



Nontraditional Therapies: A Clinician's Perspective

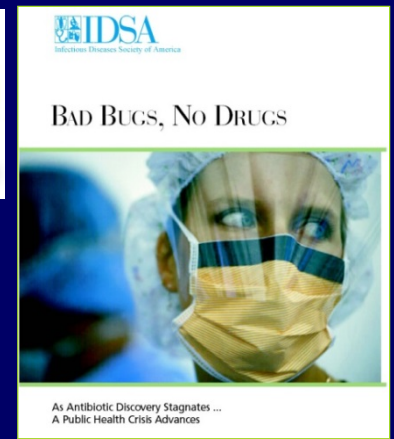
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Disclosures

- **Data Monitoring Committee**
 - Shire
- **Scientific Advisory Board**
 - Merck
- **Editor**
 - ID Clinics of North America
 - Antimicrobial Agents and Chemotherapy
- **Treasurer, Infectious Diseases Society of America**
- **Member, ID Board and ID Test Writing Committee, American Board of Internal Medicine**
- **Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)**

Nontraditional Therapies

Clinician's Perspective

Requirements – nontraditional therapies:

- **Need to work**
 - **Effective**
 - **Acceptably safe**
 - **Better than traditional antibiotics?**
 - **Additive to traditional antibiotics?**
- **Feasible path to study and use**
- **Reasonable reimbursement**

Potential Exemplar for NT Therapy

Sternal Wound Infections

- **Common 0.5-5%**
 - **Predictable risk factors**
 - **Female**
 - **Obese**
 - **Diabetic**
 - **smoker**
 - **Surgery complicated with bleeding, open chest, etc.**

Case Presentation

- 50 year old female 1 ppd smoker with HTN, hyperlipidemia, poorly controlled diabetes, obesity underwent coronary bypass x 4 Jan 07
- Readmitted 2 weeks later
 - High fevers
 - Purulent drainage from sternal wound
- Cultures + MRSA
- 1/27 bedside debridement
- 1/30 OR debridement with placement of titanium plates, pectoralis flap
- February – wound dehiscence
- OR 2/22 debridement, I&D, pectoralis flap

Case Presentation

- **March/early April**
 - Long term IV vancomycin
 - Wound developed drainage, patient developed chest pain, lost weight
 - WBC, inflammatory markers rose
- 4/19 admitted, CT + collection at sternum
- 4/20 OR plate removed, wound left open with vacuum dressing
- 4/27 OR for delayed closure
- Long term IV vancomycin with trough 15-20 mcg/ml
- Completed therapy 8/9/07

Case Presentation

Follow-up

- 8/23 presented with chest pain
- A bone scan + chronic sternal osteomyelitis, although a tagged wbc scan did not show any increased uptake in the sternum
- **Admission blood cultures 8/23/2007 + MRSA**
- TTE + small vegetation on the tricuspid valve
- Antibiotics were changed to IV daptomycin
- Chest pain improved, surveillance blood cx neg
- Discharged home on 8/31 after PICC line placement on IV daptomycin

Case Presentation

Follow-up

- 12 weeks IV therapy
- Follow up tagged wbc scan negative
- Follow up TEE (done in error)
 - New (?) aortic vegetation
- Surgery not deemed a safe option
- 8+ weeks IV therapy
- Follow-up TEE Feb '08 – aortic veg 2mm (smaller), wbc normal, documented weight gain
- Switched to suppressive Bactrim
- Did well and lived until 2018
 - 11 years after surgery

Sternal Wound Infection

- **Some sternal wound infections fail to respond to conventional antibiotics**
- **Many have significant morbidity**
- **Some are fatal**

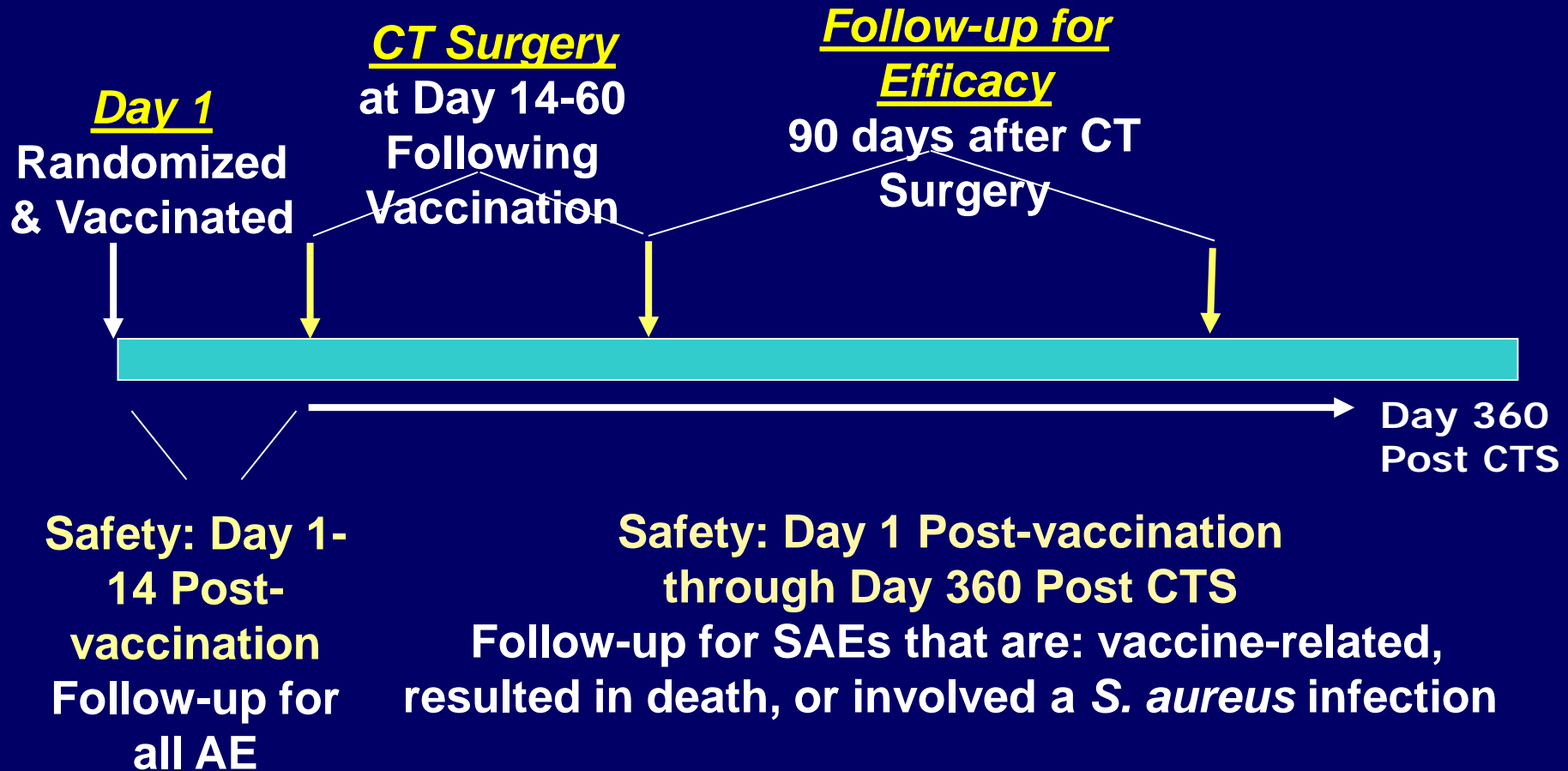
- **How much is preventing a sternal wound infection worth?**
 - **To the patient**
 - **To the hospital/payor**
 - **To society**

Nontraditional Therapies

Feasible Path to Study and Use

- Active pre-operative vaccination with *S. aureus* vaccine could reduce the post-operative incidence of *S. aureus* infections
- Rationale for cardiac surgery population:
 - *Acute period of risk of infection following surgery*
 - *Significant morbidity and mortality*
- Potential to generalize to other surgical populations

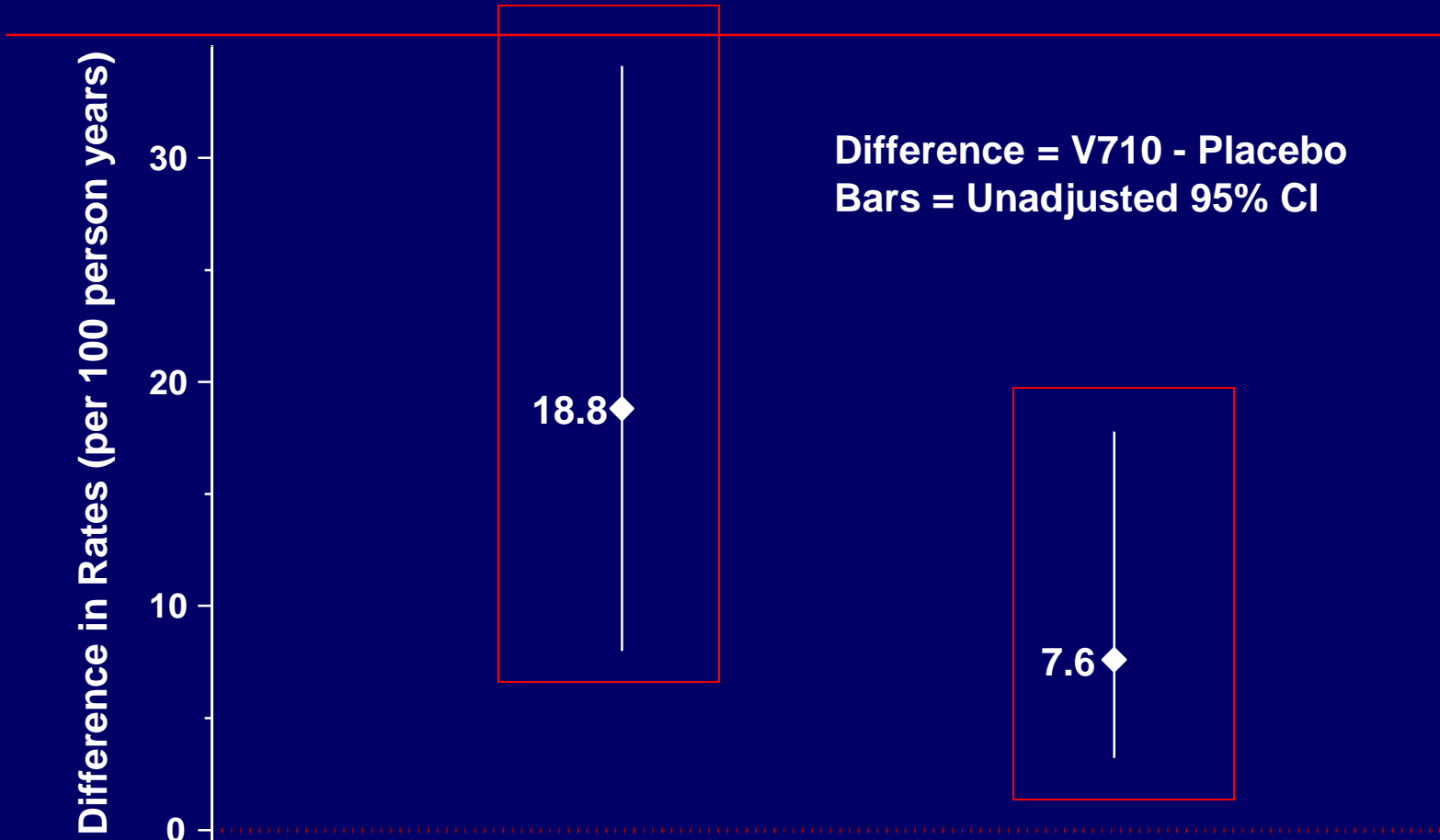
V710-003 Study design: overview



Analysis of *S. aureus* Infections

	V710 60mcg	Placebo	Vaccine Efficacy (%) (95% CI) [†]	p-Value (one-sided)
Number of Subjects Randomized	4005	4005		
Number of Subjects Randomized and Vaccinated	3981	3982		
Number of Subjects included in the FAS population	3528	3517		
Primary Hypothesis				
Number of <i>S. aureus</i> Bacteremia and/or DSWI infections	22 (0.6)	27 (0.8)	18.5 (-48.6, 55.8)	0.584
✓ <i>Bacteremia</i>	15 (0.4)	21 (0.6)	28.6	-----
✓ <i>DSWI - Mediastinitis</i>	9 (0.3)	9 (0.3)	0.0	-----
✓ <i>DSWI - Deep Incisional SSI Involving the Sternal Wound</i>	7 (0.2)	9 (0.3)	22.2	-----
MSSA	11 (0.3)	19 (0.5)	42.1	-----
MRSA	11 (0.3)	8 (0.2)	-37.5	-----

Analysis of Mortality and Multi-Organ Failure in Subjects with *S. aureus* Infections



Any <i>S. aureus</i> Infection	
V710	73
Placebo	96

Mortality		
Deaths	Follow-Up Time (yrs)	Rate (per 100 person-yrs)
15	65.2	23.0
4	94.4	4.2

Mortality due to MOF		
MOFs	Follow-Up Time (yrs)	Rate (per 100 person-yrs)
5	65.9	7.6
0	94.5	0.0

Conclusions: V710

- Was not efficacious in preventing *S. aureus* bacteremia and/or deep sternal wound infection
 - Even though it elicited a robust antibody response
- Increased mortality with SAB among vaccinated individuals
 - Appeared to be associated with multi-organ system failure (p-values not adjusted for multiplicity)
- Biological basis for this possible association is unknown but requires further study
- **Study extremely well done in a reasonable time frame**

2nd Potential Exemplar for NT Therapy:

***C. difficile* Infection (CDI)**

US burden close to 500,000 infections/year

- Magnitude of burden highly dependent on diagnostic test(s) used

National efforts to control and prevent CDI:

- Incentives for public reporting of hospital rates
- Hospital “pay for performance”

Up to 25% + recurrence - risk for recurrence:

- age >65 years
- severe underlying medical disorders
- need for ongoing therapy with concomitant antibiotics during treatment for CDI
- lack of an antibody-mediated response to toxin B

Clinical Impact of Nontraditional Therapy

Case

58 year old lady with giant cell myocarditis s/p OHTx 2013 (CMV +/-, EBV +/-, Toxo +/-) presented in 2015 with refractory *C. difficile* colitis and CMV

— Heart working well, no rejection

Recent Case

History:

- **Pre-transplant**
 - Shock, need for BiVAD support
 - *S epidermiditis* sternal osteomyelitis
- **Post-transplant**
 - Bleeding, delayed closure POD #4
 - Pneumonia/HCAP
 - Deep venous thromboses
 - Renal failure requiring CVVHd
 - Prolonged rehab c/w HCAP, CABSI
 - Early grade 2A rejection

Present History

Nov '13

- Diarrhea x 3 days – dx *C. difficile*
 - oral vancomycin

April '14

- Watery diarrhea , cramps, nausea; Dx CMV and *C. difficile*
 - fidaxomicin and ganciclovir
- Heart biopsy no rejection

July '14

- Watery diarrhea, *C. difficile* positive, fidaxomicin
-longer courses, evaluation/tx of other infections
- Total of 5 *C. difficile* episodes within 12 months
- Concern re: safety of FMT in transplant patient
- Successful FMT January 2015
- **Doing well to date**

Lessons from these cases

- **Infections caused by resistant pathogens are serious**
 - **This could happen to you or your children**
 - **Traditional antibiotics, even if we had the robust and renewable pipeline we need, are not always successful**
- **Having nontraditional therapies is and will be useful to clinicians and patients**
- **It is possible to study NT therapies in a feasible manner**
- **Preventing infections is important despite challenges**

Clinical Trials of Nontraditional Therapies are Hard

- Developing nontraditional therapies is surprisingly hard outside of a few specific areas:
 - Tractable:
 - Preventing pneumonia
 - FMT for *C. difficile*
- But, a path is desperately needed for nontraditional therapies
 - Rex & Outtersen

Nontraditional Therapies

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Requirements – nontraditional therapies:

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- **Feasible path to study and use**
 - Stewardship key to use
- Reasonable reimbursement

Regulatory Progress: TJC/CMS

Joint Commission
Requirement

Official Publication of Joint Commission Requirements
New Antimicrobial Stewardship Standard

APPLICABLE TO HOSPITALS AND CRITICAL ACCESS HOSPITALS

Effective January 1, 2017

Medication Management (MM)

Standard MM.09.01.01

The [critical access] hospital has an antimicrobial stewardship program based on current scientific literature.

Elements of Performance for MM.09.01.01

- Leaders establish antimicrobial stewardship as an organizational priority. (See also LD.01.03.01, EP 5)
Note: Examples of leadership commitment to an antimicrobial stewardship program are as follows:
 - Accountability documents
 - Budget plans
- The [critical access] hospital educates staff and licensed independent practitioners involved in antimicrobial ordering, dispensing, administration, and monitoring about antimicrobial resistance and antimicrobial stewardship practices. Education occurs upon hire or granting of initial privileges and periodically thereafter, based on organizational need.
- The [critical access] hospital educates patients, and their families as needed, regarding the appropriate use of antimicrobial medications, including antibiotics. (For more information on patient education, refer to Stan-

Core Elements of Hospital Antibiotic Stewardship Programs

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion



Healthcare IT News

TOPICS ↓ SIGN UP MA

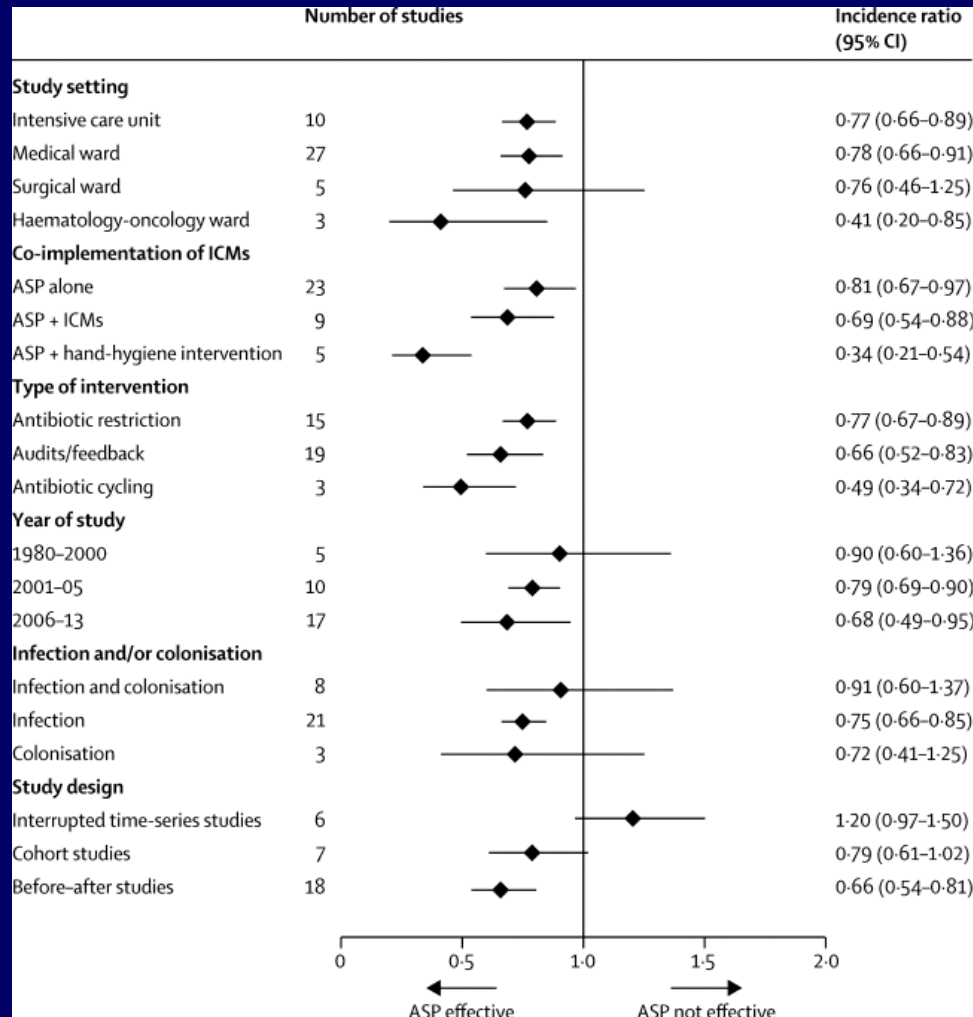
Proposed CMS rule tackles overuse of antibiotics, aims to boost infection control

New measures could save hospitals up to \$284 million annually, officials say.

By [Susan Morse](#) | June 15, 2016 | 09:11 AM

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Effect of Antibiotic Stewardship on Antibiotic Resistance



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Incentives

Principles

- Robust, understandable, predictable to motivate industry/private investors
- Target areas of greatest unmet need
- Aligned with efforts to promote stewardship, maintain access

Push Incentives

- CARB-X, BARDA, NIH ARLG etc.

Pull Incentives

- Market Entry Rewards
- Priority Review Vouchers (PRV)
- Tax Credits
- Licensing model – CMS/FDA
- Transferrable IP Rights (TIPR)

Final Thoughts - Clinician's Perspective on Nontraditional Therapies

Current status 2018

- Forced to use drugs and NT therapies with extremely limited/negative data
 - Case reports (phage)
 - Small series (FMT, monoclonal AB therapies)

Looking ahead:

- Traditional clinical development plans, NI or superiority studies may not be feasible
 - Small clinical studies
 - Data quality key (efficacy/safety)
 - Trial networks
 - Feasible studies focused on pragmatic endpoints
 - e.g., Desirability of Outcome Ranking (DOOR)
 - Including multiple body sites and infection types provides useful data for clinicians

We Need to Act Now!

Premature Death



**Rebecca Lohsen
(17 yr)--Dead**



**Mariana Bridi da Costa
(22 yr)--Dead**



**Carlos Don
(12 yr)--Dead**



**Ricky Lannetti
(21 yr)--Dead**

Life-altering Disability



Tom Dukes: colostomy, lost 8" colon



**Addie Rereich, 11yo
Double lung transplant
Stroke, nearly blind
\$6 million hospital bill**



Thank You!

- **K. Beaulac**
- **S. Doron**
- **E. Cox**
- **A. Jezek**
- **K. Outtersen**
- **J. Rex**