Antimicrobial Stewardship Workshop

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LEARNING OBJECTIVES

- DISCUSS POTENTIAL IMPLEMENTATION STRATEGIES
- IDENTIFY POTENTIAL ROLES FOR PHARMACISTS IN AN ANTIMICROBIAL STEWARDSHIP PROGRAM
- IDENTIFY POTENTIAL RESOURCES TO HELP FACILITATE AN ANTIMICROBIAL STEWARDSHIP PROGRAM

Target Antimicrobial Agents

- Expensive Agents (ex. Linezolid)
- Agents with Broad Spectrums of Activity (ex. Carbapenems)
- Agents with Severe Side Effect Profiles (ex. Aminoglycosides)
- Agents easily converted to oral formulations (ex. Fluoroquniolones)

Role of Clinical Pharmacist

- Provides cost-optimizing recommendations for patients receiving target directed antimicrobial therapy.
  - 2011: $2.15 billion / $21 Billion was due to systemic anti-infectives
  - Ex. Treatment of MRSA infections (Vancomycin vs. Linezolid vs. Daptomycin, etc.)

Total Percentage of Each Isolate Sensitive To Each Panel Antibiotic

	Total Number of Isolates	Ampicillin	Ciprofloxacin	Clindamycin	Ceftriaxone	Erythromycin	Gentamicin	Levofloxacin	Linezolid	Moxifloxacin	Nitrofurantoin	Oxacillin	Penicillin	Rifampin	Synercid	Tetracycline	Trimethoprim/Sulfamethoxazole	Vancomycin
OTHER CULTURES		**AMP**	**CIP**	**CD**	**CAX**	**ERY**	**GM**	**LEV**	**LZD**	**MXF**	**FD**	**OX**	**PEN**	**RIF**	**FYN**	**TE**	**TS**	**VA**
Staph aureus	1024	*	93	88	*	77	99	94	100	94	*	100	38	100	100	97	98	100
Staph aureus (MRSA)	588	*	48	64	*	15	97	50	100	50	*	0	0	98	100	93	97	100
Staph (coag neg)	198	*	55	58	*	43	83	56	100	56	*	52	12	97	100	81	64	100
Streptococcus pneumoniae	89	*	*	*	100	*	*	95	*	*	*	*	100	*	*	86	76	100
Enterococcus sp.	465	91	84	*	*	*	*	86	100	*	*	*	92	*	13	22	*	100
Enterococcus faecium	16	0	0	*	*	*	*	0	100	*	*	*	0	*	100	0	*	0
URINE CULTURES		**AMP**	**CIP**	**CD**	**CAX**	**ERY**	**GM**	**LEV**	**LZD**	**MXF**	**FD**	**OX**	**PEN**	**RIF**	**FYN**	**TE**	**TS**	**VA**
Staph aureus	28	*	56	*	*	*	100	59	100	63	100	100	33	96	100	100	100	100
Staph aureus (MRSA)	18	*	20	*	*	*	93	20	100	20	100	0	0	100	100	90	95	100
Enterococcus sp.	170	88	74	*	*	*	*	75	100	*	*	*	88	*	7	15	*	100
Enterococcus faecium	12	8	0	*	*	*	*	0	100	*	9	*	0	*	*	25	*	8

Recommendation to alter current therapy

Antimicrobial Agents	Recommend alternative agent(s)if patients do not meet any ONE of the following criteria for the listed agents:
Carbapenems Doripenem Meropenem	☐ Documented treatment failure with Zosyn* ☐ Evidence/history of ESBL producing organisms ☐ Penicillin allergy
Daptomycin	☐ Documented treatment failure with vancomycin* ☐ Evidence/history of vancomycin intermediate or resistant organisms ☐ Vancomycin allergy
Linezolid	☐ Diagnosis or suspicion of MRSA pneumonia ☐ Documented treatment failure with vancomycin* ☐ Evidence/history of vancomycin intermediate or resistant organisms ☐ Vancomycin allergy ☐ Necrotizing infection/toxic shock
Tigecycline	☐ Documented treatment failure with 2 other anti-MRSA agents*
Voriconazole	☐ Documented treatment failure with fluconazole* ☐ Diagnosis or suspicion of invasive aspergillosis[1]

*Treatment failure is defined as development of resistant organisms, or clinical decline (persistent fevers or hypothermia, increasing WBC, persistent or worsening signs and symptoms, organ failure, septic shock, etc.)

Role of Clinical Pharmacist

- Monitor Antimicrobial Therapy/Evaluate Appropriateness of use
  - Discuss desired empiric coverage with Prescriber/ ID Physician
  - Guidelines are just that… Guidelines!

experience were taken into account. These initial empiric therapy recommendations require modification based on knowledge of the predominant pathogens in any specific clinical setting and the local patterns of antibiotic susceptibility. In addition, once

  - Follow up on cultures and sensitivities
  - De-escalate/ Adjust Antimicrobial Therapy
    - Take into sensitivities and agent specific characteristics into account

Guidelines for the Management of Adults with Hospital-acquired , Ventilator-Associated, and Healthcare-associated Pneumonia. Am J Respir Crit Care Med Vol 171. pp.388-416, 2005

Role of Clinical Pharmacist

- Encourage change in prescribing habits
  - Staff Education
    - Institution-Specific Antibiogram
    - Interpretation of guidelines
    - Review of Formulary Options
- Facilitate discharge planning
  - Take into account patient compliance and availability of resources
  - Work with prescribers and case management staff
  - Provide discharge education

Discharge education

- RPh's can help to increase patient satisfaction scores by providing medication related education
- Drug –Drug Interactions
  - Empiric Dose reduction of Warfarin
    - Sulfamethoxazole/Trimethoprim
    - Fluoroquinolones
    - Azole antifungals
  - Serotonin Syndrome and Linezolid
  - Stress appropriate follow up and medication compliance

Discharge education

- Drug Food Interactions
  - Recommended MRSA dose: Sulfamethoxazole/Trimethoprim DS 2 tabs PO BID
    - Very GI Toxic!!! Food may help to alleviate
  - Antifungals:
    - Itraconazole and Posaconazole: Take with HIGH FAT MEAL!
      - Avoid acid-suppressing medications

Formulary restrictions

- Restriction of Broad Spectrum or Expensive Antimicrobial Agents
  - Ex. Linezolid, Daptomycin, Carbapenems, etc.
  - Develop specific criteria for use
    - Failure of therapeutic agent
    - Documented history/risk of MDR organisms
    - ID Physician Approval
- Pharmacy Driven Protocols
  - Automatic IV to Oral Conversions
  - Pharmacy to Dose Orders

Automatic IV to Oral Conversion Protocol

- Benefits of Oral Conversion
  - Decrease length of Hospital Stay
  - Decrease in Hospital Costs
- Inclusion Criteria
  - Have received > 48 hours of intravenous antimicrobial therapy
  - Afebrile for > 24 hrs.
  - Are able to take oral antibiotics (as evidenced by other oral medications)
  - WBC < 15,000/mm^3

Automatic IV to Oral Conversions

- Medications that can easily be converted
  - Cefazolin IV to Cephalexin Oral
  - Levofloxacin IV to Levofloxacin Oral
    - For Pneumonia: Levofloxacin
    - For UTI: Ciprofloxacin
  - Metronidazole IV to Metronidazole Oral
  - Clindamycin IV to Clindamycin Oral
  - Linezolid IV to Linezolid Oral

Intervention and feedback

- Interventions should be discussed/ shared on a regular basis
  - Pharmacy & Therapeutics Committee
  - Hospitalist Group.
- Provide Targeted Feedback
  - Seek support from ID Specialists/ Hospital Administration when antimicrobials are being used inappropriately
- Report Financial impact of interventions

Emerging Fluoroquinolone resistance

Total Percentage of Each Isolate Sensitive To Each Panel Antibiotic

	Total Number of Isolates	Amikacin	Amoxicillin/Clavulanic Acid	Ampicillin	Ampicillin/sulbactam	Aztreonam	Cefazolin	Cefepime	Cefotaxime	Cefotetan	Cefoxitin	Ceftazidime	Ceftriaxone	Cefuroxime	Cephalothin	Chloramphenicol	Ciprofloxacin	Ertapenem	ESBL	Gentamicin	Imipenem	Levofloxacin	Meropenem	Nitrofurantoin	Nitrofurantoin	Piperacillin	Piperacillin/Tazobactam
URINE CULTURES		AK	AUG	AMP	SAM	AZT	CFZ	FEP	CFT	CTN	CFX	CAZ	CAX	CRM	CF	C	CIP	ERT	EXS	GM	IMP	LEV	MEM	FD	NIN	PI	TZP
Enterobacter cloacae	9	100	0	0	0	89	11	100	89	11	11	89	89	33	0	*	*	100	100	*	100	100	100	100	33	100	78	100
Escherichia coli	669	100	74	50	58	95	87	92	94	96	93	94	94	88	44	*	80	100	***	93	100	72	100	97	81	68	97
Klebsiella pneumoniae	94	100	98	0	78	100	99	100	100	100	98	100	100	97	95	*	99	100	0	98	100	99	100	94	100	30	97
Proteus mirabilis	53	100	100	80	92	98	92	98	98	100	98	98	98	98	92	*	87	100	*	94	100	86	100	0	88	92	100
Pseudomonas aeruginosa	44	95	*	*	*	85	*	81	*	*	*	95	*	*	*	*	50	*	*	75	91	48	83	*	*	*	100
OTHER CULTURES		AK	AUG	AMP	SAM	AZT	CFZ	FEP	CFT	CTN	CFX	CAZ	CAX	CRM	CF	C	CIP	ERT	EXS	GM	IMP	LEV	MEM	FD	NIN	PI	TZP
Acinetobacter baumanii gp	40	100	*	*	79	*	*	67	*	*	*	56	*	*	*	*	75	*	*	84	87	60	100	*	*	44	*
Enterobacter cloacae	49	100	7	0	31	81	0	96	81	23	0	77	74	38	0	83	87	100	*	89	98	87	100	*	*	66	85
Escherichia coli	584	100	75	50	59	93	84	91	92	96	91	92	92	86	46	67	75	100	8**	90	100	79	100	*	*	59	94
Klebsiella pneumoniae	158	100	95	0	86	97	96	97	97	100	90	97	97	87	85	100	89	100	4**	100	100	88	100	*	*	10	97
Proteus mirabilis	59	100	98	88	92	100	92	100	98	96	92	100	98	96	92	50	90	100	*	97	100	89	100	*	*	95	100
Pseudomonas aeruginosa	364	89	*	*	*	63	*	72	*	*	*	74	*	*	*	*	64	*	*	80	77	63	77	*	*	*	83
Serratia marcescens	30	100	0	0	7	100	0	100	93	93	17	100	93	0	0	50	77	100	*	0	100	90	100	*	*	90	97
S maltophilia	76	*	*	*	*	*	*	*	*	*	*	40	*	*	*	72	*	*	*	*	*	76	*	*	*	*	*

Empiric Management of UTI

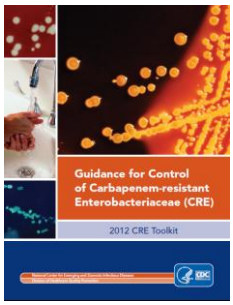
i. The threshold of 20% as the resistance prevalence at which the agent is no longer recommended for empirical treatment of acute cystitis is based on expert opinion derived from clinical, in vitro, and mathematical modeling studies (B-III).

5. The fluoroquinolones, ofloxacin, ciprofloxacin, and levofloxacin, are highly efficacious in 3-day regimens (A-I) but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis (A-III).

Gupta K, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Disease Society of America and European Society for Microbiology and Infectious Diseases. CID 2011: 52 (5): e103-e120

Carbapenem resistant enterobacteriaceae (CRE)

http://www.cdc.gov/hai/organisms/cre/cre-toolkit/



Restriction of Carbapenems

- Restricting the use of carbapenems has been linked with a lower incidence of carbapenem- resistant Pseudomonas
- Use of Carbapenems may also be correlated with increased resistance to other β- lactams (Ceftazidime and PIP/TAZ)

Restriction of Carbapenems

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Enterobacter cloacae	9	100	0	0	0	89	11	100	89	11	11	89	89	33	0	*	100	100	*	100	100	100	100	33	100	78	100
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Klebsiella pneumoniae	94	100	98	0	78	100	99	100	100	100	98	100	100	97	95	*	99	100	0	98	100	98	100	54	100	30	97
Proteus mirabilis	53	100	100	80	92	98	92	98	98	100	98	98	98	98	92	*	87	100	*	94	100	86	100	0	88	92	100
Pseudomonas aeruginosa	44	95	*	*	*	*	85	*	91	*	*	*	95	*	*	*	*	50	*	*	75	91	48	83	*	*	*	100
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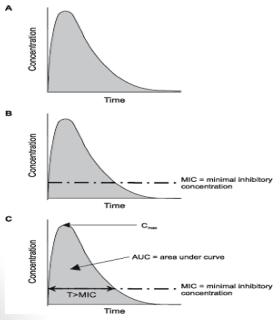
Pseudomonas aeruginosa	364	89	*	*	*	63	*	72	*	*	*	*	74	*	*	*	84	*	*	80	77	63	77	*	*	*	83
Serratia marcescens	26	100	0	0	7	100	0	100	93	93	17	100	93	0	0	50	77	100	*	0	100	90	100	*	*	90	93
S maltophilia	76	*	*	*	*	*	*	*	*	*	*	40	*	*	*	72	*	*	*	*	*	76	*	*	*	*	*

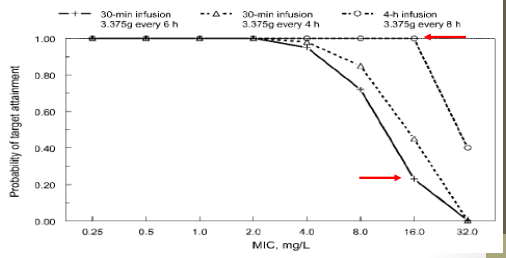
Pharmacokinetic pharmacodynamic targets



- C_{max}:MIC
- %T > MIC
- AUC:MIC

Maglio D, et al. Methods Find Exp Clin Pharmacol. 2004;26(10):781-8.

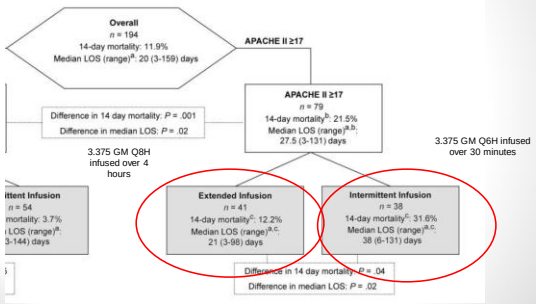
Piperacillin/tazobactam for *P. aeruginosa* Infection: Clinical implications of extended-infusion dosing strategy



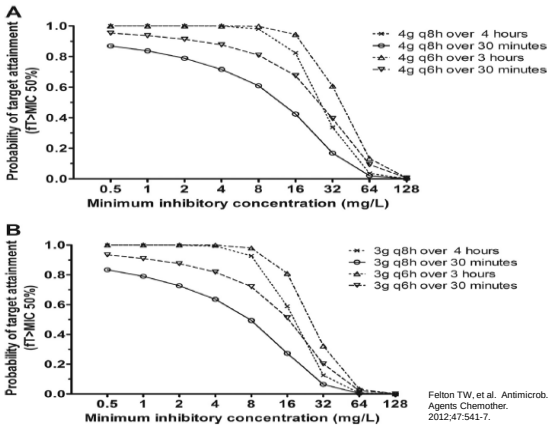
Target = piperacillin/tazobactam concentration > MIC for 50% dosing interval

Lodise TP, CID 2007;44:357-63

Piperacillin/tazobactam for *P. aeruginosa* Infection: Clinical implications of extended-infusion dosing strategy



Lodise TP, CID 2007;44:357-63.



Felton TW, et al. Antimicrob. Agents Chemother. 2012;47:541-7.

Piperacillin/tazobactam Extended Infusion Regimen

Antimicrobial Agent	CrCl ≥ 20 (mL/min)	CrCl < 20 (mL/min) or ESRD	Continuous Renal Replacement Therapy
Piperacillin/ Tazobactam	3.375 gm IV Q8H over 4 hours	3.375 gm IV Q12H over 4 hours	3.375 gm IV Q8H over 4 hours
Piperacillin/ Tazobactam	4.5 gm?		

Piperacillin/tazobactam Extended Infusion Regimen

Considerations

- Diagnostic Tests
  - Utilize 4 hour non-infusion window
  - Adjust default times
  - Continue infusion if possible
- Operating Room
- Infusion volume

Aminoglycosides

High Dose Extended-Interval Pharmacokinetics

Aminoglycoside therapy

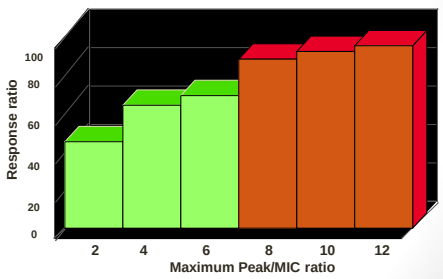
- Use decreased in the 1980s when broad spectrum β-lactam antibiotics became available
  - Carbapenems
  - Broad spectrum cephalosporins
  - β-lactam/β-lactamase inhibitor combination
- In the ICU, patients that have acute renal failure have a higher probability of death
- Due to increased gram negative resistance, aminoglycoside (AG) use is increasing and optimization of therapy is critical

Drusano GL, et al. Antimicrob. Agents Chemother. 55:2528-31.

Rationale for extended-interval dosing

- Concentration-dependent bactericidal activity
- Post-antibiotic effect (PAE)
- Adaptive resistance
- Minimize toxicities
  - Nephrotoxicity
  - Ototoxicity
- Efficacy
- Cost savings

Concentration-dependent bactericidal activity
Aminoglycoside Peak/MIC Ratio



Adapted from Moore RD et al. *J Infect Dis.* 1987;155:93-9

Cost savings

- Decreased pharmacy preparation time
- Decreased nursing administration time
- Potentially decreased drug concentration monitoring