ANTIMICROBIAL THERAPY OF INTRA-ABDOMINAL INFECTIONS

Classification of Peritonitis

TYPE	CAUSE	OPERATION
Primary	Spontaneous	None
Secondary	Enterogenous	Control of perforation
Tertiary	Nosocomial opportunistic	Repeated Laparotomy

Wittney

Experimental Model of Intra-abdominal Infection

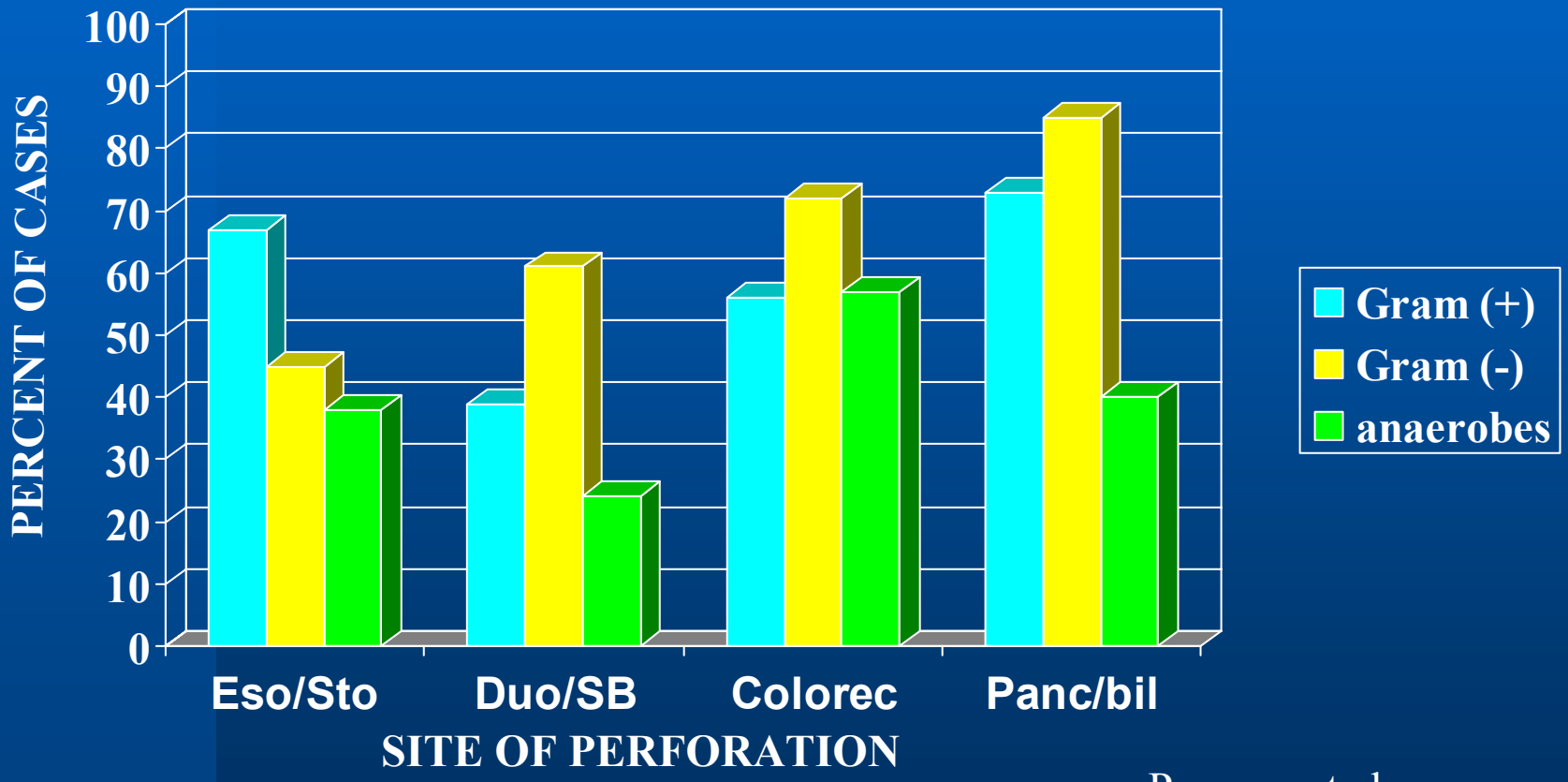
Two-Stage Disease Process

PATHOLOGY	ORGANISM
❖ Acute Peritonitis	E. coli
❖ Intra-abdominal Abscess	B. fragilis

- defined pathogenesis of IAI
- used to test efficacy of antibiotic regimens

Gorbach 1981
Bartlett 1995

Peritoneal Isolates in IAI



Poenaru et al
Can J Surg 1990

Peritoneal Isolates in IAI

ORGANISM	SOLOMKIN	MOSDELL	LAUDICO
Gram - negative			
E. coli	**56.8**	**68.4**	**46.0**
Enterobacter	13.5	6.1	19.0
Klebsiella	15.4	17.0	
Anaerobes			
B. fragilis	**22.8**	**44.5**	**67.0**
Gram – positive			
Nonenterococcal Strep	**35.8**	**25.9**	

Solomkin 1990, Mosdell 1991, Laudico 1993

Peritoneal Isolates in IAI

ORGANISM	SOLOMKIN	MOSDELL	LAUDICO
Gram-negative			
E. coli	**56.8**	**68.4**	**46.0**
Enterobacter	13.5	6.1	19.0
Klebsiella	15.4	17.0	
P. aeruginosa	14.8	19.1	6.0
Proteus	6.2	2.7	4.0
S. marcescens	1.2	4.1	
Morganella morganii	1.2	---	
Citrobacter	3.1	3.4	
Others	3.7	7.5	

Solomkin 1990, Mosdell 1991, Laudico 1993

Peritoneal Isolates in IAI

ORGANISM	SOLOMKIN	MOSDELL	LAUDICO
Anaerobes			
B. fragilis	**22.8**	**44.5**	**67.0**
Other Bacteroides	21.0	---	
Clostridium	17.9	5.8	
Peptococci/Streptococci	7.4	16.0	
Fusobacterium	6.2	5.1	
Lactobacillus	5.6	---	
Enterobacterium	4.3	---	
Others	12.4	3.7	

Solomkin 1990, Mosdell 1991, Laudico 1993

Peritoneal Isolates in IAI

ORGANISM	SOLOMKIN	MOSDELL
Gram – positive		
Nonenterococcal Strep	**35.8**	**25.9**
Enterococci	23.5	10.5
S. aureus/S. epidermidis	10.5	10.5
Yeast		
Candida sp.	18.6	4.1

Solomkin, Ann Surg 1990
Mosdell, Ann Surg 1991

Diagnosis of Acute Peritonitis

1) Clinical Findings
   - peritoneal irritation on P.E.

2) Diagnostic Imaging for Atypical Presentation

Diagnostic Imaging in Acute Peritonitis

- **ABDOMINAL ROENTGENOGRAPHIC SERIES**
  - Useful in GIT perforation & obstruction
  - Sensitivity of upright x-ray : 38 %

RADIOGRAPHIC SIGN	SENSITIVITY
RUQ air	41%
Rigler's sign	32%
Falciform ligament sign	2%
Football sign	2%
Inverted V sign	0%
Overall for supine x-ray	59%

Levine et al
Am J Roent 1991

Diagnostic Imaging in Acute Peritonitis

ULTRASOUND

- Immediate ultrasound is neither essential nor justifiable in most acute admissions to the surgical ward (Walsh, Clin Radio 1990)
- best used in pediatric or female patient with RLQ or pelvic pain

COMPUTED TOMOGRAPHY

- thin collimation helical scanning is diagnostic modality of choice for imaging the surgical abdomen

MAGNETIC RESONANCE IMAGING

- no significant diagnostic advantage over CT

Diagnostic Imaging in Acute Peritonitis

LAPAROSCOPY FOR INTRA-ABDOMINAL INFECTIONS

Prospective Study (n=154)

- only one abscess not identified
- 96 % successfully treated using laparoscopy
- 5 patients required laparotomy

-Need RCT to determine selection criteria, cost-implications and outcomes

Geis & Kim
Surg Endos 1995

Therapeutic Strategy for Intra-Abdominal Infections

I. Correction of Functional Impairment
II. Surgical Intervention
III. Antimicrobial Therapy

Kirschner et al
Arch Chir 1926

Physiologic Support

RESTORE AND MAINTAIN ADEQUATE PERFUSION

- volume expansion
- maintain arterial oxygen saturation

Surgical Intervention

THREE FUNDAMENTAL PRINCIPLES

I. Occlusion of infectious leak (SOURCE CONTROL)

- A. Primary repair, resection or exclusion
- B. Emerging role of minimally invasive surgery

II. Reduce degree of bacterial contamination (PURGE)

- A. Aspiration of purulent exudates and adjuvants
- B. Intra-operative peritoneal lavage

Surgical Intervention

THREE FUNDAMENTAL PRINCIPLES

III. Prevent recurrent or persistent infection

- use of drains
- post-operative peritoneal lavage
- Quality Control of repairs and purge
  - Open Abdomen (OPA)
  - Covered Abdominostomy (COLA)
  - Planned Relaparotomy (PR)
  - Staged Abdominal Repair (STAR)

Role of Peritoneal Cultures

Intra-operative cultures not cost-effective for :

- limited peritoneal contamination
- patients with minimal pre-morbid conditions who are treated promptly

Useful for:

- patients with suppressed local host immune defenses
- high-risk for persistent peritonitis

Role of Peritoneal Cultures

HIGH-RISK PATIENTS

- multiple pre-morbid medical problems
- significant delay in treatment
- acutely physiologically debilitated
- receiving immunosuppressive medications
- have altered gut flora because of recent hospitalization or antibiotic treatment

Antimicrobial Therapy

- Empirical because physiologic evidence of infection usually precedes identification of offending organisms
- Best chance for eradicating a serious infection is early in its course
- stratify antimicrobial use into two levels of therapeutic intensity
- selection based primarily on patient factors and local resistance patterns

Antimicrobial Therapy

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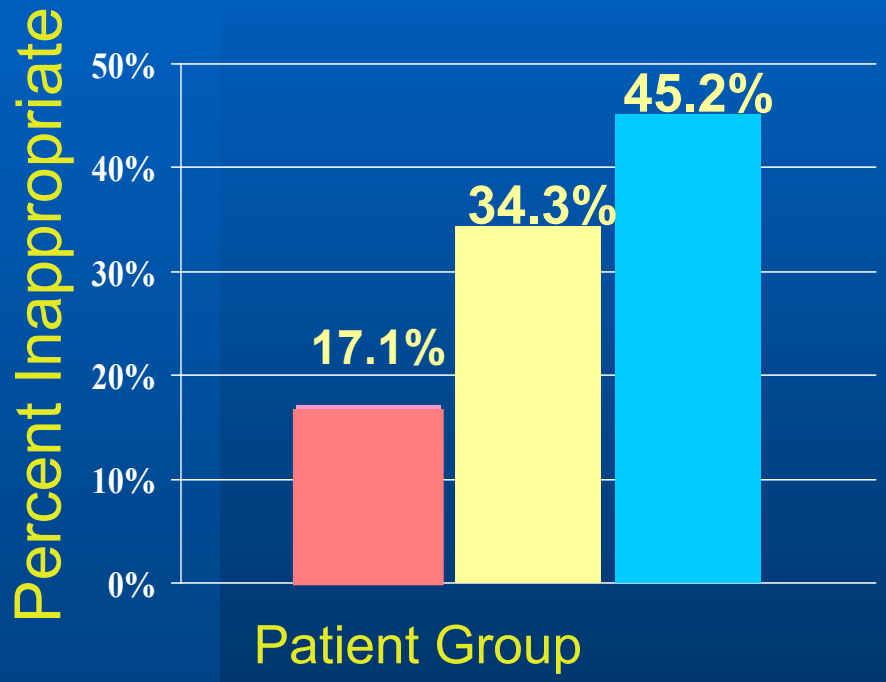
- Best chance for eradicating a serious infection is early in its course

Inappropriate Antimicrobial Therapy: Prevalence Among Intensive Care Patients

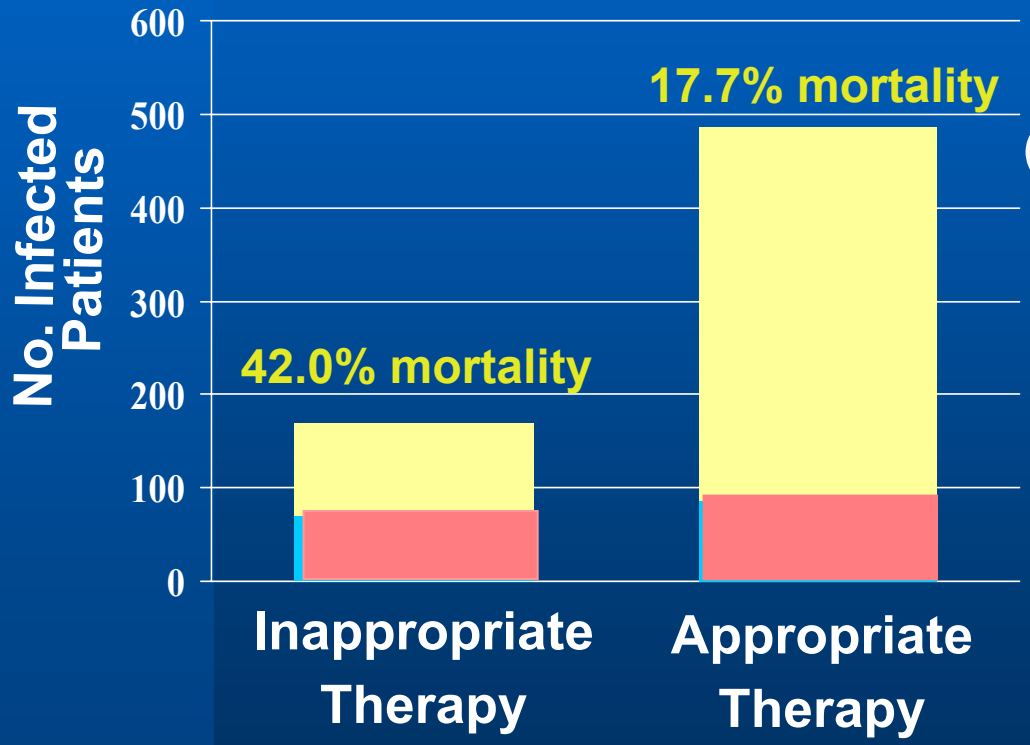


Inappropriate Antimicrobial Therapy
(n = 655 ICU patients with infection)

- Community-acquired infection
- Hospital-acquired infection
- Hospital-acquired infection after initial community-acquired infection

Kollef et al
Chest 1999

Inappropriate Antimicrobial Therapy: Impact on Mortality



Relative Risk = 2.37
(95% C.I. 1.83-3.08; *P* < .001)

Survivors

Deaths

Kollef et al
Chest 1999

COMPARISON OF OUTCOMES ACCORDING TO APPROPRIATENESS OF EMPIRIC ANTIBIOTICS

Retrospective Study (n = 480)

REGIMEN	N	MORBIDITY	MORTALITY
Excessive	77	29.9%	6.5%
Adequate	180	18.9%	5.6%
Inadequate	49	51.0%	12.2%
Non-classifiable	170	14.1%	4.7%

Conclusion: Inadequate empiric antibiotic therapy was associated with poor outcome

Mosdell et al
Ann Surg 1991

COMPARISON OF OUTCOMES ACCORDING TO CHANGES IN REGIMEN

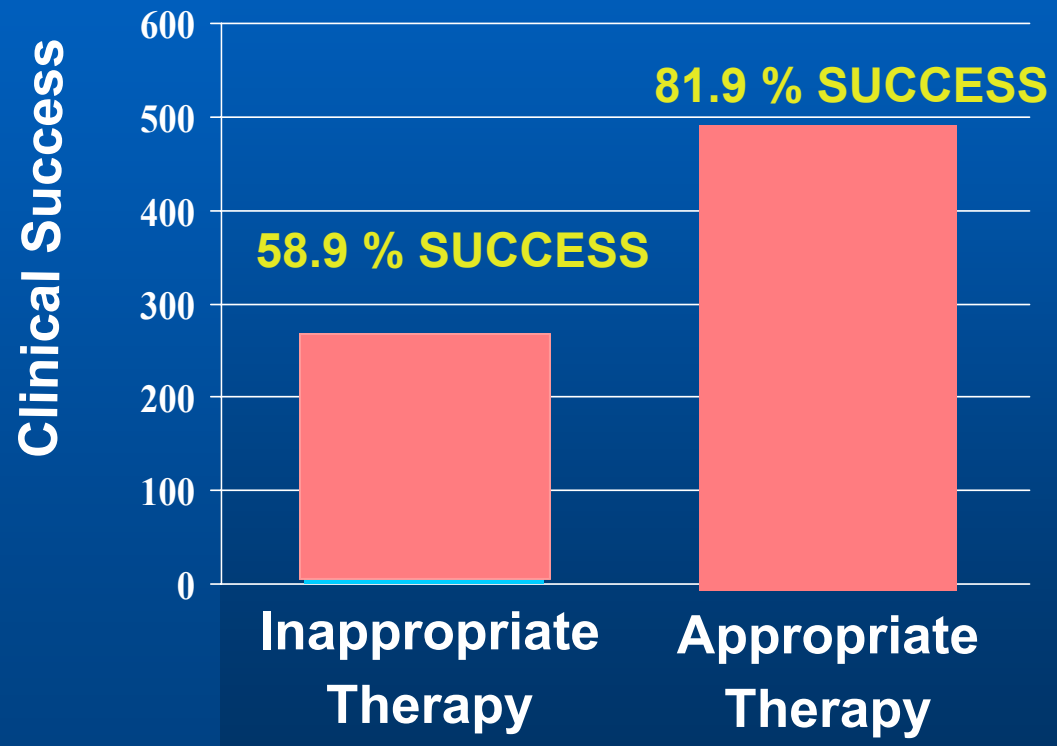
Retrospective Study (n = 480)

	INAPPROPRIATE/ NO CHANGE	APPROPRIATE CHANGE	SIGNIFICANCE
Number	36	13	NS
Length of stay	18.8	17.7	NS
Incisional SSI	31%	15%	NS
Abscess	33%	23%	NS
Re-operation	42%	23%	NS
Total complications	44%	31%	NS
Mortality	8%	23%	NS

Conclusion: Adjusting antibiotic choice based on culture data does not significantly improve outcome

Mosdell et al
Ann Surg 1991

INAPPROPRIATE ANTIMICROBIAL THERAPY: IMPACT ON CLINICAL SUCCESS



Davey 2001

Retrospective study (n =175)

OUTCOME	N	SENSITIVE ISOLATES	RESISTANT ISOLATES
Resolved infection	131	66 %	44 %
Post-op complication	44	18 %	82 %

- resistant organisms may contribute to development of postoperative infection
- significant number cured despite presence of resistant organisms

Hopkins et al
Ann Surg 1993

Prevalence of Antimicrobial-Resistant (R) Pathogens Causing Hospital-Acquired Intensive Care Unit Infections: 1999 versus 1994-1998

Organism	# Isolates	% Increase*
Fluoroquinolone-R *Pseudomonas* spp.	2,657	49%
3rd generation cephalosporin-R *E. coli*	1,551	48%
Methicillin-R *Staphylococcus aureus*	2,546	40%
Vancomycin-R enterococci	4,744	40%
Imipenem-R *Pseudomonas* spp.	1,839	20%

* Percent increase in proportion of pathogens resistant to indicated antimicrobial

Source: National Nosocomial Infections Surveillance (NNIS) System

Diagnose and Treat Infection Effectively

Target the pathogen

Fact:

Appropriate antimicrobial therapy

(correct regimen, timing, dosage, route, and duration) saves lives.

Goals of Antimicrobial Therapy

1. Eliminate infecting microorganisms
2. Decrease the likelihood of recurrence
3. Shorten the time to resolution of signs and symptoms of infection
4. Prevent antimicrobial resistance

Antimicrobial Therapy

APPROPRIATE SELECTION

1) In-vitro data
2) Experience in animal models
3) Efficacy in RCTs
4) Pharmacokinetic properties
5) Safety profile
6) Cost

Regimens for treatment of IAI subjected to RCTs

SINGLE AGENTS

B-lactam/B-lactamase inhibitors

Ampicillin/sulbactam

Piperacillin/tazobactam

Ticarcillin/clavulanic acid

Carbapenems

Ertapenem

Imipenem/cilastatin

Meropenem

Cephalosporins

Cefotetan

Cefoxitin

COMBINATION REGIMENS

Aminoglycoside-based

Gentamicin, Tobramycin, Netilmycin or Amikacin plus anti-anaerobe

Cephalosporin-based

Cefuroxime plus Metronidazole

Ceftriaxone, Cefotaxime, or Cefepime plus Metronidazole

Fluoroquinolone-based

Ciprofloxacin plus Metronidazole

Solomkin et al
CID 2003

Randomized Prospective Trials in Community - Acquired IAI

Clinical Trial	N	No. evaluable	% Clinical Cure	% Bacteriologic Cure
AMPI-SULBACTAM	194	96	87%	85%
VS CEFOXITIN (Walker 1993)	191	101	78%	83%
AMPI-SULBACTAM	67	(NS)	88%	(NS)
VS.GENTA/CLINDA (Yellin 1985)	90	(NS)	98%	(NS)

CLINICAL SUCCESS RATES REVIEW OF 79 RCTs ON IAI

			CLIN SUCCESS
Ampicillin-sulbactam	2	163	87 %
Cefoxitin	6	389	88 %
Moxalactam	5	316	83 %
Cefotetan	5	395	92 %
Piperacillin-tazobactam	5	430	90 %
Imipenem-cilastatin	23	1,637	85 %
Meropenem	10	657	89 %
Cefotaxime + Metronidazole	4	236	87 %
Aztreonam + Clindamycin	5	241	89 %
Gentamicin + Clindamycin	21	1,517	80 %
Tobramycin + Clindamycin	12	561	83 %

Holzheimer et al
Eur J Med Research 2001

Antimicrobial Therapy of Intra-Abdominal Infections

Systematic Review of 79 RCTs

Clinical success rates for best-studied antibiotics is similar

Antibiotic use depends on the expected pathogens and resistance rate in clinical setting

Holzheimer et al
Eur J Med Research 2001

Antimicrobial Therapy

- stratify antimicrobial use into two levels of therapeutic intensity
- selection based primarily on patient factors and local resistance patterns

Agents Recommended for Mild-Moderate Infections

SINGLE AGENTS

B-lactam/B-lactamase inhibitor	Ampicillin-sulbactam Ticarcillin-clavulanic acid
Carbapenems	Ertapenem

COMBINATION REGIMENS

Cephalosporin-based	Cefazolin or Cefuroxime plus Metronidazole
Fluoroquinolone-based	Ciprofloxacin, Levofloxacin, Moxifloxacin or Gatifloxacin, plus Metronidazole

Solomkin et al
CID 2003

Antimicrobial Sensitivities

	FACULTATIVE AEROBES			OBLIGATE ANAEROBES		
		Gm(+) cocci				
	Gm(-)B	Entero-cocci	Other Strep	Gm(-)B	Gm(+)B	Gm(+)C
Cefoxitin	++	0	++	++	+++	+++
Ampi-Sulb	++	+++	+++	+++	+++	+++
Ticar-Clav	++	++	+++	+++	+++	+++
Ertapenem	+++	+	+++	+++	+++	+++

Incl Cefotetan and Cefmetazole

Bohnen et al
Arch Surg 1992

Agents Recommended for High-severity Infections

SINGLE AGENTS

B-lactam/B-lactamase inhibitor	Piperacillin/Tazobactam
Carbapenems	Imipenem/cilastatin
	Meropenem

COMBINATION REGIMENS

Cephalosporin-based	3rd/4th gen Cephalosporin plus Metronidazole
Fluoroquinolone-based	Ciprofloxacin plus Metronidazole
Monobactam-based	Aztreonam plus Metronidazole

Solomkin et al
CID 2003

Antimicrobial Sensitivities

	FACULTATIVE AEROBES			OBLIGATE ANAEROBES		
		Gram(+) cocci				
	Gm(-)B	Entero cocci	Other Strep	Gm(-)B	Gm(+)B	Gm(+)C
Aminoglycosides	+++	0	0	0	0	0
Aztreonam	+++	0	0	0	0	0
3rd/4th Gen Ceph	+++	0	++	+	++	+++
Ciprofloxacin	+++	+	++	0	0	0
Metronidazole	0	0	0	+++	+++	+++
Clindamycin	0	0	++	+++	+++	+++

Incl Gentamicin, Tobramycin, Netilmycin,Amikacin
Incl. CefotaximeCeftriaxone, Ceftazidime, Cefoperazone, Ceftizoxime

Bohnen et al
Arch Surg 1992

Antimicrobial Sensitivities

	FACULTATIVE AEROBES			OBLIGATE ANAEROBES		
		Gram (+) cocci				
	Gm(-)B	Entero cocci	Other Strep	Gm(-)B	Gm(+)B	Gm(+)C
Imipenem	+++	++	+++	+++	+++	+++
Meropenem	+++	++	+++	+++	+++	+++
Pip-Tazo	+++	+++	+++	+++	+++	+++

Bohnen et al
Arch Surg 1992

EBCPG on Treatment of Acute Appendicitis

PROPHYLAXIS FOR UNCOMPLICATED APPENDICITIS

- Ampicillin – sulbactam
- Amoxicillin - clavulanate
- Cefoxitin
- Gentamicin plus Clindamycin

LEVEL I EVIDENCE
CATEGORY A RECOMMENDATION

Phil. College of Surgeons
Comm. on Surg Infxns 2003

EBCPG on Treatment of Acute Appendicitis

TREATMENT OF COMPLICATED APPENDICITIS

A. Adults

- Ertapenem
- Piperacillin - Tazobactam
- Ciprofloxacin plus Metronidazole

B. Pediatric Patients

- Ticarcillin - Clavulanate
- Imipenem - Cilastatin
- Gentamicin plus Clindamycin

LEVEL I EVIDENCE
CATEGORY A RECOMMENDATION

Phil. College of Surgeons
Comm. on Surg Infxns 2003

EBCPG on Treatment of Cholecystitis

A. **UNCOMPLICATED ACUTE CHOLECYSTITIS**

- Cefazolin
- Cefuroxime
- Cefoxitin
- Fluoroquinolone +/- Metronidazole

B. **COMPLICATED ACUTE CHOLECYSTITIS**

- Beta-lactam/ Beta-lactamase inhibitors – Ampicillin/Sulbactam
- Cefoxitin
- Ertapenem
- Fluoroquinolone plus Metronidazole

LEVEL I EVIDENCE
CATEGORY A RECOMMENDATION

Phil. College of Surgeons
Comm on Surg Infxns 2003

Duration of Antimicrobial Therapy

- Establish duration of therapy at outset based on intra-operative findings and immuno-competence of the patient
- prophylactic or preemptive vs. treatment

Duration of Antimicrobial Therapy

A. **RESECTABLE SOURCE OF INFECTION SURROUNDED BY LOW-GRADE PERITONEAL INFECTION**

acute appendicitis (A-1)

acute cholecystitis (B-2)

gastroduodenal perforation < 24 hrs duration (B-2)

traumatic enteric perforation < 12 hrs duration (A-1)

intestinal infarction without perforation (A-1)

Management:

Short-course of antibiotics ≤ 24 hours

Solomkin et. al.
CID 2003

Duration of Antimicrobial Therapy

B. **ESTABLISHED INTRA-PERITONEAL INFECTION**

-pre-determined duration based on intra-operative findings and patient's immunocompetence

Management: 5 day course

C. **SOURCE OF PERITONEAL INFECTION CANNOT BE COMPLETELY RESECTED NOR DEBRIDED**

PROLONGED PERITONEAL TOILET NECESSARY WITH RE-EXPLORATION

Management: prolonged course of antibiotics

Duration of Antimicrobial Therapy

Retrospective Study (n = 157)

- Gentamicin/Fosfomycin plus Metronidazole for 5 days

	N	CLINICAL SUCCESS
Perforated Appendicitis	53	94 %
Gastroduodenal Perforation	17	88 %
Small Bowel Necrosis	3	100 %
Peritonitis (any source)	84	93 %

Andaker 1987

Duration of Antimicrobial Therapy

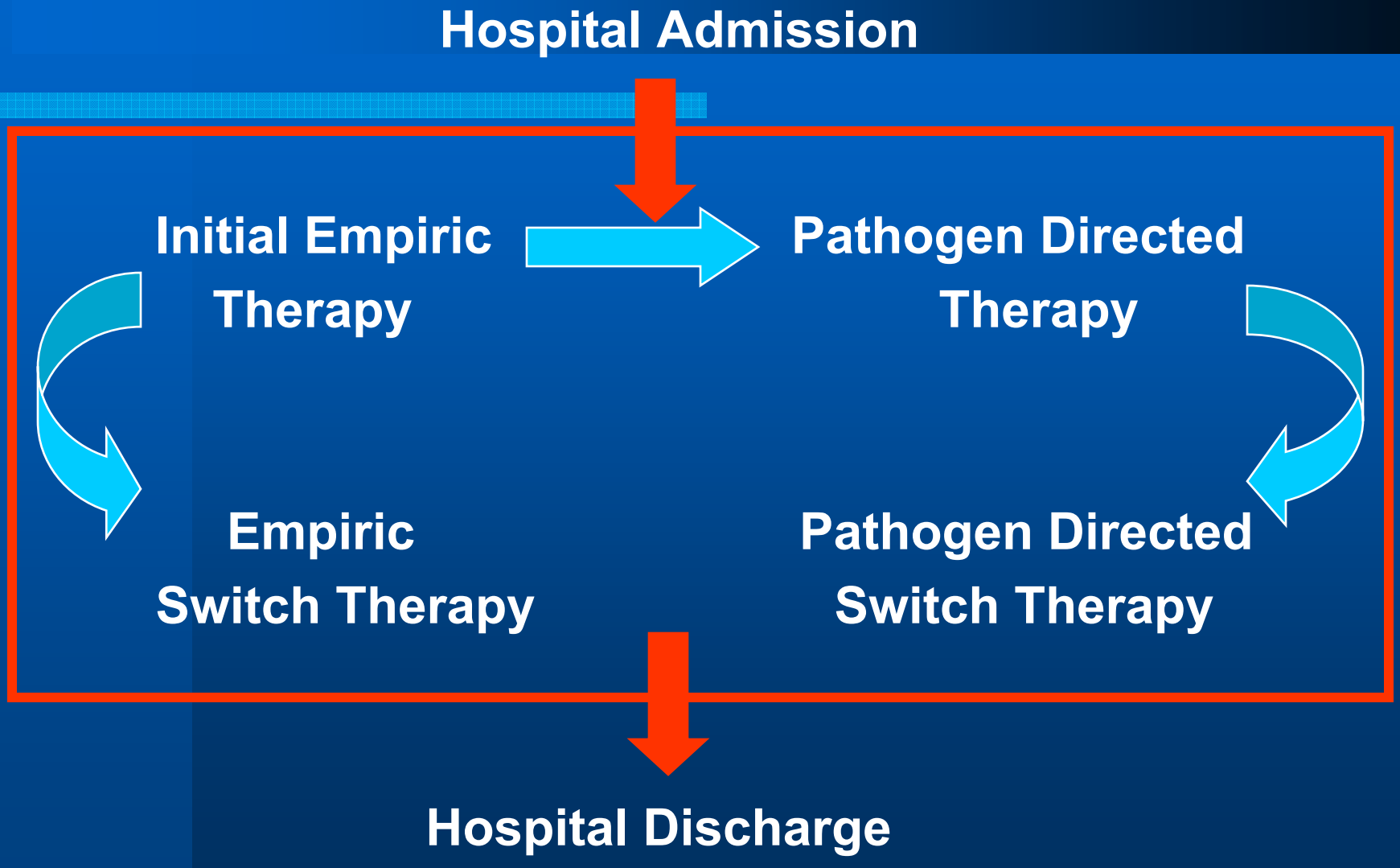
(n = 71)

- Ampicillin + Gentamicin + Metronidazole
- Ceftriaxone + Metronidazole

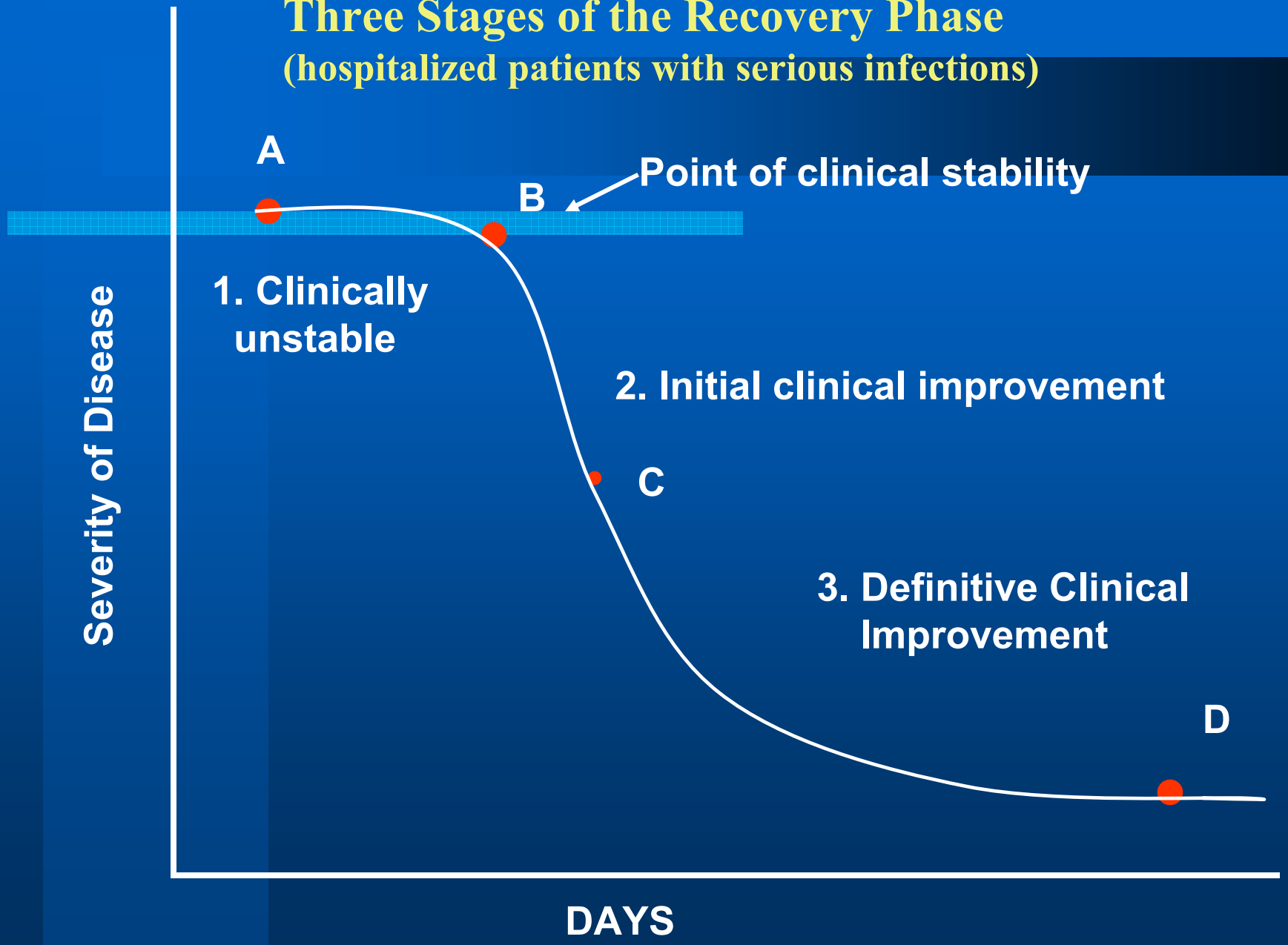
	LOCALIZED PERITONITIS	GENERALIZED PERITONITIS
Duration of Treatment	2 days	3 - 5 days
Clinical Success Rates	88 %	83 %
Mortality Rates	2 %	4 %

Schein 1994

Selection of oral antibiotics for Switch Therapy



Three Stages of the Recovery Phase
(hospitalized patients with serious infections)

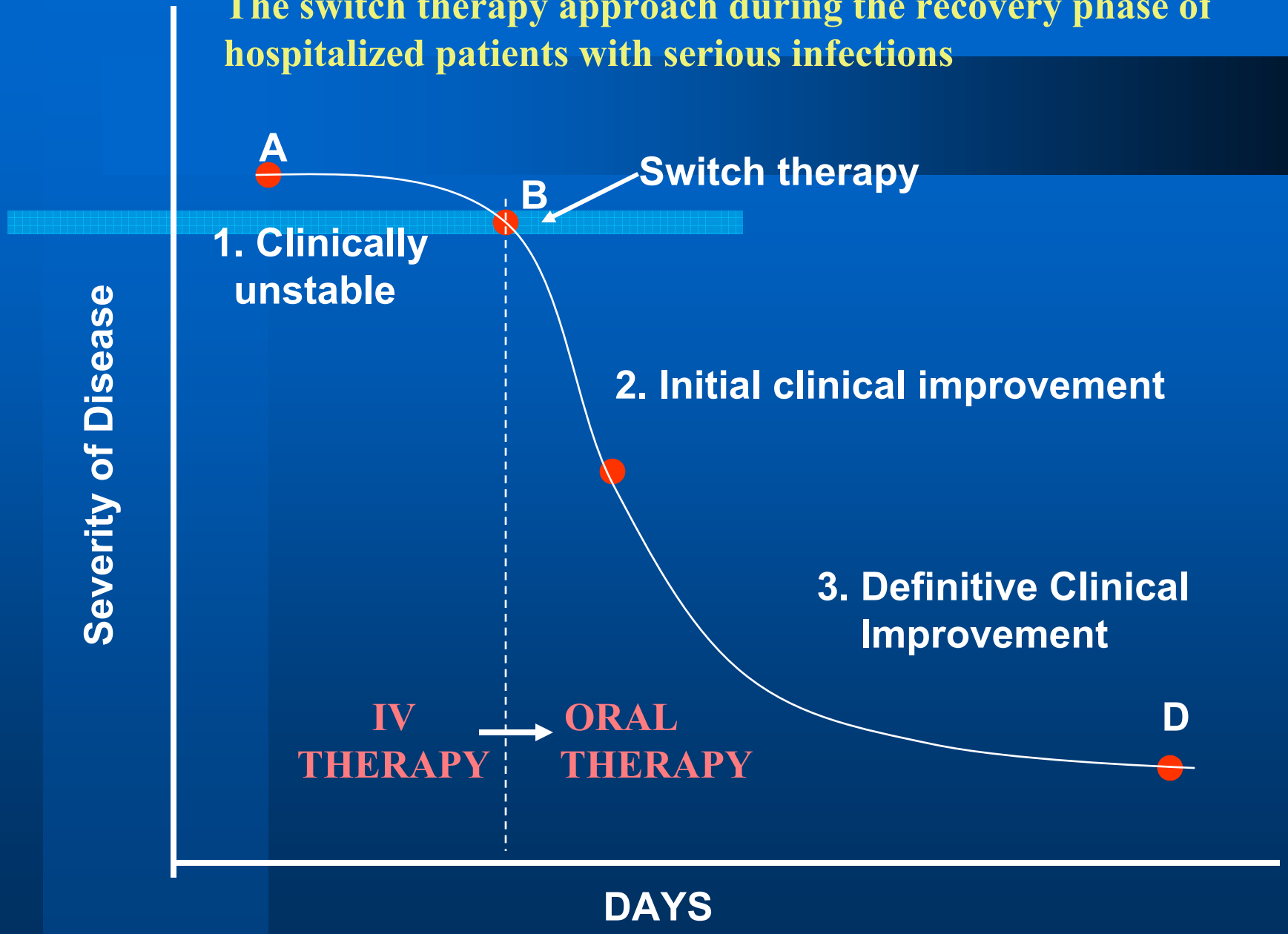


Switch Therapy from Intravenous to Oral Route

CRITERIA FOR CLINICAL STABILITY

- Subjective and objective evidence of improvement from the local inflammatory response produced by the infection
- Afebrile for at least 8 hours
- WBC should trend towards normal value
- Adequate oral intake and gastrointestinal absorption

The switch therapy approach during the recovery phase of hospitalized patients with serious infections



UNASYN IM/IV (Ampicillin-sulbactam)

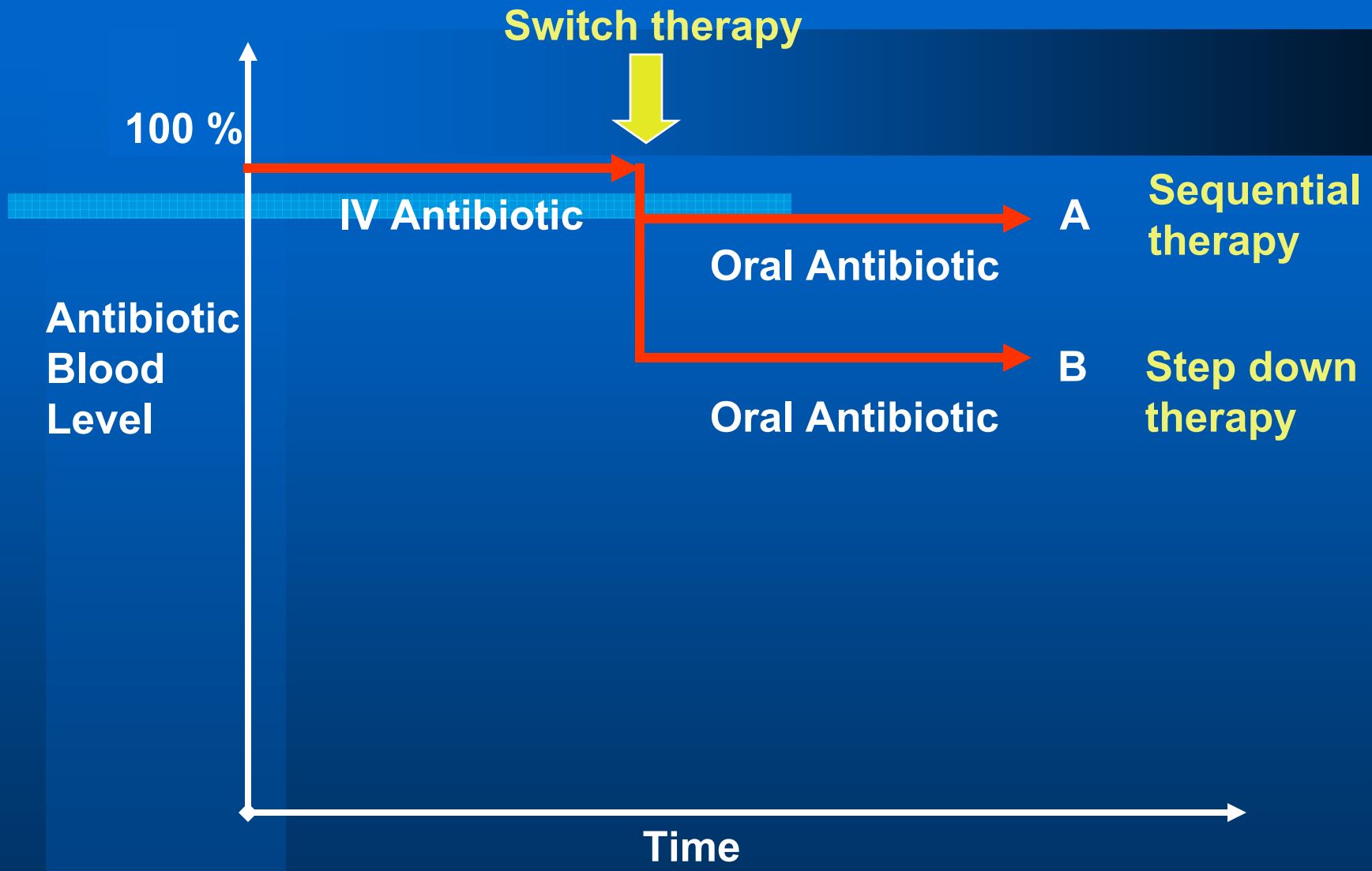
(750 mg, 1.5 g, 3.0 g)

- Twice daily, thrice daily, or four times daily dosing (IV/IM)

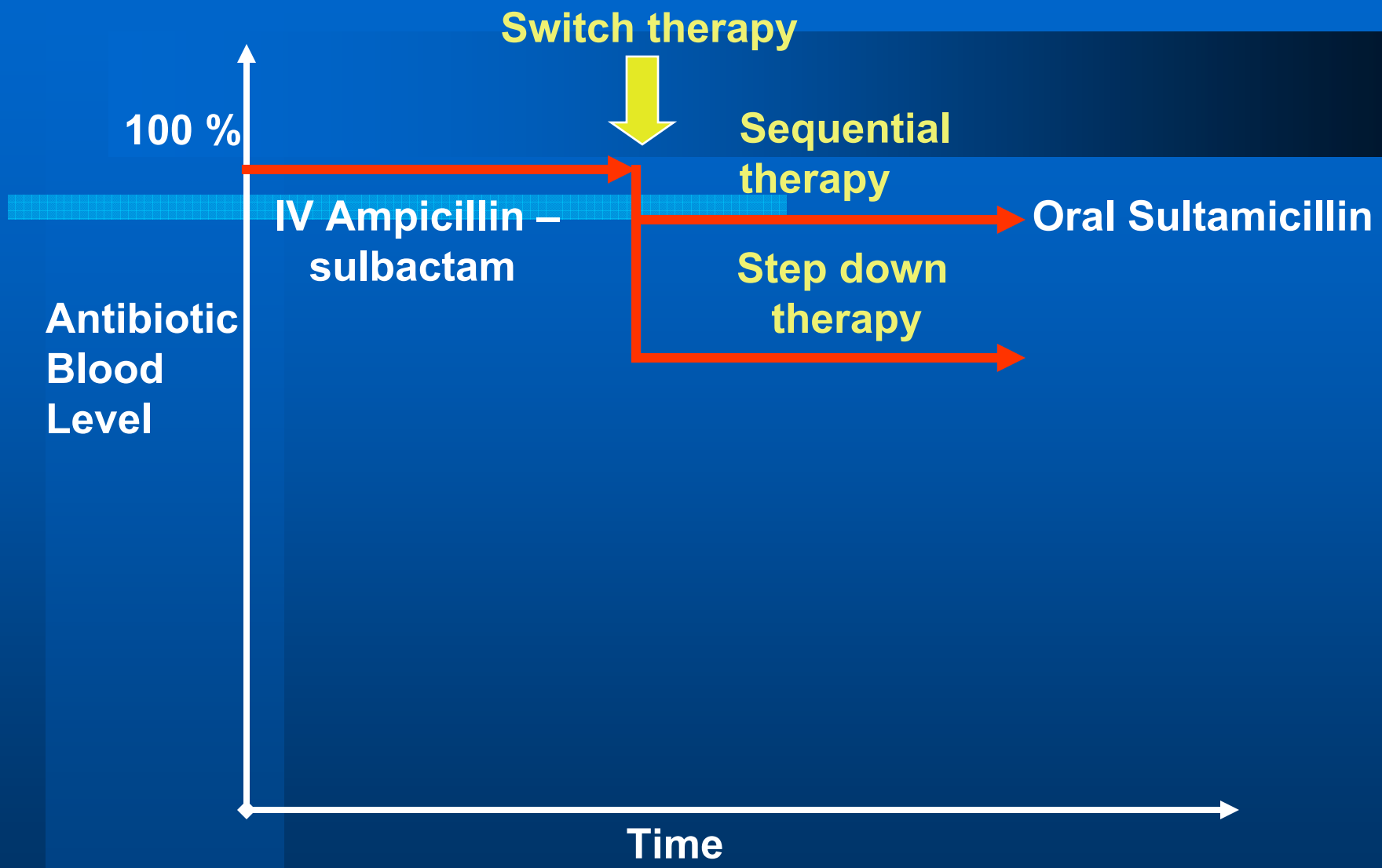
Combination of Ampicillin and Sulbactam

Ampicillin – broad antimicrobial spectrum

Sulbactam – broad spectrum B-lactamase inhibition



CLASSIFICATION OF ORAL ANTIBIOTICS FOR SWITCH THERAPY (based on bioavailability)



CLASSIFICATION OF ORAL ANTIBIOTICS FOR SWITCH THERAPY (based on bioavailability)

UNASYN IM/IV (Ampicillin-sulbactam)

(750 mg, 1.5 g, 3.0 g)

- Twice daily, thrice daily, or four times daily dosing (IV/IM)

SEQUENTIAL THERAPY

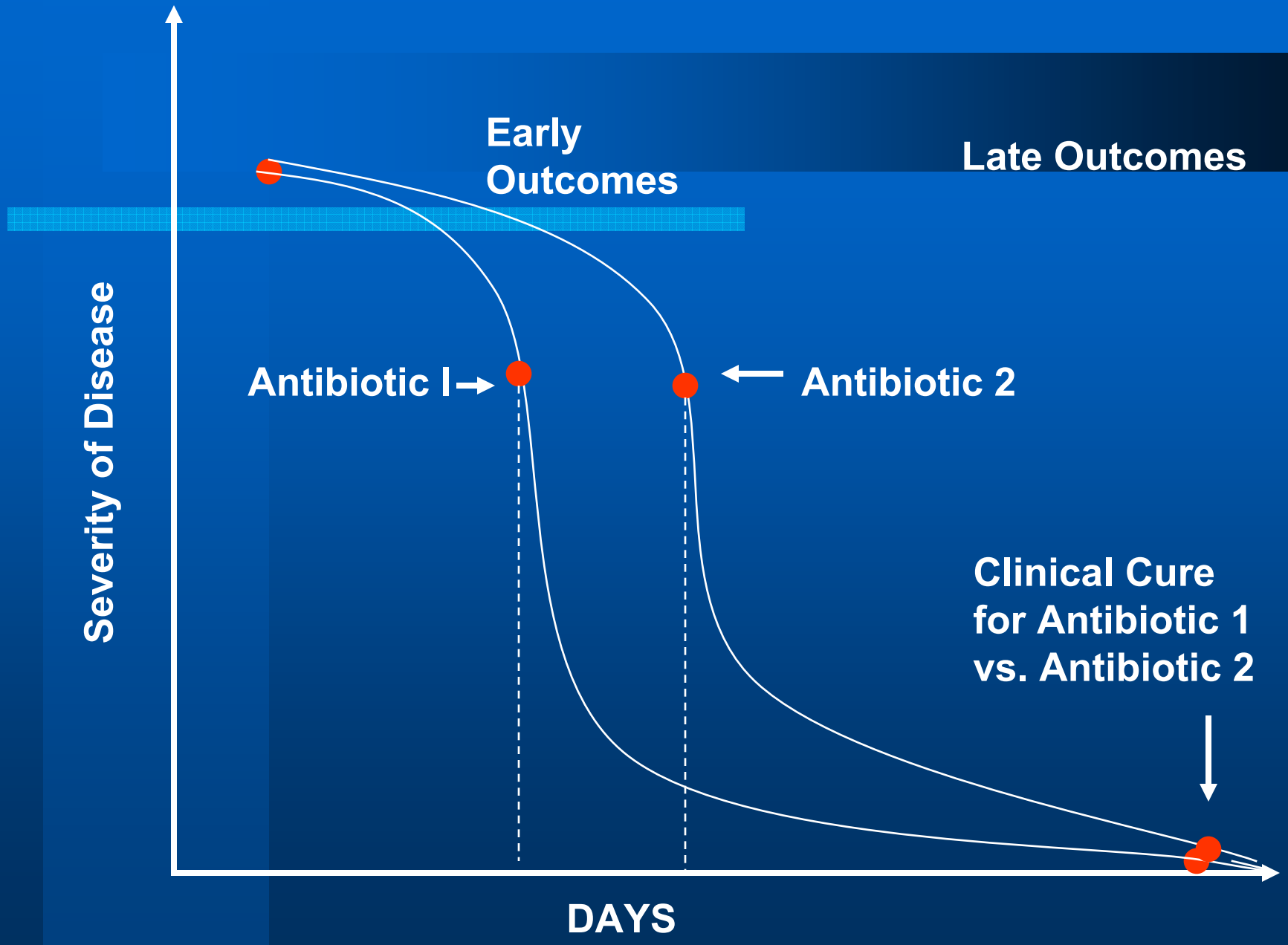
UNASYN Oral (Sultamicillin)

(750 mg and 375 mg tablet

250 mg/ 5 ml pediatric oral suspension)

- Twice daily dosing (oral)

EARLY AND LATE OUTCOMES OF SERIOUS INFECTIONS



Switch Therapy from Intravenous to Oral Route

RCT (n=459)

		CLINICAL RESOLUTION		
	N	OVER-ALL	SEQUENTIAL TX	SSI
PIP-TAZO	57	63%	70%	19%
CIPRO/METRO	64	74%	85%	11%

Consider sequential oral therapy when GI function has returned

Cohn et. al.
Ann Surg 2000

Switch Therapy from Intravenous to Oral Route

	N	CIP/MTZ IV	CIP/MTZ IV/PO	IMI IV
INTENT-TO-TREAT	671	82%	84%	82%
BACT CURE	330	84%	86%	81%

Consider sequential oral therapy when GI function has returned

Solomkin et. al.
Ann Surg 1996

Duration of Antimicrobial Therapy

Prospective study (n = 65)

- afebrile & clinically well at conclusion of therapy

WBC COUNT	N	INTRA-AB INFXN	NOSOCOMIAL INFXN
≤ 10,000	30	0 (0%)	4 (13%)
> 10,000	21	7 (33%)	2 (10%)

Lennard et al
Ann Surg 1983

Duration of Antimicrobial Therapy

CLINICAL CRITERIA TO DETERMINE LENGTH OF THERAPY

Review of 11 prospective trials (n=2,567)

TEMPERATURE (37.5 ± 0.5^0C)	+	+	+
LEUKOCYTE COUNT ($8,500 \pm 2,500/mm^3$)	NC	+	+
BANDS $\leq$ 3%	NC	NC	+
RISK OF RECURRENCE	19%	3%	0%

Stone et al
Arch Surg 1985

Duration of Antimicrobial Therapy

RCT (n=33)

PARAMETERS FOR DISCONTINUING ANTIBIOTICS

- afebrile for 24 hours
- ability to tolerate oral intake
- normal WBC count with ≤ 3% band forms

Predictive Value of Criteria : 97%

PredictIve Value of Criterion Mismatch : 100%

Hoelzer et al
Arch Surg 1999

Special Pathogens

ROLE OF ENTEROCOCCUS

- recovered in 10-20% of cases

  Enterococcus faecalis - 90 %

  Enterococcus faecium -10%

- animal studies failed to define any role in intra-abdominal sepsis

Special Pathogens

ROLE OF ENTEROCOCCUS

6 RCTs using antibiotics not active against Enterococci

- isolation rate in primary cultures : 14-33%
- no treatment failure due to Enterococci

Gorbach et al
CID 1993

Special Pathogens

- specific therapy for enterococcus is currently not recommended for most immune competent patients with community-acquired IAI

- RCT needed to determine whether outcomes can be improved by treatment of high-risk patients or of all patients with IAI

Teppler et al
Surg Infxn 2002

Special Pathogens

Pseudomonas aeruginosa

- isolation rate : 9-25%
- studies showed that neither an aminoglycoside nor a drug with activity against Pseudomonas is necessary in community-acquired IAI
- prudent to add coverage if with positive culture especially if patient's course is complicated

Prototypical Outcomes of Acute Peritonitis

1. Resolution of peritonitis
2. Fulminant course leading to septic response
3. Development of intra-abdominal abscess

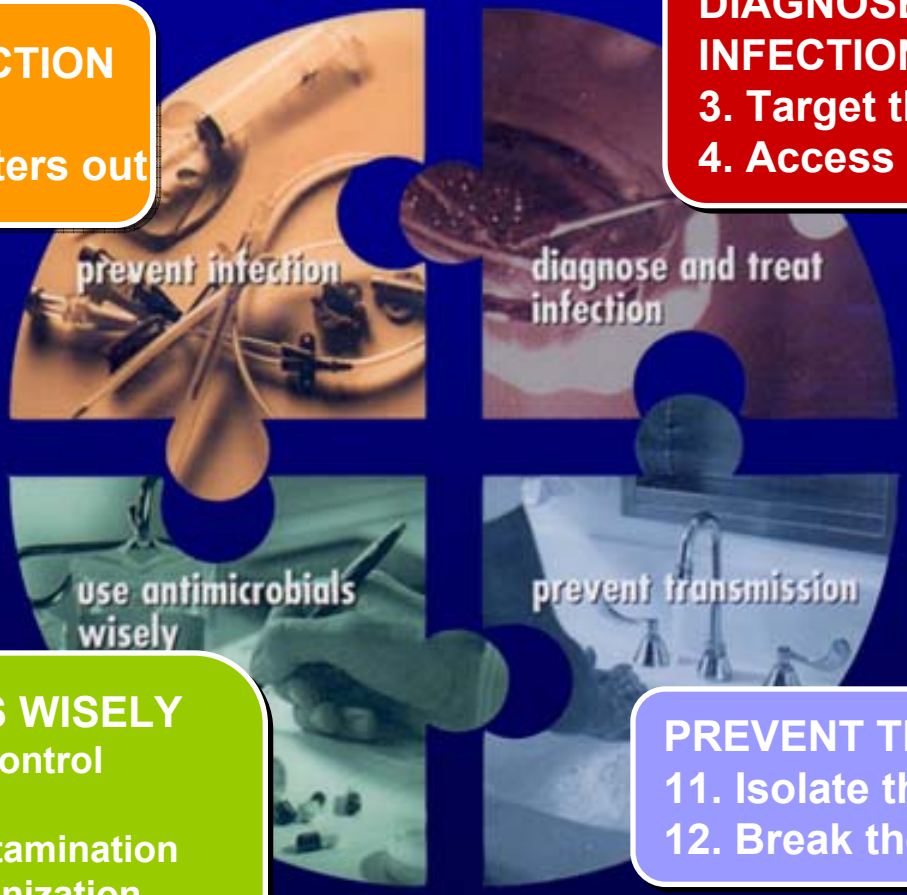
12 Steps to Prevent Antimicrobial Resistance

- **Targeted intervention programs for clinicians caring for high- risk patients**
  - *hospitalized adults*
  - *hospitalized children*
  - *geriatric patients*
  - *emergency patients*
  - *obstetrical patients*
  - *critical care patients*
  - *dialysis patients*
  - *surgical patients*
- **Goal: Improve clinician practices and prevent antimicrobial resistance**
- **Partnership with professional societies; evidence base published in peer-reviewed specialty journals**
- **Educational tools – Web-based/didactic learning modules, pocket cards, slide presentations, etc**

12 Steps to Prevent Antimicrobial Resistance in Hospitalized Adults

PREVENT INFECTION
1. Vaccinate
2. Get the catheters out

DIAGNOSE AND TREAT INFECTION EFFECTIVELY
3. Target the pathogen
4. Access the experts



USE ANTIMICROBIALS WISELY
5. Practice antimicrobial control
6. Use local data
7. Treat infection, not contamination
8. Treat infection, not colonization
9. Know when to say “no” to vanco
10. Stop treatment when infection is cured or unlikely

PREVENT TRANSMISSION
11. Isolate the pathogen
12. Break the chain of contagion

CDC. Drug Resistance/Healthcare Web site.

Ideally, a properly managed intra-abdominal infection will result in

- 1. Reduced mortality
- 2. Decreased need for re-operation and second line therapy
- 3. Reduced duration of intravenous antibiotic therapy
- 4. Shorter hospital stay
- 5. Lower cost of treatment

DIAGNOSE AND TREAT INFECTION EFFECTIVELY

- Target the pathogen

USE ANTIMICROBIALS WISELY

- Use local data
- Treat infection, not contamination
- Stop treatment when infection is cured or unlikely

Surgeons hold the solution!

" Bacteriology has revolutionized surgical pathology. All wound complications and most inflammatory lesions which come under the treatment of the surgeon are caused by microorganisms; hence the necessity of proper **recognition of the importance of bacteriology as an integral part of the science and practice of modern surgery**."

Nicholas Senn (Surgical Bacteriology, 1889)
-first American textbook solely on bacteriology

Thank You