April 3, 2016

The Dark Side of Evidence-Based Medicine

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By the end of this conference, participants should…

"If you only knew the power of the Dark Side."

—Darth Vader

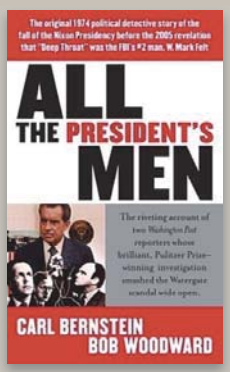
Conflicts of Interest

- None
- I have no relevant financial relationships to disclose
- I will not be discussing off-label/investigative uses of commercial devices

Three ways evidence-based medicine fails us

- Study results, though initially promising, can't be reproduced
- The conclusion drawn from the evidence is based on flawed logic
- The evidence is tainted by conflict of interest, or even fraudulent

Tabloid vs. scientific journal:
What do their editors have in common?



Sometimes Results Can't Be Reproduced

Original Contribution | July 13, 2005

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research FREE

John P. A. Ioannidis, MD

JAMA The Journal of the American Medical Association

- How frequently are highly cited studies contradicted by subsequent research?
- "A third of the most-cited clinical research seems to have replication problems"

Original Contribution | October 24/31, 2012

Empirical Evaluation of Very Large Treatment Effects of Medical Interventions FREE

Tiago V. Pereira, PhD; Ralph I. Horwitz, MD; John P. A. Ioannidis, MD, DSc

JAMA The Journal of the American Medical Association

- "Trials with very large effects have limited evidence"
- "When additional evidence is obtained, most of the very large treatment effects become much smaller"
- "Most large treatment effect estimates should be considered with caution; many are spurious findings"
- "Well-validated very large effects for mortality or even life-threatening clinical outcomes are exceedingly rare"

The NICE-SUGAR Study: NEJM 2009

- International multi-center trial
- 6104 ICU patients randomized either to:
  - blood glucose 81-108 mg/dl *or*
  - blood glucose less than 180
- Primary end point: Death (any cause) within 90 days
- Intensive glucose control ***increased*** risk of death **2.6%**

nature International weekly journal of science

Reproducibility: A tragedy of errors

David B. Allison, Andrew W. Brown, Brandon J. George & Kathryn A. Kaiser

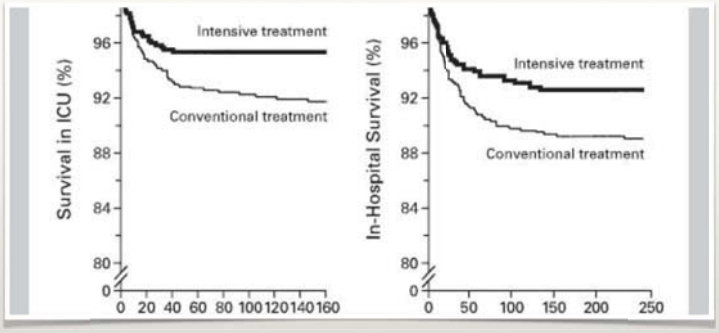
03 February 2016

Mistakes in peer-reviewed papers are easy to find but hard to fix, report David B. Allison and colleagues.

- Mistaken design, analysis, calculation
- Editors unable/reluctant to take speedy, appropriate action
- Journals reluctant to issue retractions; some even fine authors for retractions, or charge to publish letters with corrections
- No standard mechanism exists to request raw data

"This metric might not be a valid measure"

- *J Thorac Cardiovasc Surg*. 2014: Reviewed outcome data on 1700 patients after cardiac surgery, with postoperative 6 a.m. glucose < 200 or >200 mg/dl
- Level < 200 "not associated with improved risk-adjusted mortality, morbidity, or hospital resource usage"
- Conclusion: "postoperative glucose control should not be used as a measure of quality after cardiac surgery"



Van den Berghe et al., NEJM, 2001

Intensive Insulin Therapy in Critically Ill Patients

>1500 SICU patients randomly assigned to tight glucose control, 80-110 mg/dl, or conventional treatment, glucose 180-200 mg/dl

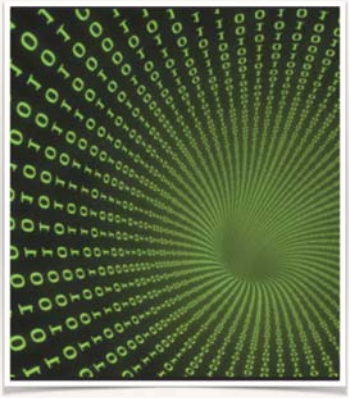
SCIP news, January 28, 2015

- "Data collection and reporting for SCIP-Inf-4 measure: *Cardiac Surgery Patients With Controlled Postoperative Blood Glucose*, is suspended immediately"
- "There are concerns that it may adversely affect the way clinicians and hospitals provide care"

Flawed logic:
The "post hoc ergo propter hoc" fallacy

The risk of mining "big data"

- Assuming that association equals causation
- "Post hoc ergo propter hoc"



Polio in 1950s

- 1952 pandemic: 58,000 American children infected; 3,000 died; 20,000 left with significant residual paralysis
- Observation: yearly rates of polio infection rose in spring and summer, as ice cream consumption increased
- Deduction: excess sugar from ice cream increases polio risk

ARB and 30-day Mortality

- *Anesthesiology,* May, 2015: retrospective review of non-cardiac surgery in 30,000 VA patients 1999-2011
- Patients who resumed ARB by postoperative day 2: **1.3%** 30-day mortality
- Patients who did *not* resume ARB: mortality **3.2%**

Science News *from research organizations*

Withholding angiotensin receptor blockers after surgery increases risk of postoperative death

Date: June 4, 2015

AIDS in 1980s

Prior to discovery of the human immunodeficiency virus (HIV), the rapid spread of AIDS was associated with the recreational use of inhaled nitrites

Time Out: Cause or Association?

- Could it be that ARBs weren't restarted because the patients couldn't tolerate it?
- "It is possible that failure to restart ARB and mortality are common effects of unmeasured aspects of being frail or sick."
- "Given the retrospective observational nature of the data, we are unable to make statements of causality."

The Pseudoscience of Quality Improvement

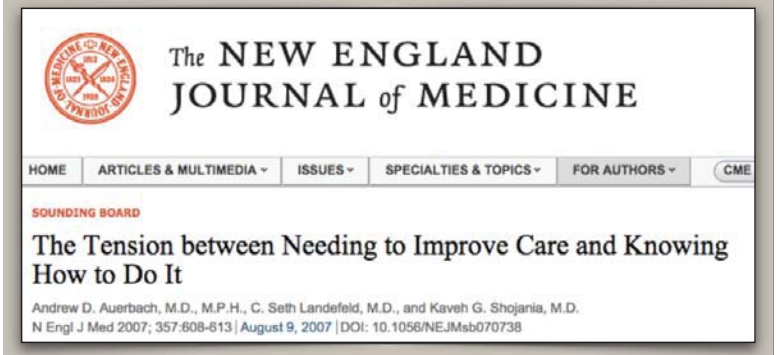
Focus on process of improving quality trumps science and reason

Leaping without looking first

- Point: "We cannot wait — the need to improve quality is urgent"
- Counterpoint: The need to improve treatment of disease is equally urgent, yet we demand rigorous evidence that a treatment works before recommending it
- Law of unintended consequences

Rapid Quality Improvement: Pro & Con

- Point: Any effort to improve quality is better than the present state of affairs
- Counterpoint: Understanding the potential risk and cost of any change is important; net benefit may be zero
- Point: Innovation is good; we should try strategies that have promise though they may be unproven
- Counterpoint: Interventions may turn out to be ineffective or even harmful—but their champions defend them rather than admit failure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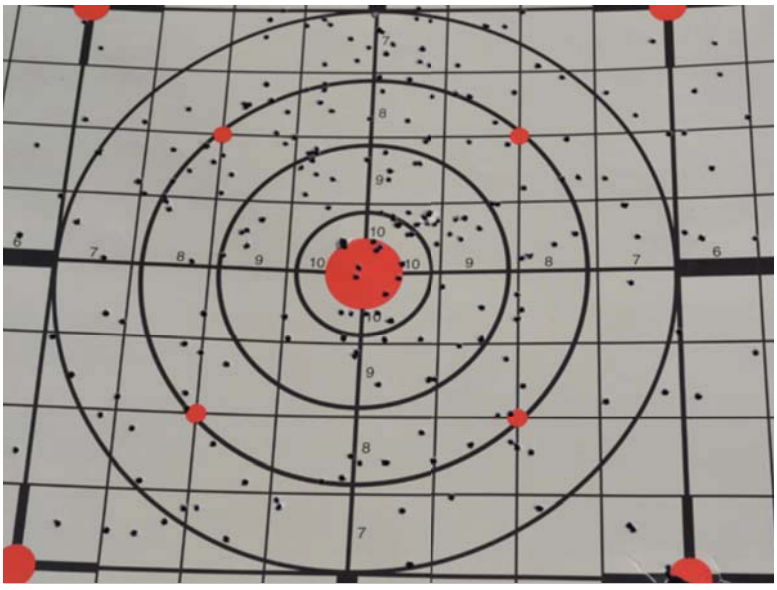
The Tension between Needing to Improve Care and Knowing How to Do It

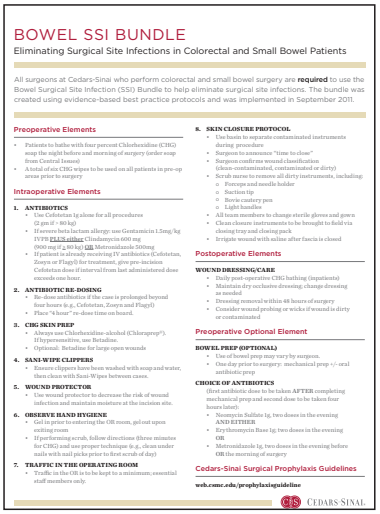
Andrew D. Auerbach, M.D., M.P.H., C. Seth Landefeld, M.D., and Kaveh G. Shojania, M.D.
N Engl J Med 2007; 357:608-613 | August 9, 2007 | DOI: 10.1056/NEJMsb070738



Surgical Site Infections

2011: Cedars-Sinai Medical Center undertook major quality initiative to reduce SSI in small bowel and colorectal operations

Mandated implementation of "care bundle" with 12 **major** elements involving changes in practice



BOWEL SSI BUNDLE

Eliminating Surgical Site Infections in Colorectal and Small Bowel Patients

All surgeons at Cedars-Sinai who perform colorectal and small bowel surgery are **required** to use the Bowel Surgical Site Infection (SSI) Bundle to help eliminate surgical site infections. The bundle was created using evidence-based best practice protocols and was implemented in September 2011.

Preoperative Elements

- Patients to bathe with four percent Chlorhexidine (CHG) soap the night before and morning of surgery (order soap from Central Issues)
- A total of six CHG wipes to be used on all patients in pre-op areas prior to surgery

Intraoperative Elements

1. **ANTIBIOTICS**
   - Use Cefotetan 1g alone for all procedures (2 gm if > 80 kg)
   - If severe beta lactam allergy: use Gentamicin 1.5mg/kg IVPB PLUS either Clindamycin 600 mg (900 mg if > 80 kg) OR Metronidazole 500mg
   - If patient is already receiving IV antibiotics (Cefotetan, Zosyn or Flagyl) for treatment, give pre-incision Cefotetan dose if interval from last administered dose exceeds one hour.
2. **ANTIBIOTIC RE-DOSING**
   - Re-dose antibiotics if the case is prolonged beyond four hours (e.g., Cefotetan, Zosyn and Flagyl)
   - Place "4 hour" re-dose time on board.
3. **CHG SKIN PREP**
   - Always use Chlorhexidine-alcohol (Chloraprep®).
   - If hypersensitive, use Betadine.
   - Optional: Betadine for large open wounds
4. **SANI-WIPE CLIPPERS**
   - Ensure clippers have been washed with soap and water, then clean with Sani-Wipes between cases.
5. **WOUND PROTECTOR**
   - Use wound protector to decrease the risk of wound infection and maintain moisture at the incision site.
6. **OBSERVE HAND HYGIENE**
   - Gel in prior to entering the OR room, gel out upon exiting room
   - If performing scrub, follow directions (three minutes for CHG) and use proper technique (e.g., clean under nails with nail picks prior to first scrub of day)
7. **TRAFFIC IN THE OPERATING ROOM**
   - Traffic in the OR is to be kept to a minimum; essential staff members only.
8. **SKIN CLOSURE PROTOCOL**
   - Use basin to separate contaminated instruments during procedure
   - Surgeon to announce "time to close"
   - Surgeon confirms wound classification (clean-contaminated, contaminated or dirty)
   - Scrub nurse to remove all dirty instruments, including:
     - Forceps and needle holder
     - Suction tip
     - Bovie cautery pen
     - Light handles
   - All team members to change sterile gloves and gown
   - Clean closure instruments to be brought to field via closing tray and closing pack
   - Irrigate wound with saline after fascia is closed

Postoperative Elements

WOUND DRESSING/CARE
- Daily post-operative CHG bathing (inpatients)
- Maintain dry occlusive dressing; change dressing as needed
- Dressing removal within 48 hours of surgery
- Consider wound probing or wicks if wound is dirty or contaminated

Preoperative Optional Element

BOWEL PREP (OPTIONAL)
- Use of bowel prep may vary by surgeon.
- One day prior to surgery: mechanical prep +/- oral antibiotic prep

CHOICE OF ANTIBIOTICS
(first antibiotic dose to be taken **AFTER** completing mechanical prep and second dose to be taken four hours later)
- Neomycin Sulfate 1g, two doses in the evening **AND EITHER**
- Erythromycin Base 1g; two doses in the evening **OR**
- Metronidazole 1g, two doses in the evening before **OR** the morning of surgery

Cedars-Sinai Surgical Prophylaxis Guidelines

web.csmc.edu/prophylaxisguideline

CEDARS SINAI

Retraction Watch

Tracking retractions

Does anesthesiology have a problem? Final version of report suggests Fujii will take retraction record, with 172

with 7 comments

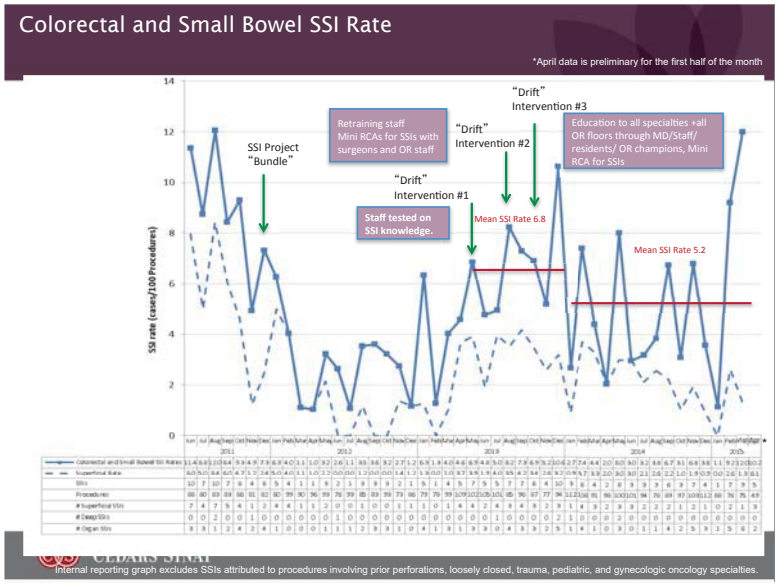
Japanese investigators have concluded that Yoshitaka Fujii, an expert in postoperative nausea and vomiting whose findings drew scrutiny in 2000 but who continued to publish prolifically for a decade after, fabricated his results in at least 172 published studies.

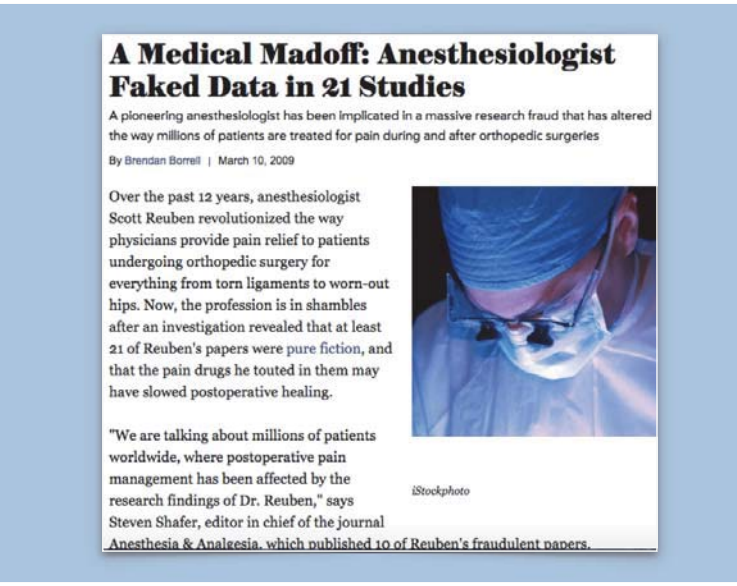
日本麻酔科学会 Japanese Society of Anesthesiologists

That number nearly doubles that of the current unofficial retraction record holder, Joachim Boldt.

Don't believe everything you read

Dr. Joachim Boldt, a German anesthesiologist, published 102 studies on colloid infusions, 88 of which have been withdrawn from the medical literature





A Medical Madoff: Anesthesiologist Faked Data in 21 Studies

A pioneering anesthesiologist has been implicated in a massive research fraud that has altered the way millions of patients are treated for pain during and after orthopedic surgeries

By Brendan Borrell | March 10, 2009

Over the past 12 years, anesthesiologist Scott Reuben revolutionized the way physicians provide pain relief to patients undergoing orthopedic surgery for everything from torn ligaments to worn-out hips. Now, the profession is in shambles after an investigation revealed that at least 21 of Reuben's papers were pure fiction, and that the pain drugs he touted in them may have slowed postoperative healing.

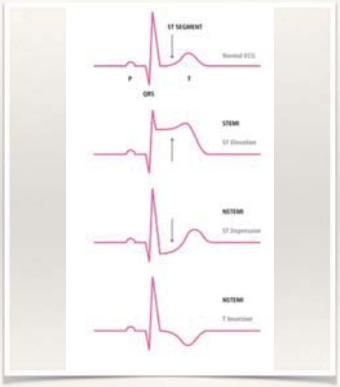
iStockphoto

"We are talking about millions of patients worldwide, where postoperative pain management has been affected by the research findings of Dr. Reuben," says Steven Shafer, editor in chief of the journal Anesthesia & Analgesia, which published 10 of Reuben's fraudulent papers.

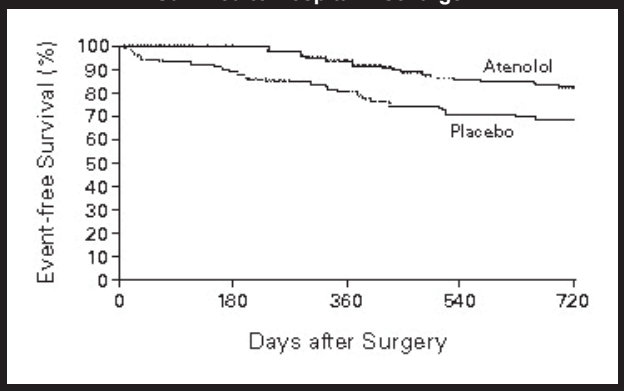
Fraud

The Saga of Beta-Blockade

- In 1980s, beta-blockers and other antihypertensives were routinely withheld before surgery
- In 1990s, role of beta-blockers in preventing perioperative ischemia began to emerge



Event-free Survival in the Two Years after Noncardiac Surgery among 192 Patients in the Atenolol and Placebo Groups Who Survived to Hospital Discharge.



Mangano DT et al. N Engl J Med 1996;335:1713-1721.

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Table 3
Effects of study treatment on primary and secondary outcomes at 30 days

	Metoprolol group (n=4174)	Placebo group (n=4177)	Hazard ratio	p value
Cardiovascular death, non-fatal myocardial infarction, or non-fatal cardiac arrest*	244 (5·8%)	290 (6·9%)	0·84 (0·70–0·99)	0·0399
Cardiovascular death	75 (1·8%)	58 (1·4%)	1·30 (0·92–1·83)	0·1368
Non-fatal myocardial infarction	152 (3·6%)	215 (5·1%)	0·70 (0·57–0·86)	0·0008
Non-fatal cardiac arrest	21 (0·5%)	19 (0·5%)	1·11 (0·60–2·06)	0·7436
Total mortality	129 (3·1%)	97 (2·3%)	1·33 (1·03–1·74)	0·0317
Myocardial infarction	176 (4·2%)	239 (5·7%)	0·73 (0·60–0·89)	0·0017
Cardiac revascularisation†	11 (0·3%)	27 (0·6%)	0·41 (0·20–0·82)	0·0123
Stroke	41 (1·0%)	19 (0·5%)	2·17 (1·26–3·74)	0·0053
Non-fatal stroke	27 (0·6%)	14 (0·3%)	1·94 (1·01–3·69)	0·0450
Congestive heart failure†	132 (3·2%)	116 (2·8%)	1·14 (0·89–1·46)	0·3005
New clinically significant atrial fibrillation†	91 (2·2%)	120 (2·9%)	0·76 (0·58–0·99)	0·0435
Clinically significant hypotension†	625 (15·0%)	404 (9·7%)	1·55 (1·38–1·74)	<0·0001
Clinically significant bradycardia†	277 (6·6%)	101 (2·4%)	2·74 (2·19–3·43)	<0·0001
Non-cardiovascular death	54 (1·3%)	39 (0·9%)	1·39 (0·92–2·10)	0·1169

Data are n (%) or hazard ratio or relative risk (95% CI).
*Some patients had more than one event.

The Lancet, May, 2008

PeriOperative ISchemic Evaluation (POISE)

Patients starting metoprolol 2-4 hours before surgery had fewer MIs but more strokes, hypotension, bradycardia, and higher overall mortality

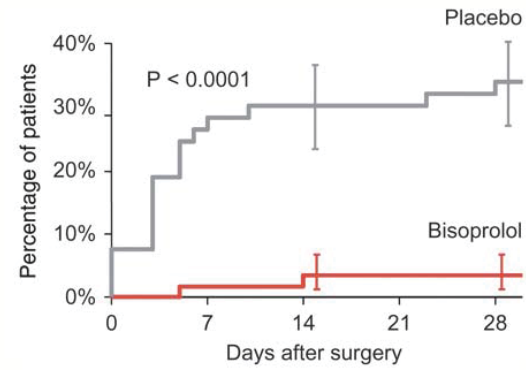

Figure 1
DECREASE showed that in high-risk patients undergoing non-cardiac surgery, perioperative beta-blockade with bisoprolol significantly reduced the combined primary endpoint of cardiac death and myocardial infarction. Reproduced with permission from Poldermans *et al.*[9]

Table 2
Grounds on which the DECREASE family of trials are considered discredited

DECREASE VI	Fictitious methods. 97% of the patients did not undergo a stress echo and the surgery as specified. No consent forms. Falsified description of method of outcome adjudication Fictitious database.
DECREASE V	Falsified methods of patient assessment (myocardial infarction and renal failure) Fictitious adjudication committee No record of the stress echo images or of the '5-member panel' said to have evaluated them No research patient records No evidence of written informed consent
DECREASE IV	Fictitious 'adjudication committee' of cardiologist, anaesthiologist and surgeon (in reality adjudications made by surgeon alone). Fictitious events that did not match hospital records or clinical discharge reports
DECREASE III	Not investigated in detail because: No source data could be found to investigate No written consent forms. No contemporaneous documentation, only current verbal assurances
DECREASE II	Fictitious method of establishing outcome
(DECREASE I	Not investigated as it was more than 10 years old)

British Medical Journal, 2013

DECREASE trials critically reevaluated

2011: Dr. Don Poldermans, lead author, is fired for using "fictitious data", resigns from European Society for Cardiology Committee for Practice Guidelines

Quality leaps forward

- 1996: New ACC/AHA guidelines recommend starting BB before non-cardiac surgery in patients who have hypertension, CAD, "cardiac risk factors"
- SCIP Quality Measure: All non-cardiac surgery patients on BB prior to admission must receive BB on day prior to or day of surgery, and on POD 1 or POD 2

What are we to do?

- If your patient for non-cardiac surgery is ***not*** already on a beta-blocker, don't start one prophylactically
- If your patient takes a beta-blocker routinely, continue it
- Avoid hypotension

American Society of Anesthesiologists

ANESTHESIOLOGY 2013

GLOBAL PARTNERS IN QUALITY OUTCOMES AND PATIENT SAFETY

Meanwhile, in Kansas…

- Cynthia Kirk, PhD, filed a whistleblower lawsuit against CareFusion under the False Claims Act
- As VP of Regulatory Affairs for the Infection Prevention Business Unit of CareFusion, she pointed out compliance violations: ChloraPrep ***not*** FDA-approved for prevention of infection or reduction of SSIs
- U.S. government and 31 states joined her lawsuit in 2011, suing for damages arising from Carefusion's "off-label marketing practices and kickbacks that induced false claims to be made to Medicare and Medicaid"

ChloraPrep vs. Betadine

Cleveland Clinic reports six operating room fires in past year, three patients injured

Charles Denham, MD

- Co-chaired National Quality Forum (NQF) Safe Practices Committee 2006, 2009, 2010
- He championed a new NQF "Safe Practice" guideline issued in 2010, recommending the use of chlorhexidine/alcohol skin prep to prevent SSI

Forbes / Business

FEB 14, 2014 @ 12:42 AM 13,405 VIEWS

The Money, the MD and a $12 Million Patient Safety Scandal

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ORIGINAL ARTICLE

Chlorhexidine–Alcohol versus Povidone–Iodine for Surgical-Site Antisepsis

Rabih O. Darouiche, M.D., Matthew J. Wall, Jr., M.D., Kamal M.F. Itani, M.D., Mary F. Otterson, M.D., Alexandra L. Webb, M.D., Matthew M. Carrick, M.D., Harold J. Miller, M.D., Samir S. Awad, M.D., Cynthia T. Crosby, B.S., Michael C. Mosier, Ph.D., Atef AlSharif, M.D., and David H. Berger, M.D.

N Engl J Med 2010; 362:18-26 | January 7, 2010 | DOI: 10.1056/NEJMoa0810988

Share:

Dr. Darouiche reports receiving research and educational grants from Cardinal Health; Dr. Wall, receiving a research grant from Cardinal Health; Dr. Itani, receiving consulting fees from Klein and Company and a research grant from Cardinal Health; Dr. Otterson, receiving consulting fees and a research grant from Cardinal Health; Dr. Webb, receiving a research grant from Cardinal Health; Dr. Awad, receiving consulting and lecture fees from Cardinal Health; Ms. Crosby, being employed by Cardinal Health; and Dr. Berger, receiving a research grant from Cardinal Health. No other potential conflict of interest relevant to this article was reported.

JUSTICE NEWS

Department of Justice

Office of Public Affairs

FOR IMMEDIATE RELEASE — Thursday, January 9, 2014

CareFusion to Pay the Government $40.1 Million to Resolve Allegations That Include More Than $11 Million in Kickbacks to One Doctor

CareFusion Corp agreed to pay $40.1 million to settle a federal government lawsuit accusing it of paying kickbacks to boost sales of a pre-surgical skin treatment, and marketing the product for unapproved uses.

The accord announced on Thursday by the U.S. Department of Justice resolves allegations that CareFusion violated the federal False Claims Act by paying $11.6 million to a doctor to promote its ChloraPrep product to healthcare providers.

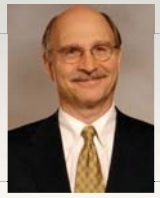
That doctor, Charles Denham, received the kickbacks while serving as co-chair of the safe practices committee of the nonprofit National Quality Forum, which makes recommendations on healthcare practices, the Justice Department said.

Patient-safety expert Denham will pay $1 million to settle kickback allegations

By Lisa Schencker | March 2, 2015

Dr. Charles Denham, a former leader of the National Quality Forum's Safe Practices Committee, has agreed to pay the federal government $1 million to settle allegations that he accepted cash in exchange for influencing the committee's recommendations.

NQF severed ties with Dr. Denham



This concludes our tour of the Dark Side.

Journal of the American College of Surgeons

Comparative Effectiveness of Skin Antiseptic Agents in Reducing Surgical Site Infections: A Report from the Washington State Surgical Care and Outcomes Assessment Program

Timo W. Hakkarainen, MD, MS, E Patchen Dellinger, MD, FACS, Heather L. Evans, MD, MS, FACS, Farhood Farjah, MD, MPH, Ellen Farrokhi, MD, FACS, Scott R. Steele, MD, FACS, Richard Thirlby, MD, FACS, David R. Flum, MD, MPH, FACS for the Surgical Care and Outcomes Assessment Program Collaborative

Received: August 17, 2013; Received in revised form: November 13, 2013; Accepted: November 20, 2013; Published Online: December 02, 2013

Conclusions

For clean-contaminated surgical cases, this large-scale state cohort study did not demonstrate superiority of any commonly used skin antiseptic agent in reducing the risk of SSI, nor did it find any unique effect of isopropyl alcohol. These results do not support the use of more expensive skin preparation agents.

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The observations of Karen Sullivan Sibert, MD a Los Angeles anesthesiologist, writer, and mother.

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