Financial Disclosures:
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Advisory Boards
Rib-x  Boehringer-Ingelheim
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Xoma  Sanofi-Aventis
BD Diagnostics

Research Study support
Vestagen
Honorarium-Travel Funds
3M
Co-evolution of Infection Control and Antibiotic Resistant Pathogens: What Works?

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Medical College of Virginia
Virginia Commonwealth University
Legendary Inheritance of Sex, Violence and Tragedy Surrounding Staphylus

Zeus
- Supreme ruler
- Mt. Olympus
- Married to Hera
- Numerous liaisons
- Father to Helen

Semele
- Mortal priestess
- Asked Zeus to reveal his glory - Bolts of lightning led to death

Minos
- King of Crete

Pasiphaë

Dionysus
- God of wine
- Hera had Titan lure and attack him remaining heart back into Semele. "Twice born"

Ariadne
- Loved Theseus who "had no joy for her" on Naxos

Staphylus
- God of wine
- Traveled with Jason for Golden Fleece
Staphylococcus Aureus

100 abscesses
Some in chains
Some in indigo-colored clumps
Reproduce abscess in mice by injection
Aureus: Latin – "gold"

Sir Alexander Ogston

Arch Klin Chir 1880; 25:588-
Significance of Bacteremia Caused by *Staphylococcus Aureus* (n=122)

- **Case Fatality:** 82%
- **Total Cases:**
  - 33 cases (aged 10-20)
  - 20 cases (aged 20-30)
  - 16 cases (aged 30-40)
  - 15 cases (aged 40-50)
  - 14 cases (aged 50-60)
  - 9 cases (aged 60-70)
  - 3 cases (aged 80+)

**Recovered Patients:**
- 4 patients (aged 10-20)
- 4 patients (aged 20-30)
- 4 patients (aged 30-40)
- 0 patients (aged 40-50, 50-60, 60-70, 80+)

Antibiotic Resistance in *S. aureus*
Following the Great Discovery of Penicillin

"An enzyme from bacteria Able to destroy Penicillin"

Extract of *E. coli* with a "substance destroying property of penicillin" – penicillinase

Sir Alexander Fleming

Abraham and Chain
*Nature* 1940; 146:837-
S. Aureus Bacteremia and Effective Antibiotic Rx

Abboud and Waisbren Arch Intern Med 1959; 104:226-33

% survival

(n=52) 0%

(n=29) 69%

≥ 6 ≤ 6

MIC (µg/mL) To Penicillin

Abboud and Waisbren Arch Intern Med 1959; 104:226-33
Attributable Impact of Penicillin

Estimated

- absolute 50% attributable survival -

Crude Mortality %

prior to penicillin

with

estimated attributable mortality

82%

31%

51%

Arch Int Med 1941; 68:851-75
Arch Int Med 1959; 104:226-73
Staphylococcal Toxin*
by P.N. Panton and F.C. O. Valentine

Denys and Van de Velde in 1895 described destruction of WBC after *S. aureus* injected into pleural cavities of rabbits: subsequent anti-leukocidin antibody

7/22 strains: strong leukocidin, weak hemolysis
- 6/7 severe infections, all 4 "pyemic" cases and
- 2/4 rapidly fatal after carbuncle

9/22 strains: weak leukocidin, strong hemolysis:
- saprophytes

Antisera continuing anti-leukocidin antibodies
- "chiefly efficacious with pyemic cases" in man

*Lancet* 1932 (March 5): 5068

* Gene later found to be on a phage virus integrated to Staph
Penicillin-Resistant *S. aureus*: Lessons after 30 years 1940-70

- **CLONAL SPREAD**
- **VIRULENT STRAIN**

**Most 80/81 Phage type**

- 80/81: all U.S. epidemics in maternity wards
- Half of UK outbreaks
- 1/3 colonized -> BSI
- 2.5% if non 80/81

**Decline of 80/81**

- Other phage types

**% resistance**

- 1940
- 1950
- 1960
- 1970

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*Lancet* 1959; 1:190-5
*BMJ* 1959; 5153:658-62
*Lancet* 2005; 365:1256-8
Vancomycin Use in the US

Drug introduced: 1958
Isolation Precautions: 1983
hVISA CA-MRSA: 1998; 42:1303-4
VRSA: 1999
IC bundles: 2008
IMS 2010
AAC 1998; 42:1303-4
Enterococci Contain Sex-Pheromone Induced Plasmid Transfer

Plasmid containing donor

Plasmid free recipient

consenting (responsive) - synthesize protein adhesin facilitating mating

secrete family of heat-stable protease
pheromones (5 to 6) - 7 or 8 AA result - transfer
frequently $10^5 - 10^6$ fold after transfer - specific plasmid pheromone shut down

Clewell
*Cell* 1993; 77: 9-12
Eleven Cases of VRSA

Time Line for VRSA

Michigan (8)
NY (1)
PA (1)
DE (1)

CDCinfo@idsociety.org 5/6/10
Fully Vancomycin-Resistant
*S. aureus* (n=11) 2002-2010

All prior: Vanco Rx, MRSA, VRE

<table>
<thead>
<tr>
<th>Condition</th>
<th>No</th>
<th>Age</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.M.</td>
<td>8</td>
<td>40s-50s</td>
<td>7</td>
</tr>
<tr>
<td>Obesity</td>
<td>4</td>
<td>60s-70s</td>
<td>4</td>
</tr>
<tr>
<td>ESRD</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any above</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal Extremity</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PHENOTYPE:**
- Middle-aged adult
- Insulin resistance
- Distal extremity wound

CDC. IDSA [Info@society.org] 5/6/10
MRSA Infections in 422 ED Patients - 2004

S. aureus - 76% SSTI (MRSA 59%)

USA 300 – 97%
SCC IV, PVL – 98%

USA 300 – 31%
PVL – 42%

MSSA 41%
MRSA 59%

Moran et al *NEJM* 2006; 355:666-74
USA 300 More Virulent than USA 400
Rat Pneumonia Model

Comparison of USA300 and USA400 lethality
*P<.01, Fisher's exact test.

Montgomery et al JID 2008; 198:561-70
Descendants of 80/81 Re-Emerging as CA-MRSA: Lessons after 70 years 1940-2010

- CLONAL SPREAD
- VIRULENT STRAIN

% resistance

- Most 80/81 Phage type PVL (+)

Decline of 80/81

Studies of Portions of:
7 housekeeping genes
8 variable genes

USA-300 PVL(+)

Robinson et al. Lancet 2005; 365:1256-8
So Far...

- *S. aureus* infections and modern hospitals have been constant companions.
- Resistance patterns arise primarily from horizontal gene transfer.
- Evolution of *S. aureus* is clonal.
  - Some strains (meth® USA 300 *nee* PEN® 80/81) are more virulent, spread more rapidly than others, and dominate.
The Role of Modern Infection Control

CDC decennial meetings

- UVA
- NNIS
- SHEA
- HIS
- SCOPE
- SENTRY

APIC

70s 80s 90s 00s 2010

- Defining the unacceptable (descriptive)
- Modelling the possible (analytical)
- Testing the interventions (intervention)
- Executing good practice (policy)
Milestones in Surgery

- Control bleeding
  - Cauterize
  - Sutures

- Abandon Blood-letting
- Transfusion
- Anesthesia

- Handwashing
- Antisepsis
- Sterile surgery

Ambrose Pare (1510-1590)

John Snow (1813-1858)

Joseph Lister (1827-1912)

Ignaz Semmelweis (1818-1865)
Silk Sutures Reduce Infecting Dose of *S. aureus* by 4 logs

Similar Data:
- SubCU Injection
- Skin incision

EFFECT OF SUTURES

Tied suture $3 \times 10^4$ organisms:
2/2 "very large stitch abscess"

Suture $3 \times 10^2$ organisms:
"small stitch abscess"

Elek and Conan *Brit J Exp Path* 1957; 38: 573-86
Niels Danbolt
Norwegian dermatologist
(1900-1984)

Typing - Coagulase
Biochemical Reaction
Necrotizing toxin (skin)
Clumping with specific rabbit antibody

Furunculosis (n=50): 77% nasal carriage same strain
Recurrent furunculosis (n=24): 22 had same strain in nose
Healthy controls – 40% carry Staphylococci
Courtesy of Niels Chr. Danbolt, PhD, University of Oslo
Median of 55% of *S. aureus* Surgical Site Infections are Endogenous

Elimination of Coincident *S. aureus* Nasal and Hand Carriage with Mupirocin

**Percent colonized**

<table>
<thead>
<tr>
<th>Time</th>
<th>Controls</th>
<th>Mupirocin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Post Rx</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>4 wks</td>
<td>88</td>
<td>82</td>
</tr>
<tr>
<td>12 wks</td>
<td>50</td>
<td>58</td>
</tr>
</tbody>
</table>

97% same clone on hand and nose

---

Intranasal Mupirocin to Prevent *S. aureus* Post-Surgical Infection

- **Mupirocin**
  - All patients: 2.3%
  - Carriers: 3.7%
- **Placebo**
  - All patients: 2.4%
  - Carriers: 5.9%

Perl, Cullen, Wenzel et al *NEJM* 2002; 346:1871-7
Subset of *S. epidermidis* Secrete Esp 
Inhibiting *S. aureus* Nasal Colonization

45% of 960 volunteers *S. epi* inhibit biofilm of *S. aureus*

If colonized with inhibitory *S. epi*

OR=0.30 for *S. aureus* colonization

*Esp*, serine protease, plus peptide component of innate immune system (hβD2)* kill biofilm

*Esp* introduced into nares, eliminates *S. aureus* colonization

* Human β-defensin 2

Iwase et al *Nature* 20 May 2010
Doi:10.1038/nature09074
Host Genetics May Determine Persistent *S. Aureus* Carriage

Persistant Carriage is Major Risk for Auto Infection

*Lancet* 2004; 364:703-5; *NEJM* 2001; 344: 11-16

And is influenced by genetic variation in host inflammatory genes

*J Infect Dis* 2008; 197:1244-53

A significant association with persistent carriage (2006 and 2008) and sets of single nucleotide polymorphisms to CRP genes and IL-4 genes.

*J Infect Dis* 2010: 202: 924-34
Hair Follicles as a Niche for *S. aureus* in the Nose

37 cadaver noses
*S. aureus* culture 9/37
SpA-specific antibodies in 8/9

8/8 only in Vestibulum nasi
6 – only outer portions of hair follicle
2-deeper parts of hair follicle

---

ten Broeke-Smits et al.
*J Hosp Infect* 2010; 76:211-4
Preventing Surgical-Site Infections in Nasal Carriers of *Staphylococcus aureus*

- Screening
- Mupirocin
- Chlorhexidine baths

- ~60% reduction of *S. aureus* infections
- 79% reduction in deep SSIs
- 55% reduction in superficial SSIs

Chlorhexidine-Alcohol vs Povidone-Iodine for Surgical-Site Antisepsis

- Clean-contaminated surgery, randomly assigned to preoperative skin prep with either chlorhexidine-alcohol or povidone-iodine paint and scrub
- 6 hospitals
- 50% of S.aureus SSI prevented without a screening program

RR = .59

Estimates of *S. aureus* Infections Using Two Different Programs

A horizontal program reduces all infections at a specific anatomic site, whereas a Vertical program targets a single organism at that site.

So Far...

- 40% of ALL SSIs can be eliminated with a change in surgical scrub from Iodophor to Chlorhexidine-Alcohol; 60% of *S. aureus* SSIs can be eliminated with Chlorhexidine baths and mupirocin Rx of carriers.

- Combining both approaches might yield a 50% absolute reduction of all SSIs.
Increasing Antibiotic Resistance
Strains 1970-2010

Wenzel et al ICHE 2008; 29:1012-8

Health care associated MRSA 2005-2008: 28% decline in US
Kallen et al JAMA 2010; 304:641-8
The Shortcomings of Nasal Screening for *S. aureus*/MRSA

- Throat carriage only in *S. aureus*: 25%
- MRSA throat carriage only: 13-15%

*Arch Internal Medicine* 2009; 169:172-8
*Journal of Clinical Microbiology* 2008; 46:835
*Journal of Clinical Microbiology* 227; 45:385

- CA-MRSA in Nares Only in 41%

*ICH* 2007; 28:966-9

Caveat: Does extranasal carriage have same risk as nasal carriage?
Decline in Invasive MRSA Infections

CDC’s population-based surveillance
2005-08: Decline 9.4%/yr
    most prominent for BSIs
    28% decline over 4 years
National decline of MRSA BSI
2003-08: 57%
Declines began prior to MRSA-specific interventions
Possible causes: horizontal programs vs unexplained biological trends

JAMA 2010; 304:641-8
JAC 2009; 64 (supp 1):111-7
JAMA 2010; 304:687-9
Controlling Healthcare Associated BSI: Vertical vs Horizontal Approach

- **S.aureus**
- **Enterococcus**
- **Candida**
- **GNR**

**Subset MRSA**

**Subset VRE**

**Subset C. glabrata**

**Subset P. aeruginosa**

Acinetobacter
Daily 4% Chlorhexidine Baths Decreased ICU-related MDR *A. baumannii* Colonization and Bloodstream Infections by 85%

Quasi-experimental design

Before 2/01 – 2/02) – after (3/02 – 12/03) comparison

Attack rate of *A. baumannii*

BSI – decreased

4.6% => 0.6% (OR=7.6, p<.001)

Incidence density of *A. baumannii*

**BSI – DECREASED**

7.8 to 1.25/1000 pt-days (85% reduction)

Could Daily Bathing with Chlorhexidine Reduce MRSA and VRE Acquisition and Infections?

In quasi-experimental study

6 mo reg soap => 6 mo chlorhexidine

- MRSA acquisition decreased 32%
- VRE acquisition decreased 50%
- VRE BSI decreased 73%

*Crit Care Med* 2009; 37:1858-65
Medical College of Virginia Hospital
Evidence-Based Interventions
(without active surveillance for MRSA)

Neuroscience, Medical, Surgical ICUs
Device-related BSI, urine infections and VAPs fell
> 40% in each unit and MRSA infects fell >48% in each unit

1 July 2010: 914 days in MRICU wince VAP case

66% Reduction in all Catheter-related Bloodstream Infections

- 103 ICUs
- Check list approach
- Empowered team

Incidence Density
Inf/1000 Cath-days

Mean: 7.7
Median: 2.7

NEJM 2006; 355:2725-32
### Bundles to Remove all Central Cath-Related BSIs

<table>
<thead>
<tr>
<th>Insertion</th>
<th>Maintenance/Removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptic Technique</td>
<td>Remove ASAP</td>
</tr>
<tr>
<td>Maximal Barrier Precautions</td>
<td>Hand Hygiene Before</td>
</tr>
<tr>
<td>Chlorinex/Alcohol Prep</td>
<td>Clean Part With Alcohol</td>
</tr>
<tr>
<td>Avoid Femoral Site</td>
<td>Avoid 3-Way MPS</td>
</tr>
<tr>
<td>Use CVC Check List</td>
<td>Needless Adaptors For Ports</td>
</tr>
<tr>
<td>Operator Name</td>
<td>Inspect/Clean Site Daily</td>
</tr>
<tr>
<td>Completed CVC Education</td>
<td>Dedicated Lumen For TPN</td>
</tr>
</tbody>
</table>

*BMJ Qual Saf 2011; 20: 174-80*
Figure 1
All or none insertion bundle reliability over time annotated to show identification and resolution of causes of incomplete reliability. Detail is given in the online appendix 6. Reliability increased between March 2008 and August 2009.

Figure 2

U chart. Monthly central-venous-catheter-related bloodstream infection (CRBSI) acquisition as rate per device day (number of infections divided by the device days/month). The plot demonstrates the common cause variation before the interventions start. Special cause variation (downwards shift) is evidenced by a run of >6 points below the centre line from February 2008.

Reducing Ventilator-Associated Pneumonia by 71% - Cohort Study

112 ICUs and 32278 ICU – Months. Bundle:

- Semi-recumbent position
- Adjustment of sedation to allow patient to follow commands
- Daily assessment of readiness to extubate
- Stress Ulcers Prophylaxis
- Prophylaxis to decrease DVTs

Caveats: No controls; no uniform surveillance definition

ICHE 2011; 32:305-14
Reducing Ventilator Associated Pneumonia by 71% - Cohort Study

**Figure 1.** Quarterly ventilator-associated pneumonia (VAP) rate through 28–30 months after implementation. Shown are the median and mean (95% confidence intervals) VAP rates over time. *P* < .001 (2-sample Wilcoxon rank-sum test) for comparison of the preimplementation baseline period with 16–18-month and 28–30-month postimplementation periods.
### Why Do Horizontal Programs Work? They Are Population-based: BSI example

Comparison of infection control approaches assuming 10,000 admissions and 500-1000 infections (5-10% rate)

<table>
<thead>
<tr>
<th></th>
<th>Population based</th>
<th>MRSA-Subset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloodstream infections*</td>
<td>50-100</td>
<td>7-14†</td>
</tr>
<tr>
<td>Number of deaths estimated**</td>
<td>13-25</td>
<td>2-4</td>
</tr>
<tr>
<td>Attributable deaths***</td>
<td>7-13</td>
<td>1-2</td>
</tr>
<tr>
<td>Lives saved if attributable deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevented by 50%</td>
<td>4-7</td>
<td>1-1</td>
</tr>
<tr>
<td>National estimates of lives saved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(assume 35 million admissions – 3500 fold greater than 10,000)</td>
<td>14,000-24,500</td>
<td>3,500</td>
</tr>
</tbody>
</table>

Wenzel et al. *ICHE* 2008; 29:1012-18
Controlling Pathogens in the Hospital: Vertical vs. Horizontal Approach

- MRSA
- MSSA
- VRE
- Acinetobacter
Controlling Pathogens in the Hospital:
Vertical vs. Horizontal Approach
Infection Control in 2011

Current data support the argument that we have the ability to reduce all nosocomial infections by 50%, including MRSA, VRE, and MDR Acinetobacter

See Also:
Infect Control Hosp Epidemiol 2011; 32:101-14

Caveat: Will we begin to see Chlorhexidine resistant strains emerge?
From 2011...

How do we prevent the existing infections by another 50% in the next 3-4 years... achieving a 75% total reduction by 2014-2015?
Key Infection Control Safety Question

On a platform of an effective infection control program (~50% reduction in all infections every 3-4 years), what is the incremental value of an adjunctive vertical program (MRSA screening)?
Emergence of New Delhi Metallo-β-lactamase

- Increasing use of Carbapenams
- Increasing use of Cefalosporins
- ESBLs
  - CTX-M-IS gene
- K. Pneumoniae KPCs
- BLA NDM-1 gene


Reference: Lancet Inf Dis 2010; 10:597-602
NDM-1 in India, Pakistan, and UK

Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency’s national reference laboratory from 2003 to 2009. The predominant gene is blaNDM-1, which was first identified in 2008. The other group includes diverse producers of KPC, OXA-48, IMP, and VIM enzymes.

*Lancet Inf Dis* 2010; 10:597-602
Final Questions

- Can we begin to think about infection control and antibiotic resistance as a global health problem?
- Can we construct global health policies and strategies that benefit the developing and developed world equally?