Antimicrobial Stewardship and Emerging Resistance:The perspective from and ID Physician

Barry C Fox MD
Division of Infectious Diseases
University of Wisconsin, Madison WI
May 2012

Background in Antimicrobial Use

MAGNITUDE OF ANTIMICROBIAL USE

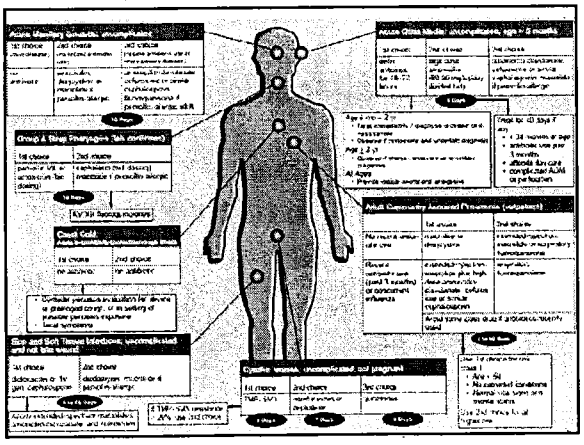
- Antibiotics are the second most commonly used class of drugs in the United States
- More than 8 billion dollars are spent on anti -infectives annually
  - 200-300 million antimicrobials prescribed annually
- 25-40% of all hospitalized patients receive antibiotics

Community based program for Preventing Antibiotic Resistance and Promoting Appropriate Antibiotic Use

Strategies for Optimal Care and Satisfied Patients

WARN
WISCONSIN ANTIBIOTIC RESISTANCE NETWORK

www.warnwisconsin.org

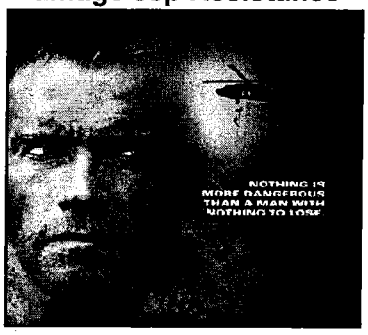


50% of antimicrobial use in hospital is either unnecessary or inappropriate

GENERAL FACTORS AFFECTING HOSPITAL PRESCRIBING PATTERNS

- Increased complexity of infectious disease issues
- Desire to use the "best" antibiotic
- Spiraling empiricism
- "Bigger is better" philosophy
- Inappropriate prophylaxis
- Fear of litigation
- Pharmaceutical detailing
- Emerging antimicrobial resistance

We forget about: Collateral (Antibiotic) Damage esp Resistance



Campaign to Prevent Antimicrobial Resistance in Healthcare Settings

12 Steps to Prevent Antimicrobial Resistance: Hospitalized Adults

Are Clinicians Perceptions of the Problem of Resistance (AR) in the Hospital Realistic?

Arch Intern Med 2004;164,1662

- Questionairre: AR bigger national issue(95% vs 77%) than own institution or own practice (95%vs65%)
- Focus groups: (93%) nationally vs (46%) institution or practice
- Barriers in Campaign steps
  - Treat infection, not colonization(35%)
  - Stop when cured or infection unlikely(35%)
  - Practice antimicrobial control(33%)

Relationship between hospital antimicrobial use and resistance: Is it clear?

- Comparisons of hospital use measure (DDD) don't measure individual exposure
- "Pressure" occurs on an individual level and depends upon pharmacodynamic variables
- Not all AB are equal for selecting AB resistance
- Effect of human population densities
- Resistance not a static phenomena

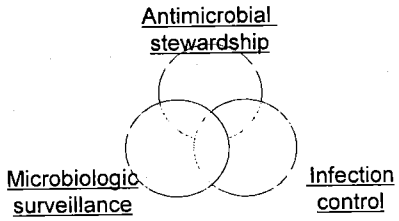
THEREFORE:

- **Antimicrobial use in hospitals is one of many variables in assessing antimicrobial resistance.....but likely the most important one**

Evolution of Terminology

- ~~Antibiotic Control~~
- Antimicrobial Management
- Antimicrobial Stewardship-team based

Core Hospital Services



Shlaes DA et al. SHEA and IDSA Joint Committee on the Prevention of Antimicrobial Resistance: Guideline for the Prevention of Antimicrobial Resistance in Hospitals. CID 1997; 18: 584-599.

Goals of Antimicrobial Stewardship

- Promote quality healthcare
- Improve antimicrobial use
- Improve patient outcomes
  - –Improve cure rates
  - –Decreased failure rates
  - –Fewer adverse drug events
  - –Decrease antimicrobial errors
- Limit emergence of resistance
- Improve institutional outcomes
- Decrease healthcare costs

Classification of Programs and Review of Selected Studies

- Education and Guideline Implementation Strategies
- Formulary and Restriction Strategies
- Review and Feedback Strategies
  - – Use Antimicrobial Order Form
- Computer Assisted Strategies

EDUCATIONAL PROGRAMS

- Least rigorously studied
- Difficult to assess because of complex educational variables
- One-on-one instruction most successful
- Results extinguish rapidly
- Cannot stand alone, but should be the cornerstone of any Antimicrobial Management Program

Classification of Programs and Review of Selected Studies

- Education and Guideline Implementation Strategies
- Formulary and Restriction Strategies
- Review and Feedback Strategies
  - – Use Antimicrobial Order Form
- Antibiotic Cycling Strategies
- Computer Assisted Strategies

ANTIMICROBIAL FORMULARY RESTRICTION

- Most direct method to influence antimicrobial utilization
- IDSA Guidelines
  - Minimum number of agents required for effective therapy
  - Eliminate duplicate agents within each class
  - Consider susceptibility patterns of nosocomial pathogens
  - Restrict certain agents (indication, toxicity, cost)
  - Periodic review
- Efficacy well documented
  - Woodward et al. Am J Med 1987;83:817-23
  - Himmelberg et al. Am J Hosp Pharm 1991;48:1220-7

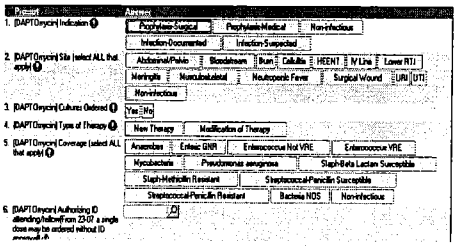
PRIOR APPROVAL PROGRAMS

- Multiple approaches
  - Phone approval
  - Automatic stop orders
  - Direct interaction
- Most onerous to physicians
- Most effective single intervention
  - McGowan and Finland. J Infect Dis 1974;130:165-8
  - Recco et al. JAMA 1979;241:2283-6
  - Coleman et al. Am J Med 1991;90:439-44

What has been done at UW Hospital?

- Antibiotic Order Form
- BEST PRACTICE ALERTS
- SETNET- Electronic based antimicrobial monitoring
  - Linked to microbiology results!
- Targeted educational programs
- Clinical research in high use anti-infective areas

Antibiotic Order Form



What has been done at UW Hospital?

- Antibiotic Order Form
- SETNET(Premier)- Electronic based antimicrobial monitoring
  - Linked to microbiology results!
- Targeted educational programs
- Clinical research in high use anti-infective areas

SAFETY SURVEYOR

Zosyn New Starts	Patient name	0889253	GYNUROL-F&N	piperacillin/tazobactam	07/13/2005
Linezolid use without MRSA or VRE		0131388	TLC-South-8883	linezolid	07/13/2005
Five days of amp/sulbac, cefepime,imipenim,meropenim,pip/tazo, or ticar/clav		1851323	PULM-D&/5	ampicillin/sulbactam	07/13/2005
Five days of amp/sulbac, cefepime,imipenim,meropenim,pip/tazo, or ticar/clav		1912415	GYNUROL-F&N	ampicillin/su/bactam	07/13/2005
Fungal Double Coverage: voriconazole & caspofungin		1807522	CSH-D4/4	voriconazole	07/13/2005
Fungal Double Coverage: voriconazole & caspofungin		1807522	CSH-D4/4	caspofungin	07/13/2005
Gm- Double Coverage: cefepime & moxifloxacin		1884314	HEMBMT-B&N	cefepime	07/13/2005
Gm- Double Coverage: cefepime & moxifloxacin		1884314	HEMBMT-B&N	moxifloxacin	07/13/2005
Gm- Double Coverage: cefepime & moxifloxacin		1843768	HEMBMT-B&N	cefepime	07/13/2005
Gm- Double Coverage: cefepime & moxifloxacin		1843768	HEMBMT-B&N	moxifloxacin	07/13/2005
IV to PO protocol drugs		0823691	PULM-D&/5	ciprofloxacin	07/13/2005

Quantiative tracking of Anti-infective Use-DDD and Patient Days of Use

INTRAVENOUS(select one)		07/03-09/04	Annualized	07/04-12/04	07/05-09/04	09/04-12/04	07/03-09/04	Annualized
PATIENT DAYS 09/04-127,952	DDD	Patient Days	Patient Days	Patient Days	Use Days/1000	Use Days/1000	Patient Days	Patient Days
PATIENT DAYS 07/03-09/04 61,781	Value	of Use (by ddd)	of Use (by ddd)	of Use (by ddd)	days (by ddd)	days (by ddd)	of Use (Actual)	of Use (Actual)
ANTIFUNGALS								
amphotericin B lipid complex	350	271.3	812	306	2.1	5	491	660
amphotericin B liposomal	350	81.5	1646	823	0.6	1.3	78	135
caspofungin	50	1628.5	1997	998.5	12.7	16.1	1546	1912
fluconazole	0.2	27446	31276	15638	21.4	25.3	2522	2818
fluconazole-oral data to compar	0.2	48707	55156	27578	38.8	44.6	4600	5070
voriconazole	0.4	4938	665	3325	3.9	5.4	573	668
voriconazole-oral data to comp	0.4	11188	1207	6035	8.7	9.8	1247	1308
TOTAL		101954	12071.8		43.1	54.6	10330	11256
BETALACTAMS								
ampicillin	2	48085	31656	15828	38	25.6	2040	1316
ampicillin/sulbactam	6	48821	65556	33378	38.9	54	3849	5162
piperacillin/tazobactam	13.5	7789	7240	3620	60.7	58.6	10504	9812
TOTAL		173936	17081.2		157.1	159	16338	16310

Antimicrobial Stewardship Alerts

Changes in Health Link/EPIC to Improve Anti-infective Prescribing

Classification of Programs and Review of Selected Studies

- Education and Guideline Implementation Strategies
- Formulary and Restriction Strategies
- Review and Feedback Strategies
  - Use Antimicrobial Order Form
- Computer Assisted Strategies

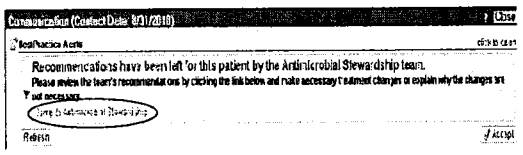
THERAPEUTIC SUBSTITUTION AND STREAMLINING PROGRAMS

- Alternative to "policing" programs
- Possibly more effective in private practice settings
  - Perceived as less punitive
- Less likely to be strictly enforced
- Three approaches:
  - Therapeutic equivalent within a class
  - Change to a different class (usually IV to PO)
  - Refine choice based upon culture results

What has been done at UW Hospital?

- Antibiotic Order Form
- BEST PRACTICE ALERTS
- SETNET- Electronic based antimicrobial monitoring
  - Linked to microbiology results!
- Targeted educational programs
- Clinical research in high use anti-infective areas

De-escalation Alert



- Click on "Jump to Antimicrobial Stewardship" to review recommendations, manage orders and address alert

Sample AMS Note 1

Antimicrobial Stewardship Recommendations

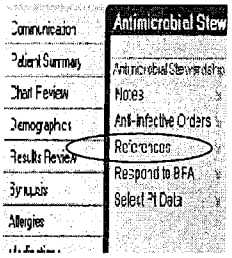
Patient: Hospice Omega Zzztestx 70 year old MRN# 2449978
Location: IDSPICE Rm 089
Primary Service: Nc service for patent encounter. - **Attending:** Weston,Carl B,MD
Admit Date: 4/20/2010 - **Hospital Day:** 223

Recommendation: Your patient is on piperacillin/tazobactam and metronidazole, both of which have anaerobic coverage. Unless the patient has an undrained abscess OR has both an infection and clostridium difficile one of the anti-anaerobic antibiotics should be discontinued.

Sincerely,

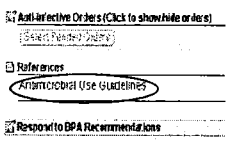
Submitted by: *D RPH ZZZDuotham, RPH - 1/1/29/2010 - 4:42 PM*

Navigator



- **Notes**
  - Review AMS recommendations
- **Anti-infective Orders**
  - D/C, modify or add orders
- **References**
  - Links to anti-infective references
- **Respond to BPA**
  - thoughtful response to AMS leads to D/C of alert
- **Select Pt Data**
  - WBC, SCr, micro results

References



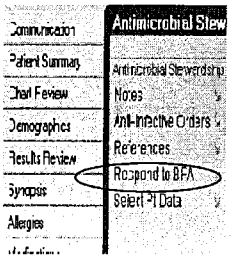
- Click on hyperlink to open references

ANTIMICROBIAL USE GUIDELINES

University of Wisconsin Hospital and Clinics
Pharmacy and Therapeutics Committee
Department of Pharmacy
Center for Drug Policy

July 2010 to June 2011
Twentieth Edition

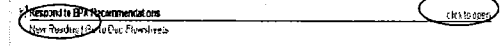
Navigator



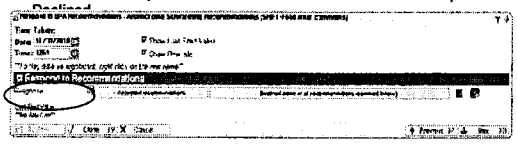
- **Notes**
  - Review AMS recommendations
- **Anti-infective Orders**
  - D/C, modify or add orders
- **References**
  - Links to anti-infective references
- **Respond to BPA**
  - thoughtful response to AMS leads to D/C of alert
- **Select Pt Data**
  - WBC, SCr, micro results

Respond to Recommendations

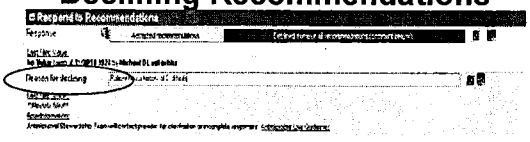
- Select New Reading or "click to open" to open flowsheet for responding to recommendations
- Response files to Doc Flowsheets, not to Progress Notes



- **To document response to recommendations click either Accepted or Declined**

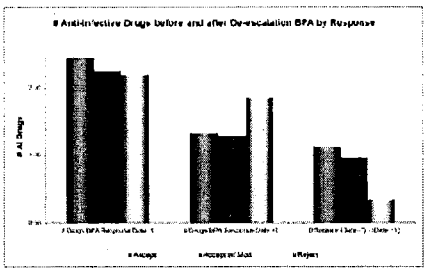


Declining Recommendations



- **If recommendations are declined, a comment field opens for provider to indicate reason**
- **AMS will follow-up with team for as needed for clarification/incomplete responses**

De-escalation BPA results



What has been done at UW Hospital?

- **Antimicrobial Stewardship Team**
- **Antibiotic Order Form**
- **Safety Surveyor- Electronic based antimicrobial monitoring**
- **Targeted educational programs**
- **Formulary and Antimicrobial approval**
- **Clinical research in high use anti-infective areas**
- **CPOE-Computer based order entry, hopefully with decision support**

A Prospective Study of De-escalation of Antimicrobial Therapy in an ICU

B.C. Fox, J.T. Fish, L. Zheng, D.G. Maki
University of Wisconsin Medical School, Section of Infectious Diseases and Center for Drug Policy

Timely reporting of microbiologic data has a significant impact on the quality and quantity of antimicrobial therapy in the ICU and can in theory eliminate unnecessarily prolonged therapy in up to 25% of antimicrobial courses

Efforts to obtain appropriate cultures before beginning or modifying antimicrobial therapy are essential.

- Unnecessary antimicrobials were still continued for as many as 50 hours after positive microbiologic results became available, but even longer when the results of cultures were negative (120 hours), and longer still, when cultures were not obtained (131 excess hours).

- Improved early reporting, especially of positive microbiologic studies can not only improve antimicrobial therapy in the ICU but, putatively, reduce antimicrobial resistance, but..... only if clinicians are willing to modify therapy *expeditiously*, as microbiologic data becomes available.

Respiratory Therapy Induced Sputum Protocol and Quantitative Microbiology in ICU

- If expectored sputum(60% acceptable) unable to be obtained, RT induces sputum to determine etiology of CAP of HAP
- 60% of specimens are also deemed "acceptable" by lab criteria, allowing for targeted antibiotic RX

Microbiology NoStaph/Nopseudomonas

- For Sputum samples that have either 5 or more organisms on the gram stain
- For sputum sample with acceptable criteria gram stain but no organisms seen/hpf-instead of reporting ALL results
- Allows de-escalation from antiMRSA and antiPseudomonas antibiotics

TABLE 3. Outcomes

	Intermittent	Prolonged	Difference & Means (95% CI)
Total days of therapy,* mean, days	4.97	9.14	0.17 (−1.65 to 2.39)
Days of therapy in ICU,* mean, days	7.16	6.31	−0.85 (−2.14 to 0.28)
Ventilator days,* mean, days	16.5	9.6	−7.7 (−17.4 to −0.4)†
ICU length of stay,* mean, days	15.5	10.7	−4.8 (−9.3 to −0.4)†
Hospital length of stay,* mean, days	33.9	22.4	−9.5 (−18.7 to −1.2)†
Mortality,* %	21.7%	12.4%	Odds ratio, 0.54 (0.18–1.66)

Adjusted for age, severity of illness (APACHE II), site of infection, prior antimicrobials while on study therapy, and organisms recovered during treatment not sensitive to primary therapy.
*Includes 121 evaluable patients.
†Significant difference.

(Ogbu Dr Clin Pract 2011;39:413-417)

Optomization of PK/PD-

Retrospective Study of Prolonged Versus Intermittent Infusion Piperacillin-Tazobactam and Meropenem in Intensive Care Unit Patients at an Academic Medical Center

What has been done at UW Hospital?

- Antibiotic Order Form
- Cereplex- Electronic based antimicrobial monitoring
- Targeted educational programs
- Unit Specific Antibiograms
- Clinical research in high use anti-infective areas

Hospital and Unit Specific Antibiograms

GRAM NEGATIVE ORGANISMS

ORGANISMS (NUMBER ISOLATES TESTED) (N=3314)	PERCENT SUSCEPTIBLE BY MIC BREAK POINT (MCG/ML)								
	CEFAZOLIN	CEFTAZIDIME	CEFEPIME	PIPERACILLIN/TAZOBACTAM	IMIPENEM	MEROPENEM	TICARCILLIN/CLAVULANIC	CIPROFLOXACIN	LEVOFLOXACIN
	≥ 8	≥ 8	≥ 8	≥ 16	≥ 8	≥ 4	≥ 64/16	≥ 1	≥ 2
Acinetobacter baumanii (11)			91	54	100	100	91/100	73	73
Citrobacter species (12)		67		67	100	100		92	92
Enterobacter aerogenes (19)		84		84	100	100		91	91
Enterobacter cloacae (35)		86		86	100	100		91	94
Escherichia coli (47)	93	100		94	100	91		93	83
Klebsiella oxytoca (8)	50	100		100	100	100	100/NT	100	100
Klebsiella pneumoniae (36)	92	100		89	100	100	100/NT	75	78
Proteus mirabilis (10)	50	100		100	100	100		100	89
Pseudomonas aeruginosa (51)			78	76*	90	90	80/70	57	
Serratia marcescens (15)		100		100	100	100		100	100
Stenotrophomonas maltophilia (40)									98

Cross ResistanceAntibiograms: Optomizing Empiric Antibiotics

Table 2. Cross-table dual susceptibility assays of 604 hospital-wide gram-negative bloodstream and lower respiratory tract isolates, University of Wisconsin hospital and clinics, 2004-2006

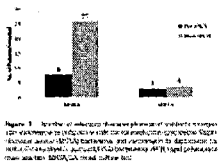
	Cefepime	Piperacillin-tazobactam	Imipenem	Ciprofloxacin	Ceftazidime
Cefepime	88	91	96	93	93
Piperacillin-tazobactam		87	96	94	94
Imipenem			99	96	95
Ciprofloxacin				88	91
Ceftazidime					88

Table 3. Cross-table dual susceptibility assays of 145 CU gram-negative bloodstream and lower respiratory tract isolates, University of Wisconsin hospital and clinics, 2004-2006

	Cefepime	Piperacillin-tazobactam	Imipenem	Ciprofloxacin	Ceftazidime
Cefepime	88	91	96	93	93
Piperacillin-tazobactam		88	93	92	92
Imipenem			98	96	95
Ciprofloxacin				88	91
Ceftazidime					88

Rapid Diagnositic Testing for MRSA(CepheidXPERT) and other blood culture techniques

An Antimicrobial Stewardship Program's Impact with Rapid Polymerase Chain Reaction Methicillin-Resistant *Staphylococcus aureus*/*S. aureus* Blood Culture Test in Patients with *S. aureus* Bacteremia



Peptide nucleic acid in situ hybridization-PNA-FISH

ELSEVIER

DISEASE

Mycology

Cost savings with implementation of PNA FISH testing for identification of *Candida albicans* in blood cultures

Barbara D. Alexander[a,*], Elizabeth Dodds Ashley[a], L. Barth Reller[a,b], Shelby D. Reed[c]

Classification of Programs and Review of Selected Studies

- Education and Guideline Implementation Strategies
- Formulary and Restriction Strategies
- Review and Feedback Strategies
  - Use Antimicrobial Order Form
- Antibiotic Cycling Strategies
- Computer Assisted Strategies

COMPUTERIZED ANTIBIOTIC ASSISTANT;LDS HOSPITAL CLINICAL OUTCOMES

- Significant reductions in:
  - –Orders for drugs with reported allergies (35 vs. 146)
  - –Excess drug dosages (87 vs.405)
  - –Antibiotic-susceptibility mismatches (12 vs. 206)
  - –Mean number of days of excessive dosages (2.7 vs. 5.9)
  - –Adverse events (4 vs. 28)

Evans et al. N Engl J Med 1998; 338:232-8

COMPUTERIZED ANTIBIOTIC ASSISTANT: LDS HOSPITAL

Institutional Outcomes

Evans et al. N Engl J Med 1998; 338:232-8

If all else fails