

Antimicrobial Management: A Tale of Two cities

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Signet Classics

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A Tale of Two Cities

150TH ANNIVERSARY EDITION

WITH AN INTRODUCTION BY FREDERICK BUSCH



ABC's of Antimicrobial resistance

- E nterococci - VRE
- S taphylococcus aureus – MRSA, VRSA
- K lebsiella – KPC – carbapenem resistant
- A cinetobacter – Multi Drug Resistant
(MDR – susceptible to < 3 antibiotics)
- P seudomonas - MDR
- E SBL

Why Antibiotic Management?

- MDR bacteria spreading rapidly
 - Like pre-1940's in therapeutic options
- No new classes of pipeline drugs
 - No new Gram negative classes
 - New Gram Positives in development may be ineffective with heterozygous MRSA strains
- Present options associated with toxicity, early resistance and no clinical studies
 - Polymyxins are associated with neuro and nephrotoxicity

Infectious Disease Issues

- Void in antibiotic studies since mid-80's
 - AIDS epidemic captured leaders in ID field
 - Other societies developed own guidelines
 - Drug companies decreased funding to studies or left the field. (Lily, BMS, etc)
 - Unable to enroll large numbers in studies
- Length of therapy = Lunar Cycle or number of digits on attending
- Many diseases are “accepted practice” based on retrospective reviews or case reports

Societal Problems!

1. Detectable levels of antibiotics (& antidepressants in drinking water.)

2. Antibiotics in animals associated with VRE in humans

Major water sources positive for pharmaceuticals

At least one pharmaceutical was detected in 28 tested finished drinking water. Test results vary widely. Some water systems said tests had been negative, but the AP found independent research showing otherwise.

Pharmaceuticals in drinking water

- Water tested positive for pharmaceuticals
- Water tested negative for pharmaceuticals
- Water not tested for pharmaceuticals
- Test results pending



* In Virginia Beach, pharmaceuticals were found in source water but not in treated drinking water.
** Drinking water in Austin, Texas, was tested for only one prescription drug, a synthetic birth control chemical.

NOTE: All places include some surrounding areas except: Albuquerque, N.M.; Arlington, Texas; Fresno, Calif.; Long Beach, Calif.; Los Angeles; Memphis, Tenn.; New Orleans; New York City; and Orlando, Fla.

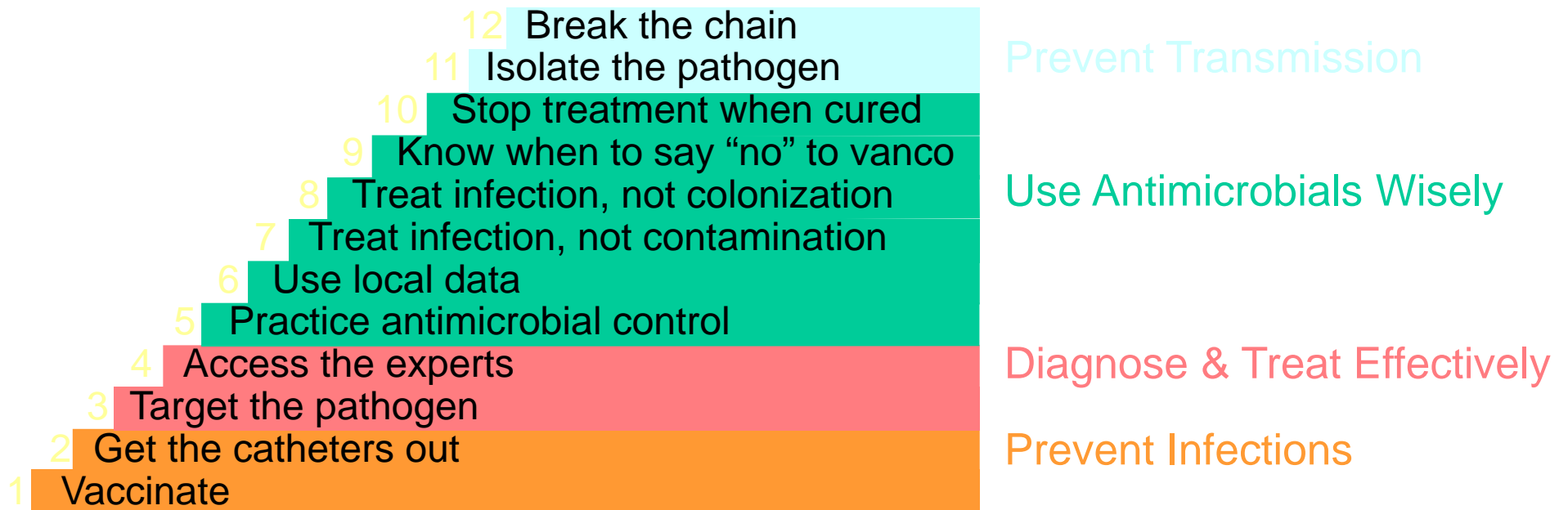
Major Reasons for Antibiotic Control

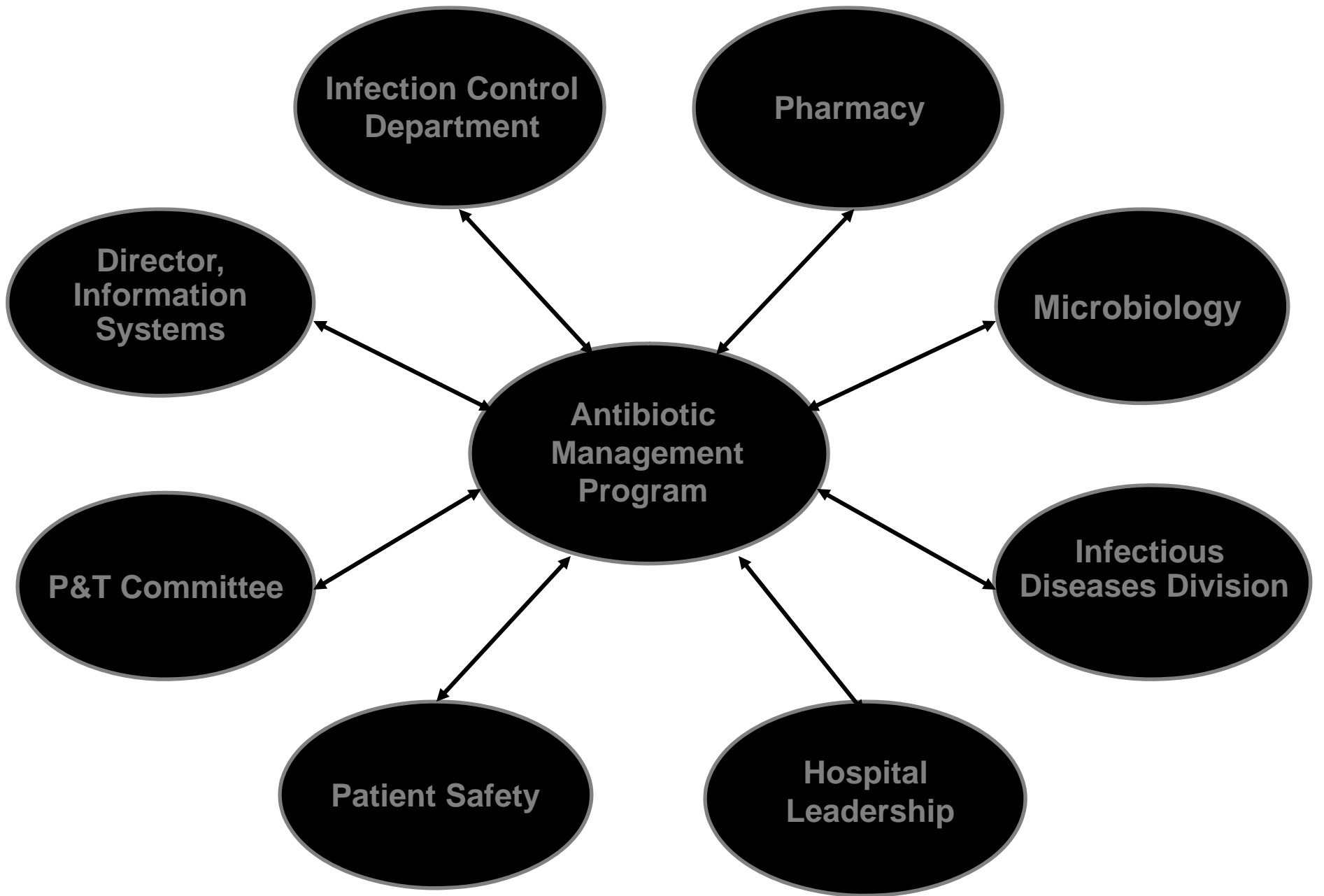
- Medicare No Pay Rule
 - Starts 10/1/08
 - Not reimburse at highest Diagnostic related group
 - Vascular-catheter related infections
 - Catheter associated infections
 - Surgical Site Infections (sternal wound especially)
 - VAP and *C. difficile* were removed as the AMA said they were not preventable!!
- Lawyers
 - Over 400 lawyers advertising to call if you “have MRSA or VRE” and were in hospital
 - Settlements by hospitals not recorded

State and Other Mandates

- Certain states mandate reporting of hospital acquired infections from resistant bacteria
 - Reporting bias
 - Affects tertiary care centers as referred in frequently
 - Do not test do not see infection
- Most States mandates pain management and suicide training for licensure
- Most institutions mandate pain management for privileges
- Why do none of them mandate learning basic antibiotic utilization?

12 Steps to Prevent Antimicrobial Resistance: Hospitalized Adults





Perspective

- Oncologists
 - Can perform Bone Marrow, FISH the smear and perform flow cytometry in 24 hours to identify gene markers causing disease
 - Can provide directed therapy to leukemia based on these results and give prognosis and response to therapy
- Infectious Disease
 - Start broad antibiotic therapy for several days until culture results
 - Treat all positive cultures until can determine if colonizer, contaminant or infection
 - Prognosis linked to empiric therapy



It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

Essential Elements of a Program

- Hospital Support
 - Why:
 - Changing behavior is difficult (and time-consuming)
 - For a big institution, months of full time work may be needed to get a system in place
 - How:
 - Funding for an ID faculty member
 - Funding for an ID pharmacist
 - Support from other hospital leadership
 - Chief Medical Officer or equivalent
 - Quality Improvement leadership and IT
 - Pharmacy leadership
 - Chief of Infectious Diseases
 - Director of Microbiology laboratory

Essential Elements of a Program

- Relationship with Pharmacy
 - Why:
 - Pharmacy has to enforce your rules
 - How:
 - Funding for at least one ID pharmacist is CRUCIAL
 - Address pharmacy issues (drug supply, compliance)
 - Review antibiotic orders
 - Dosing recommendations
 - Recruitment of other clinical pharmacists to be involved
 - Conferences directed at all levels of pharmacy
 - Antibiotic Subcommittee of P&T

Essential Elements of a Program

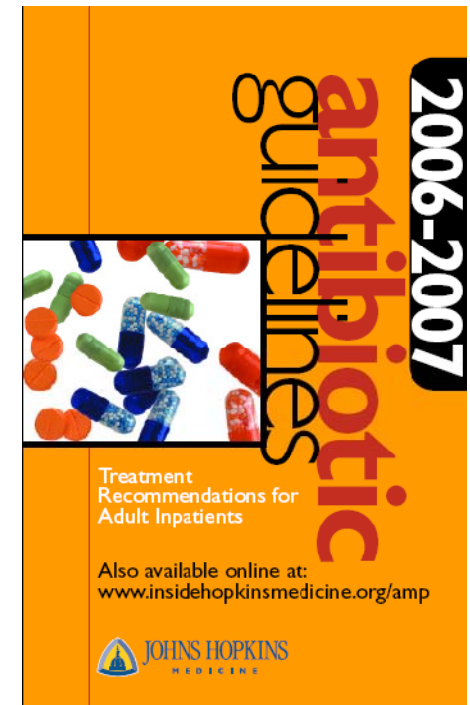
- Guidelines

- Why:

- Evidenced-based recommendations
 - Standardization of recommendations
 - Adherence to the use of formulary drugs
 - Intellectual back-up for people who hold the approval pager

- How:

- Develop and/or steal
 - Involve a “content expert” from all areas covered (OB/GYN, surgery, critical care, etc.)
 - Budget for their production (book vs web site)



Targeted interventions

- Do not try to do everything initially
 - Start IV-PO
 - Decrease length of usage i.e. 8 days for VAP
 - Early spectrum narrowing
- Do not maximize cost savings initially
 - How to please administrators
 - “What have you done for me lately”
- Identify Strange practices
 - Double anaerobe coverage
- Medicolegal
 - Making residents document clearly aminoglycoside usage, levels and early discontinuation

Automated Antimicrobial Surveillance Programs

- Computerized and automated programs allow for real time interventions and tracking
- Monitor and intervene on patients on antimicrobials
- Can focus on specific interventions and report outcomes

Essential Elements of a Program

- Relationship with microbiology
 - Why:
 - Many clinical decisions are made on the basis of what they report
 - Antibiogram development and interpretation
 - Other resistance data
 - Rapid testing – earlier reporting associated with better outcomes, less antibiotic usage
 - How:
 - Working group/weekly meeting

Comparison of services

- Maryland
 - Hospital Support
 - Physician support
 - Pharmacy
 - Computer support
 - automated
 - Microbiology
 - PNA FISH and PCr surveillance
- OHSU
 - Hospital Support
 - Physician support
 - Pharmacy
 - *Computer support*
 - *Microbiology*

Case 1

- 50 yo man in MICU. Previous VRE
- Has allogenic SCT, resolved neutropenia, but still thrombocytopenic.
- 2 large tunneled catheters present
- Report GPC from blood culture drawn 10/15 on 10/16.
- What to do?
 - Do we start vancomycin, linezolid or daptomycin?
 - Do you pull the line?
 - How long can you wait?

Continued

- 10/16 Daptomycin started 6mg/kg (630mg)
 - Cost \$750
- Both Catheters removed as continued fever
 - IR removed, Cost \$1000
- 10/17 Identified as Staph. Species
- 10/18 Final Coag Negative Staph, all other cultures negative. Changes to Vancomycin
- 10/18 New Catheter – bled heavily, needed transfusions, stayed 3 extra days in MICU
 - 3 extra days in ICU, Cost \$20,000
- Total Extra Expenses - \$21,750

Using PNA FISH

- 10/16 would know Coagulase negative staphylococci
- Vancomycin for 7 days
- Retain tunneled catheters
- Would have left MICU same day
- Cost PNA FISH - \$50!

Case 2 - Endocarditis

- 43 yo woman, IVDU. Previous TV replacement for MRSA endocarditis
- Admitted to MICU 9/5 with fevers, hypotension after using drugs
- 8 hours later Growing GPC in blood
- What to start?

Continued

- 9/5/08 Vancomycin/ gentamicin and rifampin started
- 9/6/08 Still bacteremic, reported Enterococcus Species.
- 9/7/08 Still bacteremic, identification still not returned
- 9/8/08 Enterococcus faecalis
 - Ampicillin Sensitive
 - Vancomycin Resistant!

Continued

- Antibiotics changed to Ampicillin high dose with gentamicin
- Rifampin stopped not before having increased LFT's which lead to CT and US of abdomen. Cost \$1200
- Patient refused surgery, but cleared in 48 hours on correct antibiotic therapy

Case 3

- 57 yo man with DM, HTN and ESRD transferred on medical floor after 5 days in MICU for aspiration pneumonia.
- Has no lines and an A-V fistula
- Gram Positive Cocci in clusters from BC 1 day prior is called to team
- What to do?
 - Keep line and give vanco as outpatient?
 - Repeat BC, Ultra Sound fistula?

Continued

- Remained in hospital 48 hours more
- Only received one more dose on vancomycin as renal failure
- Had 2 further negative blood cultures
- Had ultrasound of fistula
- Had CXR
- Once found out Coag negative staph – patient sent home.

GPC in Clusters!

- Overuse of empiric antibiotic therapy
 - Excess vancomycin usage
- Delayed hospital discharge¹
 - Extends length of stay
 - Decreases bed utilization
- Excess further unnecessary testing
- Average hospital cost for contaminated blood culture is \$4000²
- Emergence of other resistant bacteria
 - ie VRE

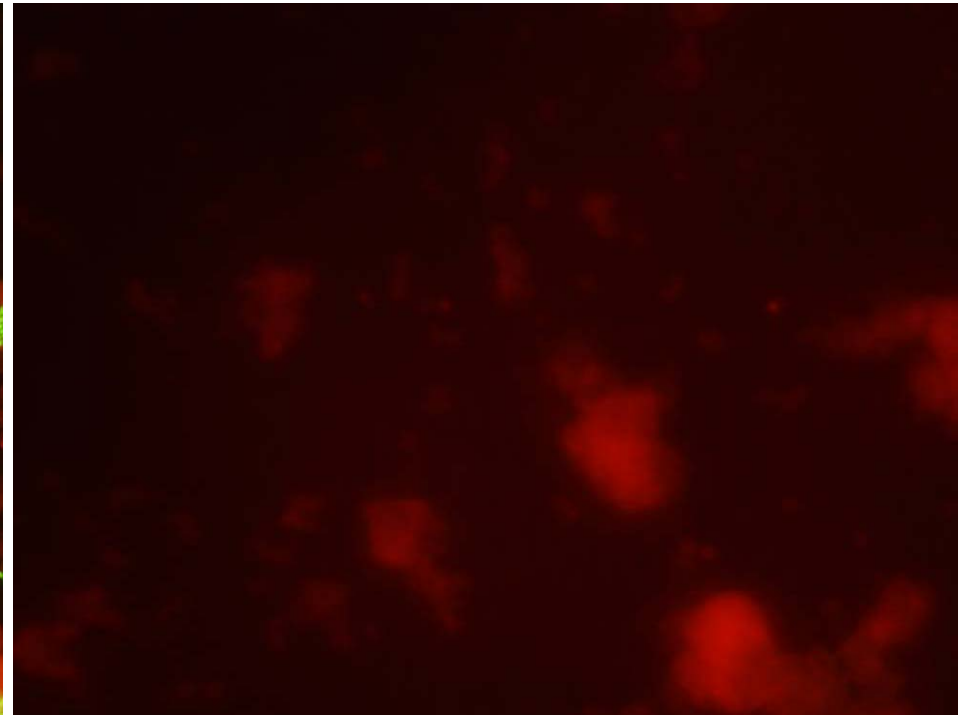
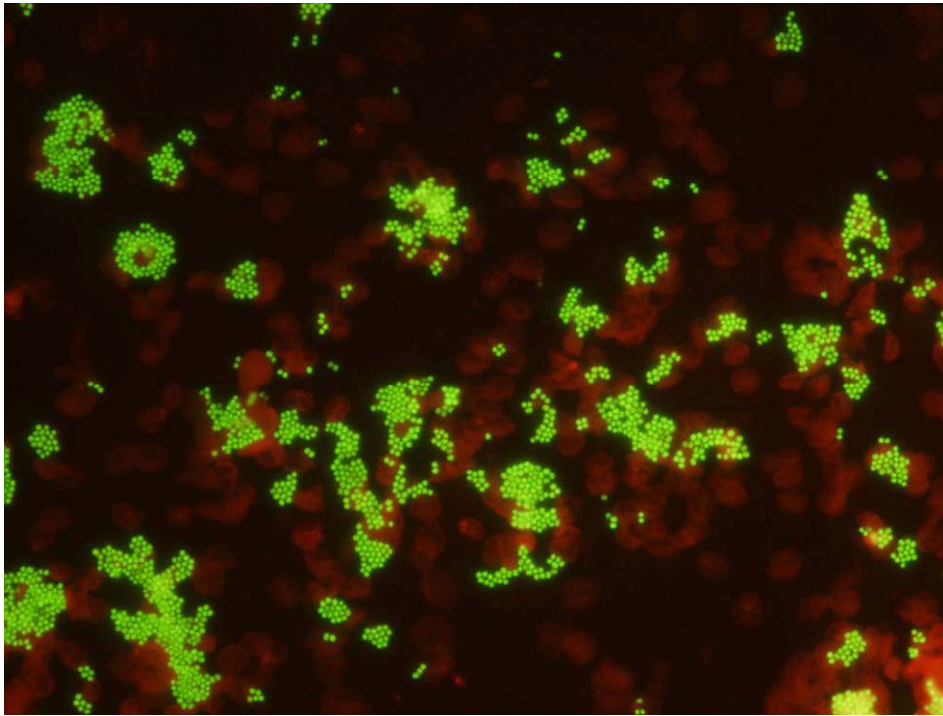
1. Diekema et al. J Clin Micro 2003; 41:3655

2. Dunagan WC. Am J Med 1989; 87:253.

S. aureus PNA FISH

S. aureus

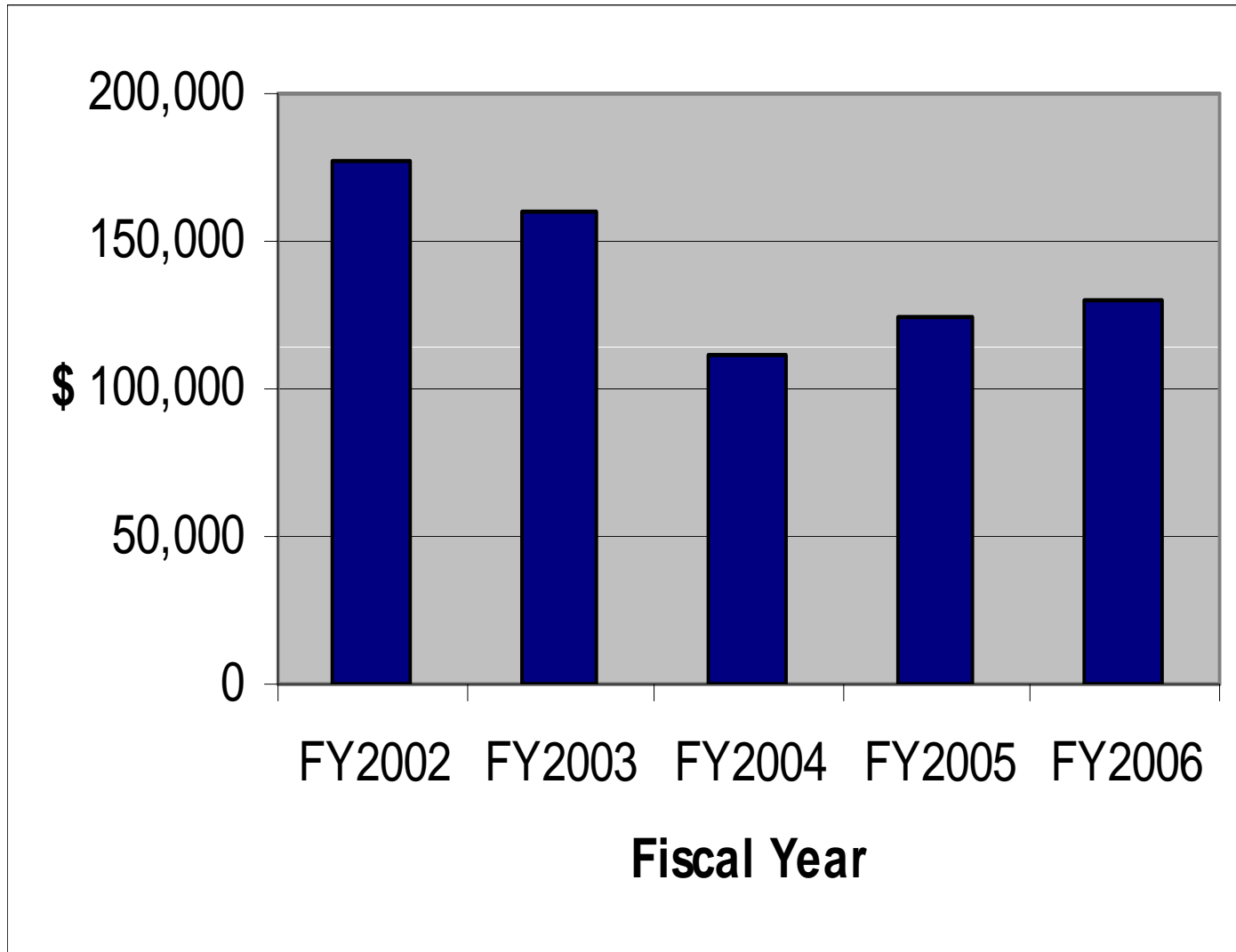
CONS



How Long to Treat Coagulase Negative Staphylococci?

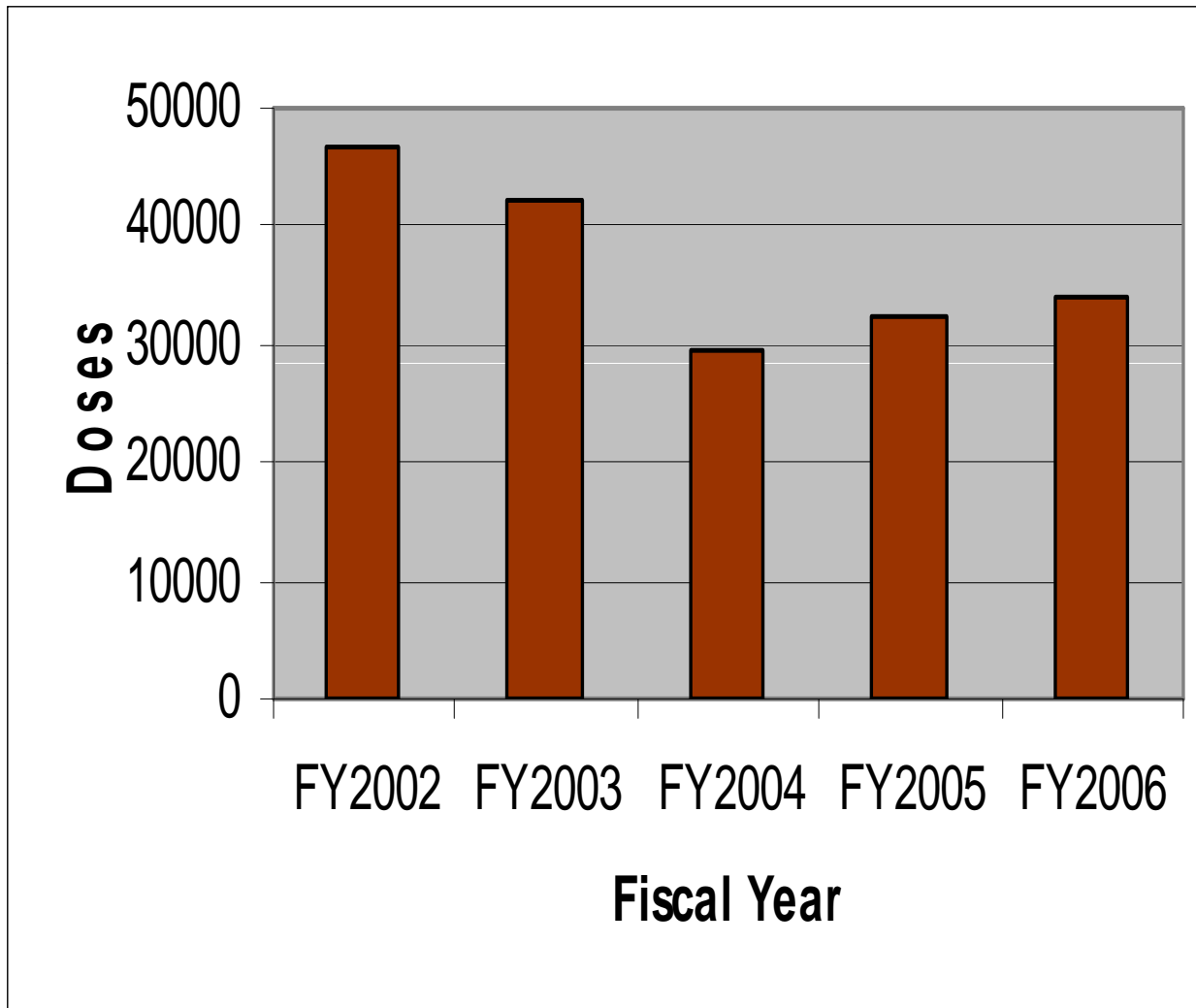
- Varying opinions
- Most treat lines 3-5 days
- Length when no lines ??
- Definite therapy
 - Non removeable intravascular device
 - AICD, Pacemaker, Balloon pump, LVAD, Jarvik
 - Recent prosthetic valve or endovascular graft
 - IVDU with recent endocarditis
 - Cancer center

Vancomycin Costs per Fiscal year At UMMS



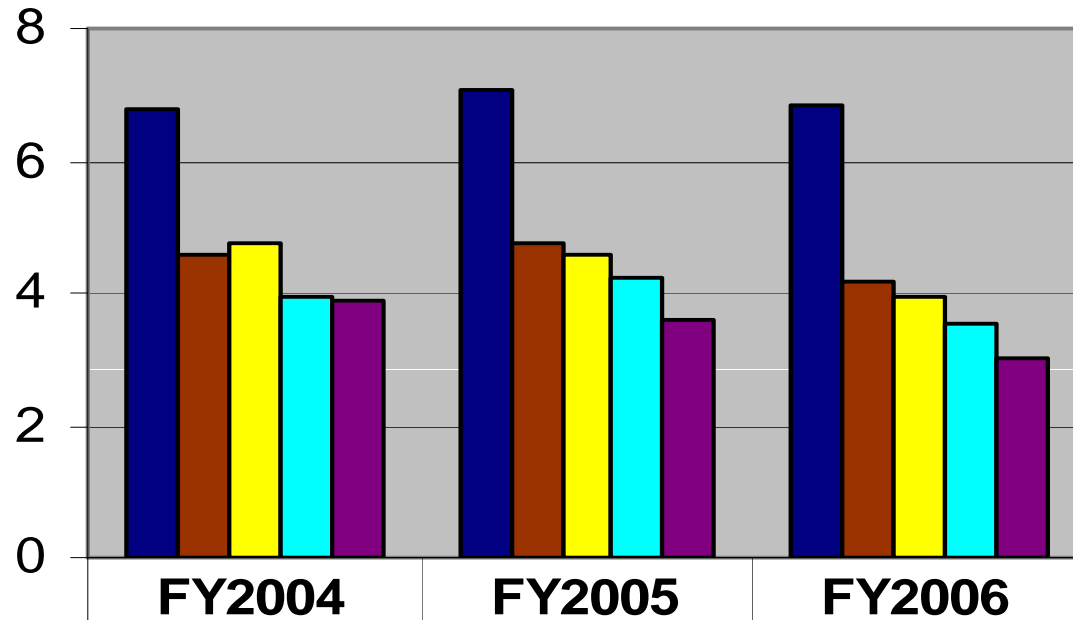
***Vancomycin restriction removed 6/2004 for FY2005**

Vancomycin Doses used by Fiscal Year



***Vancomycin restriction removed 6/2004 for FY2005**

Median reduction in length of stay since 2004 by Service



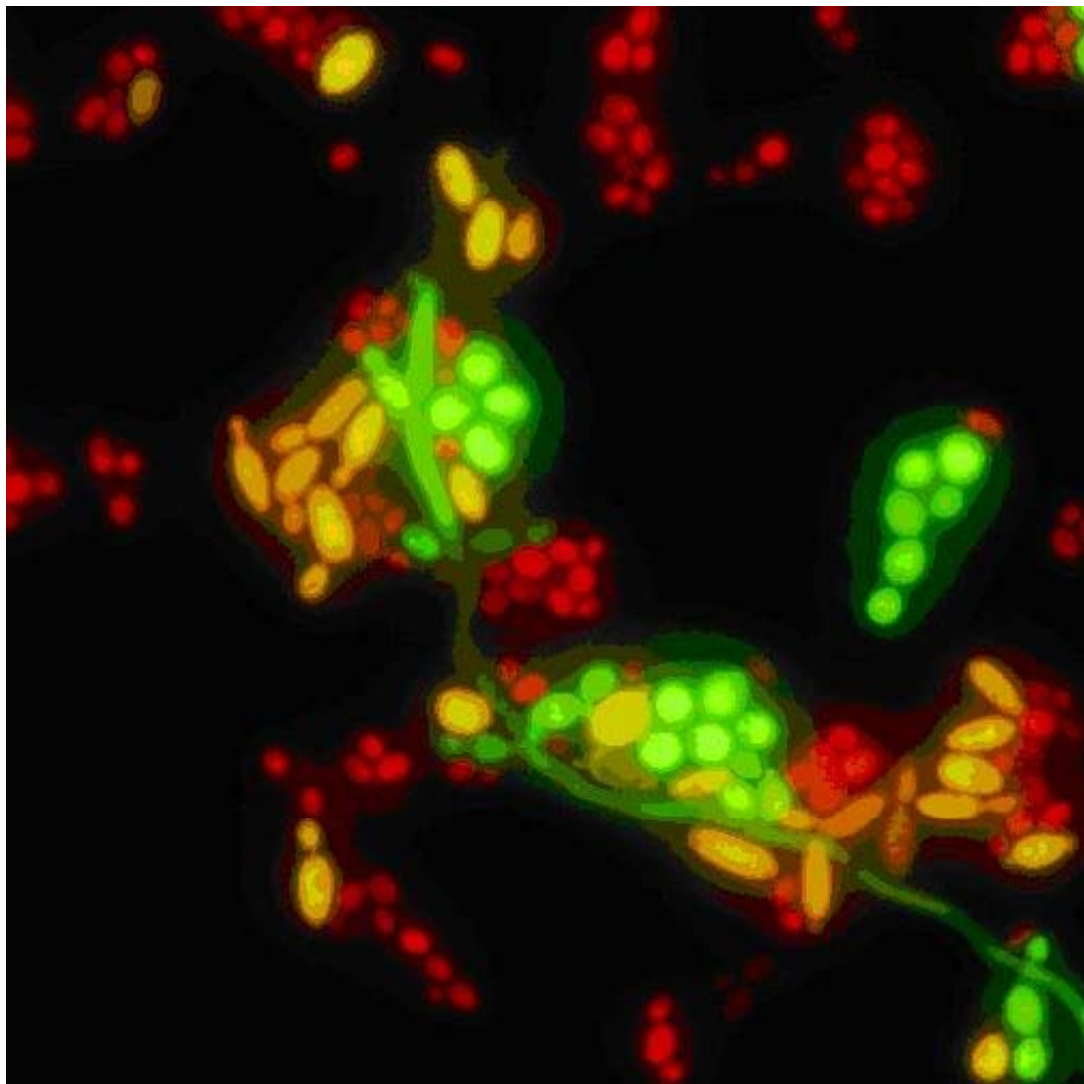
■ SICU	6.79	7.09	6.8375
■ Gen Surgery	4.6075	4.7525	4.1725
■ Gen medicine	4.75	4.5925	3.9475
■ Gen medicine	3.9625	4.2325	3.5225
■ Telemetry	3.8575	3.5925	3.0425

Case 4

- 57 yo man with DM, HTN and ESRD transferred on medical floor after 5 days in MICU for aspiration pneumonia.
- Has HD catheter
- Yeast from BC 3 days prior is called to team. Follow up BC negative.
- What to do?
 - Give echinocandin through a new PICC?
 - Oral fluconazole?

Continued

- HD catheter removed by IR (\$300)
- PICC line placed and micafungin started.
- After 3 days found out to be *C. albicans*
- 2 further days and fluconazole sensitive
- PICC line removed and patient discharged on oral fluconazole
- 4 extra days in hospital



C. Albicans Treatment algorithm

- UMMS Patient
 - Fish +ve – Oral fluconazole*
 - Fish Negative – Oral fluconazole* unless used prior or known resistant species
 - FISH –ve and HIV/AIDS – Fluconazole IV and automatic Cryptococcal antigen order
- Non-UMMS Patient
 - FISH +ve* – Oral fluconazole
 - Fish Neg – IV Micafungin

*Intravenous Fluconazole could be used in hemodynamically unstable patients

Prospective Intervention Study

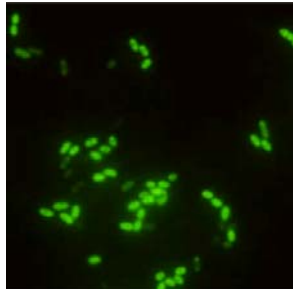
- 8 month randomized study at Washington Hospital
- Batched, twice daily
- Alternately reported to physician with intervention by pharm D or fellow
- 202 cultures run
- 101 in each arm
- Age, sex, catheter status similar both groups

Results (Ly et al)

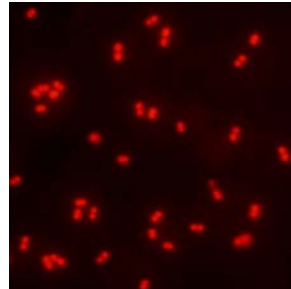
- Reduction in Non-ICU LOS (8 vs 6.5 days)
- Less vancomycin use in Intervention arm (40% vs 15%)
- Decreased mortality in *S. aureus* ICU group
- Median savings of \$1500 in CNS group and \$6200 in *S. aureus* group.

Enterococcus PNA FISH

- Fluorescent PNA probe hybridizes to ribosomal RNA (rRNA)
- *E. faecalis* and other enterococci identification directly from GPCPC+ blood culture bottles in **2.5 hours**



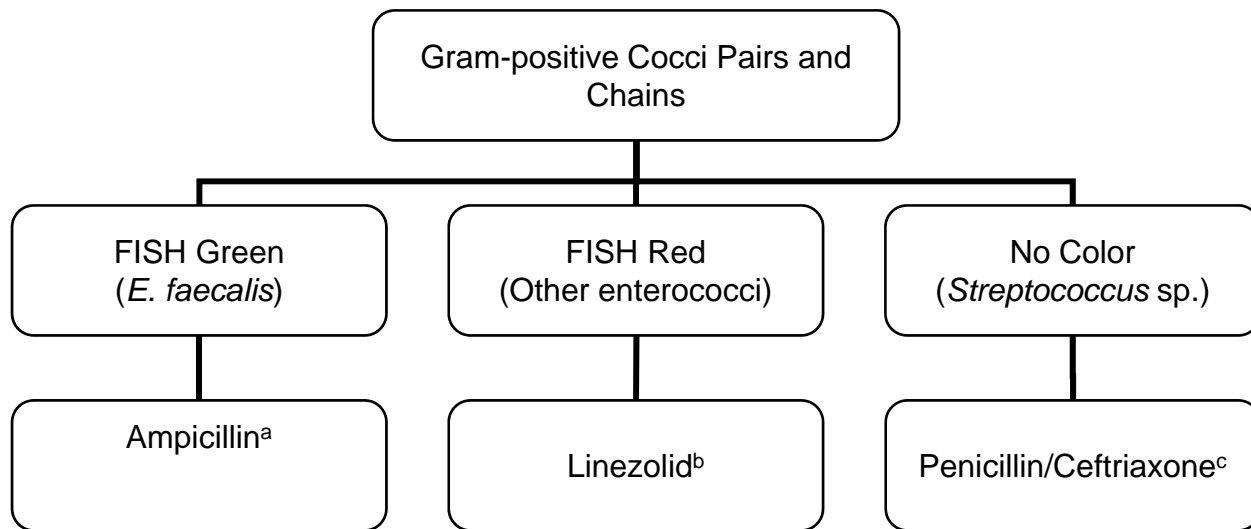
E. faecalis



non-faecalis enterococci



non-enterococci GPCPC
(Presumptive Strep.)



Case 2

- 35 yo woman, IVDU and 2 months post delivery
- Abdominal and back pain, fevers, weakness in ER
- Become hypotensive and in shock
- Transferred to MICU on Nafcillin and vancomycin
- Blood cultures grew GPC Pairs and chains in 6 hours. No change in Abx
- Next morning, WCC 35,000, 3 pressors

Case Cont.

- Asked lab for urgent PNA on blood in AM
 - Culture +ve 10PM
- Result *E. faecalis* by FISH by 10AM
- Changed to Ampicillin and gentamicin
- TEE showed MV endocarditis
- CT- splenic abscess and brain abscess
- Culture 3 days later showed *E. faecalis* resistant to vancomycin
- If waited, 3 days of ineffective therapy
- Patient had MV repair and alive.

PNA FISH

- PRO's

- Very Specific (98-100%)
- Very Sensitive (95-100%) off blood cultures
- Small equipment, space and maintenance requirements
- Tech friendly
- Can tell living organisms
- More Probes and 1 hour resulting!
- Rapid reliable reporting and Quality assurance
- Easy to develop treatment algorithms

- Cons

- Limits of detection of 10^4 organisms –only performed off blood cultures at present
 - Future flow cytometry
 - Direct specimen testing
- Limited number of probes
- Cost for real time reporting

Problems!

- Hospital Administrations see the Microbiology lab as an individual cost center rather than an integrative part of patient management.
 - What have you done for me lately phenomenon?
- Continuity of lab techs is poor.
 - Modern technology is needed to maintain interest.
- Many laboratories are being outsourced
 - increasing the time to get answers to cultures.
- Traditional culture system has not adjusted to managed care
 - again time for results = delay in discharge = lost income (Paid by diagnostic related groups)

Conclusion

1. Rapid testing with an organized antimicrobial program can result in:
 1. Improved patient safety
 - Early **appropriate** and **effective** antibiotic therapy
 - Decrease mortality in some situations
 2. Decreased Antimicrobial utilization
 3. Decreased hospital length of stay
 4. Significant (often unrecognized) cost savings
 5. Development of new therapeutic guidelines

Conclusion cont.

- PNA Fish
 - Easy and inexpensive to run.
 - Can be run in real-time for sick patients
 - Ensure technician comfortable with test
 - One month evaluation before implementation
- Future
 - Utility of Gram negative probes
 - Utilization on other sterile fluids – flow cytometry
 - Automation

If You Were Septic, Would
You Like to Wait 48-72 Hours
to Know if you are Receiving
Appropriate or Unnecessary
Antibiotic Therapy?