Multidrug resistance
We can use narrow-spectrum antibiotics in critical care.

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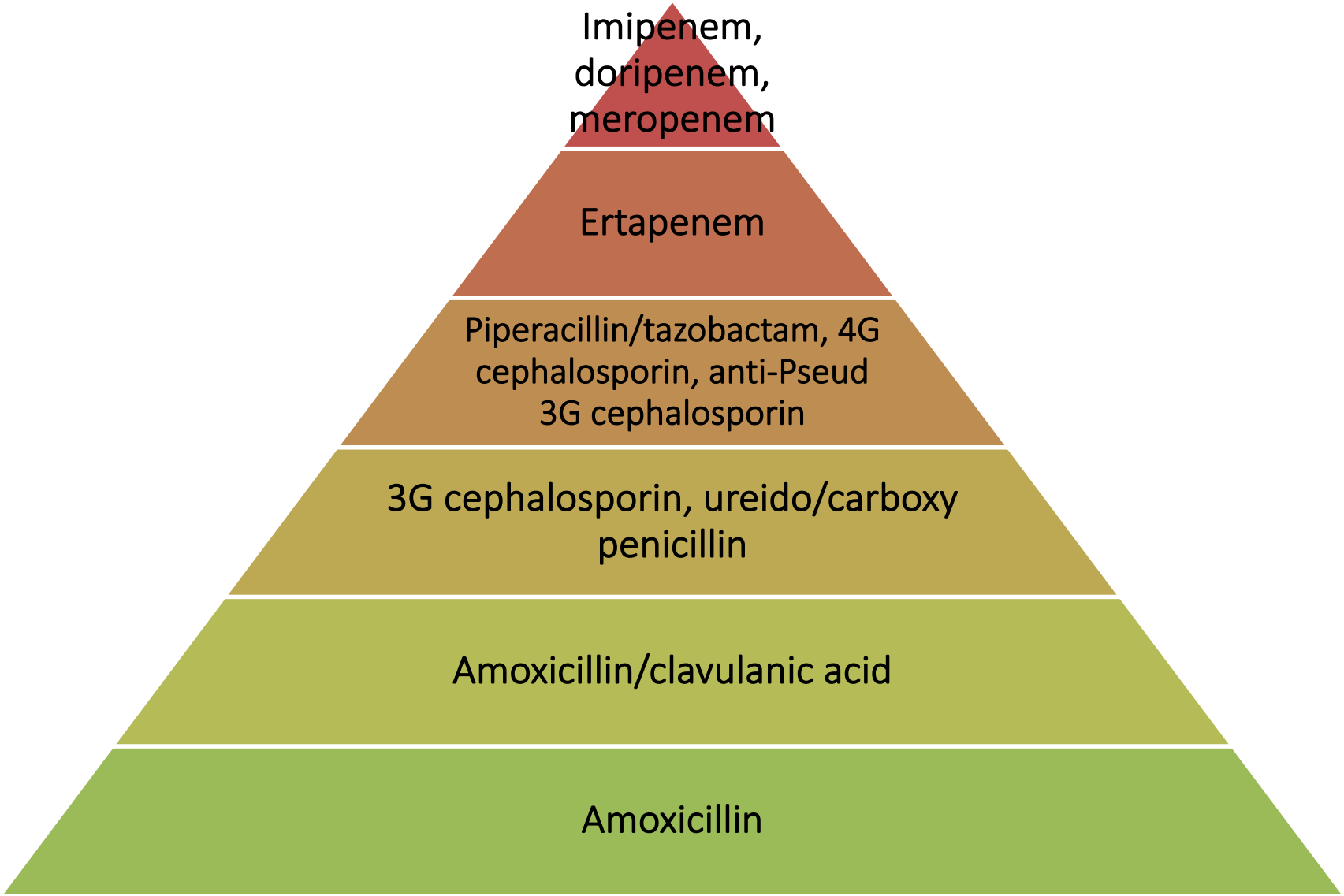
Defining narrow spectrum antibiotics

- Gram-positive or Gram-negative only
- Ecological impact

- No consensus
- Depends on setting
- Ranking most often within classes of antibiotics

Ranking antibiotics



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Weiss, E. Clin Microbiol Infect 2015 7:649.e1-10

Conventional wisdom

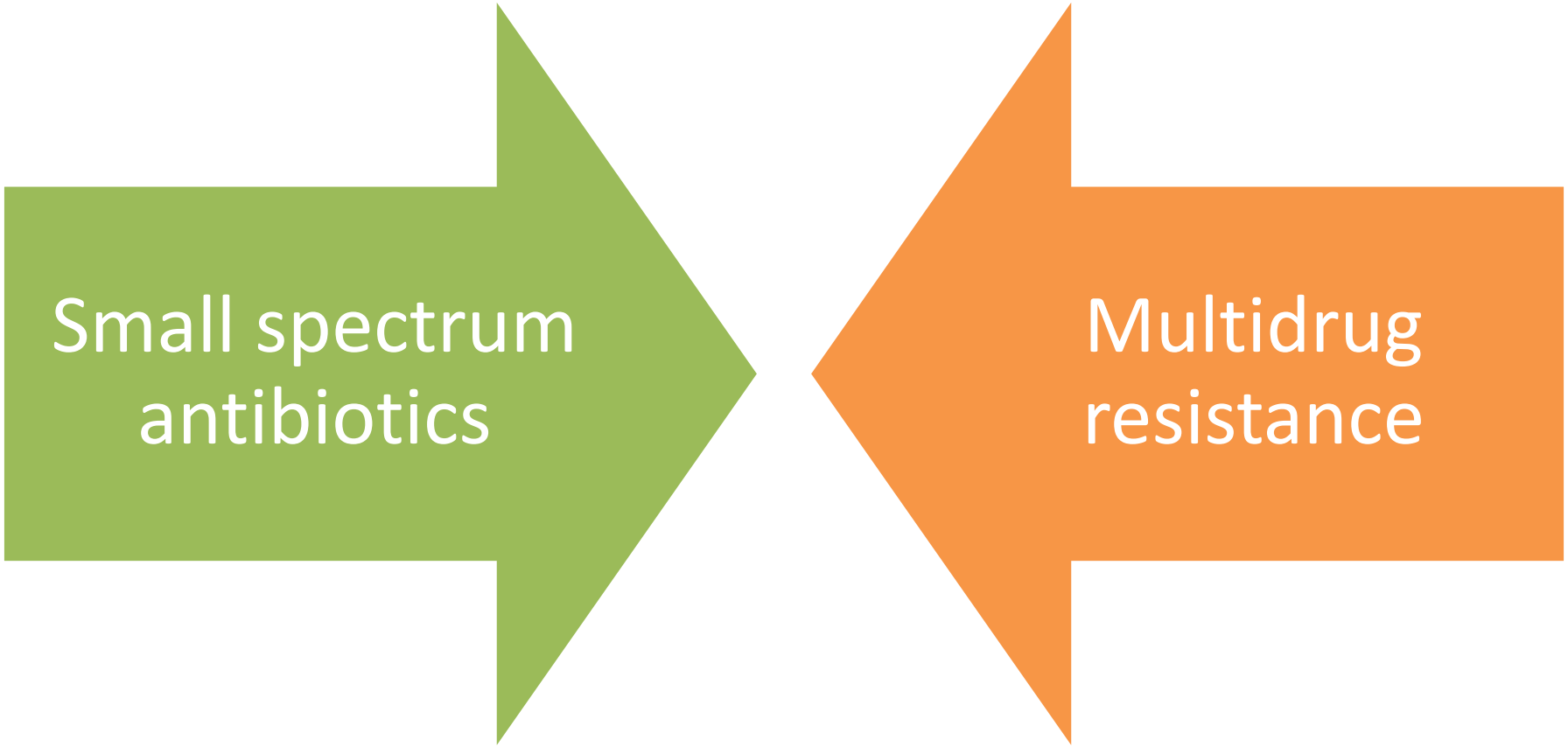

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Table 3. Factors Associated With Antimicrobial De-escalation

Factors Associated With ADE
Positively associated
Initially appropriate empiric antimicrobial therapy
Broad-spectrum empiric therapy
Compliance with national prescribing guidelines
Treatment with multiple and "companion" antimicrobials
Positive microbiological cultures
Lower severity of illness scores at
Baseline
Time of ADE
Day 5 of therapy
Negatively associated
Isolation of a multiresistant pathogen
Polymicrobial infections
Intra-abdominal infections

Tabah, A. Clin Infect Dis 2016 8:1009-1017

Indications – empirical therapy

Limited use of narrow-spectrum antibiotics

- Driven by local ecology
- Community acquired infections
- Early-onset HAP and cIAI

- Impact of rapid diagnostics may facilitate role of narrow spectrum antibiotics

Indications – directed therapy

Certainly an option in MDR

- Antibiotic de-escalation
  - Changing the backbone antibiotic
- Guided by susceptibility testing
- MDR infections do not necessarily require multiple antibiotics

Indications – antibiotic de-escalation

1: : Escherichia coli +-

	1
Amoxicilline	R
Amoxy-clavulaanzuur	S
Cotrimoxazol	R
Cefuroxim (IV)	R
Tobramycine	S
Temocilline	S
Ofloxacine/levofloxacine	S
Amikacine	S
Piperacilline/tazobactam	S
Cefotaxim/ceftriaxone	R
Ceftazidime	R
Meropenem	S
ESBL	R

1: : Klebsiella pneumoniae +++
2: : Escherichia coli ++

	1	2
Amoxicilline	R	R
Amoxicilline-clavulaanzuur	R	R
Cotrimoxazol	S	S
Cefuroxim (IV)	R	R
Tobramycine	R	R
Temocilline	S	S
Fosfomycine	R	
Ofloxacine/levofloxacine	R	R
Amikacine	S	S
Piperacilline/tazobactam	R	R
Cefotaxim/ceftriaxone	R	S
Ceftazidime	R	S
Meropenem	S	S
Tigecycline	R	

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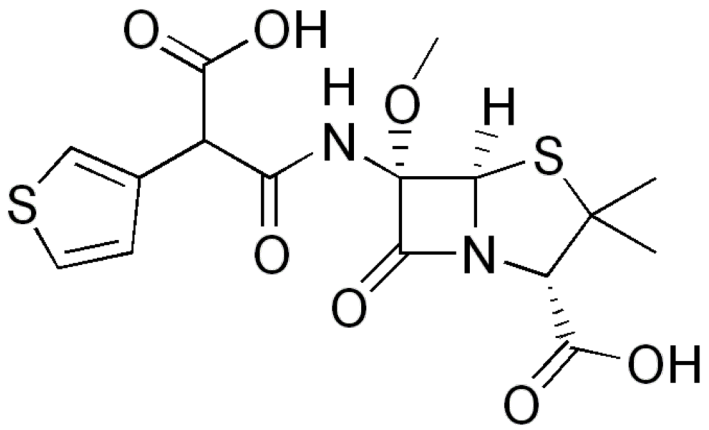
Temocillin

- Active against many ESBL and derepressed ampC cefalosporinase producing Enterobacteraceae
- Limited availability
- Licensed for UTI, sepsis and LRTI
- Up to MIC 8 – up to 6g/24h
- Clinical experience limited
  - Cure rates >80% for LRTI and cIAI
- KPC?



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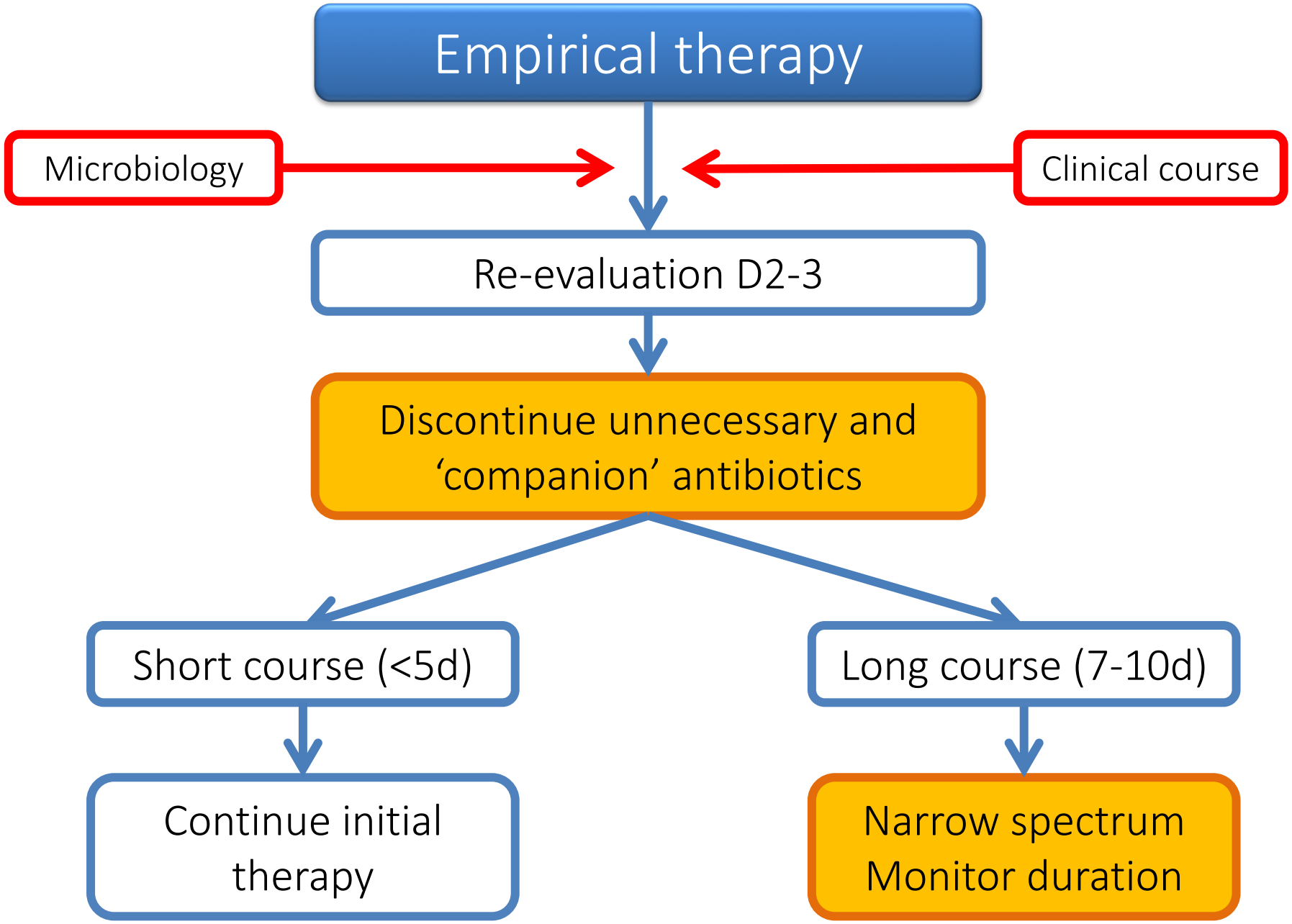
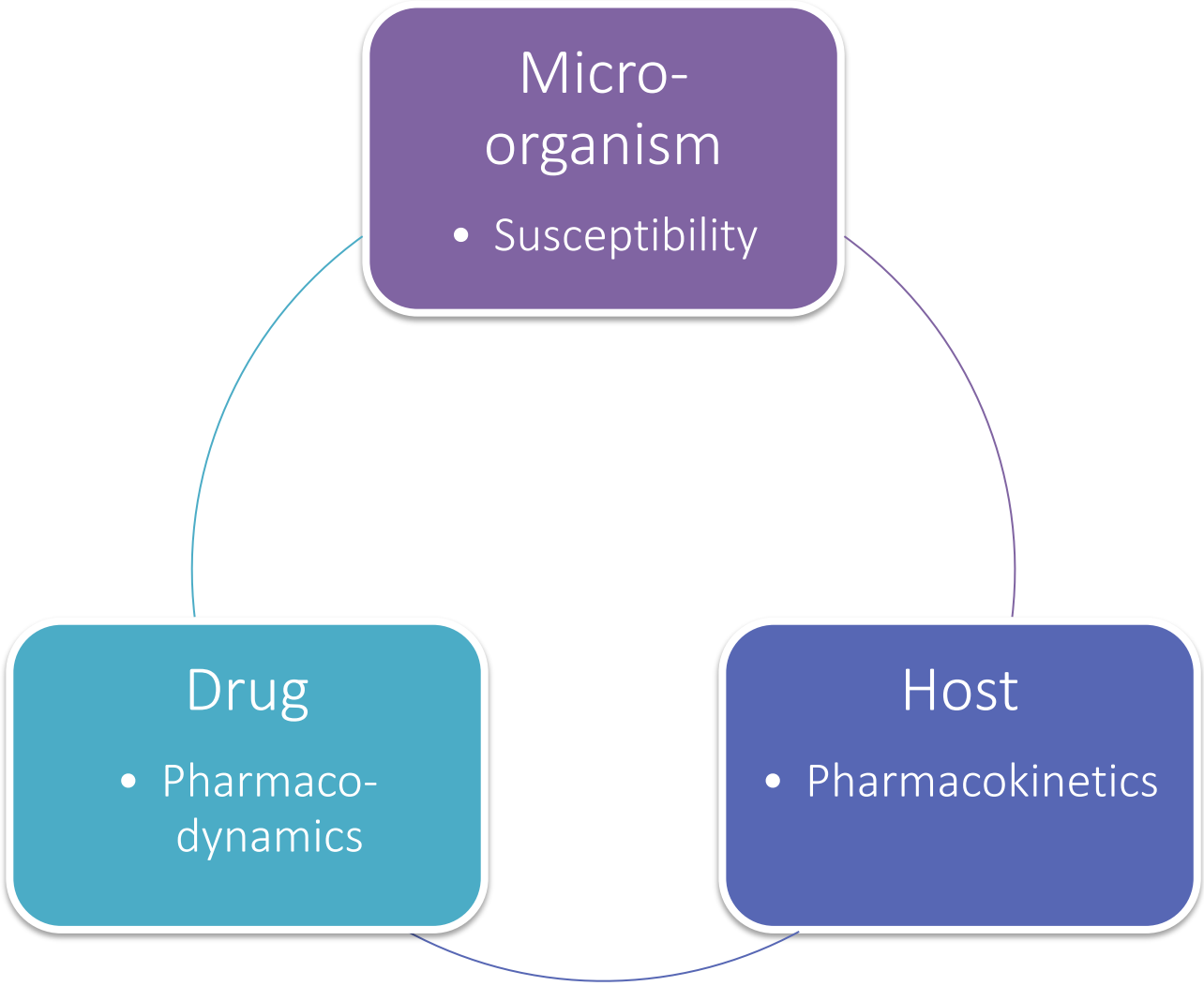
Karaiskos, I. Expert Opin Pharmacother 2014 10:1351-1370
Laterre, PF. J Antimicrob Chemother 2014
Alexandre, K. J Antimicrob Chemother 2016 7:1899-1904


Empirical therapy
Microbiology
Clinical course
Re-evaluation D2-3
Discontinue unnecessary and 'companion' antibiotics
Short course (<5d)
Long course (7-10d)
Continue initial therapy
Narrow spectrum
Monitor duration

Antibiotic efficacy determinants



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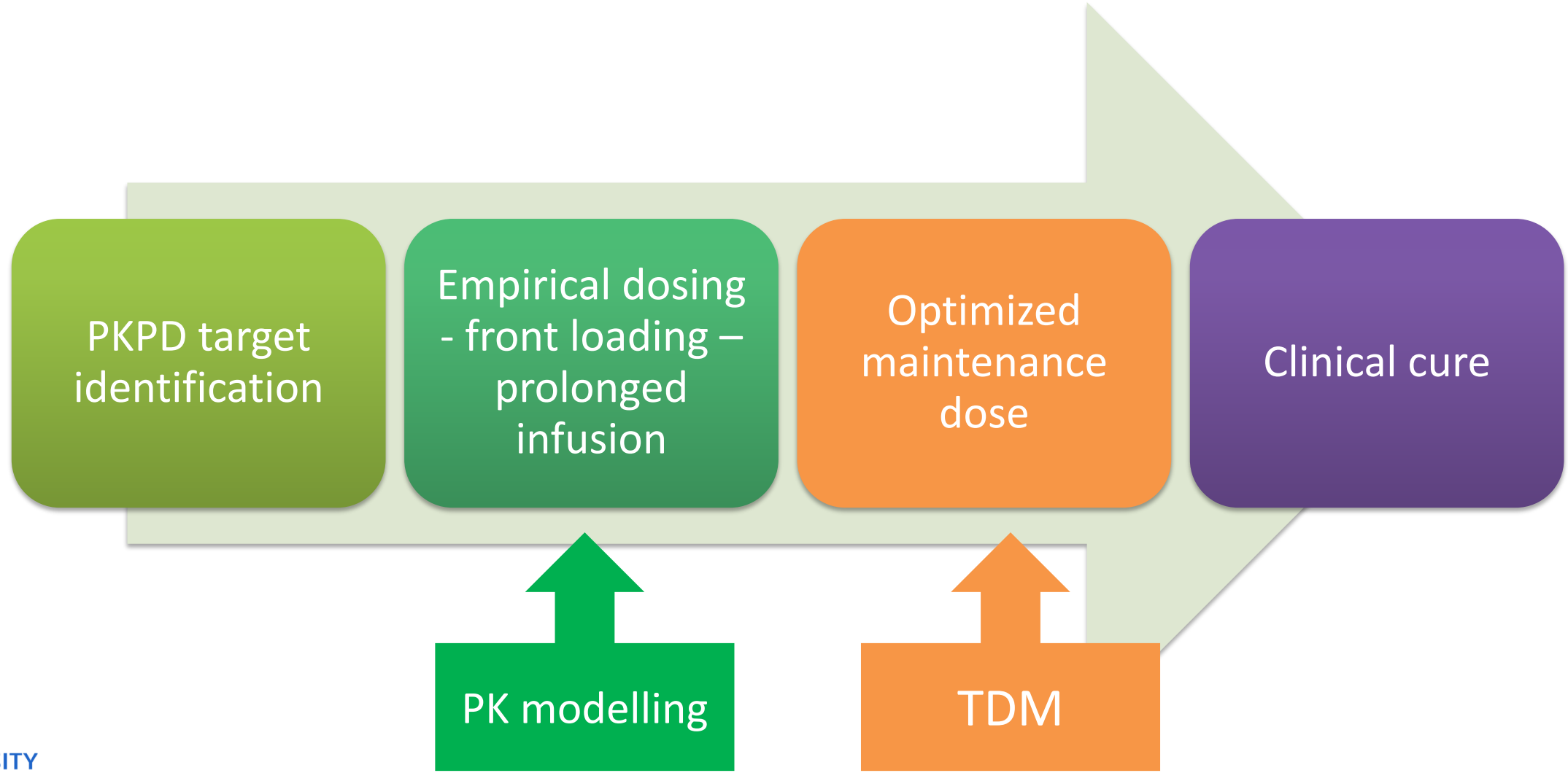
PK/PD optimized approach



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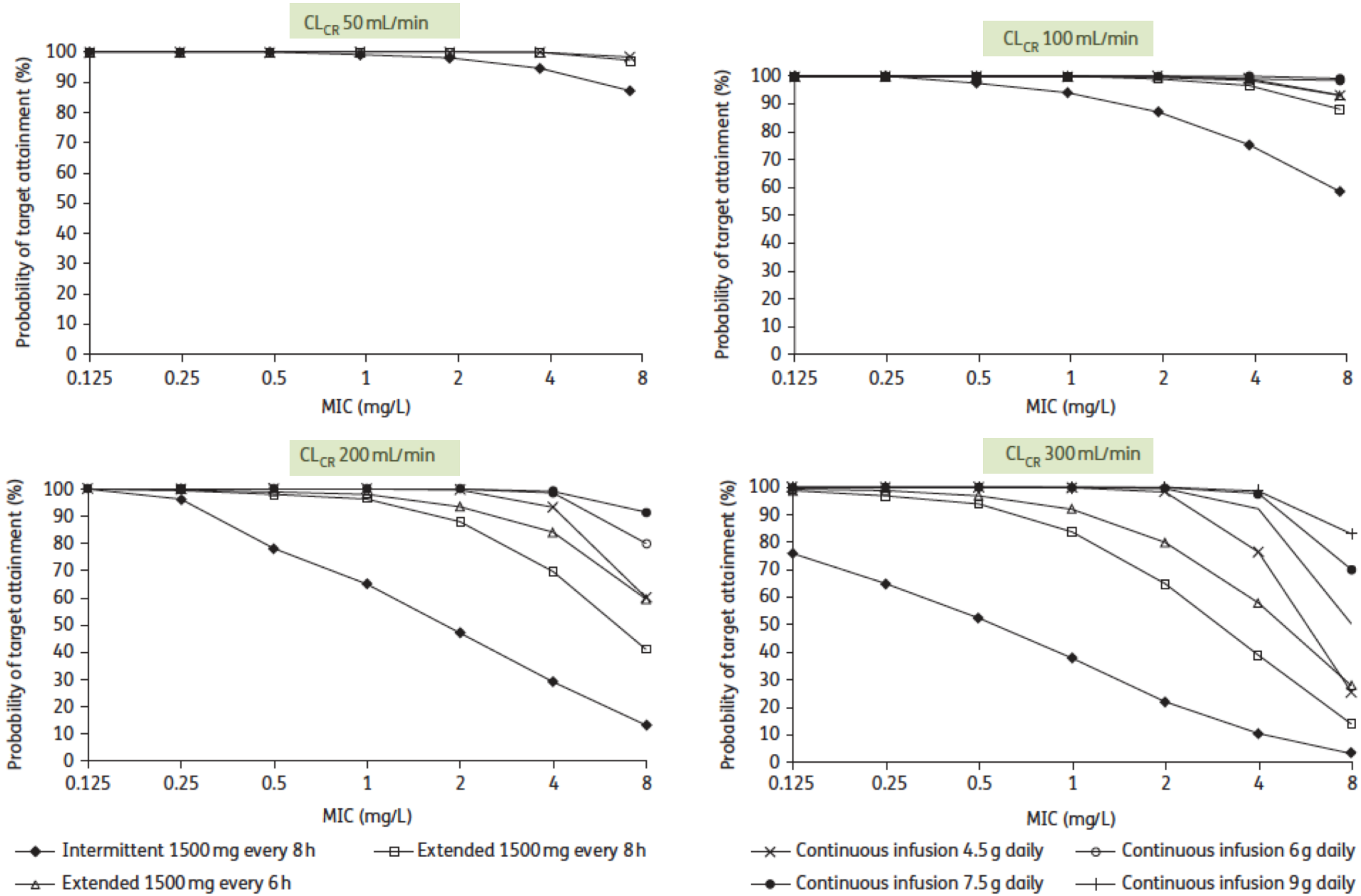

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Carlier, M. J Antimicrob Chemother 2014 10:2797-2803

Amoxicillin in ICU patients

	MIC					
	<4 mg/L		8 mg/L		16 mg/L	
Dose	50% $fT_{>MIC}$	100% $fT_{>MIC}$	50% $fT_{>MIC}$	100% $fT_{>MIC}$	50% $fT_{>MIC}$	100% $fT_{>MIC}$
Creatinine clearance 30 mL/min						
II 0.5 g q6h						
II 0.5 g q8h	+	+	+	+	+	–
II 1 g q8h	+	+	+	+	+	+
II 1 g q6h	+	+	+	+	+	+
Creatinine clearance 50 mL/min						
II 0.5 g q6h	+	+	+	+	+	–
II 1 g q8h	+	+	+	+	+	–
EI 1 g q8h	+	+	+	+	+	+
II 1 g q6h	+	+	+	+	+	+
CI 4 g q24h	+	+	+	+	+	+
Creatinine clearance 130 mL/min						
II 1 g q8h	+	–	–	–	–	–
II 1 g q6h	+	+	+	–	–	–
EI 1 g q6h	+	+	+	–	+	–
CI 4 g q24h	+	+	+	+	–	–
II 1 g q4h	+	+	+	+	+	–
CI 6 g q24h	+	+	+	+	+	+

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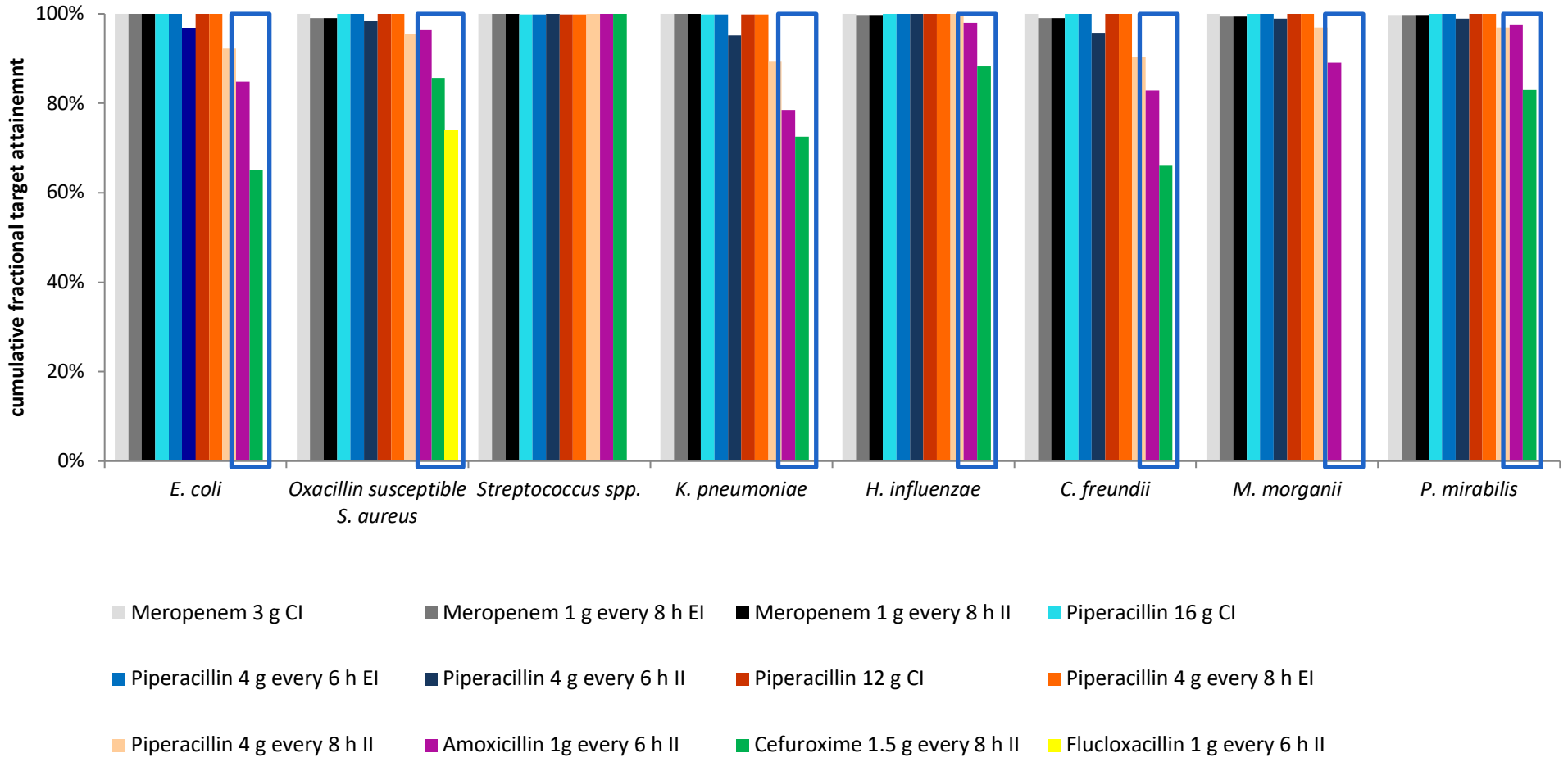
Carlier, M. J Antimicrob Chemother 2013 11:2600-2608

PK/PD target attainment in de-escalation



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Carlier, M. Antimicrob Agents Chemother 2015 8:4689-4694

Empirical use of narrow(er) spectrum antibiotics

Opportunity to reduce AB resistance

- Favourable local epidemiology
- Improved risk stratification
- Low to intermediate probability of infection

Integrated in antibiotic stewardship programs

Pitfalls in use of narrow spectrum antibiotics

- Microbiology
  - Not obtaining microbiology
  - Overinterpretation of colonisation cultures
- Impact on ecology
- Beware of prolonged therapy

Challenges for the future

- Better understanding of PK of narrower spectrum antibiotics
- Impact on microbiome to be determined
- Evaluate risk of potential superinfection with non-covered pathogens
- Role of TDM

In conclusion

- Narrow spectrum antibiotics have a potential role in MDR infections
- Definition context dependent
- Overall sensible approach even in ICU
- Empirical therapy
- Directed therapy – de-escalation
- Unexplored areas remain
- Integral part of antibiotic stewardship programs