home programs, and all the rest of team care. The Council for Medical Services issued a report addressing this issue, and there was considerable discussion.

Participation of community physicians on hospital staffs was a particular concern of resolution 701. There is a growing gap between physicians who work on hospital staffs and physicians who work in the community. While this is a particular issue for primary care, many specialists are focused on outpatient medicine, as well. Retaining the interest and participation of community physicians on hospital staffs is difficult, but essential if proper coordination between in-patient and out-patient care is to be achieved.

The AMA has decided once again to maintain dues at their present level. Dues have remained the same for the past 11 years. The AMA has increased membership over the last four years, after a long decline. This, together with the obvious increase in the involvement of medical students in the organization at all levels, is very good news.

At the presidential inauguration ceremony, Board of Trustees Chair David Barbe, MD, Mountain Grove, administered the oath of office to the incoming President of the AMA, Robert M. Wah, MD, of McLean, Virginia. Dr. Wah is a career Navy physician. A reproductive endocrinologist by specialty, he has been strongly involved in the information technology activities of the Department of Defense, and is currently involved in the computer sciences industry.

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Retail-Based Clinics & the Patient-Centered Medical Home

by Kirsten Weltmer, MD, Nasreen Talib, MD & Keith Mann, MD

The American Academy of Pediatrics concludes that retail-based clinics are not appropriate sources of primary medical care for children due to the fragmented, episodic nature of the care they provide.

With drive-thru banking, fast food restaurants, Twitter, and 1-hour photo, is it any wonder that we would come to expect our health care in a similar manner? It is estimated that there are over 1,600 retail-based clinics[1,2] operating now and these numbers are growing in response to health care consumers seeking convenient, quick, accessible and affordable care.

Most of these retail-based clinics are do not require appointments, have extended clinic hours on evenings and weekends and are more affordable than a trip to the local emergency room.[3,4] Initially designed to provide care for a limited number of pressing but non-emergency conditions, some retail-based clinics are now marketing on their websites preventative care, physicals, health screening services, vaccines and chronic disease monitoring.

Patient-Centered Medical Home

The American Academy of Pediatrics (AAP) continues to question the role of retail-based clinics in the care of children in a recent policy statement.[5] The AAP concludes that retail-based clinics are not appropriate sources of primary medical care for children due to the fragmented, episodic nature of the care they provide. Fragmented care often doesn't have necessary follow up and lacks integration with the patients' primary medical home. Coordinated, longitudinal care associated with the transformation many practices see when adopting a medical home model has been associated with improved outcomes and, at least in adults, at a lower cost of care.[6,9,10] With this in mind, the standard of care for children should be a medical home



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where the physician has received specialty training in the care of children and their specific health care problems. The physician should have an ongoing relationship with the patient and family. The care provided in the medical home should be high quality, coordinated, long-term and 'whole person' health care. (See Figure 1.)

Addressing the Gap

While the principles of the patient-centered medical home are hard to argue, retail-based clinics that provide episodic, acute care outside the traditional medical home have clearly found a place in the pediatric health care market. Patients are consumers of health care, and in their use of retail-based clinics they are sending a clear message that convenience, efficiency, extended hours, and cost are important, especially in the context of acute care. This should not be surprising. When asked what factors most influence the choice of primary care physicians, patients most commonly state convenience and proximity to the home or workplace followed by quick relief from acute illness.[7] Once continuity of care is established, comprehensive and coordinated care becomes more valued. Pediatricians are thus stuck with what appears to be competing patient demands; the need to provide comprehensive, coordinated, and holistic care while being flexible enough to allow for walk in or same day appointments with extended hours. This is increasingly difficult to achieve, especially in smaller practices, while also maintaining a modicum of work-life balance.

Merging Continuity and Convenience

A patient in a medical home has a single primary care provider that is responsible for all aspects of health care, including preventative and wellness care, chronic disease management and acute care. A number of studies document improved outcome measures and improved patient and provider satisfaction when a single provider is in charge of the patient's medical care.[8-10] In the medical home, the patient should have the reasonable expectation to see their primary care provider who best understands their medical history and future health care needs for both preventative care and acute care needs. To match patient demands, scheduling processes should allow for same-day access to the primary care provider for acute visits. If health care consumers use these occasions to seek care from retail-based clinics, the opportunity for the primary care provider to address chronic disease management and preventative care is missed. Adding value to each patient visit by addressing preventative care needs or chronic disease management may provide the impetus to the consumer to return to the primary care office.However, when visit types were compared between retail-based clinics and visits to the primary care office, in only 11% of the visits to the primary care office were preventative care ordered or delivered.[11] In order to compete with the convenience factor, primary care offices should be willing to work to add increased value at every patient encounter offering preventative care and chronic disease management when applicable.

Health care consumers reported that an advantage to retail-based clinics were their close proximity to home, walk-in appointments, little to no wait times and accessible hours including evenings and weekends. In order to compete, medical home practices should be willing to meet the needs of their patients by providing same day access and access to routine and acute appointments outside of regular business hours. With the available advances in technology and increasingly tech-savvy patients, providing timely clinical advice by phone, patient portals or by secure electronic communication during and outside of regular business hours meet the demands of convenient access.

For practices unable to meet the demands of both continuity and convenience, the AAP suggests developing collaborative relationships with retail-based clinics to expand access to their patients while continuing to foster the principles of the medical home. In such a model, both parties should agree to the scope of practice, disease specific evidenced based standards of care, shared medical records and/or prompt communication, and referral back to the medical home for ongoing care.[5]

Providing Cost Efficient Care

For patients seeking care from retail-based clinic, it is estimated that nearly one-third of health care consumers are paying out-of-pocket compared to 10% in the primary care setting.[11] Indeed, the retail-based clinic may offer out-of-pocket savings for the uninsured consumer seeking health care for minor illness when the alternatives include high cost emergency room care. Despite the short term cost savings offered by the retail-based clinic, it is fragmented, episodic based care that has contributed to the current state of inefficient and costly health care system that is not sustainable.[12] Bringing care back to the medical home, with a focus on prevention, follow up and continuity can help drive positive outcomes without adding to the global fixed costs of health care (i.e. space, salaries for presumably unnecessary retail-based clinics).

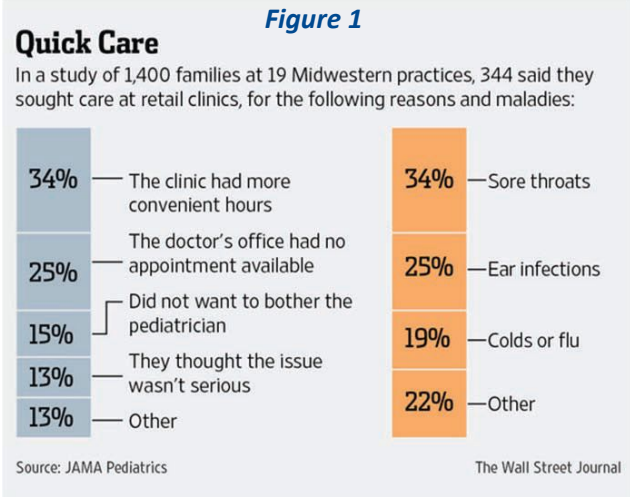
The policy statement put forth by the AAP expresses the view that the standard of medical care for children is

the medical home with a provider specifically trained in children's health care issues. The AAP further states that retail-based clinics are inappropriate source for primary care for children. In order to meet the demands of the pediatric health care consumers, the primary care medical home must provide quality, organized and evidence based care that is also accessible and convenient. That's what patients expect from us.

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Figure 1



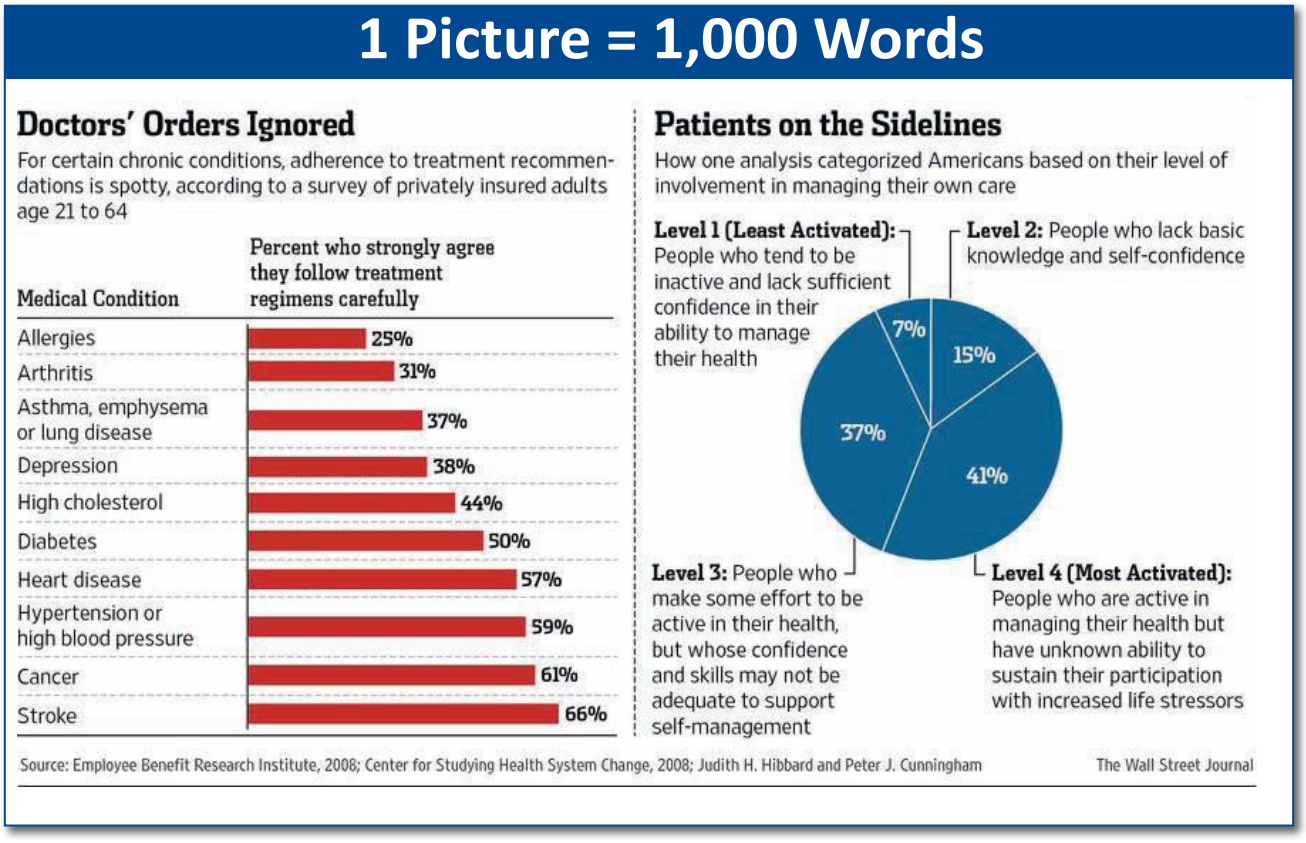
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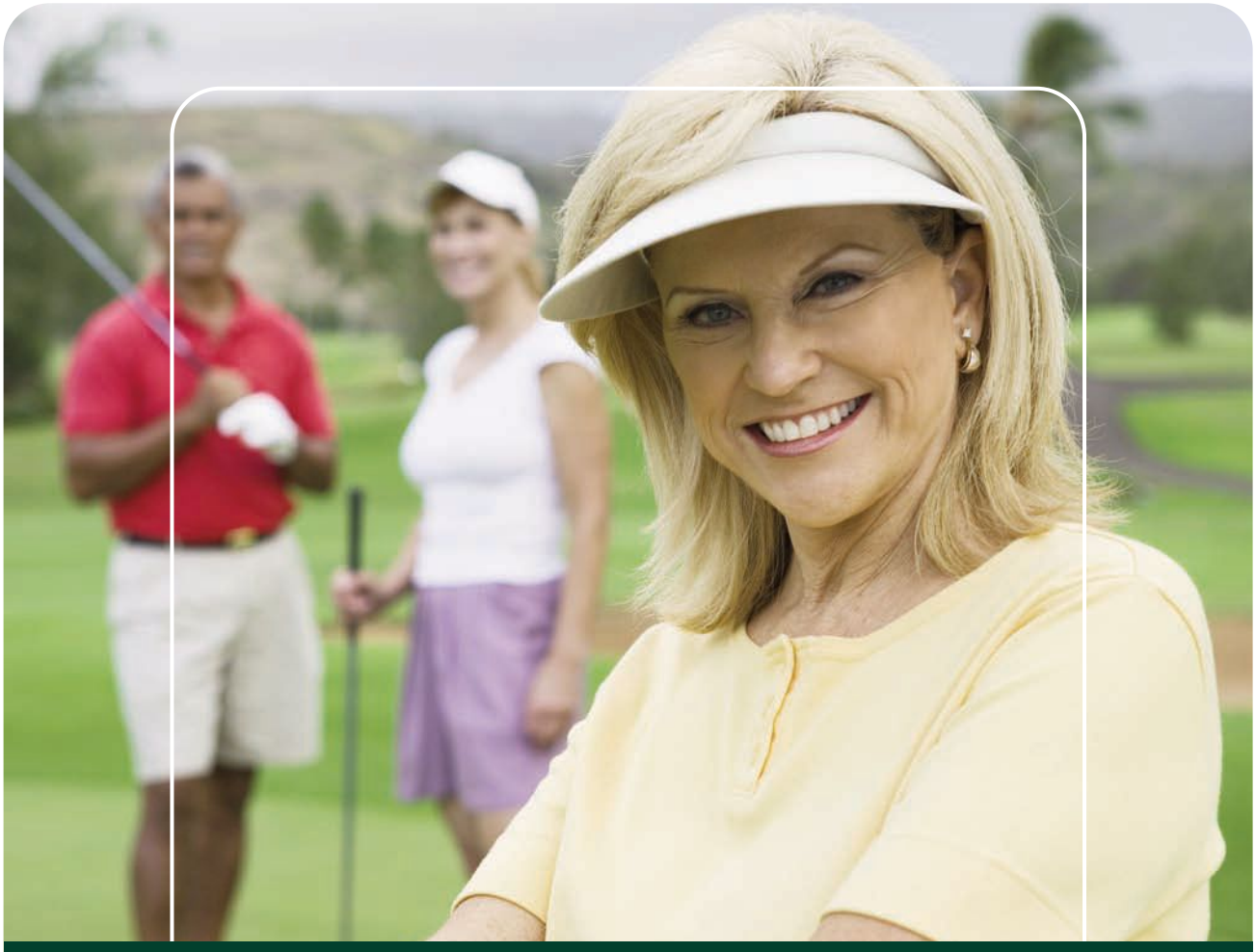
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Figure 1: JAMA Pediatrics/Wall Street Journal

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1 Picture = 1,000 Words





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Research Continues on New Vaccines and Biologics at the Saint Louis University Center for Vaccine Development

by Daniel F. Hoft, MD, PhD

In 1989 Robert B. Belshe, MD, founded the Saint Louis University (SLU) Division of Infectious Diseases & Immunology and the SLU Center for Vaccine Development (CVD). At its inception there were four Infectious Disease faculty members. Over the past 25 years the Division has grown to include 17 faculty members. In 2011, Dr. Belshe stepped down from being division chief, and Daniel F. Hoft, MD, PhD, became the new Director of the Division of Infectious Diseases, Allergy & Immunology. The SLUCVD involves the majority of the Division's faculty members in its research mission. Dr. Belshe remains the overall Director of the SLUCVD, with Dr. Hoft directing the laboratory and international components of the center, and Sharon E. Frey, MD directing the clinical vaccine trials unit. Overall during the last 25 years, the SLUCVD has conducted more than 100 funded studies comprising a portfolio of diverse Phase I, Phase 2, Phase 3 and Phase 4 trials that enrolled approximately 7,000 volunteers.

The SLUCVD is a multi-disciplinary research center designed to conduct basic and clinical research on new vaccines and biologics. The Center is made up of highly-trained researchers who have a long track record of successfully conducting vaccine studies. Researchers at the Center recognize the increasing need for a multidisciplinary approach to vaccine development which encompasses an understanding of pathophysiology, immunology, molecular biology and epidemiology. This diversity of expertise is found at the SLUCVD. Some of our key scientific contributions to date include clinical development of the Flumist vaccine (the live attenuated influenza vaccine), development of safe and effective vaccines for Smallpox and other potential bioweapons, defining the detailed human immunologic responses induced by BCG vaccines with the goal to develop more effective TB vaccines, and testing of new experimental vaccines designed to protect against pandemic influenza, herpes simplex, hepatitis C, Dengue, pneumococcal pneumonia/meningitis and pertussis. In addition, the SLUCVD has figured prominently in national preparedness efforts to enhance protection against emerging infectious diseases (e.g. - emergent 2009 H1N1 and H7N9 pandemic influenza vaccine testing), prompting visits by Secretary of Health and Human Services Kathleen Sebelius to our center and awards from BARDA.

This year will mark 25 years of continuous NIH funding for the SLUCVD. More than $150 million have been attracted to SLU for research on vaccines due to the presence of the CVD and its investigators. One large NIH contract, the NIAID-sponsored Vaccine & Treatment Evaluation Unit (VTEU), accounts for about 30-40% of the $6-8 million in extramural funding received annually by the center for more than the last 10 years. The majority of the non-VTEU extramural dollars awarded to SLUCVD investigators represent RO1, R21 and other NIH grants awarded to individual investigators in our group. The SLUCVD successfully re-competed for the next cycle of VTEU funding in 2013. This next 10 year VTEU cycle will continue until 2023 and is expected to bring at least another $50-75 million to SLU for vaccine development work.

The following *Missouri Medicine* feature focuses on five major current research interests of faculty within the SLUCVD. **MM**



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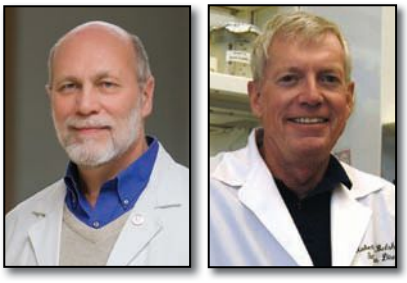
SAINT LOUIS UNIVERSITY

Center for Vaccine Development

Progress Toward the Development of Universal Influenza Vaccines

by Daniel F. Hoft, MD, PhD & Robert B. Belshe, MD

Influenza remains a major threat to human health and improved vaccines with broader heterotypic/ heterosubtypic cross-reactivity are needed.



Daniel F. Hoft, MD, PhD, (left) is Professor and Director, Division of Infectious Diseases, Allergy & Immunology, and Robert B. Belshe, MD, MSMA member since 2013, is the Adorjan Endowed Professor of Medicine Pediatrics and Molecular Microbiology in the Departments of Internal Medicine & Molecular Microbiology at Saint Louis University.
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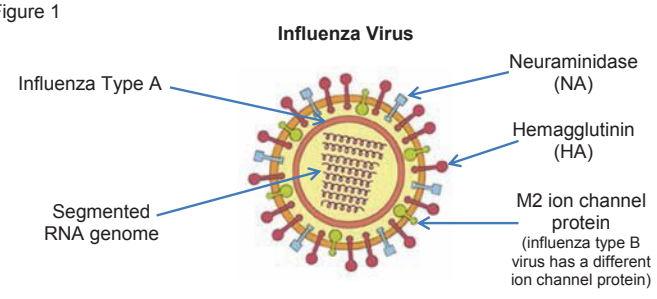
Abstract

Influenza remains a major problem causing significant morbidity and mortality annually and periodic pandemics with the potential for 10-100 fold increased mortality. Conventional vaccines can be highly effective if generated each year to match currently circulating viruses. Ongoing research focuses on producing cross-protective vaccines that induce T cell and/ or antibody responses specific for highly conserved viral epitopes. The Saint Louis University Center for Vaccine Development (SLUCVD) is highly engaged in multiple efforts to generate universally relevant influenza vaccines.

Introduction

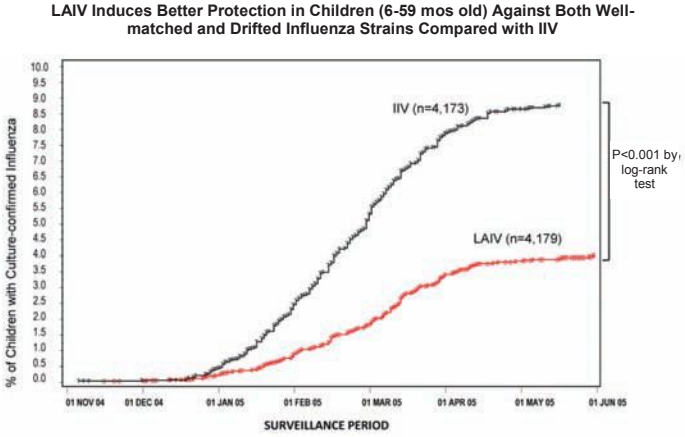
Influenza continues to be a major threat to human health. Every year, thousands of persons in the U.S. die from complications of influenza infection. Usually the elderly, young children and pregnant women are particularly susceptible to severe complications, but with some pandemic strains, over-exuberant inflammation in response to lower respiratory infection seems to disproportionately affect the middle-aged and younger adult populations. Effective vaccines have been available for the past 50 years, but must be given annually to optimally protect against the diversity of new strains that circulate over time. The influenza genome contains eight segments (See Figure 1), and is prone to high error rates during viral replication. The high mutation rate results in extensive genetic diversity, especially within the surface proteins Hemagglutinnin (HA) and Neuraminidase (NA). These molecules are constantly under intense immune pressure as major targets for viral specific, immunoprotective antibodies. The random mutation or genetic drift, combined with the selection of immune escape mutants, renders vaccine immunity involving primarily HA/NA specific antibodies of only transient efficacy against the seasonally emerging strains that disseminate worldwide. Current vaccines targeting primarily the induction of HA-reactive antibodies specific for seasonal circulating strains must be administered yearly to be maximally effective. Some years when the vaccines are poor matches for the major strains that unpredictably emerge, significantly increased influenza morbidity and mortality occurs. Additionally some groups (elderly and young children)

Figure 1



- 8 genome segments (reassortment →pandemic shifts)
- HA/NA highly variable (antigenic drifts)
- Internal proteins more conserved

Figure 2



respond less well than healthy adults to HA antigen when it is injected as vaccine.

The segmented influenza genome also presents the opportunity for genetic reassortment between different viral strains when the same human, pig, bird or other animal is infected simultaneously with two influenza viruses. This reassortment generates new chimeric viruses with some genomic segments derived from each of the infecting strains. Occasionally reassorted viruses can efficiently replicate within and transmit between humans, as well as express HA and NA types that have not previously circulated in contemporary human populations. The resulting pandemic virus with shifted surface proteins may result in cataclysmic public health consequences. It is believed that the 1918 H1N1 pandemic strain killed 50-100 million persons in a period of about 18 months. These features of the biology of influenza continue to present major challenges for public health efforts focused on prophylactic vaccine strategies.

There are two major types of influenza vaccines currently available. The inactivated influenza vaccines (IIV) contain primarily HA protein (and some NA protein that co- purifies with HA during manufacture). The HA is derived from 3 (trivalent vaccine) or 4 (quadrivalent vaccine) strains representing the major circulating viral pathogens each season. High (for elderly), standard (for ages >3) and low doses (for children 6-35 months) are licensed for intramuscular administration and some (licensed in Europe but not the U.S.) have included adjuvants. One intradermally administered vaccine is available. These IIV induce HA-specific antibodies, with a serum endpoint titer in highly standardized hemagglutination inhibition (HAI) *in vitro* assays of at least 1:40. This titer is known to provide at least some protection against influenza strains expressing the specifically targeted matching HA sequences. The IIV can be highly protective if given annually to young and middle aged populations but are less effective in infants, the elderly and the immunosuppressed.

Live attenuated influenza vaccines (LAIV) are reassortment viruses generated with genomic segments expressing nonstructural proteins with attenuating mutations and HA/NA-encoding segments from seasonally circulating viral strains. These LAIV are delivered intranasally. Work led by Dr. Belshe and our Saint Louis University Center for Vaccine Development (SLUCVD) demonstrated that LAIV vaccination was more effective in children than IIV vaccination (See Figure 2).[1] The improved efficacy in children is most likely due to the induction of serum antibodies, secretory IgA (sIgA) and cell-mediated immunity (CMI); i.e., a more complete immune response than is seen in children given IIV. In adults LAIV is also effective, however several comparative studies have suggested equal efficacy or a modest advantage to IIV. Of interest, HA-specific serum antibody responses induced by LAIV in adults have not been highly predictive of protective immunity, further suggesting that either sIgA and/or CMI can be important.

The additional immune responses induced by LAIV responsible for inducing increased protection in children and the protection in adults seen in the absence of increased serum HAI antibodies are unclear. As mentioned above, LAIV has been shown to induce T cell responses and sIgA which likely are involved. Dr. Hoft's lab has recently shown that LAIV induces influenza-specific CD4+, CD8+ and γδ

T cell responses in children not induced by IIV in children, including T cells specific for highly conserved epitopes encoded by internal/nonstructural viral proteins.[2] These T cell responses may be the reason for the LAIV enhanced immunity compared with IIV in children, and could provide cross-protection against widely diverse influenza A strains. In support of this latter possibility, Dr. Gorse in our group also has demonstrated that LAIV induced Cytotoxic T Lymphocyte (CTL) responses with greater heterotypic cross-reactivity than IIV.[3] However, because LAIV is given intranasally, it also induces mucosal immune responses not induced by IIV, and influenza-specific sIgA and/or regional T cell responses in the respiratory mucosa also may contribute to the enhanced immunity induced by LAIV in children, and/or the protection seen in adults in the absence of increased serum HAI responses. Relevant for this latter hypothesis, Dr. Hoft's lab has recently shown that in adults LAIV uniquely induced influenza-specific sIgA responses, without inducing increased serum HAI responses or increased T cell responses (manuscript in preparation). Therefore, depending on the population being vaccinated with LAIV, serum HAI antibodies, T cell responses and/or sIgA all can be important for protective immunity. In contrast, IIV appears to induce predominantly serum HAI antibodies in the absence of major T cell and sIgA stimulating activity.

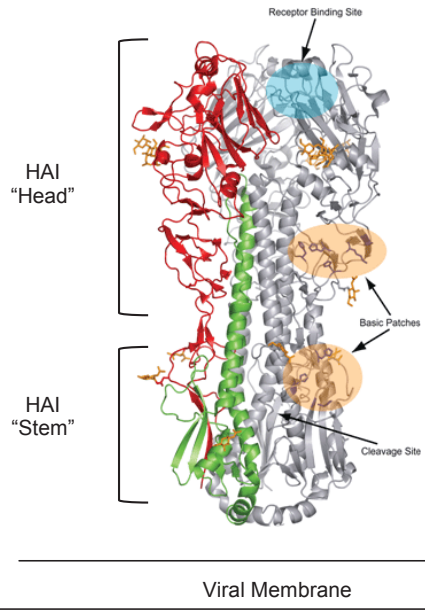
In any case, current influenza vaccines have been developed and optimized based on the induction of immune responses capable of specific recognition of the currently circulating influenza strains, and not for the optimal induction of cross-reactive heterotypic immunity capable of universal protection against all influenza strains capable of being generating during viral evolution. The rest of this manuscript focuses on a summary of ongoing work attempting to develop vaccines capable of inducing more broadly cross-protective influenza immunity, and how the SLUCVD is contributing to these efforts.

Broadly Neutralizing Antibody Strategy

The HA molecule contains both a "head" or HA1 domain that contains the sialic acid/receptor binding pocket important for infection, and a "stem" or HA2 domain that houses the fusion machinery required for delivery of infectious genomes into host cell compartments for efficient viral replication (See Figure 3). HA1 and HA2 are produced as a single protein which is cleaved by host proteases. HA proteins fold into trimeric spike structures on the influenza viral envelope, and most of the HA-specific protective antibodies induced by natural infection

Figure 3

Structure of Influenza Hemagglutinin



and/or current vaccines block interactions between HA and sialic acid receptors preventing infection. The immunodominant HA epitopes that induce the majority of these antibodies usually contain highly variable residues such that the antibodies produced provide protection only against viral strains expressing the exact or highly similar HA molecules, but not against many of the rapidly evolving viral populations.

Over the past decade rare monoclonal antibodies have been generated that display broad heterosubtypic neutralization capacity.[4] Some of these antibodies can recognize and block the HA sialic acid receptor binding site on the top of widely diverse HA "heads," while others bind to the relatively more conserved "stem" domain and block viral fusion. Furthermore, antibodies capable of broad neutralization of influenza B strains appear to prevent virus progeny release from infected cells (SeeTable 1).

Many of these broadly neutralizing antibodies show evidence of extensive somatic hypermutation compared with germline immunoglobulin sequences, which indicates that these antibodies were generated by repeated restimulation of a B cell clone to generate higher affinity antibody variants. This evidence of somatic hypermutation is so extensive in some of these broadly neutralizing antibodies, that it is unlikely that current vaccine technology could efficiently induce these responses. However, at least some of these antibodies with broad neutralizing activity

Table 1
Potential Mechanisms for Influenza Broadly Neutralizing Abs

Targets
Anti-HA "head" sialic acid binding receptor
Anti-HA "stem" fusion blocking
Anti-NA detachment/release inhibition

Challenges
Extensive somatic hypermutation
Immune escape with selective pressure

Table 2
Strategy for Generation of T cell Targeting Pandemic Vaccines

Step 1.	Bioinformatics to identify highly conserved epitopes
Step 2.	Murine studies in HLA transgenic mice to confirm immunogenicity
Step 3.	Immunogenicity confirmation with human PBMC
Step 4.	Vaccine construction/HLA transgenic mouse immunization
Step 5.	GMP/human trials

have been shown to use the VH1-69 germline segment with only a relatively little or moderate degree of somatic hypermutation, suggesting that their induction could be achieved with standard prime/boost regimens using vaccines with the correct antigenic structure. Some progress in inducing these broadly neutralizing antibody responses has recently been reported in Nature using influenza nanoparticle vaccines.[5]

The SLUCVD is engaged in clinical research developing broadly neutralizing antibody responses for avian viruses that have the potential to cause human disease, including H5 and H7 expressing viruses. One strategy has been prime/boost vaccination schedules with vaccines including different HA variants; for example priming with one HA subtype 5 strain and boosting with another. The resulting antibodies were cross reactive for both H5 variants. Another approach has been to induce immune responses directed against the relatively conserved M2 protein involved in viral uncoating inside the infected host cell. We hope to be testing additional candidates focused on the induction of broadly neutralizing antibody responses in the future, as this is a highly promising area for pandemic influenza vaccine development.

Conserved T cell Epitope Strategy

The internal nonstructural proteins in general are much more conserved than HA and NA. Dr. Hoft's group has identified a sequence subset within these proteins conserved by widely diverse influenza A viral strains including H1N1, H2N2 and H3N2 seasonal and past pandemic strains, as well as H5N1 and H7N9 bird flu strains that over the last decade have been found to cause highly severe human infections. Fortunately, most of the H5 and H7 bird flu infections have occurred in limited areas of Asia in subjects with direct contact with poultry or other birds, without evidence of human-to-human transmission. However, if these bird flu strains evolve and develop the ability for efficient person-to-person transmission, they could lead to major future pandemics responsible for massive worldwide morbidity and mortality. We further have identified predicted CD4 and CD8 T cell epitopes within the highly conserved sequence set shared by widely diverse heterosubtypic influenza viruses, and demonstrated that at least some of these T cell epitopes are immunogenic in humans and can induce T cells with the capacity to inhibit influenza viral replication inside human macrophages.[2]

Dr. Hoft has received a new NIH R21 grant recently to generate new "universally relevant" vaccines capable of inducing protective T cell responses against the highly conserved epitopes identified (See Table 2). Our ongoing approach is to use "humanized mice" that express no mouse major histocompatibility complex (MHC) antigens but express single human lymphocyte antigen (HLA) class I and class II alleles. Using dendritic cells generated from these humanized mice, pulsed with our predicted "universally relevant" T cell epitopes, we are vaccinating these same mice and confirming the immunogenicity of individual epitopes in IFN-γ ELISPOT assays. The epitopes confirmed to have immunogenic potential will be included in new DNA and other recombinant vaccines for testing their protective potential in the humanized mouse model. Our current work focuses on identifying protective epitopes restricted by HLA-DR1 and HLA-A2, the 2 most common human class II and class I alleles, respectively, that theoretically could induce immunity in 40-50% of the world's population. Iterative studies with epitopes for additional major HLA alleles will be pursued to design new vaccines capable of inducing immunity in most persons worldwide.

Priming With Single H5/H7 HA in Seasonal Vaccines

"Bird flu" strains expressing H5 or H7 HA subtypes have significant pandemic potential and represent major

threats to public health. Because there have been no H5 or H7 viral subtypes circulating widely among humans during the last 100 years, all human populations are immunologically naïve and highly susceptible to severe disease. These viruses so far have not adapted for efficient human transmission and may never do so. Developing new H5/H7 vaccines with the old HA-specific HAI optimization methods annually for efficacy against the viral strains circulating seasonally in birds could lead to a massive drain on public health resources without any actual benefit.

At Saint Louis University, we are conducting additional studies of another potentially more practical approach. With our VTEU colleagues we have conducted prime/boost clinical trials investigating whether an inactivated H5 HA vaccine derived from a clade 1, Vietnamese strain of H5N1 virus, can prime for enhanced and more rapid immune responses induced by boosting with an inactivated H5 HA vaccine derived from a clade 2, Indonesian strain of H5N1 virus. This is an important question because in persons that are immunologically naïve with regard to a new HA subtype, two doses of standard influenza vaccines (either IIV or LAIV) given at least a month apart are necessary for induction of sero-protective antibody titers. If we could prime with one subtype of H5 HA, and then get more rapid responses to a subsequent distinctly heterotypic H5 vaccine at the beginning of a newly recognized pandemic with the latter H5 subtype, without the need for two doses of the pandemic vaccine, this would greatly facilitate public health efforts to reduce pandemic morbidity and mortality.

In our recent H5 clade 1 priming/H5 clade 2 boosting studies, vaccine-induced immune responses sequentially induced by these two different heterosubtypic H5 vaccines can model for exposure to subsequent seasonal evolution of viral strains associated with annual genetic drift. Almost all volunteers were found to have little to no background HAI activity reactive with either H5 subtype before both the priming and boosting with these vaccines. The clade 1 H5 priming induced heterosubtypic-specific antibodies with HAI activity with clade 1 H5 HA, but only low levels of serum antibodies with HAI reactivity against the clade 2 H5 HA. However, after a single boost with the clade 2 heterosubtypic vaccine given 12 months later, sero-protective levels of antibodies specific for the boosting H5 HA were detectable within eight days and peaked at day 14 (manuscript in preparation). This reduced the time from vaccination to potential protection by months compared with volunteers given placebo during the clade 1, H5 HA priming step. This more rapid achievement of vaccine effect could save thousands to millions of lives during an actual H5 pandemic. Therefore, a possible approach for future seasonal vaccines could be to add H5 HA and/or H7 HA components to prime for more rapid booster effects in time of need.

In addition to studying serum HAI antibody responses with the heterosubtypic H5 clade 1 priming/H5 clade 2 boosting study, we have investigated whether T cell responses directed against the boosting H5 HA antigen or directed against the "universally relevant" T cell epitopes we have previously identified were enhanced compared with unprimed subjects. Similar to the antibody studies described above, clade 2 H5-specific and highly conserved T cell responses were enhanced by this heterosubtypic H5 prime/boost strategy (manuscript in preparation). This priming effect for enhanced T cell responses was detected in subjects boosted one to two years later. Therefore, the addition of an H5 and/or H7 HA component to standard seasonal influenza vaccines may be able to prime for enhanced protective humoral immunity and CMI against future "bird flu" pandemics in humans.

Summary and Conclusions

Influenza remains a major threat to human health and improved vaccines with broader heterotypic/heterosubtypic cross-reactivity are needed. Recent research has provided hope for the development of more "universally relevant" influenza vaccines that target both broadly neutralizing antibody responses and T cell responses directed against highly conserved influenza epitopes. The SLUCVD is involved and committed to this important area of research.

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Disclosure

None reported. **MM**

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Development of Vaccines to Control the Worldwide Tuberculosis Pandemic

by Daniel F. Hoft, MD, PhD

Tuberculosis remains an important world problem, but several promising areas of research focused on the development of improved TB vaccines are underway.



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Abstract

***Mycobacterium tuberculosis* (Mtb) infection and tuberculosis (TB) disease are major public health problems. Available BCG vaccines are partially effective against severe disease, but have not reduced the overall prevalence of TB infection and disease. A third of the world's population is latently infected with Mtb, and therefore more effective prophylactic and therapeutic vaccines are urgently needed. The Hoft laboratory and the Saint Louis University Center for Vaccine Development (SLUCVD) are actively pursuing these important goals.**

Introduction

Mycobacterium tuberculosis (Mtb) infection and tuberculosis (TB) disease are major worldwide public health problems (See Figure 1). A third of the world's population is Mtb infected and one to two million people die from the complications of TB each year. Increasing rates of Mtb drug resistance threaten to render all of our current chemotherapy regimens useless, and the HIV pandemic has greatly amplified the risks of TB infection, transmission and disease progression. Strains of attenuated *M. bovis* Bacillus Calmette-Guérin (BCG) have been used extensively since the 1920s to reduce TB infection and disease.[1] BCG induces partially protective TB immunity, providing 70-80% efficacy against the worst TB outcomes including TB meningitis and mortality in children even when given within the first week after birth. However, standard intradermal BCG vaccination of infants does not reliably prevent TB infection and/or pulmonary TB disease in adults, and thus has not affected the overall prevalence of TB infection and disease. Revaccination with BCG in adulthood has not enhanced protective TB immunity. Improved TB vaccines are urgently needed. Dr. Daniel F. Hoft's laboratory (The Hoft lab) at the Saint Louis University Center for Vaccine Development (SLUCVD) has conducted 20 years of research focused on this goal.

Classic dogma defines TB latency and active disease as two opposite poles of both the immunologic and bacteriologic spectra. During TB latency, it has been believed that the immune system successfully contains the bacilli and drives them into a nonreplicating/low metabolic state, while conditions of waning immunity allow TB reactivation with recurrent high levels of Mtb replication and active disease progression. Dormant Mtb bacilli are able to survive

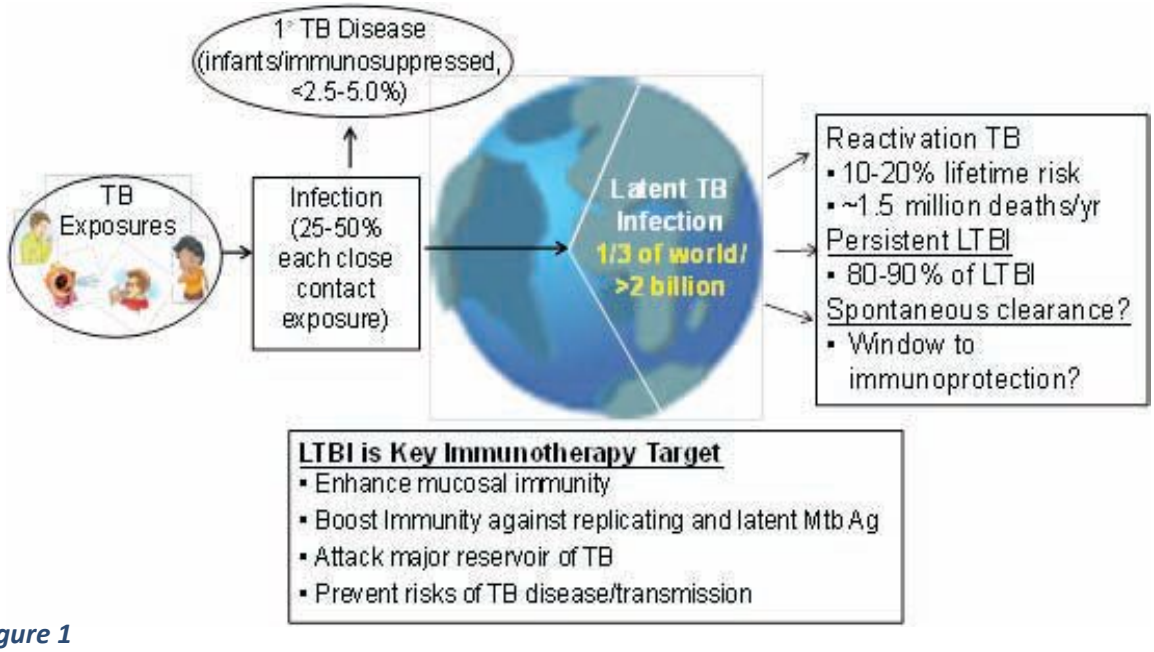


Figure 1

Latent TB Infection (LTBI) is the Major Public Health Problem

With each TB close contact, risk of infection is 25-50%. Repeated exposures are common in the developing world and provide a larger challenge for treatment and prevention strategies. TB active disease occurs early after infection (1° disease) in the immunosuppressed, or more commonly after LTBI reactivation LTBI (10-20% lifetime risk). Vaccines are unlikely to protect the immunosuppressed, but immunocompetent subjects with LTBI could benefit from immunotherapy that enhanced TB immunity enough or redirected immune responses appropriately to eliminate/reduce bacterial burden. Mucosal immunity directed against Mtb antigens expressed by replicating and dormant bacilli is predicted to be important for LTBI immunotherapy. The rate of spontaneous LTBI clearance is unknown but thought to be low.

prolonged periods (up to 12 years) of *in vitro* stress.[2] The Wayne model utilizing progressive reductions in oxygen concentrations *in vitro* developed in the early 1990s identified and further characterized "non-replicating persistent" states of Mtb.[3-5] These studies, combined with clinical evidence that asymptomatic latent TB infection (LTBI) can persist *in vivo* for eight to nine decades, have led to the belief that LTBI is a state of mycobacterial dormancy during which the immune system contains virtually all persisting Mtb organisms in a static state within granulomas.

Certain observations regarding LTBI are difficult to reconcile with this static view of latency. First, prolonged isoniazid (INH) monotherapy given for six to nine months to patients with LTBI is very effective in preventing TB reactivation disease, strongly indicating that this therapy eradicates all viable Mtb organisms during latency in vivo. This finding is inconsistent with the static model of LTBI in that INH is bactericidal only for replicating organisms. Second, modern imaging techniques, combining positron emission tomography (PET) with high resolution computed tomography (CT), suggest that despite the paucibacillary nature of LTBI, the associated granulomatous lesions display wide ranges of Mtb metabolic and host immunologic activity. Specifically, these PET/CT scans integrate images of fluorodeoxyglucose uptake and detailed anatomic structure to clearly localize hypermetabolic activity in specific tissues. PET/CT studies done in patients and non-human primates (NHP) with LTBI and TB disease have detected distinct granulomatous regions ranging from "cold" quiescent lesions to "hot" expanding lesions present side-by-side in a single individual/animal.[6,7] Together this suggests that both active TB and LTBI represent dynamic spectra, with variable levels of actively replicating and inactive bacilli in granulomas ranging from small and immature lesions to large and mature encapsulated lesions with necrotic/hypoxic centers (See Figure 2).

The immune response can greatly alter the proportions and absolute numbers of actively replicating Mtb in infected persons with concomitant changes in TB disease risks. Major challenges for vaccine development include the need to induce the optimal combination of immune responses effective against both replicating and inactive bacilli, with the capacity to protect the major tissues infected including the lung (See Figure 3). Because the infection is largely

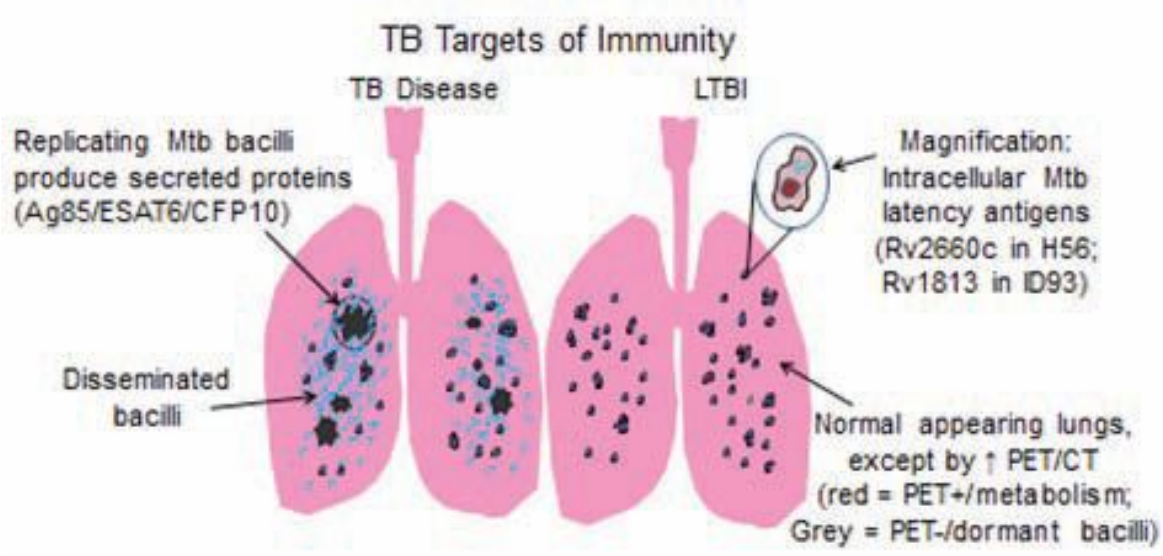


Figure 2

Both LTBI and active TB disease represent dynamic spectra of interactions between host immunity and dormant/replicating organisms. In TB disease, there is much higher overall bacillary load (intracellular and extracellular) with destructive immune responses causing cavity formation, but smaller, scattered granulomatous lesions with predominantly dormant bacilli are also present. In LTBI, much lower bacillary loads (predominantly intracellular) and smaller granulomas are present. Even in LTBI some granulomas are "hot" for FDG uptake by PET/CT, while others appear "cold". Optimal LTBI immunotherapy will need to induce potent mucosal lung immunity directed against antigens expressed by both actively replicating and dormant bacilli.

intracellular during early primary infection, paucibacillary LTBI and early reactivation disease, T cell responses are critically important for protective immunity. CD4+ Th1 cell and CD8+ T cell responses are involved in the control of Mtb replication *in vivo*, as are the cytokines they produce (e.g.-IFN-γ, TNF and IL-2).[1] These responses alone appear insufficient for bacterial clearance as these T cell subsets peak during active TB disease and decrease after spontaneous immunologic control or drug-induced cures. Other immune subsets which tend to accumulate in mucosal tissues, including $\gamma_9\delta_2$ T cells and mucosa-associated invariant T (MAIT) cells, also contribute to the levels of protective responses.[8-12] The relative importance of these less studied subsets for TB immunity and their detailed mechanisms of action, especially for immunotherapeutic-induced protection against LTBI persistence and reactivation, are unknown. The prominent localization of these unconventional T cell subsets to lung mucosa suggests they may be significant contributors to local containment and perhaps even elimination of Mtb pulmonary infection. $\gamma_9\delta_2$ T cells and MAIT cells are not classically HLA-restricted but respond to highly conserved ligands in the context of nonpolymorphic restriction elements, suggesting that the same antigens could induce protective T cells in all recipients of immunotherapeutic vaccines. Both $\gamma_9\delta_2$ T cells and MAIT cells have anti-mycobacterial protective effects *in vitro* and *in vivo*, specific antigens capable of inducing these T cell subsets have recently become available, and both subsets are depleted during HIV/AIDS progression when the risks of opportunistic bacterial and other pathogens greatly increase, further suggesting their importance for human immunity. Although controversial, Mtb-specific antibody responses may provide vaccine-induced protection against initial TB infection in the lung and/or dissemination/transmission of extracellular bacilli during peaks of Mtb replication.

Considering the optimal Mtb antigens to include in vaccines, Mtb has a highly remarkable capacity to adapt in vivo to a variety of stressful conditions. Pathogenic Mtb can replicate intracellularly in professional mononuclear phagocytes despite numerous mechanisms available to kill intracellular bacilli. The pathogen switches from predominant glucose metabolism when replicating at high rates extracellularly, to lipid-based metabolism after uptake into the phagosomes of mononuclear phagocytes. The organism thrives in aerobic conditions reaching its highest levels of replication, but can also survive prolonged periods of microaerophilic and even anaerobic conditions. Certain

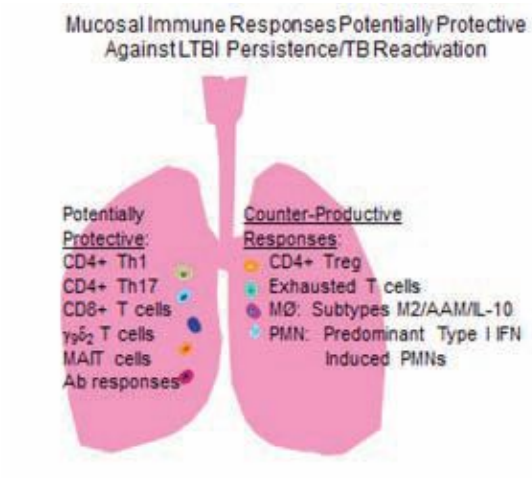


Figure 3

TB-specific mucosal immune responses are important for protection against LTBI reactivation. Lung CD4+ Th1 and Th17 cells, CD8+ T cells, $\gamma_9\delta_2$ T cells, MAIT cells and sIgA/IgG antibody responses could protect against the majority of LTBI reactivation and reduce both TB disease and TB transmission. All of these T cell responses are considered major targets for immunotherapy because they can recognize intracellular Mtb, the major pathogen reservoir during LTBI. Mucosal antibody also could protect against initial infection and transmission, and is the focus of other funded work by our group. CD4+ Treg, T cell exhaustion, alternatively activated macrophages unable to kill intracellular Mtb and type I IFN induced PMNs can negatively regulate protective immunity in the lung and will assessed for their roles in reducing LTBI immunity.

gene sets or regulons are activated intracellularly (e.g.-DosR), and thought to be involved in persistence of Mtb during LTBI.[13] Other genes associated with reactivation of LTBI have been identified (e.g.-resuscitation-promoting factors).[14-16] Although previous data suggest that TB immunity is predominantly directed against secreted proteins produced by replicating Mtb, there is a growing body of evidence that latency-specific antigens are targeted as well. New vaccines may need to include antigens expressed by both actively replicating and inactive bacilli.

Another major goal important for vaccine development is to learn how to optimize host immunity with immunotherapies capable of clearance/reduction in Mtb load in persons already with LTBI. Important research required to facilitate the development of effective post-infection immunotherapies include: 1) determining the proportion of subjects with LTBI who spontaneously eliminate their Mtb bacillary burden and are no longer at risk of TB disease unless reinfection occurs, 2) development of biomarkers for distinguishing subgroups of patients that eliminate or indefinitely contain Mtb growth and others at high risk of failing to prevent TB reactivation, and 3) learning to manipulate host defenses to optimize containment and/or clearance.

Most primary and reactivation TB disease occurs in the lung, and pulmonary TB is the main source of TB transmission. These clinical facts combined with the accumulated knowledge described above indicate that optimally effective prophylactic and immunotherapeutic vaccines for TB will need to target 1) mucosal immunity in the lung, 2) antigens expressed by actively replicating and inactive Mtb, and 3) intracellular and extracellular Mtb organisms. The Hoft lab and the SLUCVD are currently working to accomplish these goals. The potential significance of this work is profound as up to one-third of the world's population currently have LTBI, the HIV/TB co-pandemics in many places in the world are spiraling out of control, and drug-resistant strains of Mtb are increasing and threatening to render all current TB public health control measures useless.

Lessons Learned from a Recently Conducted TB Vaccine Efficacy Trial

BCG is derived from an attenuated *M. bovis* strain, another member of the Mtb complex of mycobacteria, and expresses thousands of different antigens also produced by Mtb. The major BCG antigens and immune subsets responsible for inducing the partially protective immunity are largely unknown. In animal models, Mtb/BCG secreted proteins (e.g.-members of the antigen 85 complex and ESAT-6) have been shown to induce potent protection against actively replicating Mtb infections, and have been pursued as important subunit vaccine candidates. The first new TB vaccine to enter efficacy trials in almost 100 years was a recombinant Modified Vaccinia Ankara engineered to express the Mtb secreted protein Ag85A (rMVA/85A) developed at Oxford University. The results of this efficacy trial were published last year in the *Lancet*.[17] Infants were given BCG at birth and randomized to receive rMVA/85A or a control vaccination four to six months later. Unfortunately, over the three-year follow-up, no increased protection was detected in rMVA/85A boosted children, and the reasons for this failure are unknown. Major hypotheses include: 1) Ag85A and/or secreted proteins alone are not the optimal antigens for induction of enhanced protective immunity in humans, 2) the rMVA/85A vaccine predominantly induces only CD4+ T cell responses without inducing other important immune subsets, and 3) BCG alone is protective in infants and booster vaccines

may not be able to enhance this protection in the first few years of life.

Many groups have identified additional Mtb antigens that are protective in animal models. None of these used alone or as boosters for BCG vaccination have reproducibly induced better protection in mice, guinea pigs and/or nonhuman primates than BCG vaccination alone. Research has focused on identifying Mtb antigens uniquely expressed during LTBI. The thought is that once LTBI is established, the expression of secreted proteins may be greatly reduced by relatively dormant persisting organisms and therefore additional antigenic targets must be targeted by the immune system. There are several vaccines containing "latency antigens" in development, including some being studied in the SLUCVD that may provide future enhancements in TB protective immunity.

In phase I and II trials, rMVA/85A was shown to predominantly induce CD4+ T cells with little induction of CD8+ T cells. Standard protein antigens such as Ag85A would not be expected to induce protective $\gamma_9\delta_2$ T cells and MAIT cells because these T cells have been shown to be induced by phosphorylated lipids and vitamin metabolites, respectively. Current vaccines in development are being formulated to induce both CD4+ and CD8+ T cells, and novel vaccines are being explored that also induce $\gamma_9\delta_2$ T cells and MAIT cells. It is not known if these vaccines will be able to boost BCG immunity in infants better than rMVA/85A, but these questions must be addressed in future TB vaccine trials.

rMVA/85A or similar vaccines possibly can be used to enhance protection against TB disease in adolescents and/or adults. The rMVA/85A efficacy trial followed infants for one to three years after vaccination. Relevant memory immune responses may persist longer after BCG priming followed by MVA/85A boosting than after BCG alone. This possibility will require long-term follow up of vaccinated infants. Another possibility is that rMVA/85A boosting of infants cannot improve long-term immunity, but boosting of adolescents with MVA/85A or similar vaccines may enhance protection. Future trials must address this issue as well.

Additional TB Vaccine Approaches

Another viral-vectored, subunit vaccine in clinical development is AERAS-402, a recombinant attenuated adenovirus expressing 2 secreted and 1 latency specific Mtb antigens (Ag85A, Ag85B and TB10.4). (See Table 1.) This vaccine was developed by scientists at Crucell in collaboration with the Aeras Global TB Vaccine Foundation. The Aeras Foundation has been funded by large grants from the Bill & Melinda Gates Foundation specifically to focus on clinical development of promising TB vaccine strategies. Aeras funded our SLUCVD to study the ability of AERAS-402 to boost BCG immunity in adults. This work has already been published demonstrating that AERAS-402 was safe, significantly boosted T cell responses directed against all 3 Mtb antigens, and induced the highest responses in TB-specific CD8+ T cells detected to date.[18] AERAS-402 is now in phase II trials in Africa and we should have efficacy data soon.

Another strategy instead of boosting BCG immunity, is to construct recombinant BCG (rBCG) that overexpress key Mtb antigens not highly expressed by attenuated BCG or unique to Mtb. In collaboration with the Aeras Foundation, we have tested 2 rBCG to date in phase I trials and demonstrated the proof-of-principle that these vaccines can induce significantly better immune responses directed against the overexpressed Mtb antigens in humans[19] (and manuscript in preparation). These and additional rBCG strains are in various stages of clinical development, but human efficacy data so far have not been reported.

With funding from our NIH Vaccine and Treatment Evaluation Unit (VTEU) contract, Dr. Hoft has completed 3 phase I trials of oral BCG vaccination. Oral delivery of BCG was the initial route that Calmette and Guérin used to deliver BCG to infants, and was used for decades in Brazil. Because of this history, we know that BCG is safe. No efficacy trials of oral BCG have demonstrated protection in humans, and there were no previous data indicating whether or not oral BCG can uniquely induce mucosal immune responses. Recent work has demonstrated that oral BCG does induce significant increases in TB-specific secretory IgA in respiratory secretions and TB-specific T cells among bronchoalveolar lavage cells[20] (and manuscript in preparation). Future mucosal TB vaccine work in the SLUCVD will focus on clinical development of oral and intranasal vaccinations with BCG and other new TB vaccines in both animal models and human trials.

Our lab has been developing functional assays of the immune responses induced by vaccination for use in determining which of the many new TB vaccine candidates/strategies under development are most promising and should be moved forward more rapidly into expensive phase II and III trials. The TB research community believes that CD4+ T cells, CD8+ T cells, $\gamma_9\delta_2$ T cells and MAIT cells are important for protective immunity. The optimal cytokine and effector molecules produced by these cells with the most protective effects against Mtb infection, replication and persistence in humans are not known. We

Table 1
Recent and Ongoing TB Vaccine-elated Work at the SLUCVD

- Clinical studies of BCG immunity (NIH funded)
- Clinical studies of subunit boosts for BCG (NIH + Areas funded)
- Clinical and basic studies of mucosal TB vaccines (NIH funded)
- The role of $\gamma_9\delta_2$ T cells in TB immunity (NIH funded)
- The role of MAIT cells in TB immunity (NIH funded)
- Development of functional assays and challenge protocols to assess TB vaccines (NIH + FDA funded)

have developed *in vitro* assays that can measure the ability of vaccine-induced T cells to inhibit intracellular mycobacterial growth,[9,21-24] and are about to begin a new VTEU-sponsored clinical trial with the goal of optimizing a human challenge model. This challenge model will use a standard BCG strain as the challenge, administered after vaccination with new experimental TB vaccines to determine if the immunity induced can inhibit mycobacterial replication *in vivo*.

An immunotherapy given during LTBI capable of clearing TB infection or at least preventing TB reactivation disease could have an immense impact on the TB world public health problem. The major barrier for development of effective immunotherapeutic strategies is the lack of a definite signature of LTBI clearance. The Hoft lab is actively seeking additional research funds to conduct a clinical trial designed to achieve this goal.

Conclusions

Tuberculosis remains an important world problem, but several promising areas of research focused on the development of improved TB vaccines are underway. BCG, although not optimal, does provide some protection demonstrating at least proof-of-principle that vaccines can be effective. Future research needs to determine the best Mtb antigens, the optimal vaccine format, and whether mucosal approaches can improve upon BCG immunity.

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Disclosure

None reported. **MM**

SAINT LOUIS UNIVERSITY

Center for Vaccine Development

New Smallpox Vaccines for an Ancient Scourge

by Sharon E. Frey, MD

Jenner is credited with initiating the wide-spread process of vaccination with animal pox to protect against smallpox, and is considered the father of the field of modern vaccinology.



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Abstract

The potential use of variola virus, a Class A agent of bioterrorism, remains a concern. In an effort to prepare for a possible smallpox outbreak due to an intentional release of variola, the U.S. government and industry have been evaluating vaccines stored in the National Strategic Stockpile including cell culture grown ACAM2000 and modified vaccinia Ankara, IMVAMUNE, in clinical studies. This paper discusses smallpox vaccines studies conducted at the Saint Louis University Center for Vaccine Development.

Smallpox History and Introduction

Smallpox, an ancient scourge caused by infection with variola virus, is the only disease that has been eliminated through vaccination (See Table 1). Over the millennia smallpox is believed to have killed 300 to 500 million people and has caused disfiguration and blindness in survivors. In 1980 smallpox was declared eradicated by the World Health Assembly after a massive vaccine campaign by the World Health Organization that was conducted in collaboration with multiple government agencies worldwide.[1]

During the Cold War, the USSR explored the use of variola virus as an agent of biowarfare and therefore there is concern that smallpox could be intentionally re-introduced into the human population.[2] Variola major has been classified as a Class A agent of bioterrorism due to its ease of transmission from person to person, high mortality rates, potential for public panic and social disruption, and special actions required for public health preparedness.

Humans are the only known reservoir for variola which is spread from person to person via the respiratory route. The incubation period lasts approximately 12-14 days and is followed by a two to three day prodrome of fever, malaise, prostration, and severe headaches and backaches, after which a pustular rash develops[3] (See Table 2). Mortality was estimated at 30% in the general population. Vaccination successfully prevented disease when given prophylactically and as late as two to three days post exposure. If given as late as four to five days post exposure, vaccination may decrease the severity of disease in some individuals.

Vaccination against smallpox was administered by a variety of routes. In ancient China, dried pulverized scabs were delivered by blowing the powder though a thin long reed into

the nasal passages by a method called insufflation. Another process of inoculation similar to modern vaccination was to intradermally inoculate (variolation) persons with material from the smallpox cutaneous lesions of diseased patients. In 1796, Jenner vaccinated 8-year-old James Phipps with the material from a cowpox lesion after noting milk maids were immune to smallpox. Because Jenner's published results represented the first time these findings were widely disseminated in the scientific community, he is credited with initiating the wide-spread process of vaccination with animal pox to protect against smallpox, and is considered the father of the field of modern vaccinology.

Smallpox Vaccines Available in the National Strategic Stockpile

Multiple strains of replicating vaccinia were used throughout different regions of the world during the WHO eradication campaign. Vaccines using the New York City Board of Health (NYCBH) strain, lyophilized Dryavx (Wyeth), and liquid Wetvax (Aventis Pasteur), were used in the U.S. and Lister/Elstree strain was used in the United Kingdom. The remaining stores of Dryvax and Wetvax from the US smallpox eradication campaign were maintained by the US government and Dryvax was used for vaccinating individuals potentially at high risk of contracting disease and later in new clinical trials of smallpox vaccine in the U.S. civilian population beginning in 2000. Dryvax, prepared using calf lymph from inoculated cows, remained in use until it was destroyed by the government in 2010 after replacing it with ACAM2000 in the Center for Disease Control and Prevention's (CDC) Strategic National Stockpile of medical supplies. ACAM2000 (Novartis, formerly Acambis), a second generation smallpox vaccine, was developed from a single clonal strain of Dryvax made with NYCBH strain, which contained a swarm of strains.[4] In addition, ACAM2000 is propagated in Vero cell culture instead of using the traditional method of propagation by inoculation of the shaved bellies of calves. Thus it is believed that ACAM2000 had safety and production advantages compared to Dryvax and was approved by the FDA in 2007.

Replicating vaccinia virus smallpox vaccines (Dryvax and ACAM2000) are administered by a process called scarification of skin. After puncturing the skin multiple times with a bifurcated needle containing vaccinia virus, a small papule forms at the site of vaccination and evolves into a pustule (~1 cm) or primary lesion

Table 1
Smallpox Vaccination and Eradication of Disease

1796:	First vaccine developed by Edward Jenner
1949:	Last case of smallpox in the U.S.
1970:	U.S. ended biowarfare program
1971:	U.S. discontinued vaccinating the general public
1976:	U.S. discontinued vaccinating health care workers
1977:	Last naturally occurring case was in Somalia
1980:	WHO certified the world free of smallpox
1982:	Vaccine production discontinued
1982:	Vaccination no longer required for international travel
2000:	Smallpox vaccine studies began
2008:	ACAM2000 replaced Dryvax in the National Strategic Stockpile
2010:	MVA added to the National Strategic Stockpile
Currently:	Certain lab workers and military personnel are vaccinated

Table 2
Smallpox Infection and Disease

Virus:	Variola major/minor
Spread:	Person-to-person
Incubation:	12-14 days
Disease:	2-3 day prodrome of high fever, malaise, and prostration with severe headache and backache followed by rash
Rash progression:	Papules days on 1-2, vesicles by day 4-5, pustules by day 7, scab by day 14, pitted scar
Mortality:	30%
Vaccination:	Within 2 – 3 days of exposure

Table 3
Risks of Vaccination

Most common: accidental spread (usually not serious)
- Eye, genital area

Less common (more serious):
- Abnormal skin eruptions
  - -Vaccinial rash
  - -Eczema vaccinatum 38/1,000,000
  - -Vaccinia necrosum
  - -Erythematous urthiarial eruption
- Encephalitis or progressive vaccinia 3/1,000,000
- Other complications 600/1,000,000
- Death 1/1,000,000
- Revaccination – rates of adverse reactions decrease by 10-fold

Source: Lane JM et al, J Infect Dis 1970;122:30-9

Table 4
Contraindications for Non-Emergency Use of Replicating Vaccinia

- Infants <12 months of age
- Individuals with eczema or other skin conditions
- Immunocompromised persons
- Pregnant or breast-feeding
- Cardiac disease
- Household members with the above conditions

Source: http://www.vaers.hhs.gov/pdf/smallpox.pdf

("take"), eventually forming a scab that separates after 14-21 days leaving a scar. These replicating vaccines are highly effective and are associated with a variety of adverse events. There are relative contraindications for their use in non-emergent situations due to serious complications such as vaccinia necrosum and eczema vaccinatun that occur in the immunosuppressed and persons with atopic dermatitis[5] (See Tables 3 and 4).

Cases of myo-pericarditis associated with vaccination came to light in recent studies conducted in the military and civilians, and during the pre-event vaccination campaign of 2003.[6,7] The incidence of myo-pericarditis may be as high as 1 in 145 in subjects receiving Dryvax or ACAM2000 for the first time. To date there have been no reported cases of myo-pericarditis in individuals receiving MVA.[8] Because of these new findings, cardiac disease has been added to the list of contraindications of replicating vaccinia for non-emergency use of smallpox vaccine (See Table 4).

A third generation smallpox vaccine, modified vaccinia Ankara (MVA), was used in Germany during the end of the eradication campaign in adults and children, some of whom were immunocompromised, as a prime prior to vaccination with Lister strain in order to ameliorate the side effects of the replicating vaccinia.[9] Unfortunately, its effectiveness in preventing disease was never truly tested but it clearly decreased adverse events caused by the Lister strain. MVA does not replicate in human cells and was used in many vaccinia studies as a primary vaccine for smallpox and as a viral vaccine vector to carry antigens for a variety of infectious diseases such as influenza and human immunodeficiency virus as well as cancers.[10] MVA was found to be safe in immunocompromised hosts, namely in persons infected with HIV, bone marrow transplants, and anergic individuals.[11] MVA, IMVAMUNE (Bavarian Nordic), was added to the U.S. National Strategic Stockplie in 2010 for use in persons with HIV and atopic dermatitis and was approved for use by the European Commission (IMVANEX) and Health Canada (IMVAMUNE) in 2013.

Modern Clinical Trials of Smallpox Vaccine Studies with Dryvax

The first modern studies with Dryvax in civilians were initiated during April 2000 at the Saint Louis University Center for Vaccine Development. Vaccine supply was limited and had not been used in the general public for over 20 years. The objectives of the first studies were to evaluate the safety and immunogenicity of different dilutions of lyophilized Dryvax, which had remained frozen in storage since 1982.[12,13] The studies were conducted in healthy adult (≥18 years of age) subjects without a history of eczema or active skin disease who were not previously vaccinated (naïve) against smallpox and in subjects who were previously vaccinated (non-naïve) against smallpox. Dressings at the vaccination site were used to prevent auto-inoculation and inoculation of others with virus from the primary cutaneous lesion (take) which was a common event in the early studies.

In a phase 2 multi-site study of 680 adults who were not previously vaccinated (naïve) against smallpox, greater than 97% of subjects developed a mean primary cutaneous lesion (pustule size) of 12.4 mm at days 13-14 after receiving or undiluted [$10^{8.1}$ pfu/ml (range $10^{7.8}$-$10^{8.4}$)] and diluted vaccine, 1:5 [$10^{7.2}$ pfu/ml (range $10^{6.9}$ to $10^{7.5}$ pfu/ml)] or 1:10 ($10^{6.8}$ pfu/ml (range $10^{6.0}$ – $10^{7.2}$)].[13] Fever (≥100°F) occurred in 8.9% of subjects on days 7-9. Headaches were common at all times. Moderate or severe muscle aches (20.6%), chills 6.5%), nausea (3.9%), fatigue (19.7%), and pain at the injection site (33.8%) occurred on days 7-9 post vaccination. Fourteen percent of subjects had a rash distant from the vaccination site during follow-up. More than a third of subjects missed school, work or recreational activities, or had trouble sleeping due to illness. Three subjects had serious adverse events related or possibly related to vaccine including fever (104.2°F), headache and nausea, and 6.5 cm of erythema at the vaccination site.

In a phase 1 study (N=90), previously vaccinated (non-naïve subjects) adults (N=10) who received undiluted ($10^{7.5}$ pfu/ml) vaccine were compared to 80 non-naïve subjects who received undiluted ($10^{7.6}$ pfu/ml) vaccine, or diluted vaccine at 1:3.2 ($10^{7.0}$ pfu/ml), 1:10 ($10^{6.5}$ pfu/ml) or 1:32 ($10^{6.3}$ pfu/ml) doses.

All non-naïve subjects receiving undiluted vaccine had a take and greater than 90% of subjects at the 1:3.2 dilution, 81% at the 1:10 dilution, and 53% at the 1:32 dilution had a take.[14] The mean pustule sizes within 12-15 days of vaccination were 8.4 mm in the previously vaccinated (non-naïve) group compared to a mean size of 10.7 mm in the not previously vaccinated (naïve) group ($p=.04$).

Adverse events were similar between the groups except fever was significantly less common in the previously vaccinated subjects (9.4%) than in the vaccinated subjects (60%) ($p=0.02$).

Of note, these studies illustrated that vaccination with one-tenth the normal dose of Dryvax resulted in takes

Table 5
Animal Rule

In selected circumstances, when it is unethical or infeasible to conduct human efficacy studies, the FDA may grant marketing approval based on adequate and well-controlled animal studies when the results of those studies establish that the drug or biological product is reasonably likely to produce clinical benefit in humans.
Source: Federal Register: 21 CFR 314.600 for drugs; CFR 601.90 for biologics

which correlated with protection after vaccination. This finding was critical as it allowed the expansion of available doses in the National Strategic Stockpile by 10-fold. The titer of undiluted Dryvax in the studies was consistent with the titer in the package insert.

Studies with ACAM

In a phase 1 study, ACAM2000 (N=30) was compared to Dryvax (N=30) in subjects who were not previously vaccinated (naïve).[15] The adverse events profiles between the ACAM2000 and Dryvax groups were similar. The common AEs occurring in ≥50% of subjects were injection site pruritus, injection site pain, fatigue, lymph node pain, headache, malaise and myalgia. Only two to three subjects in each group had a temperature of ≥100°F. There were no significant differences between the groups. The majority of AEs were mild to moderate. All the ACAM2000 and Dryvax recipients developed a take, the clinical correlate of protection, with a mean pustule size of approximately 13 mm. These take rates are similar to another studies comparing ACAM2000 to Dryvax in subjects not previously vaccinated.[16]

There was no significant difference in four-fold titer rise for ACAM2000 (90.0%) and Dryvax (96.7%). Plaque reduction geometric mean neutralizing titers (GMT) remained high at 45 days post vaccination after the administration of one dose of ACAM2000 titers (103.5) and one dose of Dryvax (171.5).[15] There were no statistically significant differences in comparison of quantitative T cell responses at day 45 between the two groups. For Dryvax and ACAM2000, respectively, the cytotoxic T lymphocyte (CTL) median lytic units were 12.5 and 15.95; the median number of spot forming units by ELISPOT per 10^6 peripheral blood mononuclear cells was 264 and 296; and the median stimulation indices for lymphocyte proliferation were 23.05 and 24.95.[15] Both humoral and cellular immunogenicity responses are thought to play an important role in protection against smallpox and healing of the primary cutaneous lesion after vaccination.

The importance of these findings rest in the knowledge that ACAM2000 has a similar adverse event and immunogenicity profile as Dryvax but offers the advantage of being manufactured using a single clone of virus grown in cell culture under modern safety and quality standards, with limited risk due to adventitious agents.

Studies with MVA

A major drawback of ACAM2000 is its potential for uncontrolled replication in immunocompromised hosts and persons with a history of atopic dermatitis. MVA, a non-replicating virus in human cells, is given by injection, typically subcutaneously, and because it does not replicate in humans there is no pustule formation at the site of injection eliminating the possibility of autoinoculation or dissemination of the virus. MVA was initially designed specifically to limit the major adverse events of replicating virus.

In a phase 2 study, two doses of MVA (Bavarian Nordic) given four weeks apart ameliorated the side effects and pustule size from Dryvax (used as a vaccinia challenge) administered four months after the last dose of MVA.[17] Of note, the decreased size of the Dryvax pustule suggests that MVA is capable of limiting disease due to orthopox viruses. Plaque reduction neutralizing antibodies titers in the sera of subjects receiving two doses of MVA were high and comparable to those of recipients receiving a single dose of Dryvax. Antibody studies with sera from the vaccinees found MVA to be comparable to Dryvax in its ability to neutralize variola virus in vitro.[18]

Current Plans for Smallpox Vaccination

In 2002, President Bush announced an unprecedented plan to vaccinate civilians against a disease that did not exist. It was the first time in 30 years that smallpox vaccine was given to civilians. The three-stage pre-event campaign started in January 2003, and was designed to vaccinate volunteers: 1) 500,000 health care workers, 2) 10 million first responders, 3) the general public. The campaign failed to meet its numbers due to concerns among the public about adverse events and financial compensation; approximately 39,000 civilians were vaccinated by year's end and the campaign was closed. Currently, there are no plans to prophylactically (pre-event) vaccinate the civilian population. The government has made extensive plans to respond rapidly to a post-event threat. Studies are ongoing with MVA to evaluate best doses and shortest vaccination schedule

necessary to develop a sufficient antibody titer during a post event scenario.[19] Although a titer of 1:32 after vaccination with replicating virus is thought to be adequate to protect against smallpox, a protective titer for MVA has not been established.

Future Directions

Since smallpox is no longer present from natural causes, new smallpox vaccine developed for use in the U.S. can only be approved by the FDA according to the animal rule (See Table 5). Aerosolized monkeypox animal models are being used to measure the protective effect of ACAM2000 and MVA.[20, 21] Newer vaccines under study include protein subunit, peptides with adjuvants, and DNA vaccines which have met with some success in animals.[22,23] Immunoinformatics and systems biology will provide newer tools for the development of new smallpox vaccines.[24,25] Saint Louis University continues to participate in NIH-funded smallpox and other important biodefense vaccine studies.

Conclusion

As a result of recent smallpox vaccine research, new second, ACAM2000, and third, IMVAMUNE, generation vaccines were added to the national strategic stockpile. Based on human and animal studies the vaccines appear to be as protective as Dryvax, however their true efficacy has not been tested due to the successful and unprecedented smallpox eradication campaign.

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Disclosure

None reported.

MM

Saint Louis University

Center for Vaccine Development

Prospects for a Dengue Vaccine: Progress and Pitfalls

by Sarah L. George, MD

Clinicians are advised to consult the CDC website if their patients are traveling to potentially dengue endemic areas, or they are treating a case of possible dengue in a returning traveler.



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Abstract

Dengue virus is now the world's most common arboviral infection and has spread to the continental United States. The *Aedes* mosquito which transmits dengue is prevalent throughout Missouri, so clinicians should be familiar with dengue. While there are no licensed vaccines, five are in human trials including two tested at the Saint Louis University Center for Vaccine Development. Our deepening understanding of the correlates of protective immunity to dengue improves near-term prospects for a vaccine.

Introduction to Dengue Virus and Dengue Disease

Dengue virus (DENV) has spread rapidly in recent decades and is now the world's most common human arboviral infection. Up to 390 million people are infected with DENV annually; of these perhaps 100 million develop dengue fever, and 22,000 die.[1] Conservative estimates place over half the world's population at risk for dengue. There are four dengue viral serotypes (DENV 1, 2, 3, and 4), and a fifth was reported in 2013. All dengue viruses are transmitted by *Aedes* mosquitoes, which have spread over the American southeast, and are now found throughout Missouri (http://www.cdc.gov). Symptoms of dengue include fever, headache, eye pain, myalgia, arthralgia, rash, leukopenia, and nausea (See Table 1). The symptoms begin 3-14 days after a bite by an infected mosquito and the illness usually lasts for 4 to 7 days, followed by a convalescent period of several weeks. There is no available treatment other than supportive care. In the past five years, sporadic cases of dengue disease have been reported in people who have not traveled outside the United States and so must have acquired the infection locally. DENV re-appeared in 2009 in Key West after 50 years[2]; since then south Florida has reported approximately 20 locally-acquired cases of dengue annually. In 2013, seven locally acquired cases of dengue were reported in south Texas and one locally acquired case was reported in Suffolk County New York. A fatal case of dengue (in an immunocompromised person) occurred in Santa Fe New Mexico in 2013. While locally acquired DENV has not been reported to date in Missouri, given the spread of the

disease, local acquisition is a real possibility in mosquito season (April-October) and clinicians should be aware of the symptoms of dengue.

Infection with one of the four DENV serotypes generally induces life-long protective immunity against reinfection with viruses of the same serotype but increases the risk of severe disease (dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS)) or death during a subsequent infection with a virus from one of the other three serotypes[3, 4] (See Figure 1). DHF/DSS symptoms usually begin just before or after the fever subsides; the signs include bleeding and easy bruising due to thrombocytopenia, abdominal pain, nausea, vomiting, and shortness of breath, ascites, hepatomegaly, and pleural effusions due to capillary leak. While an estimated 22,000 deaths from dengue occur worldwide each year,[1] with proper care the mortality rate of DHF/DSS can be <1%. Suspected cases of dengue should be treated with supportive fluids and analgesics such as acetominophen, but aspirin, heparin, NSAIDS, or anticoagulant administration should be avoided. Extensive epidemiologic studies have shown a correlation between the introduction of a new dengue virus into an already endemic area and a spike in DHF/DSS cases[5] (See Figure 1). Exactly why people develop DHF/DSS is not completely understood; it is thought that antibodies from a prior DENV infection are unable to successfully neutralize infection with DENV of a different serotype.[4, 6] Instead, the antibodies bind to the newly infecting virus and facilitate uptake into Fc-receptor bearing cells, such as monocytes and macrophages. These are the host cells where DENV

Table 1: Key clinical findings in dengue fever and dengue hemorrhagic fever/shock syndrome.

Dengue Fever:	
Symptoms:	
	Fever
	Headache
	Arthralgia
	Myalgia
	Retro-orbital pain
	Rash
	Nausea
	Diarrhea
Laboratory findings:	
	Leukopenia
Dengue hemorrhagic fever/dengue shock syndrome:	
Symptoms:	
	Bleeding or petechiae
	Hypotension
	Pleural effusion, ascites
	Hepatomegaly
	Abdominal pain
Laboratory findings:	
	Thrombocytopenia

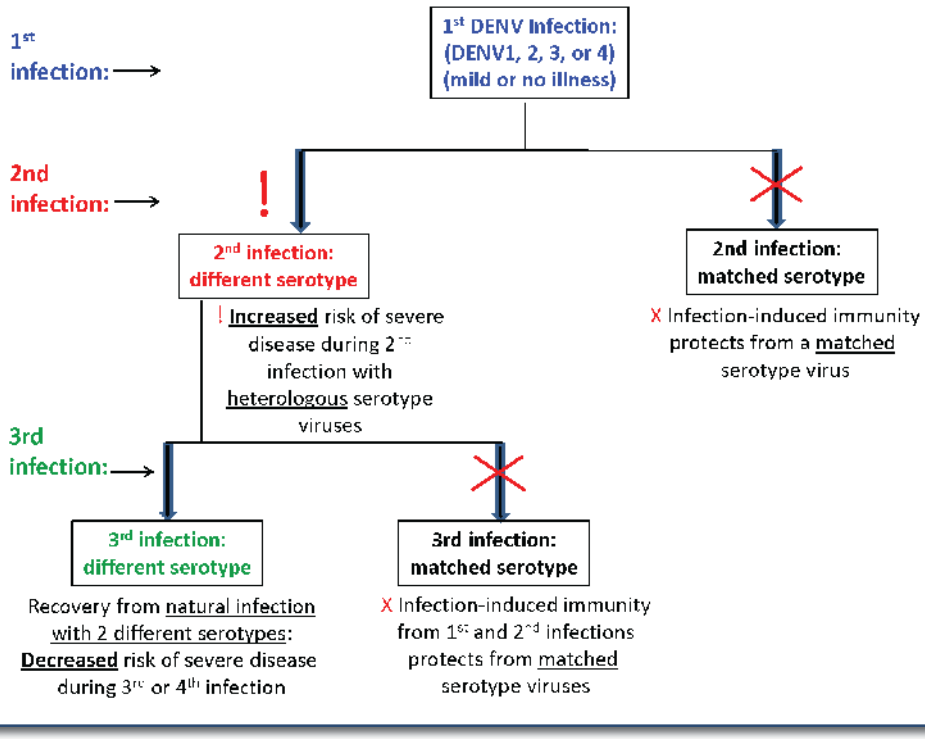


Figure 1 Association of Sequential Dengue Infections with Risk of Severe Disease

There are 4 or 5 serotypes of DENV. Recovery from infection with a virus of one serotype usually confers protection against reinfection with other viruses of the same serotype (15) (X), but increases the risk of severe disease (!) during infection with a virus of another serotype. However sequential infection with viruses from two different serotypes reduces the risk of severe disease during subsequent dengue infections.

replicates, thus antibodies to a prior DENV infection with a different viral serotype paradoxically increase viral replication by facilitating entry into the host cell. It should be emphasized that while this phenomenon has been demonstrated *in vitro*, it is not certain this is the cause, or the sole cause, of DHF/DSS *in vivo*.[7] DHF/DSS could also be due to excessive inflammatory cytokine production by T cells, such as production of TNFα instead of IFNγ[8,9], or insufficient T cell-mediated killing of dengue-infected cells. What is known is that DHF/DSS patients usually have higher levels of DENV in blood, and either infection or dysfunction of endothelial cells, leading to platelet consumption, bleeding, capillary leak, and shock. However it should be emphasized that most people with secondary dengue infections, even with a virus from a different serotype, don't develop DHF/DSS.

Diagnosis of dengue fever requires either development of specific antibodies (IgM or IgG) to dengue, or detection of dengue virus in serum by RT-PCR assay, in a patient with compatible symptoms. The patient should have had exposure to mosquitos within the past two weeks, but travel to a known dengue endemic area should not be considered an absolute pre-requisite for the diagnosis of dengue, given the rapid spread of the disease. Diagnosis of DHF/DSS requires a history of fever and dengue-like illness complicated by bleeding, thrombocytopenia, and evidence of plasma leakage such as hemoconcentration, ascites, pleural effusions, and liver enlargement (www.cdc.gov/dengue).

While increased risk of severe dengue (DHF/DSS) is seen in people experiencing a second dengue infection with a different viral serotype, epidemiologic data also demonstrate that once people have recovered from a second infection with a virus from a different serotype, the risk of severe disease with a third or fourth infection decreases dramatically.[10] Thus sequential natural infection with dengue viruses from different serotypes induces protective immunity against severe disease, though it does not protect from infection. The reasons for this are under investigation, and may include maturation of the antibody response and development of cross-neutralizing antibodies against key viral epitopes.[11,12] Thus a protective vaccine against dengue disease should be possible, if a vaccine can successfully mimic and expand this naturally occurring process. The criteria for a completely successful vaccine would be: 1) inducing protective responses against all four viral serotypes, and 2) inducing protection against all dengue disease, and not just DHF/DSS. However even a partially successful vaccine which protected from DHF/DSS and reduced the morbidity of dengue disease would be a major advance.

Overview of Dengue Vaccines

Development of a safe dengue vaccine which provides durable immunity to all four DENV is a top global health priority, and the Saint Louis University Center for Vaccine Development has assisted in this effort by completing two first-in-man studies of candidate dengue vaccines (described below). Dengue vaccine development has been hampered by several factors: 1) The need to simultaneously induce protective immunity to four different viral serotypes, or at least to multiple serotypes. 2) The concern that vaccine-induced immunity if inadequate or too narrowly focused might increase risk of DHF/DSS after natural infection with a virus to which the vaccine did not induce immunity. However, it must be emphasized that this phenomenon has not been seen in vaccine trials.[13] 3) Inadequate knowledge of the correlates of protective immunity to dengue disease. It has been thought based on in vitro studies and by analogy with other Flaviviruses, such as Yellow Fever virus and Japanese encephalitis virus, that sufficient titers of neutralizing antibodies to the viral envelope protein, which mediates entry to the host cell, should be adequate for protection. However, the relatively poor protective efficacy against dengue disease in a recent trial of a live attenuated tetravalent dengue vaccine candidate which induced high titer neutralizing antibodies to the envelope protein of all four dengue viruses has called this assumption into question.[14] It has recently been argued that dengue-specific T cell responses are required for effective immunity,[15] though whether this is correct and what T cell responses must be induced for protection is not clear. 4) Since a protective dengue vaccine should induce immunity to four viruses simultaneously, the conventional approach has been to administer four attenuated viruses concurrently in a single dose. However, this is complicated by the problem of viral interference, whereby not all of the vaccine viruses replicate equally and thus immunity to only the most highly replication competent viruses is induced. This phenomenon has been noted in all three live attenuated viral vaccines currently under development.[16-18] Despite these difficulties, dengue vaccine development has advanced considerably in the past 10 years and it is hoped an effective vaccine will be available soon.

Table 2: Summary of Dengue Vaccine Candidates currently in Human Trials:

Vaccine	Components	Manufacturer	Testing Phase	Schedule
CYD	*DV 1-4 prM and E proteins expressed in live attenuated Yellow Fever 17D vaccine	Sanofi-Pasteur	Phase 3 Results expected in 2014	0, 6, 12 months
DENVax	Live attenuated whole DV2 virus; DV1, 3, and 4 prM and E proteins expressed in attenuated DV2 viruses	Takeda	Phase 2, with plans for phase 3 in 2014	0 and 3 months
TV003	Live attenuated whole DV 1, 3, and 4 viruses; DV2 prM and E proteins expressed in attenuated DV4 virus	NIAID	Phase 2	single dose
V180	Recombinant E protein of DV 1-4 adjuvanted with Iscomatrix	Merck	Phase I	0, 1, 2 months
TDENV	Purified inactivated adjuvanted whole DV 1-4	GlaxoSmithKline	Phase I	0 and 1 month

*DV = DENV

There are currently five dengue vaccine candidates in human clinical trials, and others in preclinical testing (See Table 2). The first candidate vaccine which will complete a phase 3 efficacy trial is the live attenuated Yellow Fever vaccine-vectored dengue vaccine (CYD) (Sanofi-Pasteur), in which the premembrane (prM) and envelope (E) coding sequences of DENV 1, 2, 3, and 4 were inserted into the Yellow Fever 17D vaccine virus, resulting in 4 chimeric replication competent viruses.[16] This vaccine has a good safety profile and induces neutralizing antibodies to all four DENV viral envelope proteins, but the 3-dose schedule administered at 0, 6, and 12 months makes administration difficult in resource-limited settings, or for use in travelers or in the event of an outbreak. The CYD vaccine was only 30% protective against dengue disease in a study of 3673 Thai children, and did not provide any protection against disease from DENV2, the most pathogenic of the dengue viruses.[14] The vaccine was however partially protective against disease from DENV1, while the reduction in the number of cases of DENV3 and DENV4, though the numbers were small, suggested some protection. There was no evidence of increased protection after the second and third doses of vaccine, suggesting that most of the immunity achieved may have been derived from the first dose, even though three doses were required to induce neutralizing antibodies to all 4 viruses. Only ~11% of the YF 17D-vectored dengue vaccine is dengue proteins (the remainder are yellow fever vaccine virus proteins), and the first dose of vaccine failed to protect against vaccine viremia after the second and third doses.[16] This indicates the vaccine did not induce complete protective immunity against the attenuated vaccine viruses, thus its relatively low potency in this trial was in hindsight perhaps not surprising. Data on the vaccine's protective efficacy in the phase 3 trial of approximately 30,000 people is expected in 2014.

The second candidate dengue vaccine which will enter a phase 3 study of protective efficacy is DENVax (Takeda). DENVax is based on a live attenuated DENV2 virus, whose safety has been well-characterized.[19, 20] The prM and E coding regions of DENV1, 3, and 4 were inserted into the attenuated DENV2, resulting in a vaccine consisting of 4 recombinant attenuated viruses.[21] The first human trial of DENVax was conducted at the Saint Louis University Center for Vaccine Development between 2010-2012, sponsored by the NIH Vaccine Testing and Evaluation Unit (VTEU). DENVax was safe and induced high neutralizing antibody titers to at least three dengue viruses in the majority of volunteers (manuscript in preparation). The 2-dose schedule administered 90 days apart makes this formulation more practicable in resource-limited settings and for travelers. DENVax also induces dengue-specific proliferation and IFNγ secretion by CD4+ and CD8+ T cells in people and non-human primates,[21, 22] and since 100% of the vaccine proteins are derived from dengue, immunity induced by this vaccine may be broader than immunity induced by the CYD vaccine.

A third dengue vaccine candidate (TV003),

developed by NIAID, is now in phase 2 studies. This vaccine candidate consists of attenuated whole DENV1, 3, and 4 viruses, and an attenuated DENV4 into which DENV2 prM and E protein coding regions were inserted.[17, 23] This vaccine induces neutralizing antibodies to all four dengue serotypes after a single dose, and the immune response may be more equally balanced between the different viruses than after DENVax administration, though the overall titers are lower.[17] Perhaps significantly, vaccine viremia is not seen after second doses of DENVax or TV003, unlike for the CYD vaccine, indicating the first dose of both vaccines may be able to induce sterilizing immunity to the attenuated vaccine components. Administration of the NIAID vaccine is associated with development of a mild rash, which is correlated with development of neutralizing antibodies after vaccination.[17]

The fourth and fifth dengue vaccine candidates currently in human trials are a recombinant dengue E protein vaccine, adjuvanted with ISCOMATRIX (Merck), and an inactivated tetravalent dengue virus vaccine, adjuvanted with alum or ASO (GlaxoSmithKline). Merck's recombinant E protein vaccine was initially tested in a clinical trial at the Saint Louis University Center for Vaccine Development in 2009, and was safe and immunogenic (manuscript pending). As the Merck vaccine is a recombinant protein, it should not have the safety concerns associated with live attenuated viral vaccines, and if effective, may be safer for use in very young children or in immunocompromised patients. The 3-dose schedule of administration at 0, 1, and 2 months is more rapid and convenient than some of the other dosing schedules. The GlaxoSmithKline vaccine was originally developed as a live attenuated tetravalent dengue virus vaccine, containing whole attenuated DENV 1, 2, 3, and 4.[18] The vaccine was safe and immunogenic, though some volunteers experienced a rash, similar to the NIAID vaccine. Since that trial, the vaccine has been reformulated as a purified inactivated tetravalent vaccine, and is currently being studied with different adjuvants in a phase I trial of two doses given 28 days apart. Both of these vaccine candidates are likely to have fewer safety issues than the live attenuated viral vaccines, but whether their immunogenicity will be adequate for protection is not yet established.

Looking Ahead

While dengue vaccine development has advanced considerably in the past decade, current approaches have been based on empiricism and trial-and-error. This has led to much time and resources being devoted to development and testing of vaccines with insufficient confidence that the phase 3 efficacy trials will show significant protection. The fundamental problem remains that we have not yet determined the correlates of protective immunity to dengue disease in people. Such correlates must exist, as life-long protective immunity to the infecting virus develops after natural infection (whether or not the infection results in disease) and two sequential natural infections significantly reduce risk of severe disease in post-secondary infections.[10] To accelerate vaccine development, we need in vitro assays of dengue immunity which are better correlated with in vivo protection. Key neutralizing epitopes in the envelope protein hinge region have recently been identified,[11,12] and the ability of vaccines to induce antibodies to these epitopes should be measured and correlated with protection in clinical trials. Development of T cell assays which correlate with protective immunity is at an earlier stage, but preliminary data point to a key role for a dengue-specific CD4+ and CD8+ T cell IFNγ response.[8, 9] Using samples collected from the DENVax clinical trial conducted at the Saint Louis University Center for Vaccine Development, we have identified a unique gene signature, including elevated expression of key KIR (killer cell immunoglobulin-like receptor) genes, immediately after vaccine administration which was highly predictive of a multivalent immune response. We have also found the development of dengue-specific T helper follicular cells after vaccination could be predictive of subsequent immune responses (manuscript in preparation). These studies help define early correlates predictive of dengue immune responses, facilitating identification of key targets for immune protection.

Finally, vaccine development could be advanced, and inadequately protective vaccines more rapidly identified, using human challenge models, whereby vaccine recipients are challenged with heterologous attenuated vaccine viruses and protection from viremia caused by the challenge virus measured.[24] Such efforts would provide more confidence that vaccines going

into phase 2 and 3 trials are likely to be protective, and would be a significant improvement on the current empirical approach.

As of this time, no licensed vaccine to dengue is available, and the best protection is mosquito avoidance and using mosquito repellents containing either DEET, picaridin, oil of lemon eucalyptus, or IR3535 (www.cdc.gov/dengue). Repellent can be applied to exposed skin or clothing, or clothing or mosquito nets impregnated with permethrin can be used. Additional mosquito control efforts in testing include Wolbachia infection of Aedes mosquitoes, which renders them less permissive for dengue infection and less able to transmit dengue.[25]

The latest dengue outbreak and risk information is available from the CDC (http://www.cdc.gov/dengue/travelOutbreaks), and clinicians are advised to consult this if their patients are traveling to potentially dengue endemic areas, or they are treating a case of possible dengue in a returning traveler. However with the identification of sporadic locally acquired cases in New York, Texas, New Mexico, and Florida in 2013, the report of a locally-acquired case of dengue in Missouri may only be a matter of time.

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Disclosure

None reported. **MM**

Chikungunya Update

by Sarah L. George, MD

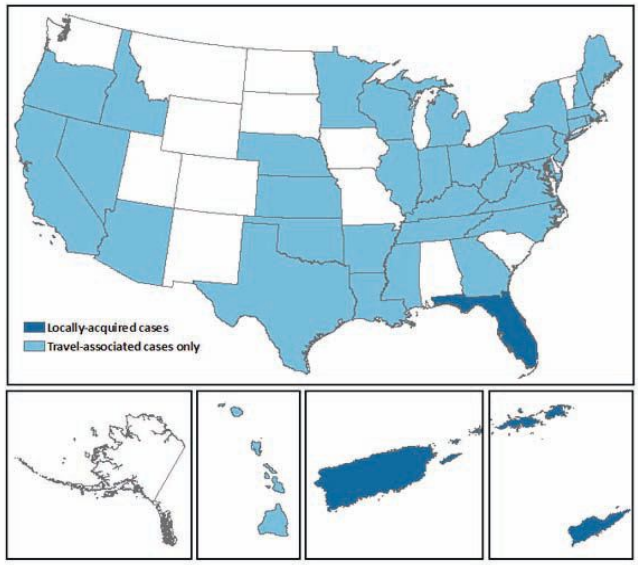
In December 2013, the World Health Organization reported the first cases of transmission of Chikungunya virus in the Americas, on the island of St. Martin in the Caribbean (cdc.gov/travel/notices/watch/chikungunya). Since that report, >2000 cases of Chikungunya have been reported from eight different Caribbean islands. As of July 11, 2014, the Pan American Health Organization had reported 259,723 suspected and 4,721 confirmed cases of locally-acquired chikungunya fever in the Americas. With over 130 cases in over 20 states reported in the U.S., the chances of having an outbreak here are increasing.

Chikungunya is an Alphavirus transmitted by *Aedes* mosquitoes, the same mosquitoes that transmit dengue. The first cases of Chikungunya were reported from Africa in the 1950s; since 2004 the disease has spread through Southern Asia and Europe and caused millions of human infections. The symptoms of Chikungunya are abrupt onset of high fever accompanied by severe joint pain and stiffness (arthralgia/arthritis/tenosynovitis), particularly of the hands and feet, but other joints can be involved. The pain is often symmetric and debilitating. A maculopapular rash may develop two to three days after the onset of fever, and may be accompanied by headache, fatigue, nausea, vomiting, and myalgias (cdc.gov/travel/yellowbook/chikungunya). Symptoms usually begin within a week of an infected mosquito bite, and while the fever typically resolves after three to five days, in 10% of cases the joint pain and debility can persist for weeks or months. Accompanying laboratory abnormalities can include lymphopenia, thrombocytopenia, elevated creatinine and liver function tests. Complications and fatalities are both rare. Treatment is supportive, including analgesics, antipyretics, and intravenous fluids if needed. There is no licensed vaccine for Chikungunya, though some candidates are entering phase I human studies. The only effective prevention is mosquito avoidance.

The diagnosis of Chikungunya is based on clinical symptoms and history of recent travel (< 2 weeks) to an area reporting disease activity. Suspected cases can be tested for Chikungunya IgM and IgG antibodies in reference laboratories, or for neutralizing antibodies at the CDC. Because people with Chikungunya have high levels of virus in blood during the first two to six days of the illness, they should be advised to remain indoors behind mosquito screens to prevent further spread of the disease. As of this writing, only a few locally-acquired Chikungunya cases have been reported from the continental U.S., but give the wide prevalence of the *Aedes* mosquito vector and the rapid spread of this disease since 2004, clinicians should remain alert for an increasing number likely to occur. Clinicians are advised to consult the CDC website for updates on this disease, particularly if they have patients who plan travel to affected areas or if they are treating a case of fever and arthritis in a returning traveler.

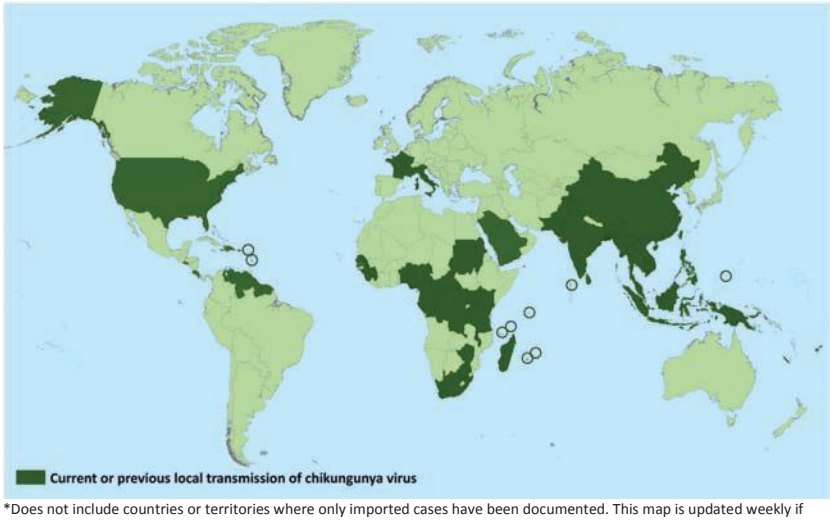
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Chikungunya virus disease cases reported by state or territory – United States, 2014 (as of July 22, 2014)



Source: http://www.cdc.gov/chikungunya/geo/united-states.html#arbonet-data

Countries and territories where chikungunya cases have been reported* (*as of July 22, 2014*)



*Does not include countries or territories where only imported cases have been documented. This map is updated weekly if there are new countries or territories that report local chikungunya virus transmission.

Source: http://www.cdc.gov/chikungunya/pdfs/ChikungunyaWorldMap_07-22-2014.pdf

SAINT LOUIS UNIVERSITY

Center for Vaccine Development

Recommended Solutions to the Barriers to Immunization in Children and Adults

by Edwin L. Anderson, MD

Health care provider barriers to immunization include lack of knowledge about indications for and contraindications to immunizations, poorly trained medical staff, and absence of a reminder system for missed vaccinations.



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Abstract

Vaccines prevent disease and mortality. They are the foremost achievement of public health programs in the United States and internationally. In the early 90s the National Vaccine Advisory Committee concluded that there were significant barriers to young children being fully immunized including inconvenient and limited clinic hours for immunization, inadequate access to health care, and vaccine administration fees. Barriers to adult immunization also have been identified. This article will discuss research addressing barriers to immunization and possible solutions.

Introduction

Vaccines are effective in preventing disease and mortality and are the premier achievement of public health programs in the United States and internationally. A recent article by Panhuis et al.[1] estimated that since 1924 vaccines have prevented over 100 million cases caused by eight contagious diseases. This estimate was arrived at by comparing incidence rates before and after vaccine licensure. Despite this remarkable success multiple resurgences of measles, rubella, mumps, and pertussis have occurred since the 1980s. These resurgences have various causes, including refusal to vaccinate, incomplete vaccination series, waning immunity, and imported cases.

This review will concentrate on barriers to immunization encountered by parents, patients, and providers and will provide recommendations for possible solutions to overcoming these barriers.

Barriers to Childhood Vaccines and Possible Solutions

Following the measles epidemics of 1989 and 1990, with 18,000 cases and 25,000 cases, respectively, the National Vaccine Advisory Committee concluded that there were significant barriers to young children being fully immunized[2]. These barriers were missed opportunities to vaccinate and impediments to immunization in the delivery system. Obstacles for parents getting their children fully immunized were identified and included inconvenient and limited clinic hours for immunization, inadequate access to health care, and vaccine administration fees. As a result, the Standards for

Pediatric Immunization Practices were published[3]. Specific recommendations were made to administer all vaccines the child was eligible for at each visit and to use all clinical encounters, including visits for mild illness, to provide needed immunization[4].

Many of the barriers to immunization found in the measles epidemics greatly reduced vaccinations provided by public health departments, where approximately 50% of all vaccines in the United States were administered. Over the next decade a survey by Taylor et al.[5] showed that there was a shift to vaccines being given in the primary care setting with about 58% administered in private practices. Their study was done to assess the association between parents' perception of barriers to vaccination and their preferences regarding specific strategies designed to reduce missed vaccination opportunities and improve the immunization status of their children. The authors surveyed parents from 177 pediatric practices. Parents of children 8 to 35 months old were asked to identify the most difficult issue about obtaining immunizations, as well as their preferences for the maximum number of vaccine injections their child should receive at one office visit. Parents were also asked whether or not their children should receive needed immunization during office visits for mild illness. Actual immunization data were collected on over 13,000 children. Two-thirds of parents who responded indicated that their children should receive no more than two immunizations at one visit. However, there was no difference in the preferred maximum number of vaccines per visit comparing between parents of children who were fully immunized at eight months of age and parents of underimmunized children (median response for both groups was two injections, $p=.62$). Also, there was no difference in vaccination coverage comparing groups with parental attitudes for or against their child receiving needed immunizations during an illness visit. The most commonly cited barrier was concern about vaccine side effects but this barrier was not associated with immunization status. Other identified barriers - including confusing vaccine schedules, the inconvenience of the vaccination process, having a child frequently too ill to vaccinate, and religious objections - were statistically associated with underimmunization. However, these barriers were identified by $<5\%$ of parents and were not thought to account for a significant number of underimmunized children. Taylor et al.[5] concluded that immunization rates could be improved by making their office-practice procedures more efficient.

A Study by Kimmel et al.[6] grouped barriers to immunization as systems barriers (eg., inadequate organization of the health care system), health care provider barriers (eg., clinicians not adequately educated about vaccines), and parent and patient barriers (eg., fear of immunization-related adverse events). The most significant systems barrier to immunization was supply and distribution. Vaccines have been in short supply at times due to inadequate manufacturing capacity. Occasionally these shortages were significant and changes had to be made in vaccination schedule, such as delaying the fourth dose in a series.[7] Currently the CDC lists certain DTaP and Tdap vaccines as being in short supply but the shortages are not great enough to warrant any changes in routine vaccination schedules (source: www.cdc.gov/VACCINes/vac-gen/shortages/).

Health care provider barriers to immunization include lack of knowledge about indications for and contraindications to immunizations, poorly trained medical staff, and absence of a reminder system for missed vaccinations. Also, there are still parents and medical staff who are uncomfortable with the number of recommended immunizations during well-child visits in the first year of life. The physician must clearly communicate to parents and office medical staff that vaccines must be given on time and according to published guidelines.

Providers face logistical barriers which include the expense of vaccines, proper vaccine storage requirements, and lack of vaccination records[6]. The MMR vaccine, live attenuated influenza vaccine, and the rotavirus vaccine have stringent storage requirements. Missed visits and failure to provide needed immunizations at every clinic visit opportunity contribute to incomplete immunization requirements. Practices with reminder systems in place can improve immunization rates. Electronic health records (EHR) may improve the efficiency of office practice by standardized record keeping, especially regarding missed visits and accurate immunization records. However, many practices have not utilized EHR systems yet.

Patient and parent barriers to immunization include: parents may lack knowledge about childhood vaccinations, have unreasonable fears about vaccine safety, or lack transportation. They may not be aware of the threat of vaccine-preventable illness or that safe and effective vaccines are available against these diseases. A study of a rural clinic showed that supportive staff, convenient office times, and limited wait time for immunizations contributed to fully immunized children[8].

Despite the many barriers described, research has shown that some interventions can improve vaccinations rates[9, 10]. For parents who are distrustful of official sources, some may be more willing to accept information from their personal physician who takes time to listen and

address their concerns about vaccine safety.[9] Studies in adults can be applicable. In adult populations one of the strongest predictors of influenza vaccination is a physician's recommendation to receive the vaccine.[10] A study of standing orders, reminders, rapid vaccination services in inner city clinics found that these steps also led to an increase in influenza immunization rates among adults.[11]

Misconceptions about vaccines exist. Some parents believe that too many immunizations will weaken their child's immune system or may cause chronic illnesses such as asthma, DM, or MS.[12] Some parents believe that vaccine-preventable diseases were already disappearing prior to the use of vaccines or that vaccines are not natural and prefer disease-induced immunity for their children. Parents who are non-vaccinators may believe they can control their child's susceptibility to infection, question the validity of vaccine information, prefer errors of omission rather than errors of commission, or believe herd immunity will protect their child from the common childhood illnesses. These and other misconceptions are addressed at the following CDC website (www.cdc.gov/vaccines/vac-en/6mishome.htm). Physicians serve as the primary source of vaccine information for most parents and patients.

Physicians must provide accurate information about the benefits and risks associated with immunization. Occasional severe adverse events do occur following vaccination but are extremely rare. Current vaccine information can be provided with CDC-supplied Vaccine Information Statements (CDC.gov/nip/publications/vis) which can be given to families or patients prior to vaccination. Time should be made available prior to vaccination for parents to express their concerns to providers.

Parents may refuse vaccination for personal, cultural and/or religious reasons, or because of a previous perceived bad experience with immunization. Physicians need to acknowledge parents' concerns and respectfully address them and attempt to correct any misconceptions.[13] Also, parents often use cognitive shortcuts to simplify complex situations and judgments and health care providers should be aware of this reasoning.[14]

Barriers to Adult Vaccination and Possible Solutions

Barriers to adult immunization have been identified to facilitate compliance with vaccine recommendations by the U.S. Public Health Service, multiple national professional healthcare, and state public health agencies. Johnson et al.[15] surveyed over 2,000 adults aged 19 to 74 years, (20 of whom were health care providers), about attitudes and knowledge regarding tetanus, influenza, and pneumococcal vaccines. Among consumers (patients), 90% to 96% were aware of the availability of influenza and tetanus vaccines. Only 65% were aware of the pneumococcal vaccine, although awareness was higher among groups for whom this vaccine was recommended (85% of respondents ≥65 years versus 50% of those <50 years, $p < 0.001$). Most consumers were aware of the tetanus vaccine but only 36% knew that adults should receive a booster every 10 years. Of the three vaccines covered in the survey, the one that most consumers (70%) remembered receiving as an adult was the tetanus vaccine.

Most consumers (79% to 85%, depending on the vaccine) indicated they were likely to receive a vaccine if their health care professional recommended it. The most consistent reason given for not receiving any of the three vaccines was the belief that a healthy person did not need to be vaccinated (60%). For tetanus vaccine, 74% believed it was necessary only when an injury occurred; for the pneumococcal vaccine, 56% said their doctor had not recommended it. Vaccine costs were not found to be a deterrent for >80% of consumers, and 83% agreed that vaccinations preventing missed days at work would be valuable.

The Johnson et al.[15] survey results of physicians and nonphysician providers (PA/NP/RN) also found some interesting differences between these provider groups, their beliefs, and their practice delivery methods. Greater than 90% of these health care professionals believed their adult patients should be vaccinated. Also, both physician and nonphysician providers claimed to discuss recommended vaccinations with their adult patients during scheduled health maintenance office visits. However, PA/NP/RN providers were more likely to discuss immunizations during sick visits (42%) than were physicians (29%, $p = 0.03$). When asked about specific vaccines, physicians and the PA/NP/RN group recommended the tetanus vaccine to all adults (85% and 88%, respectively). Recommendations were less frequent for influenza and pneumococcal immunizations and survey results showed that neither group of providers followed published recommendations for adults. Only 60% of physicians and 56% of the PA/NP/RN group stated that they used official guidelines as their source of information about adult immunizations. Most health care providers had systems in place to assure that patients got recommended vaccines while only approximately 33% actually audited rates of vaccination.

Providers were questioned about why patients might not receive tetanus, influenza, and pneumococcal immunizations.[15] Common reasons offered were failure

of patients to come in for regular well-care visits, concern about vaccine side effects, and lack of an effective reminder system in the practice. Over 50% of health care professionals acknowledged that they did not always remind patients of the consequences of missing vaccinations. The PA/NP/RN providers were significantly more likely to routinely talk to patients about the consequences of missing tetanus, influenza, and pneumococcal vaccinations.

In the U.S. pneumonia and influenza are major causes of death in the elderly. It has been estimated that the pneumococcal polysaccharide vaccine (PPV) and the influenza vaccine prevent thousands of deaths each year and yet vaccination rates in 2002 among adults 65 years and older for PPV and influenza vaccine were 55% and 66%, respectively.[9] Vaccinations rates for Hispanic and African Americans were even lower. A study from the University of Pittsburg by Nowalk et al.[16] identified patient beliefs, facilitators, and barriers to PPV and influenza vaccinations in elderly patients across a range of socioeconomic levels. This study was conducted by telephone interview of patients 66 years and older from the metropolitan Pittsburg area and included patients from several inner city clinics and suburban practices.

A total of 557 participants completed the interviews with regard to the PPV vaccination.[16] Seventy percent of respondents reported receiving this vaccine but there were significant differences by race, practice location, marital status, and physician recommended vaccination. Whites were more likely to have received PPV than African Americans (74% versus 57%, p=.005). Widowed individuals, when compared to other marital categories, were more likely to be vaccinated (76% vs 73% married, 53% single, and 50% divorced, p=.0008). A high proportion (87%) of those vaccinated reported that someone in their doctors' offices recommended PPV compared with 24% of the unvaccinated (p=.0002). Additional questions were asked to assess barriers and facilitators to vaccination. Receipt of PPV was associated with the perception that obtaining the vaccine was wise, a willingness to be given PPV at the same time as the influenza vaccination, and a specific physician recommendation. In logistic regression analyses, a doctor's recommendation for PPV was significantly related to pneumococcal vaccination status [OR, 95% CI, 4.9[0.6-42.6)], p=<.001).

Seventy-six percent of respondents were vaccinated against influenza with a greater proportion from suburban (81%) than from inner-city practices (71%; p=.006). Married persons were more likely to have received influenza vaccine than those in other marital categories (83% vs 73% widowed, 66% single, 62% divorced/separated; p<.05). More men than women (81% vs 73%; p=.03), and more whites than blacks (79% vs 61%; p=.003) were vaccinated against influenza. Individuals with incomes >$40,000 (88%) and those attending vocational or technical school (94%) had high rates of vaccination. Beliefs and attitudes found in the survey indicated that vaccinees were more likely to report that their doctor, family and/or friends recommended vaccination and they were also more likely to receive PPV if they received influenza vaccine at the same visit. Factors preventing immunization were faulty recall by the patient and failure of the physician to discuss vaccination with their patients.

Pneumococcal disease continues to cause severe illness in the elderly and in those with underlying medical conditions.[17] Despite prompt antibiotic treatment the mortality varies from 15% to 40% depending on risk factors. Therefore, it is very surprising that although the 23 valent PPV has 56% to 81% efficacy preventing invasive disease, vaccination rates continue to be 60% or less for those older than 65 years. Because 36% to 70% of patients hospitalized for pneumococcal bacteremia have been patients in the same institution during the previous five years, PPV vaccination during hospitalization as institutional policy has been a way of improving immunization rates.

Experience at Veterans' Affairs institutions has found that a Standing Orders Program (SOP) that allows clinical personnel such as nurses and pharmacists to vaccinate inpatients with PPV without a specific physician's order can improve vaccination rates in this at risk population.[17] In 2003 hospitals that were part of the University of Pittsburg Medical Center Health System initiated such institutional policies for PPV. Over the next 24 months medical personnel encountered a number of barriers to the implementation of the vaccination SOPs. Middleton and colleagues[18] identified these impediments and provided recommendations for overcoming these barriers. They found barriers related to patients, providers, and institutions. The major patient barriers were inaccurate PPV history, and patient/family concerns about safety and the actual need for vaccination. Providers' barriers included fear of increased workload, lack of information about the institutional policy, reluctance of staff to administer a vaccine without a physician order, attending physician resistance to vaccination, and PPV not being available after hours. Institutional barriers included inertia, cost-benefit questions, and determining the PPV status of hospitalized patients. Their recommendations for increasing the effectiveness of these vaccination policies included institution-wide education about the importance of PPV in high risk populations, collecting accurate information

Table 1
Recommendations for Improving Vaccination Among Adults

1. Education of potential vaccine recipients
2. Publicity promoting vaccines
3. Increased access to vaccination services such as workplaces, pharmacies
4. Reminder-recall systems and internal audits of practice vaccination rates
5. Standing order programs
6. Audit vaccination rates in practices
7. Health-care provider recommendation to patients
8. Routine assessment of vaccinations incorporated into clinical practice
9. Medical office staff trained to routinely assess vaccination needs of patients

Table 2
Recommendations for Improving Vaccination Rates Among Children

1. Increase knowledge about importance of vaccination for disease prevention
2. Stay up-to-date on latest vaccination recommendations
3. Become familiar with new vaccines
4. Assure office staff are friendly and supportive of families and encourage vaccination at every opportunity, including mild illness visits
5. Reminder/recall systems for patients, families and providers
6. Reduce out-of-pocket costs
7. Standing orders for immunizations
8. Assessment of immunization rates for individual providers

about PPV status at admission, education of staff, patients and families about the safety of vaccination, continuous education of new medical staff about the vaccination policy, and designated champions at each institution to continuously and effectively promote the vaccination program.

Conclusion

The successful prevention of severe infectious diseases by vaccination is without question. Despite this success, there is room for improvement among adults and children. Coverage rates for pneumococcal and influenza vaccines are substantially below the Healthy People targets of 90%.[19, 20] Recommendations for improving vaccines rates among adults are shown in Table 1. Recommendations for maintaining and improving vaccination rates among young children are shown in Table 2. The Center for Vaccine Development at Saint Louis University of Medicine has been involved in vaccine research for over 20 years. The work, involving a collaboration of experienced and dedicated physicians, basic researchers, nurses, laboratory, and support staff, has contributed greatly to the development of new vaccines and developing the basic science necessary for vaccines of the future. Additional research seeking to determine how to accomplish the optimal vaccination coverage of targeted populations must also continue.

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Disclosure

None reported.

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Clues from Hands Part I

Personal Details about Patients Revealed by Hand Examination

by Sherea M. Stricklin, BA, Katie S. Payne, Ryan K. Rader, BS, Karen D. Schilli, MS & William V. Stoecker, MD

The astute clinician has daily opportunities to practice these observational skills, increasing the range of detectable signs well beyond the examples present here, following in the tradition of the famous fictional detective, Sherlock Holmes.



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Abstract

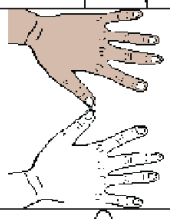
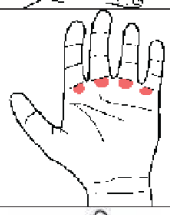
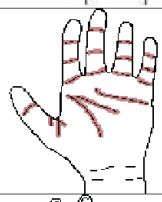
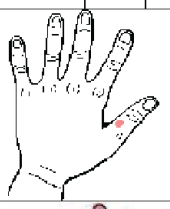
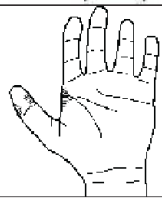
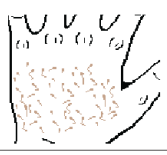
This is the first part of a two-part article on personal details revealed by the hand examination. Daily activities revealed by hand examination are the focus of Part 1, while personal details including nutrition and psychological assessment are presented in Part 2. These clues enable the examiner to discern hobbies, vocation, sporting activities, dietary information, and psychosocial information of the patient. We describe signs that may aid the clinician in determining these activities, enabling us to provide better patient care by establishing good patient rapport. Part 1, presented here, focuses on detection of visible traces on the hands of sporting activities, hobbies, and vocation. The patient through long familiarity may be oblivious to these features or may find them too insignificant to mention, yet they can provide meaningful social details for the physician.

Introduction

The social and personal history provides a powerful therapeutic adjunct. Greater knowledge of the patient can aid in optimizing therapy and treatment compliance. Through observation of a person's hands and forearms, details about a patient's daily activities can be discovered, adding a silent narrative to their social history. These details include information that patients may not be willing to share (e.g. suicidal attempts and self-induced emesis), or may find too insignificant to mention (e.g. household pets, occupational and recreational exposures), or may be unaware of (e.g. dietary deficiencies). Turning over the patient's hands to look for the hyperlinear palms of the atopic diathesis (for asthma and/or allergies) or pallor in palmar creases (for anemia) is a natural step in any examination. However, a more thorough examination can include findings that reveal more about the patient, including many daily activities. The clinician can also learn to discern the degree of fading of pigment or healing of small injuries to estimate the time since the injury or exposure. Observing features that offer insight to a patient's daily activities shows a genuine personal interest and goes a long way toward establishing patient trust in the doctor. The astute clinician then can utilize this trust to improve a patient's clinical outcome by obtaining assent for further diagnostic workup or enhancing therapeutic compliance.

Part 1 focuses on activities in the areas of sports, work and hobbies. The specific location, morphology, mechanism, and implication of

Table 1

Activity	Diagram	Location	Morphology	Explanation	Comments
Basketball (dunking)		Volar aspect of first phalanx, dominant hand	Orange skin coloring confined to dermatoglyphic ridges	Rim rust leaves orange color on hands that can dunk	Low sensitivity, as presence requires rusted basketball hoop rim and ability of player to reach rim
Golf		Entire dorsum of non-dominant hand	Pigmentation less on gloved hand (top hand on golf club)	Hand protected from sunlight	Dominant hand is the pale hand
Weightlifting for some, also rowing machine, manual labor		Distal palm at metacarpal head	Calluses	Skin adapts to weights with calluses	Nonspecific, can sometimes occur with any prolonged gripping. Very thick calluses imply weightlifting
Baseball or softball		Volar aspect of palm, hypothenar eminence, over hamate bone	Bruise	Bruise from base of bat. momentum from struck baseball transferred to palm	Axial line corresponds to rim at base of bat
Hulling walnuts		Volar hand	Brown pigment prominent in dermatoglyphic sulci	Walnut hull stain is difficult to wash away, especially from dermatoglyphic sulci	Most common in Ozarks
Yard work		Medial first proximal phalanx	Blisters commonly from rake or mower	Thin glabrous skin of medial first phalanx bears unaccustomed friction	More common during warm months; usually heal rapidly
Guitar playing		Fingertips of non-dominant hand, most prominent on 2nd-4th digits	Calluses	Steel strings make calluses	T-shirt may display band names
Car repair		Flexor hand	Black pigment in nail plate and dermatoglyphic sulci, prominent at edges of gripping surfaces	Used motor oil is difficult to wash out of nails and dermatoglyphic sulci	Not confined to males
Wood heat, burning trash		Hairs on dorsal hand	Hair tips are thicker and curled at ends	Heat from wood stove, burning trash or barbecue pit causes hair tips to thicken and curl	Males

these signs are summarized in Table 1. Detection of signs enables a clinician to elicit a more detailed patient history and gain a greater understanding of the patient through close observation of the patient's hands.

Sport participation can be noted from a hand examination. Basketball players who regularly dunk a basketball will display orange-to-rust skin coloring on the proximal interphalangeal joints on the volar skin (See Figure 1), where the hands frequently make contact with a rusted basketball hoop. Golfers tend to wear only one glove on the non-dominant hand while playing. As a result, extended sun exposure to the dominant hand causes greater pigmentation (See Figure 2). People who exercise with weights and other resistance exercise devices routinely develop heavy calluses over the metacarpal heads (See Figures 1 and 3). For children in primary school, similar calluses can be an indication of using playground equipment. The rim at the base of the bat may cause softball or baseball players to display a bruise over the hypothenar eminence, a common injury to the non-dominant palm (See Figure 4).

Hobbies/Work/ Environment

Frequent use of gardening or household tools (e.g. rakes,

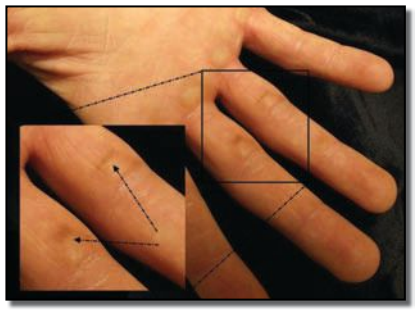


Figure 1
Rim rust marks (arrows) from dunking basketballs and calluses from weightlifting. The rim rust marks are prominent immediately proximal to the calluses.

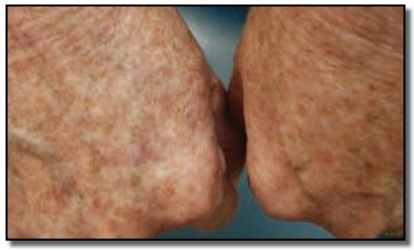


Figure 2
Golfer displaying darker skin pigmentation on nondominant hand due to wearing glove on dominant hand while playing golf.

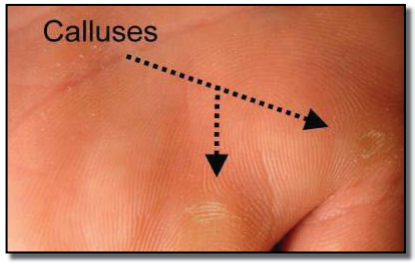


Figure 3
Calluses over metacarpal head on palms due to weight lifting.

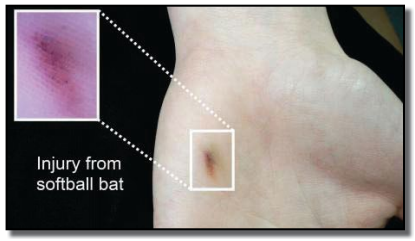


Figure 4
Bruise over hypothenar eminence of palm, nondominant hand, due to softball bat. Note hemorrhagic dots in dermatoglyphic ridges, pathognomonic for hemorrhage.

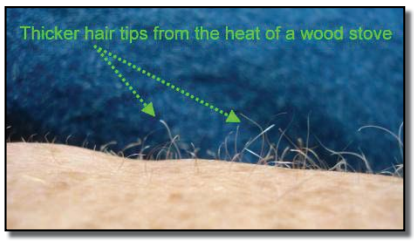


Figure 5
Thickened and curled hair tips caused by heat from a wood stove.



Figure 6
Fingertip calluses on non-dominant hand from playing guitar. Note total absence of palmar calluses in this student.

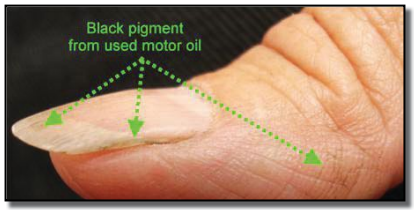


Figure 7
Black pigment from motor oil located on nail plate and in dermatoglyphic sulci at edges of gripping surfaces, in a female patient who rebuilds engines.

brooms, mops, etc) can lead to blisters and eventually calluses on the medial first proximal phalanx of ungloved hands (See Table 1). Loading wood into a hot stove, or burning trash or leaves can singe the hairs on dorsal hands and wrists (See Figure 5).

Guitarists display telltale signs of callus formation on the fingertips of their non-dominant hand (See Figure 6). These changes are prominent when the patient practices regularly, but will fade after a period of not playing. Due to the difficulty of washing motor oil from the hands, car mechanics, both vocational and recreational, can exhibit black pigment on the fingernails, fingers, and palms, with pigment persisting longest in the palmar and digital dermatoglyphic sulci (See Figure 7). Similarly, stains from hulling walnuts are also difficult to remove. These stains typically appear as brown pigmentation in the dermatoglyphic sulci on the volar side of hands and fingers, most prominently on the finger and thumb pads (See Table 1).

Conclusion, Part 1

This concludes the presentation of signs of activities present on the hands, part 1 of our two-part presentation of signs of patient activities and personality observed on the hands. Part 2 will focus on personality traits and preferences, including pet ownership, nutritional assessment, and psychological disorders. The astute clinician has daily opportunities to practice these observational skills, increasing the range of detectable signs well beyond the examples present here, following in the tradition of the famous fictional detective, Sherlock Holmes. It was a physician, Professor Joseph Bell, who inspired Sir Arthur Conan Doyle in creating the character for Sherlock Holmes. Professor Bell (1837-1911), lecturer at the University of Edinburg College of Medicine, could deduce the occupation and activities of a stranger through careful observation.[1] The wise clinician will understand that patients are mainly concerned with their medical problems, and silently incorporate these observations in the clinical assessment, and share these observations in a way to increase patient rapport.

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1. http://en.wikipedia.org/wiki/Joseph_Bell. accessed July 20, 2013

Disclosure

None reported.

MM

Intratympanic Steroid Therapy for Treatment of Idiopathic Sudden Sensorineural Hearing Loss

by Zachary W Bear, MD & Anthony A Mikulec, MD

In the primary treatment of ISSHL, achieving the correct diagnosis rapidly is paramount, as early initial treatment greatly increases the chance of hearing recovery.



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Abstract

Idiopathic sudden sensorineural hearing loss (ISSHL) is the sudden loss of unilateral hearing of unknown etiology. The standard treatment consist of a high dose oral steroid taper. This article serves to review the current literature on intratympanic steroid injections for ISSHL. Current literature suggested intratympanic steroids are equivalent to oral steroid therapy, primary combined therapy is superior to either alone and intratympanic steroids should be offered for salvage therapy in ISSHL.

Introduction

A sudden decrease in sensorineural hearing from an unknown etiology broadly defines idiopathic sudden sensorineural hearing loss (ISSHL). There is no consensus regarding the exact degree and time frame of ISSHL, but the most common definition used is a 30 decibel (dB) loss over three continuous frequencies occurring within three days. A more general definition of any noticeable and measurable loss of hearing function over the course of minutes to days is often used.[1] A recent article estimates the incidence in the U.S. to be 27 out of 100,000 people with a slight male predominance.[2] Hearing loss is usually unilateral and associated symptoms include feeling of ear fullness, tinnitus and dizziness/vertigo.[1]

A number of different etiologies have been proposed to explain ISSHL including viral infection, intracochlear membrane rupture, vascular insults, and autoimmune processes; however none of these have been proven definitively in humans.[3] A recent review article found that hypertension, diabetes, smoking history, heavy alcohol use and short sleep durations were more common in patients with ISSHL than controls.[4] The same article also found that genetic mutations associated with thromboembolic events were more common in patients with ISSHL. Most likely, each of these underlying etiologies contributes to some proportion of the total incidence of ISSHL.

Treatment strategies used for ISSHL are nearly as diverse as the proposed etiologies. Cochrane reviews exist for the use of oral steroids, antivirals, vasodilators/ vasoactive substances and hyperbaric oxygen.[5,6,7,8] These reviews concluded that the benefit of oral steroids remains unclear and the effectiveness of vasodilators remains unproven. Hyperbaric oxygen therapy significantly improved hearing, but secondary to the few number of patients and poor reporting, clinical significance remains unclear. There are ongoing reviews for intratympanic steroids, antioxidants and acupuncture. A multitude of other interventions have been attempted with minimal clinical response. Currently, the most widely used treatment for ISSHL is systemic glucocorticoids. The first published article looking at oral

steroid therapy was in 1980.[9] This placebo controlled, double blind study with 67 patients found that oral steroids resulted in 61% of patients recovering hearing as compared to 32% of the placebo group. A recent Cochrane review concluded that the evidence supporting the use is unclear[8] and a recent multicenter placebo-controlled, triple-blind study concluded that oral steroids did not seem to influence the recovery of hearing in ISSHL in 93 patients.[10]

The American Academy of Otolaryngology published a recent clinical practice guideline detailing recommendations regarding ISSHL.[11] By definition, ISSHL results in a sensorineural hearing loss so it is imperative to rule out a conductive hearing loss (such as cerumen impaction) by physical exam and audiometry. The history and physical should also assess patients for bilateral sudden hearing loss, recurrent or fluctuating hearing loss and focal neurological deficits, as these can point to underlying etiologies. The guideline recommended against routine CT scan or laboratory testing, but recommended MRI or auditory brainstem response to rule out retrocochlear pathology such as vestibular schwannoma. The guideline stated that oral corticosteroids could be offered, but then acknowledged the paucity of studies to support their use. It was stated that clinicians should not "routinely prescribe antivirals, thrombolytics, vasodilators, vasoactive substances, or antioxidants". The guideline suggested that intratympanic steroids were an alternative for primary treatment and recommended them after failure of initial management. Just as the Cochrane review suggested some benefit from hyperbaric oxygen[7] the guideline recommended offering patients with ISSHL hyperbaric oxygen treatment within three months of diagnosis. The difficulties of obtaining hyperbaric oxygen treatment were mentioned, including the relatively few number of treatment centers and lack of insurance coverage/cost to patient. Finally, the guideline reiterated the importance of follow up audiometry and offering hearing amplification for those who do not fully regain hearing.

The use of intratympanic steroid injections for inner ear disorders was described in the mid 1990s for use in patients with Meniere's disease, autoimmune inner ear disease and sudden sensorineural deafness.[12] Since that time it has grown in popularity for several reasons. As described above, the most common treatment for ISSHL is oral corticosteroids. Although no clear side effects of steroids used in ISSHL was reported in the Cochrane review[8], the side effects of long term use can include fluid and electrolyte abnormalities, hypertension, hyperglycemia, increased susceptibility to infection, osteoporosis, myopathy, behavioral disturbances, cataracts, growth arrest, fat redistribution, striae and ecchymosis.[13] Minimal systemic absorption of intratympanic steroids has been reported and the risk of systemic side effects is minimized.[14] Studies have shown that cochlear perilymph concentrations are on the order of 100 fold higher with intratympanic administration of steroids vs IV or oral.[14] Injection of steroids through the tympanic membrane comes with some associated risk such as residual perforation or increased susceptibility to infection, however few actual complications were reported in the studies reviewed in this article.



Figure 1
Injection of Intratympanic steroids using binocular otoscope. Patient in supine position. Topical phenol applied to anteriorsuperior quadrant followed by injection of steroids.

Intratympanic steroid injections are relatively simple to perform, and an increasing percentage of generalist ENTs perform them. The general procedure at this institution is similar to ones described in studies reviewed by this article. The patient is placed supine in a chair. (See Figure 1.) Topical anesthetic (often phenol) is placed on the anterosuperior quadrant of the tympanic membrane. An aqueous solution of steroid (dexamethasone, methylprednisolone) is then injected through the anesthetized region until the middle ear is full. (See Figure 2.) The patient remains supine with the injected ear pointed up for 20-30 minutes, to facilitate passage of steroid across the round window membrane. Overall the procedure is no more difficult than an in office myringotomy, which most general otolaryngologists are comfortable performing.

It has been shown that intratympanic steroids are safe and minimize the side effects associated with systemic steroids while resulting in much higher cochlear concentrations than IV or oral preparations. The questions that remain, like many of the treatments for ISSHL, is does it work and when should it be used? There are a number of articles in the literature that describe the use of intratympanic steroids for use in ISSHL. Some of the articles describe using intratympanic steroids as primary treatment, with or without other treatments (usually oral steroids). Others describe the use as secondary or salvage treatment after initial treatment has failed or there is residual hearing loss. This article will review



Figure 2
Materials for intratympanic injection: steroid (methylprednisolone and dexamethasone pictured), phenol, ear speculum, syringe with luer lock needle.

the current literature on intratympanic steroids and their use in ISSHL. The review will concentrate on randomized studies with preference for placebo controlled trials.

Literature Review

Intratympanic Therapy as Primary Treatment for ISSHL

First studies looking at the effects of intratympanic steroid therapy as a primary treatment were considered. A single randomised, placebo controlled, triple blind study comparing intratympanic steroids to a placebo therapy was found.[15] The study consisted of 50 patients with moderate unilateral ISSHL. 25 were placed in the experimental group and received intratympanic prednisolone once a day for 3 consecutive days. The control group consisted of the other 25 patients and received saline injections for 3 consecutive days. The primary outcome measured was improvement in pure tone averages. Anyone who did not show a complete recovery on day 7 in either group was treated with an oral steroid taper. Notable findings included a complete recovery in 76% of the intratympanic group on day 7 and only 20% of the control group on day 7. Also noted was no recovery on day 7 in 4% of the experimental group and 80% of the saline group. By the end of the study (after patients who did not recover by day 7 had the oral steroid taper), there was no statistical difference in the hearing thresholds of the two groups. Also of note, if a patient failed to completely respond to intratympanic steroids, they did not further benefit from additional steroids. Overall, the authors suggested that the study supported the use of steroids, whether intratympanic or oral, for first line treatment for ISSHL.[13] The article also concluded that when intratympanic steroids were used as monotherapy for primary treatment of ISSHL systemic steroids do not seem to offer any benefit when used as salvage treatment.

Another group of papers looked at primary intratympanic steroid treatment with or without systemic steroids versus systemic steroid treatment alone. A study out of Turkey in 2013 with 79 patients compared treatment of unilateral ISSHL with oral steroid therapy vs 4 intratympanic injections of methylprednisolone plus oral steroid therapy.[16] They showed an improvement of 44 dB in the intratympanic plus oral group pure tone average vs a 26 dB improvement in the oral steroid only group. The results were statistically the same for patients with an initial pure tone average of less than 70, but showed improved results with the intratympanic and oral group in those with a pure tone average of at least 70. The study concluded that the combination therapy, oral plus intratympanic steroids, was superior for primary treatment of ISSNL especially with severe hearing loss. A similar study with 158 patients out of Turkey compared systemic steroids alone vs systemic steroids in combination with intratympanic methylprednisolone.[17] They showed an improvement of 13 dB in the systemic steroid only group compared to 20 dB in the combination group. This was statistically significant and this group similarly recommended combination therapy as a primary treatment for ISSHL. Another similar article with 120 patients published in 2008 out of Korea reached a different conclusion.[18] The study compared oral steroid therapy to combination therapy with intratympanic dexamethasone. This study found a statistically significant improvement at only one frequency (250 Hz). They concluded that intratympanic steroids offered no benefit in ISSHL in comparison to oral steroid therapy alone.

The literature search also revealed multiple papers that compared systemic steroids alone vs intratympanic steroids alone; some of which had a third combined treatment group. A study out of Italy with 46 patients compared intratympanic dexamethasone alone and oral prednisone alone.[19] They found an improvement in hearing of at least 10 dB in 80% of the intratympanic group and 81% of the oral group. they concluded that either intratympanic or oral steroids alone would be equally effective in treatment of ISSHL. A Korean study from 2009 compared oral prednisone alone and intratympanic dexamethasone alone as primary therapy for ISSHL.[20] They found statistically better results in the high frequencies for oral therapy, but concluded that either modality alone could be used for primary treatment of ISSHL. A study out of the US with 51 patients compared three different groups; placebo and intratympanic dexamethasone, oral prednisone and intratympanic saline and oral prednisone and intratympanic dexamethasone.[21] They found an improvement of at least 15 dB in pure tone average in 71% of the intratympanic dexamethasone group, 44% of the oral prednisone group and 88% of the combined therapy group. There was a statistically significant improvement in the combined group vs either of the other groups. Of note this

study used a placebo for systemic therapy and intratympanic saline in the control groups. The study concluded that combined therapy was superior to intratympanic or oral steroids alone.

A study of 250 patients in the United States with ISSHL compared oral prednisone alone to four intratympanic injections of methylprednisolone alone for initial treatment.[22] The pretreatment pure tone average was 86.7 for the oral steroid group and 86.4 for the intratympanic steroid group. Following treatment the pure tone average improved 30.7 dB in the oral group and 28.7 in the intratympanic group. This was found to be statistically equivalent. This study concluded that intratympanic steroid treatment is not inferior to oral steroid treatment. In subgroup analysis, the authors noted a trend for better recovery with oral steroids in those with a pretreatment pure tone average of at least 90 dB and those who presented with dizziness.

Intratympanic Therapy as Salvage Treatment for ISSHL

In addition to initial therapy in ISSHL, intratympanic steroid injections are also being used in salvage or secondary therapy after failure of initial therapy with systemic steroids. A study from China studied 65 patients who had been admitted for treatment of ISSHL and treated with IV prednisolone who showed no improvement in hearing.[23] The patients were split into three groups: intratympanic methylprednisolone alone, methylprednisolone drops onto the tympanic membrane alone and a group the received no further treatment. 38% of the intratympanic group showed an improvement in pure tone average of at least 10 dB with zere patients in the ear drop or control group showing this degree of improvement. The authors recommended intratympanic steroid therapy for those who failed systemic steroid treatment for ISSHL. Another placebo controlled, blinded study compared intratympanic dexamethasone to intratympanic saline injections in patients who failed systemic steroid therapy.[24] The study showed an improvement of at least 10 dB in 44.4% of the intratympanic steroid group compared to only 11.1% of the intratympanic steroid group. The authors again recommended the use of intratympanic steroids after failure of systemic steroid therapy. A Korean study compared the use of intratympanic dexamethasone to no further treatment in patients with ISSHL who failed systemic steroid treatment.[25] Similar to the other studies mentioned, 47.6% of the intratympanic steroid group showed improvement compared to only 16.0% of the controls. The authors recommended use of intratympanic steroids following failure of systemic steroids.

A single study was found that compared the use of additional systemic steroids to the systemic steroids with intratympanic methylprednisolone in patients that failed initial systemic therapy.[26] Patients in the study failed conventional systemic steroids and were determined to have a 'poor prognosis'. Poor prognosis was defined as hearing loss greater than 70 dB, age older than 60, a flat or high high frequency hearing loss on audiogram, presence of severe vertigo or time exceeding 2 weeks from onset of initial treatment. 20.5% of the additional systemic steroids alone group showed an improvement of at least 15 dB in comparison to 45.9% treated with additional systemic steroids in combination with intratympanic steroids. The authors concluded that patients with 'poor prognosis' ISSHL may benefit from transtympanic therapy in combination with oral steroids for salvage treatment.

Discussion

Given the obvious morbidity associated with ISSHL, it is clear that effective treatments are needed. The "gold standard" in the United States has been high dose oral steroid therapy, but recent review articles have concluded that the efficacy of this treatment is questionable.[8,10] Reviewing the literature reveals that intratympanic steroid therapy is proving to be beneficial for patients with ISSNL.

The studies described here seem to suggest that intratympanic steroid injections alone or systemic steroid therapy alone are equally effective in the treatment of ISSHL.[15,19,20,22] Patients with uncontrolled diabetes or other medical problems may not be able to tolerate high dose systemic steroid therapy, making initial treatment with intratympanic steroids a good choice. However, in certain communities, patients may not have access to an ENT who performs intratympanic injections and patients need to be able to see this specialist as soon as possible and 3-5 times over a two week period for injections.

Although monotherapy with either systemic or intratympanic steroids appears to be equally effective, the literature described above suggests that primary combined therapy is superior to monotherapy.[16,17,21] There were, however, studies that did not conclude combined therapy was superior.[18] The study that did not recommend combined therapy did show statistically significant improvement at 250 Hz.[18] When seeing a patient with ISSHL, offering both intratympanic and oral steroid therapy initially seems reasonable.

Studies suggest that the use of intratympanic steroids for secondary/salvage treatment is more effective than no additional treatment.[23,24,25] Many patients present to the ER or primary care physicians with ISSNL and are treated with oral steroid therapy. It is important for these physicians to know that patients who fail to respond to initial oral steroids may still benefit from intratympanic steroids. Most protocols in the literature initiated intratympanic injections immediately after failure of oral steroids. Physicians should promptly refer patients to an ENT comfortable performing transtympanic steroid injections.

Optimal delivery of transtympanic steroids and absorption into the cochlea is an active area of research. A study from Taiwan advocated the use of a MicroWick placed through the tympanic membrane and had patients place a dexamethasone solution in the external auditory canal twice a day[27] in an attempt to provide continual cochlear absorption of the steroid. Other companies are investigating ways to inject steroid into the middle ear that resorb much slower than the aqueous solutions currently being used, so that only one injection is needed.

There are multiple questions regarding intratympanic steroid treatment for ISSHL that remain unanswered. First, there is no universally accepted protocol for the use of intratympanic steroids. In the articles reviewed, the number of injections varied from 3 to 8 performed over a 1 to 4 week period; dexamethasone was most commonly used followed by methylprednisolone. Future studies determining the ideal steroid and the number and frequency of injections are needed. The treatment window for ISSHL remains uncertain. It is also unclear why some patients benefit from intratympanic steroids while others do not. As described above, multiple etiologies have been proposed to explain ISSHL. Likely, only certain underlying pathologies are amenable to steroid therapy. Subgrouping patients with ISSHL may result in better treatment strategies.

Perhaps the biggest hurdle in treatment of ISSHL with intratympanic steroids is recognizing the diagnosis and achieving timely access to care. A sudden drop in hearing in one ear is often incorrectly ascribed to fluid behind the ear drum or otitis media, and treated with decongestants or oral steroids. In the absence of a formal audiogram, a Weber tuning fork test can be used to ascertain if a hearing loss is conductive or sensorineural. The test is performed by holding a tuning fork (ideally 512 Hz) firmly against the forehead. Patients with a conductive hearing loss from otitis media or similar will hear the tuning fork louder in the affected ear, while patients with ISSHL will hear it better in the non affected (normal) ear. If a tuning fork is not available, a mobile phone or pager turned to its vibrate function and pressed against the forehead will work quite well. It is distinctly clear that rapid initiation of therapy for ISSHL profoundly increases the chance for a good outcome.

Conclusion

In the primary treatment of ISSHL, achieving the correct diagnosis rapidly is paramount, as early initial treatment greatly increases the chance of hearing recovery. All patients with ISSHL should be evaluated for retrocochlear pathology by MRI with contrast, even if the hearing loss recovers. Both intratympanic steroids or systemic steroids alone appear equally effective, however the use of both intratympanic and systemic steroids together is likely superior to either used alone. Intratympanic steroids likely offer additional benefit as a secondary/salvage therapy in patients who fail initial systemic steroid therapy. Hyperbaric oxygen treatment may play a role in ISSHL treatment, although robust data is lacking and patient access to hyperbaric oxygen therapy is limited.

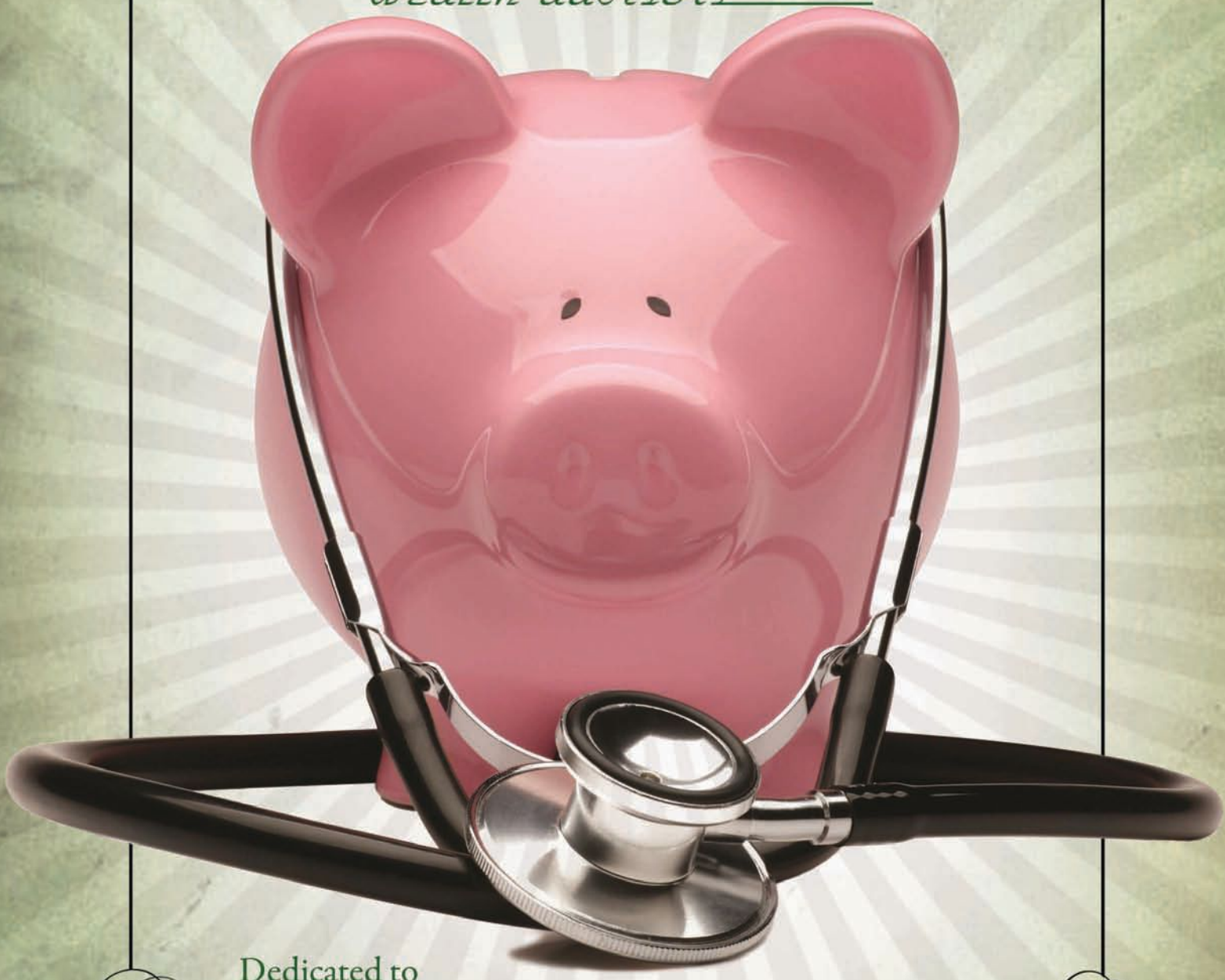
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Disclosure

None reported. **MM**

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