Systemic Antimicrobial Prophylaxis Issues

Pierre Moine
Department of Anesthesiology
University of Colorado Denver

3rd International Conference on Surgery and Anesthesia –OMICs Group Conference

The Surgical Infections Prevention and Surgical Care Improvement Projects: National initiatives to improve outcome for patients having surgery

Bratzler DW and Hunt DR, Clin Infect Dis 2006

- Surgical site infections (SSIs) complicate up to 5% of all operations in the US (30% of clean contaminated surgery)
- SSIs most frequent nosocomial infection among surgical patients (accounting for over 40% of nosocomial infections in surgical patients)
- Estimated 750,000 SSIs / 15 million surgical procedures performed
  - Increasing ICU admissions
  - Increasing the postoperative LOS by 7-10 days
  - Increasing hospital readmissions
  - Mortality rates can exceed 10% with certain infections
  - Increasing hospital costs by 300%
- Resulting in additional direct and indirect cost to both the patient and the healthcare system – An estimated $2 billion in excess healthcare expenditures annually.

Surgical Care Improvement Project SCIP quality performance measures for SSI reduction. Multidisciplinary approach

- IFN-1 Proper timing of antibiotics: Antibiotics received within 1 hour before surgical incision
- IFN-2 Appropriate antibiotic selection for probable microbial contaminants
- IFN-3 Appropriate discontinuation of prophylactic antibiotics within 24 hours post-surgically
- IFN-4 Euglycemia
- IFN-6 Maintenance of perioperative normothermia
- IFN-7 Clippers for appropriate hair removal

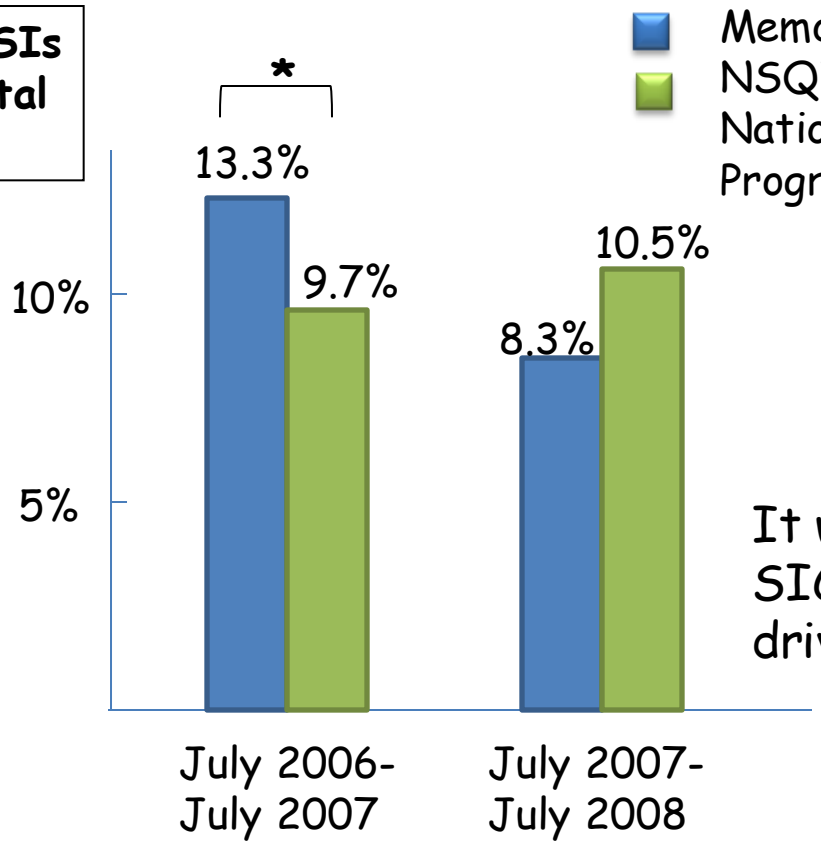
Compliance with SCIP quality performance measures is publicly reported and is tied to hospital reimbursement

Jones RS et al. Surgery 2005
Garcia N et al. Am Surg 2012

Improving surgical site infections: Using National Surgical Quality Improvement Program Data to Institute Surgical Care Improvement Project protocols in improving surgical outcomes.

Berenguer CM et al. J Am Coll Surg 2010

Rate of SSIs in colorectal surgery



Memorial University Medical Center
NSQIP [American College of surgeons National Surgical Quality Improvement Program] – 142 sites

It was unclear whether improved SICP compliance alone was the driving force for decreased SSIs

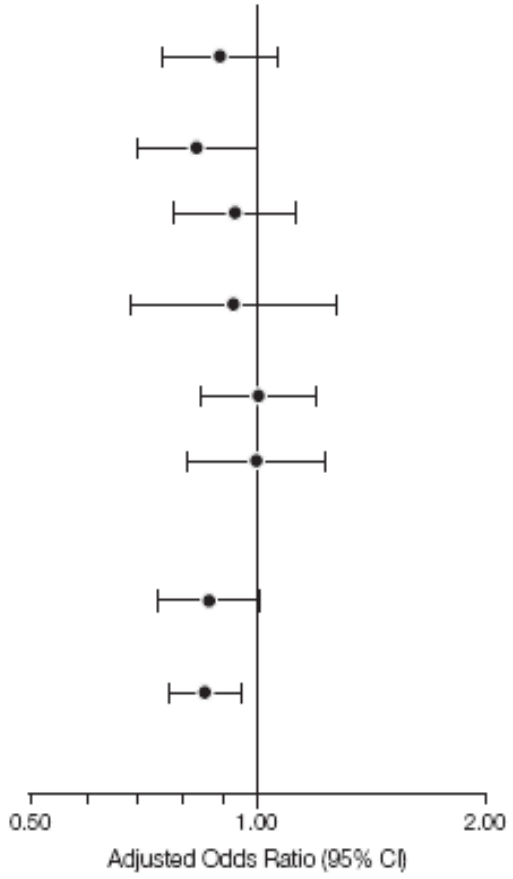
Compliance with SCIP	**38%**	**92%**

Adherence to Surgical Care Improvement Project measures and the association with postoperative infections

Stulberg JJ et al. JAMA 2010

Figure 1. Surgical Care Improvement Project (SCIP) Infection-Prevention Process Measures

	Nonadherent Discharges		Adherent Discharges		
	Postoperative Infections	Discharges	Postoperative Infections	Discharges	Adjusted Odds Ratio (95% CI)
Individual SCIP measures					
INF-1: prophylactic antibiotic received within 1 h prior to surgical incision	251	18147	1394	190925	0.89 (0.75-1.06)
* INF-2: prophylactic antibiotic selection for surgical patients	266	12670	1496	198002	0.83 (0.69-1.00)
INF-3: prophylactic antibiotics discontinued within 24 h after surgery end time	310	26499	1024	173228	0.94 (0.78-1.13)
INF-4: cardiac surgery patients with controlled 6 AM postoperative blood glucose	65	4168	362	31512	0.93 (0.68-1.27)
INF-6: surgery patients with appropriate hair removal	194	21308	3539	380111	1.00 (0.85-1.19)
INF-7: colorectal surgery patients with immediate postoperative normothermia	181	4564	676	18101	1.00 (0.81-1.23)
Composite measures					
* S-INF-Core: all 3 original Surgical Infection Prevention (SIP) project perioperative infection-prevention measures	511	44417	816	154963	0.86 (0.74-1.01)
S-INF: all patients with at least 2 recorded SCIP infection-prevention measures in a single visit	843	59356	1070	158304	0.85 (0.76-0.95)



Each estimate accounts for the surgical procedure performed, patient characteristics, and hospital characteristics. CI indicates confidence interval.

SIP – SCIP controversy

- Studies demonstrate that SCIP implementation has achieved substantial improvements in adherence
- There is minimal evidence to support that SCIP adherence improves surgical outcomes at the patient or hospital levels
- Findings are unable to support the assertion that reported adherence on these measures is directly related-associated to improved outcomes.
- Although the processes measured are best practices and should continue, they might be too simplistic or blunt to discriminate hospital quality
- We definitely need to identify contributing factors that have not been considered

Timing of surgical antibiotic prophylaxis and the risk of surgical site infection.

Hawn MT et al. JAMA Surg 2013

N = 32 459 operations
SSIs 1497 cases (4.6%)

Table 3. Relative Contribution of Model Covariates for Surgical Site Infection Risk[a]

	Overall		Orthopedic		Vascular		Colorectal	
Variable	$\chi^2 - df$	Rank	$\chi^2 - df$	Rank	$\chi^2 - df$	Rank	$\chi^2 - df$	Rank
Total	362.7		14.0		79.0		77.4	
Specialty	233.2[b]	1	...	...	...	...	...	...
Antibiotic timing	−0.5	15	1.2	5	−1.0	14	0.1	11
Antibiotic agent	17.6[b]	5	5.1[b]	2	−2.1	15	18.0[b]	2
Operative duration	31.7[b]	2	−0.6	9	9.2[b]	5	26.3[b]	1
Age	30.0[b]	3	4.9	3	14.8[b]	2	11.1[b]	4
Diabetes	19.4[b]	4	1.4	4	20.5[b]	1	1.0	10
Wound class	9.9[b]	6	...	...	13.9[b]	3	2.4	6
Dyspnea	8.9[b]	7	1.0	6	−0.5	11	11.8[b]	3
ASA class	6.2[b]	8	−1.9	14	10.0	4	2.3	7
Work RVUs	2.1	9	−0.8	11	4.5	7	2.2	8
COPD	2.0	10	−1.0	13	0.5	9	1.3	9
Emergent case	1.3	11	−0.9	12	−0.9	13	4.1[b]	5
Alcohol use	1.3	12	−0.4	8	7.7[b]	6	−0.4	12
Smoker	0.8	13	6.9[b]	1	−0.8	12	−0.9	14
Penicillin allergy	−0.1	14	−0.6	10	3.0[b]	8	−0.9	13
Steroid use	−1.0	16	−0.3	7	0.1	10	−1.0	15

Abbreviations: ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; RVUs, relative value units; ellipses, covariates not included in model.

[a] $\chi^2 - df$ is the χ^2 estimate minus the *df* for the model term. Rank is the relative contribution of the model term to the overall surgical site infection risk.

[b] Covariate is significant ($P < .05$).

Ertapenem versus cefotetan prophylaxis in elective colorectal surgery

Itani KMF et al. N Engl J Med 2006

Table 2. Adjusted Proportion of Patients with Failed Prophylaxis of Infection 4 Weeks after Surgery, According to Reason for Failure.*

Reason for Failure	Patients in Per-Protocol Analysis			Patients in Modified Intention-to-Treat Analysis		
	Ertapenem (N=338)	Cefotetan (N=334)	Absolute Difference	Ertapenem (N=451)	Cefotetan (N=450)	Absolute Difference
	no. (%)		% (*95% CI*)	*no.* (%)		% (*95% CI*)
Any failure	95 (28.0)	143 (42.8)	−14.8 (−21.9 to −7.5)	182 (40.2)	229 (50.9)	−10.7 (−17.1 to −4.2)
Surgical-site infection	62 (18.1)	104 (31.1)	−13.0 (−19.5 to −6.5)	78 (17.1)	118 (26.2)	−9.1 (−14.4 to −3.7)
Superficial incisional infection	45 (13.1)	75 (22.4)	−9.3 (−15.0 to −3.5)	56 (12.3)	81 (17.9)	−5.6 (−10.3 to −0.9)
Deep incisional infection	13 (3.7)	17 (5.1)	−1.4 (−4.7 to 1.9)	15 (3.3)	23 (5.1)	−1.8 (−4.6 to 0.8)
Organ–space infection	4 (1.2)	12 (3.7)	−2.5 (−5.2 to −0.2)	7 (1.5)	14 (3.2)	−1.7 (−3.9 to 0.4)
Unexplained use of antibiotics	23 (6.9)	25 (7.5)	−0.6 (−4.6 to 3.4)	45 (10.0)	42 (9.4)	0.6 (−3.3 to 4.6)
Anastomotic leakage	10 (3.0)	14 (4.2)	−1.2 (−4.2 to 1.8)	13 (2.9)	18 (4.0)	−1.1 (−3.6 to 1.4)
Missed follow-up assessment†	—	—	—	19 (4.2)	24 (5.4)	−1.2 (−4.2 to 1.6)
Concomitant use of antibiotics for distant-site infection†‡	—	—	—	27 (6.0)	27 (6.0)	0 (−3.2 to 3.2)

* The absolute difference is for the ertapenem group as compared with the cefotetan group. All percentages and 95% CIs were computed from a statistical model adjusting for surgical procedure; therefore, the percentages may not equal the number of patients whose treatment failed divided by the total number of patients in each treatment group. Dashes denote not applicable.

† Patients in the per-protocol analysis who missed a follow-up assessment or had concomitant use of antibiotics for a distant-site infection were excluded from the analysis.

‡ In the modified intention-to-treat analysis, the protocol deemed that prophylaxis had failed in patients who had concomitant use of antibiotics for a distant-site infection, even though these patients had no signs or symptoms of infection at the operative site. Distant-site infections included pneumonia (in 13 patients in the ertapenem group and 23 in the cefotetan group), urinary tract infection (20 in the ertapenem group and 29 in the cefotetan group), and other infections (19 in the ertapenem group and 12 in the cefotetan group). Examples of other distant-site infections included *Clostridium difficile* infection, respiratory tract infection, and bloodstream infection. Patients with multiple distant-site infections were counted only once in this category.

Antibiotic prophylaxis in colorectal surgery

Moine P and Asehnoune K. N Engl J Med 2007

Differences in antibiotic effectiveness

Inappropriate timing of preoperative antibiotic administration
PK/PD performance
- Initial loading dose
- Lack of antibiotic redosing
- Low Concentrations of cefotetan at closure

Lack of weight-based dosing in obese patients (27%)
Changing patterns of antimicrobial resistance/Cefotetan MICs
Prolonged surgeries (up to 313 minutes)

Ertapenem versus cefotetan prophylaxis in elective colorectal surgery

Itani KMF et al. N Engl J Med 2006

Table 3. In Vitro Susceptibility of Documented Pathogens in the Two Treatment Groups.*

Pathogen	Total No. of Isolates	Ertapenem		Cefotetan	
		Isolates Tested for Resistance	Resistant Isolates	Isolates Tested for Resistance	Resistant Isolates
		no.	*no.* (%)	*no.*	*no.* (%)
Patients receiving ertapenem					
Gram-positive aerobic cocci	42	24	14 (58.3)	24	18 (75.0)
Gram-positive aerobic bacilli	3	0	0	0	0
Gram-negative aerobic bacilli	17	11	1 (9.1)	11	2 (18.2)
Gram-positive anaerobic bacteria	25	24	0	24	5 (20.8)
Gram-negative anaerobic bacteria	36	33	0	33	17 (51.5)
Other unspecified bacteria	1	0	0	0	0
Total	124	92	15 (16.3)	92	42 (45.7)
Patients receiving cefotetan					
Gram-positive aerobic cocci	51	24	14 (58.3)	24	19 (79.2)
Gram-positive aerobic bacilli	0	0	0	0	0
Gram-negative aerobic bacilli	23	10	1 (10.0)	15	8 (53.3)
Gram-positive anaerobic bacteria	30	29	0	29	19 (65.5)
Gram-negative anaerobic bacteria	44	37	1 (2.7)	37	24 (64.9)
Other unspecified bacteria	3	0	0	0	0
Total	151	100	16 (16.0)	105	70 (66.7)

* Patients with infections caused by these pathogens had superficial and deep surgical-site infections, organ–space infections, and anastomotic leakage. Pathogens that occurred in more than 1% of patients in either treatment group included the following: gram-positive aerobic cocci — enterococcus species, *Staphylococcus aureus,* staphylococcus species (coagulase negative), and streptococcus species; gram-positive aerobic bacilli — bacillus species; gram-negative aerobic bacilli — *Enterobacter aerogenes, Escherichia coli, Klebsiella pneumonia, Morganella morganii, Proteus mirabilis,* and *Pseudomonas aeruginosa*; gram-positive anaerobic bacteria — peptostreptococcus species, clostridium species, eubacterium species, *Lactobacillus plantarum,* and *Propionibacterium acnes*; gram-negative anaerobic bacteria — porphyromonas species, bacteroides species, and fusobacterium species; and other unspecified bacteria — gram-negative bacillus (not otherwise specified).

Choice of intravenous antibiotic prophylaxis for colorectal surgery does matter

Deierhoi RJ et al. J Am Coll Surg 2013

5,750 elective colorectal procedures performed at 112 VA hospitals
709 SSIs (12.3%) developed within 30 days.

Table 4. Generalized Estimating Equations of Surgical Site Infection

	Overall cohort	
IV antibiotic agent	**Odds ratio[adj]***	**95% CI**
Cefazolin/metronidazole	ref	ref
Ampicillin/sulbactam	2.16	1.35–3.58
Cefotetan	2.53	1.51–4.22
Cefoxitin	2.56	1.73–3.81
Ertapenem	1.48	0.79–2.78
Fluoroquinolone/plus anaerobic	1.89	1.01–3.51
Oral antibiotic	0.37	0.29–0.46

*Adjusted odds ratio for oral antibiotic, age, body mass index, procedure work relative value units, operation duration, and dyspnea.

Timing of surgical antibiotic prophylaxis and the risk of surgical site infection.

Hawn MT et al. JAMA Surg 2013

The choice of Prophylactic antibiotic (Antibiotic agent selection) for orthopedic and colorectal procedures was associated with SSIs

Orthopedic procedures (cefazolin as reference group):
Vancomycin alone <<<< Cefazolin [adjusted OR 1.75; 95% CI, 1.16-2.65]
Nevertheless, it is unclear whether the selection of vancomycin is an indicator of patients at higher risk for SSI

Colorectal procedures (cefoxitin as reference group):
Cefazolin + metronidazole >>>> Cefoxitin [adjusted OR 0.49; 95%CI, 0.34-0.71]
Quinolone + metronidazole >>>> Cefoxitin [adjusted OR 0.55, 95% CI, 0.35-0.87]

These differences in effectiveness were not explained by the half-lifes of these agents

Antimicrobial prophylaxis for surgery : An advisory statement from the National Surgical Infection Prevention Project – Bratzler DW et al. Clin Infect Dis 2004.
Clinical practice guidelines for antimicrobial prophylaxis in Surgery – Bratzler DW et al. Am J Health-System Pharm 2013.

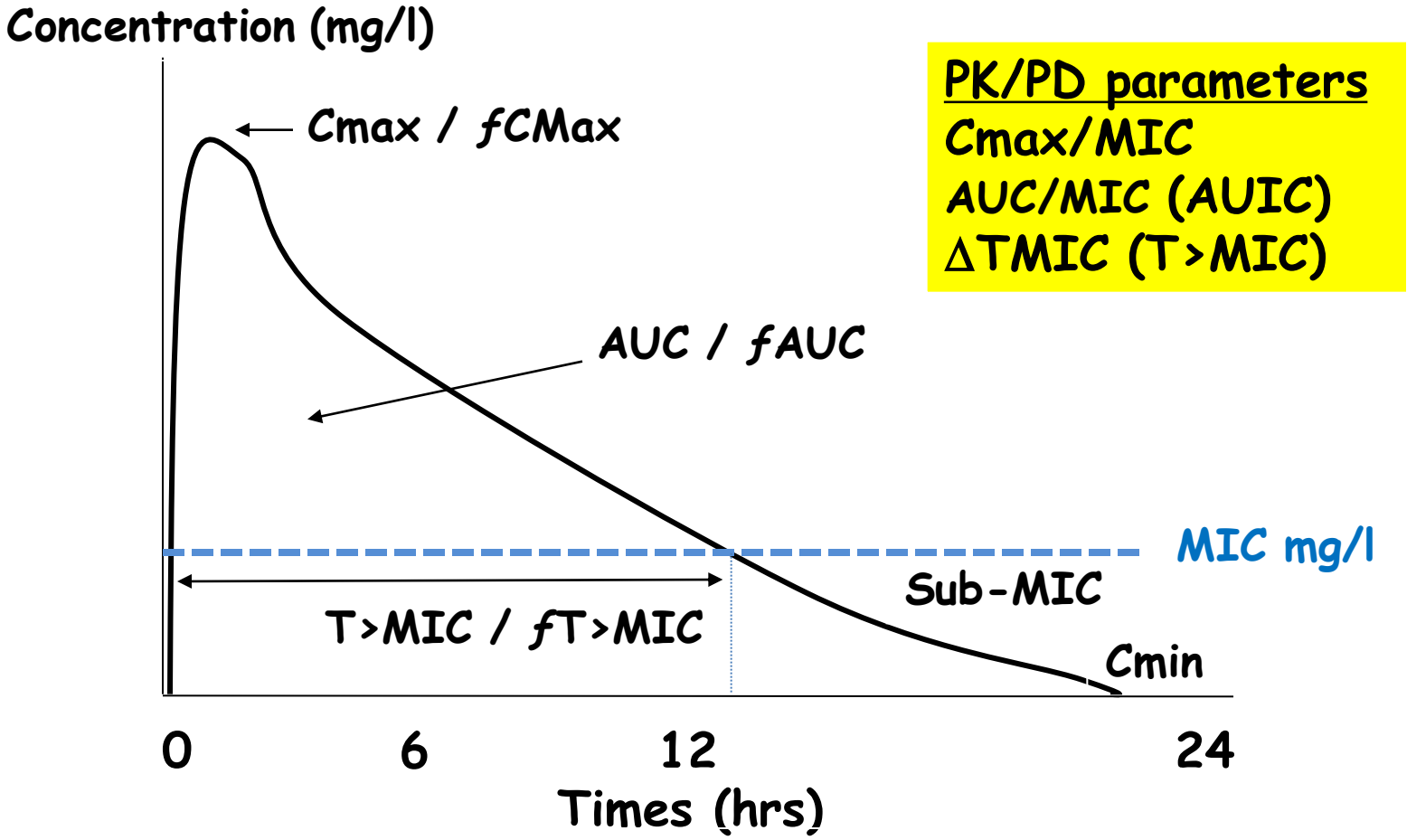
Antimicrobials	Standard Dose 2004-2006	Recommended redosing interval (h)	Standard Dose 2013	Recommended redosing interval (h)
Cefazolin	1-2 g iv (20-30 mg/kg)-2g if ≥ 80 kg	2-5	2 g 3 g for ≥ 120 kg	4
Cefotetan	1-2 g iv (20-40 mg/kg)	3-6	2 g	6
Cefoxitin	1-2 g iv (20-40 mg/kg)	2-3	2 g	2
Cefuroxime	1.5 g iv (50 mg/kg)	3-4	1.5 g	4
Ampicillin-sulbactam	1-2/0.5-1 g iv	-	2/1 g iv	2
Aztreonam	1-2 g iv (2 g)	3-5	2 g	4
Ciprofloxacin	400 mg iv (400 mg)	4-10	400 mg	NA
Vancomycin	1 g iv (10-15 mg/kg)	6-12	15 mg/kg	4-8
Metronidazole	0.5-1 g iv (15 mg/kg then 7.5 mg/kg)	6-8	1 g	6-10
Clindamycin	600-900 mg iv	3-6	900 mg	6
Cefotaxime/ceftriaxone	-	-	1 g / 2 g (2 g / -)	3 / NA
Ertapenem			1 g	NA
Piperacillin-tazobactam			3.375 mg	2
Levofloxacin			500 mg	NA
Moxifloxacin			400 mg	NA

Pharmacokinetics-Pharmacodynamics of Antimicrobial Therapy:
It's Not Just for Mice Anymore.

Ambrose PG et al. Clin Infect Dis 2007

Pharmocokinetic-pharmacodynamic PK/PD parameters

The quantitative relationship between a pharmacokinetic parameter and a microbiological parameter is labeled PK/PD index
They are used to predict in-vivo antimicrobial activity.



PK/PD parameters
Cmax/MIC
AUC/MIC (AUIC)
ΔTMIC (T>MIC)

***ƒ*: an indicator that the free, unbound (non-protein bound) fraction is used**

Pharmacodynamic modelling of intravenous antibiotic prophylaxis in elective colorectal surgery

Moine P and Fish DN. Int J Antimicrob Agents 2013

Table 3
Probability of target attainment (PTA) of surgical prophylaxis regimens against *Escherichia coli*, *Bacteroides fragilis* and *Staphylococcus aureus* at susceptibility breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI).

Antibiotic	Dose	PTA by pathogen (%)[a]											
		Escherichia coli				*Bacteroides fragilis*				*Staphylococcus aureus*			
		Time after dose (h)				Time after dose (h)				Time after dose (h)			
		1	2	3	4	1	2	3	4	1	2	3	4
SAM[b]	1.5 g	**100**	**100**	**99.7**	77.5					**100**	**100**	**99.7**	77.5
	3 g	**100**	**100**	**100**	**99.5**					**100**	**100**	**100**	**99.5**
Cefoxitin[c]	1 g	54.0	0	0	0	14.1	0	0	0	57.3	1.4	0	0
	2 g	83.8	24.5	0	0	55.2	0	0	0	**92.1**	26.4	3.2	0
Cefotetan[d]	1 g	1.0	0	0	0	1.0	0	0	0	1.0	0	0	0
	2 g	48.3	21.9	5.5	1.0	48.3	21.9	5.5	1.0	48.3	21.9	5.5	1.0
Cefazolin[e]	1 g	**100**	**100**	**100**	**100**					**92.2**	77.2	21.2	0
	2 g	**100**	**100**	**100**	**100**					**100**	**100**	**100**	**91.2**
Cefuroxime[f]	1.5 g	**100**	**100**	**100**	**91.4**					**100**	**100**	**100**	**91.4**
Ceftriaxone[e]	1 g	84.5	84.5	84.5	84.5					0	0	0	0
	2 g	**99.4**	**99.4**	**99.4**	**99.4**					0	0	0	0
Ertapenem[g]	1 g	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**98.7**	**100**	**100**	**100**	**100**

SAM, ampicillin/sulbactam.

[a] Regimens meeting the desired goal of PTA ≥ 90% at each time point are highlighted in bold text.
[b] Current CLSI breakpoints = 8 mg/L for *E. coli* and *S. aureus*, undefined for *B. fragilis*.
[c] Current CLSI breakpoints = 8 mg/L for *E. coli* and *S. aureus*, 16 mg/L for *B. fragilis*.
[d] Current CLSI breakpoints = 16 mg/L for all organisms.
[e] Current CLSI breakpoints = 1 mg/L for *E. coli*, 8 mg/L for *S. aureus*.
[f] Current CLSI breakpoints = 8 mg/L for *E. coli* and *S. aureus*.
[g] Current CLSI breakpoints = 0.25 mg/L for *E. coli*, 2 mg/L for *S. aureus*, 4 mg/L for *B. fragilis*.

Pharmacodynamic modelling of intravenous antibiotic prophylaxis in elective colorectal surgery

Moine P and Fish DN. Int J Antimicrob Agents 2013

The CFR is related to PD target attainment in that it expresses the probability of a given dosage regimen achieving desired exposures against an entire population of pathogens, rather than against organisms with only certain specific MICs to the drug.

Table 4

Cumulative fraction of response (CFR) of surgical prophylaxis regimens against *Escherichia coli*, *Bacteroides fragilis* and *Staphylococcus aureus* at different time points after dosing.

Antibiotic	Dose	CFR by pathogen (%)[a]											
		Escherichia coli				*Bacteroides fragilis*				*Staphylococcus aureus*			
		Time after dose (h)				Time after dose (h)				Time after dose (h)			
		1	2	3	4	1	2	3	4	1	2	3	4
SAM[b]	1.5 g	79.2	75.0	58.6	29.1								
	3 g	**90.0**	81.8	76.6	70.9								
Cefoxitin	1 g	**93.3**	55.5	9.6	1.5	83.9	16.1	0.1	0	**100**	36.7	0.1	0
	2 g	**97.0**	84.7	43.2	6.9	**92.2**	56.9	3.5	0	**100**	**100**	7.9	0
Cefotetan [c]													
Cefazolin	1 g	**93.0**	88.5	87.0	83.3					**90.8**	**90.2**	**90.0**	89.6
	2 g	**94.2**	**94.0**	**93.0**	**91.7**					**91.6**	**91.1**	**91.0**	**90.7**
Cefuroxime	1.5 g	**99.8**	**96.9**	**95.4**	**91.8**					**100**	**100**	**95.9**	**90.7**
Ceftriaxone	1 g	87.1	87.1	87.1	87.1					3.65	3.65	3.65	3.65
	2 g	87.3	87.3	87.3	87.3					37.9	37.9	37.9	37.9
Ertapenem	1 g	**100**	**100**	**99.9**	**99.9**	**99.3**	**99.3**	**98.3**	**97.6**	**94.5**	**94.4**	**93.4**	**92.8**

SAM, ampicillin/sulbactam; MIC, minimum inhibitory concentration; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

[a] Regimens meeting the desired goal of CFR ≥ 90% at each time point are highlighted in bold text.

[b] Current SAM MIC distributions were not available through the EUCAST website or other sources, thus CFRs could not be calculated for *B. fragilis* or *S. aureus*.

[c] Current cefotetan MIC distributions for target pathogens were not available through the EUCAST website or other sources, thus CFRs could not be calculated.

The obese surgical patient: a susceptible host for infection.

Anaya DA, Dellinger EP. Surg Infect 2006

- Obese patients do not appear to have a higher risk of postoperative complications or mortality than non-obese patients but, the risk of SSI is higher in obese patients and increases as their BMI increase

- Obesity *per se* was identified repeatedly as an independent predictor of SSI in different populations of patients.

- Obesity is a risk factor for SSI after both elective and urgent procedures

Dosing of antibiotics in obesity

Janson B and Thursky K. Curr Opin Infect Dis 2012

KEY POINTS

- There is a lack of data for most antibiotics regarding dosing in obese and morbidly obese patients.

- Knowledge of pharmacokinetics and pharmacodynamics will assist with dosing.

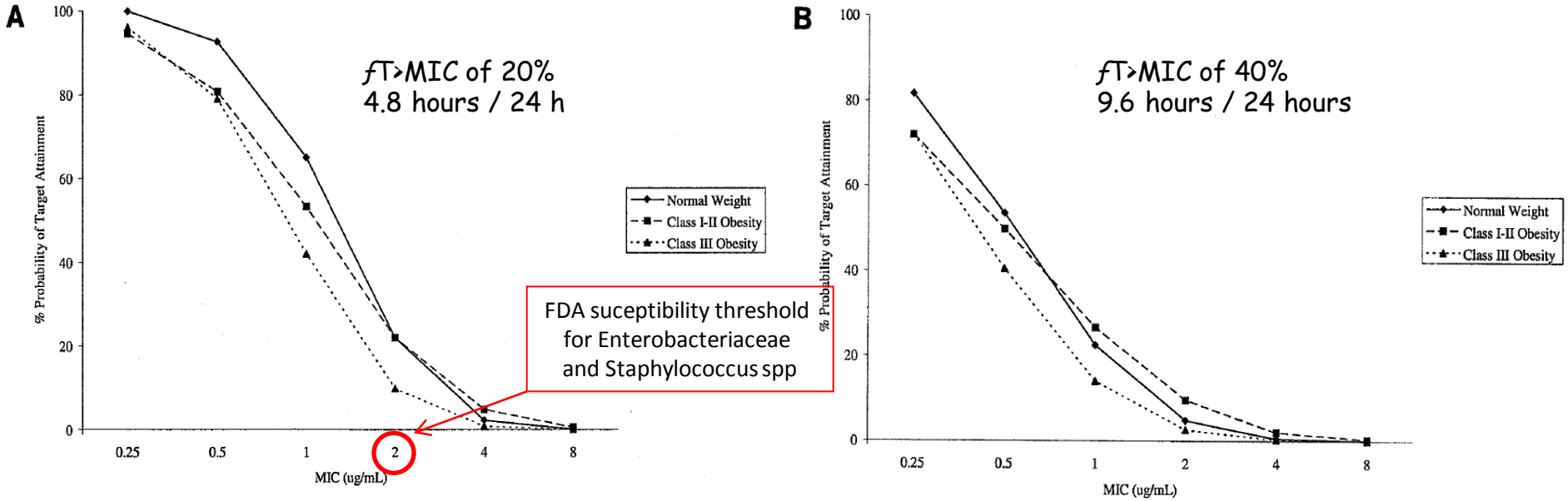
- Only a limited number of studies have been conducted to evaluate obesity-associated physiological changes and their pharmacokinetic ramifications

- Some antibiotics may require higher doses at the same frequency, whereas others may require more frequent dosing

Comparative pharmacokinetics and pharmacodynamic target attainment of ertapenem in normal-weight, obese, and extremely obese adults

Chen M et al. Antimicrob Agents Chemother 2006

ƒT>MIC of 20% and 40% of the dosing interval (24 hours) are commonly cited pharmacodynamic targets for bacteriostatic and maximal bactericidal effect, respectively.



Ertapenem current susceptibility breakpoints: 0.25 mg/L for E coli, 2 mg/L for S aureus, 4 mg/L for B fragilis

Single iv 1-g dose of ertapenem infused over

30 Normal Weight 18.5-24.9 kg/m^2 - Class I-II obesity 30-39.9 kg/m^2 - Class III obesity ≥ 40 kg/m^2

This study suggest that the standard dose of ertapenem (1 g daily) may not be sufficient to achieve 90% probability of target attainment for bacteriostatic (ƒT>MIC of 20%) or maximal bactericidal (ƒT>MIC of 40%) activity for organisms with MICs in excess of 0.25-0.5 mcg/ml in any of the BMI groups

Cefoxitin antibiotic prophylaxis: Evaluation of pharmacokinetics and pharmacodynamic target attainment of cefoxitin in obese patients.

Moine P et al. Submitted for publication

2005 National Surgical Infection Prevention Project recommendations
Cefoxitin recommended standard iv dose: 1-2 g with a redosing interval of 2-3 hours, while the weight-based dose recommendation was 20-40 mg/kg.

2013 American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) recommendations
Cefoxitin recommended standard iv dose: 2 g with a redosing interval of 2 hours. A weight-based dose recommendation was not even addressed.

Inclusion criteria: Obese patients defined a BMI >30 kg/m^2, 18 to 75 years of age, and scheduled for elective bariatric surgery anticipated to last more than 2 hours in duration.
Exclusion criteria: Allergy to cephalosporins or severe allergy to any betalactams, severe renal insufficiency (creatinine clearance < 40 mL/Min, calculated according to Cokcroft and Gault formula) or severe hepatic failure (serum bilirubin concentration >2 mg/dL).

Cefoxitin antibiotic prophylaxis: Evaluation of pharmacokinetics and pharmacodynamic target attainment of cefoxitin in obese patients.

Moine P et al. Submitted for publication

Cumulative fraction of response (CFR) of surgical prophylaxis regimens for different MICs at different time points after dosing.
Current CLSI breakpoints = 8 mg/L for *E. coli* and *S. aureus*, 16 mg/L for *B. fragilis*.

Antibiotic Regimen		CFR by Pathogen (%)								
		MICs								
	Time (h)	0.5	1	2	4	8	16	32	64	128
Cefoxitin	1	**100.0**	**100.0**	**100.0**	**99.8**	72.8	9.1	0	0	0
2g regimen	2	**100.0**	**100.0**	**97.3**	67.4	11.6	0	0	0	0
PD target defined as	3	**100.0**	**93.0**	64.0	16.8	0.4	0	0	0	0
fT>MIC of 100%	4	87.0	61.4	22.2	2.1	0	0	0	0	0
Cefoxitin	1	**100.0**	**100.0**	**100.0**	**100.0**	**91.0**	21.9	0	0	0
2g regimen	2	**100.0**	**100.0**	**100.0**	**95.3**	40.9	2.0	0	0	0
PD target defined as	3	**100.0**	**100.0**	**96.1**	60.4	9.5	0.1	0	0	0
fT>MIC of 70%	4	**100.0**	**95.8**	72.3	24.7	1.2	0	0	0	0
Cefoxitin	1	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**90.1**	24.6	0.2	0
40 mg/kg regimen	2	**100.0**	**100.0**	**100.0**	**99.5**	81.5	25.3	0.9	0	0
PD target defined as	3	**100.0**	**100.0**	**97.1**	74.7	29.5	2.4	0	0	0
fT>MIC of 100%	4	**99.4**	**92.2**	70.6	34.4	5.4	0	0	0	0
Cefoxitin	1	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**98.3**	45.4	1.4	0
40 mg/kg regimen	2	**100.0**	**100.0**	**100.0**	**100.0**	**99.1**	64.6	8.8	0	0
PD target defined as	3	**100.0**	**100.0**	**100.0**	**99.0**	77.2	23.1	0.5	0	0
fT>MIC of 70%	4	**100.0**	**100.0**	**99.1**	83.6	39.6	4.2	0	0	0

Prophylactic antibiotic Challenges/Significant limitations (non SCIP targeted measures)

- Optimal choice of antibiotic had not (and still has not) been established. Selected antibiotic agent effectiveness according to the type of surgery remains to be assessed.
- Variability in antibiotic pharmacokinetics within various type of surgical patients/populations
- Distribution of antibiotic concentrations at the "site of infection"
- Antibiotic pharmacokinetic/pharmacodynamic PK/PD characteristics
- Optimal PK/PD surrogate markers/targets within various type of surgical patients/populations or type of surgery
- Appropriate antibiotic dosing and redosing
- Patient characteristics such as obesity/HRS/sepsis/trauma…
- Changing patterns of antimicrobial resistance
  - May vary by type of surgery
  - May vary by region and by hospital
- MDR pathogens and MDR pathogen risk factors / Key pathogen susceptibilities / resistances [Prolonged hospitalization before surgery / Exposure to antimicrobial therapy / Immunosuppression / Other relevant risk for opportunistic MDR pathogen / Prior colonization-infection with MDR pathogen]