Antibiotic Stewardship in Community-Acquired Pneumonia

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CAP: magnitude of the problem

UNITED STATES

>4,000,000 people develop CAP every year

>1.3 million hospitalizations

Cost of care for patients with CAP: $40 billion

EUROPE

5-10 cases per 1000 inhabitants per year

>65 yrs old, >15 cases per 1000 inhabitants per year

CAP results in an annual expenditure of €10.1 billion

Mortality ranges from <1% to 48%

CAP is one of the leading indications for antibiotic prescription

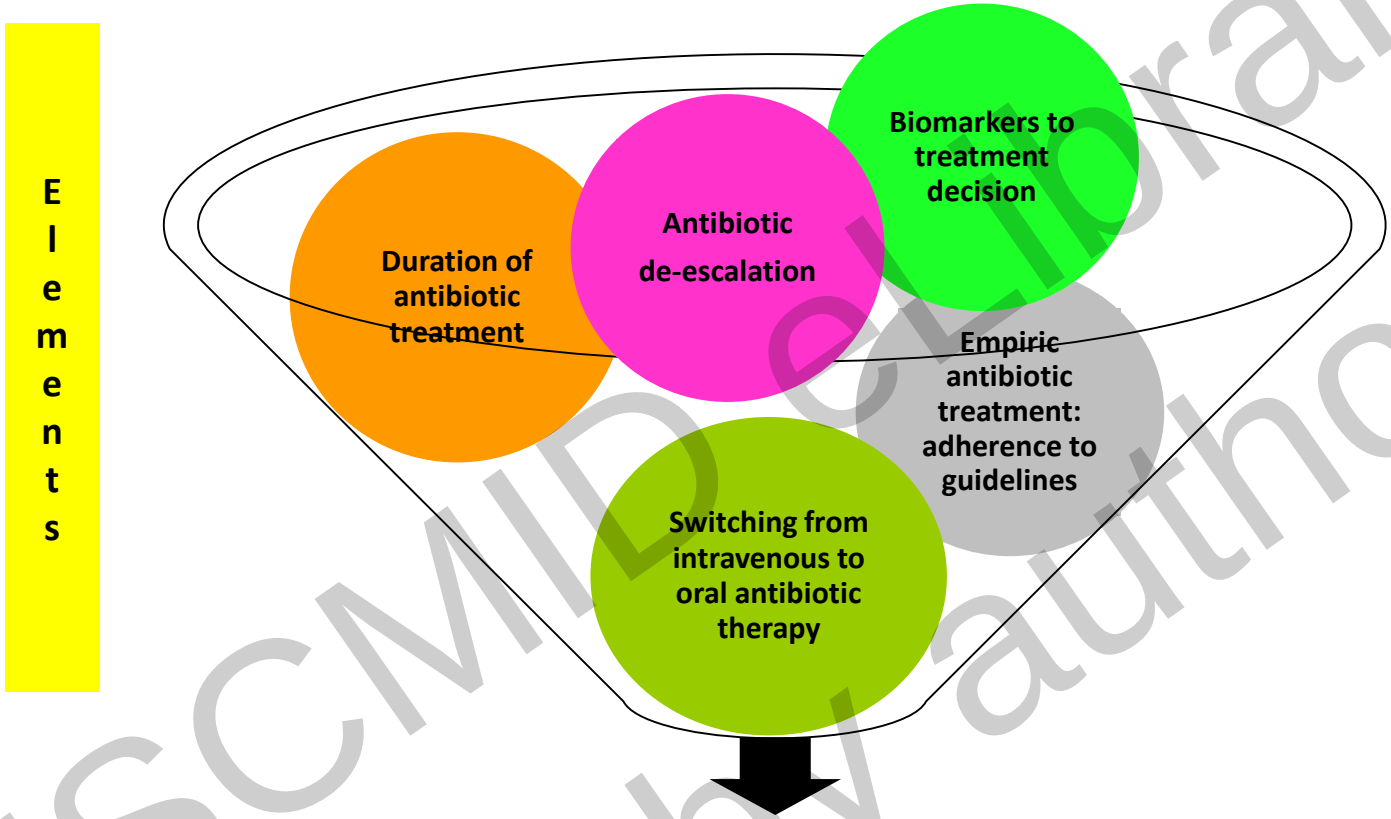
Niederman MS. Semin Respir Crit Care Med 2009

Welte T. Thorax 2012

Goals of antimicrobial stewardship

- Achieve optimal clinical outcomes with antimicrobial use.
- Minimize toxicity and other adverse events, including CDAD and other secondary infections.
- Reduce the costs of health care for infections, by encouraging and developing more cost effective approaches.
- Limit the selection pressures for antimicrobial-resistant strains.

Antimicrobial stewardship in CAP



Viasus D. Expert Rev Anti Infect Ther 2017

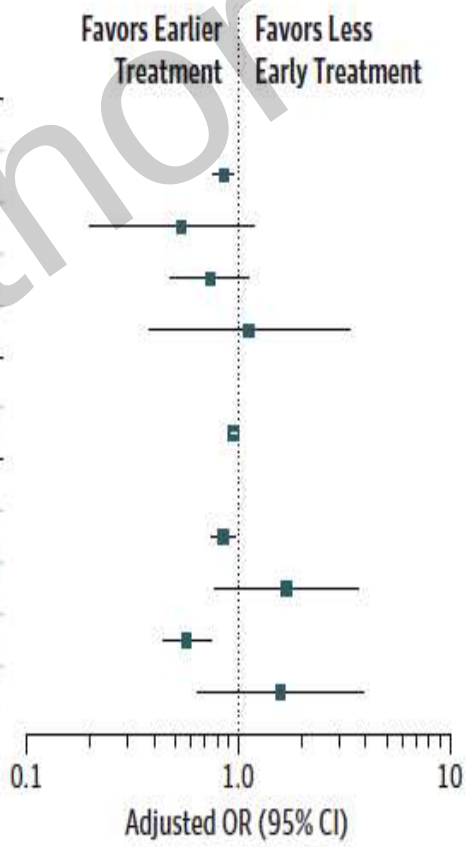
Misdiagnosis of CAP and inappropriate utilization of antibiotics: side effects of the 4-h antibiotic administration rule

Variable	January to June 2003	January to June 2005	*P*
Diagnosis of CAP without radiographic abnormalities	20.6%	28.5%	0.04
Antibiotics within 4h of triage	53.8%	65.8%	0.007
Final diagnosis of CAP	75.9%	58.9%	<0.001
Mean antibiotics utilized per patient	1.39 ± 0.58	1.66 ± 0.54	<0.001

Kanwar M. Chest 2007

Studies assessing initiation of antibiotic therapy within various thresholds and short-term mortality for hospitalized patients with CAP

Source	Outcome	<Time Threshold		>Time Threshold		Adjusted OR (95% CI)
		No. of Patients	No. (%) Who Died	No. of Patients	No. (%) Who Died	
Threshold evaluated <4 h						
Houck et al,[15] 2004	30-d Mortality	8388	973 (11.6)	5383	684 (12.7)	0.85 (0.76-0.95)
Waterer et al,[23] 2006	In-hospital mortality	NR	NR	NR	NR	0.54 (0.20-1.19)
Lee et al,[24] 2011	30-d Mortality	1619	107 (6.6)	443	34 (7.7)	0.74 (0.48-1.13)
Simonetti et al,[22] 2012	30-d Mortality	477	33 (6.9)	797	37 (4.6)	1.12 (0.38-3.33)
Threshold evaluated <6 h						
Lee et al,[8] 2014	30-d Mortality	1102555	122384 (11.1)	67467	7421 (11.0)	0.95 (0.93-0.98)
Threshold evaluated <8 h						
Meehan et al,[13] 1997	30-d Mortality	NR	NR	NR	NR	0.85 (0.75-0.96)
Dedier et al,[14] 2001	In-hospital mortality	809	NR	253	NR	1.69 (0.78-3.66)
Arnold et al,[21] 2007	In-hospital mortality	NR	NR	NR	NR	0.57 (0.44-0.74)
Simonetti et al,[22] 2012	30-d Mortality	1030	58 (5.6)	244	12 (4.9)	1.58 (0.64-3.88)



Lee JS. JAMA 2016

Recommended empirical antibiotic therapy for CAP

Inpatients, non-ICU treatment

- A respiratory fluoroquinolone (strong recommendation; level I evidence)
- A β-lactam **plus** a macrolide (strong recommendation; level I evidence)

Inpatients, ICU treatment

- A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin (level II evidence) **or** a respiratory fluoroquinolone (level I evidence) (strong recommendation) (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)

IDSA/ATS Guidelines on the Management of CAP. CID 2007

Improving outcomes in elderly patients with CAP by adhering to national guidelines

Aim: to define whether elderly patients hospitalized with CAP had better outcomes if they were were treated with empirical antimicrobial therapy adherent the 2007 IDSA/AST guidelines

Design: secondary analysis of the CAPO database. 43 centers in 12 countries

Patients: 1649 (975 regimen adherent, 465 undertreated, 195 overtreated)

Outcome	Adherence	Non-adherence	*P*
Clinical stability by 7 days	71 %	57 %	<.01
Length of stay, days	8	10	<.01
Overall in-hospital mortality	8 %	17 %	<.01

Arnold FW. Arch Intern Med 2009

Antibiotic stewardship programs to improve adherence to antibiotic prescribing guidelines for CAP

Study	Intervention	Pts in the intervention group	Pts in the control group	Results
Mcintosh 2011	Audit and feedback report, academic detailing, PowerPoint presentations for group feedback sessions, letter to prescribers, wall posters, and prescribing prompts	Audit 2: 503 Audit 3: 462	Audit 1: 518	Concordant ATB prescribing improved from 6% in audit 1 to 25% and 22% in audits 2 and 3, respectively; *P*<. 001
Høgli 2016	Pre-intervention audit (empirical antibiotic, dose, and total treatment duration). Intervention with oral feedback and distribution CAP guideline pocket version	253	155	Prescribing of appropriate empirical ATB increased from 62% to 83%; *P*<.001

Mcintosh KA. Int J Qual Health Care 2011. Høgli JU. BMC Infect Dis 2016

Studies evaluating antibiotic de-escalation in CAP

Study	Population	De-escalation n (%)	Results
Khasawneh Inf Drug Res 2014	60 pts with bacteremic CAP	33 (55.5)	No differences in mortality and LOS
Carugati CMI 2015	261 pts with bacteremic CAP	165 (63.2)	Higher mortality in the non-DE group
Yamana J Infect 2016	11159 pts with CAP	1258 (11.3)	No differences in 5-day and in-hospital mortality
Viasus JAC 2016	1410 pts with CAPP	166 (11.7)	No differences in 30-day mortality Shorter LOS in DE

Impact of antibiotic de-escalation on clinical outcomes in community-acquired pneumococcal pneumonia (CAPP)

1410 episodes of CAPP (1995-2014)

Antibiotic de-escalation (<72 h) was performed in 166 cases (11.7%)

- Antibiotic de-escalation was not associated with a higher risk of 30-day mortality (OR 0.8, 95% CI 0.2-2.8), but it was a protective factor for prolonged LOS (OR 0.5,95% CI 0.3-0.7).
- Similar results were found in pts classified into IV-V PSI classes, those with clinical instability and those with bacteremia.
- No significant differences were documented in adverse events.

Viasus D. J Antimicrob Chemother 2016

Effectiveness of early switch from intravenous to oral antibiotics in severe CAP: a multicentre randomised trial

Setting: 7 teaching hospitals in the Netherlands.

Participants: 265 pts in non-intensive care wards with severe CAP.

Intervention: 3 days of iv antibiotics followed, when clinically stable, by oral antibiotics or 7 days of iv antibiotics.

Outcome	Intervention (n= 132)	Control (n= 133)	Mean difference (95% CI)
Clinical cure	110 (83)	113 (85)	2% (-7% to 10%)
Mean (SD) LOS, days	9.6 (5.0)	11.5 (4.9)	1.9 (0.6 to 3.2)

Oosterheert JJ. BMJ 2006

Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in CAP

Objective: to determine whether the use of a 3-step critical pathway is safe and effective in reducing duration of iv antibiotic therapy and LOS in hospitalized adults with CAP

Design: randomized controlled trial (ISRCTN 17875607)

Setting: 2 tertiary hospitals in Barcelona

Intervention: 3-step critical pathway or usual care

Primary end point: LOS

Secondary end points: duration of iv antibiotic therapy, adverse drug reactions, need for readmission, and overall case-fatality rate

Carratalà J. Arch Intern Med 2012

3-Step Critical Pathway in CAP

1 EARLY MOBILIZATION

Movement out of bed:

> 20´ during the first 24 hours of hospitalization

progressive movement each subsequent day

2 SWITCH TO ORAL ANTIBIOTIC THERAPY

Ability to maintain oral intake, stable vital signs (temperature ≤37.8ºC, RR ≤24´, SBP ≥90 mmHg) and absence of exacerbated comorbidities

3 HOSPITAL DISCHARGE

Meeting criteria for oral antibiotic therapy, baseline mental status, and adequate oxygenation on room air (PaO_2 ≥60 mmHg or pulse oximetry ≥90%)

Carratalà J. Arch Intern Med 2012

Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in CAP

Outcomes	3-step pathway (n= 200)	Usual care (n= 201)	P
Primary end point			
Length of stay, median, days	3.9	6.0	<.001
Secondary end points			
Length of iv antibiotic therapy	2.0	4.0	<.001
Adverse drug reactions	5 %	16 %	<.001
Phlebitis	4 %	10 %	.02
Subsequent admission	9 %	8 %	.59
Overall case-fatality rate	2 %	1 %	.45

What prevents the intravenous to oral antibiotic switch?

Twenty doctors working in a teaching hospital in north-east England participated in semistructured interviews to explore their decisions around switching iv to oral antibiotics.

Decisions about the choice of iv over oral antibiotics were influenced by three key issues:

- Consumerism and “complaints culture”
- Hierarchy of the medical team structure
- Mythical properties of intravenous antibiotics
  “iv anything is better than oral…”

Broom J. J Antimicrob Chemother 2016

Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis

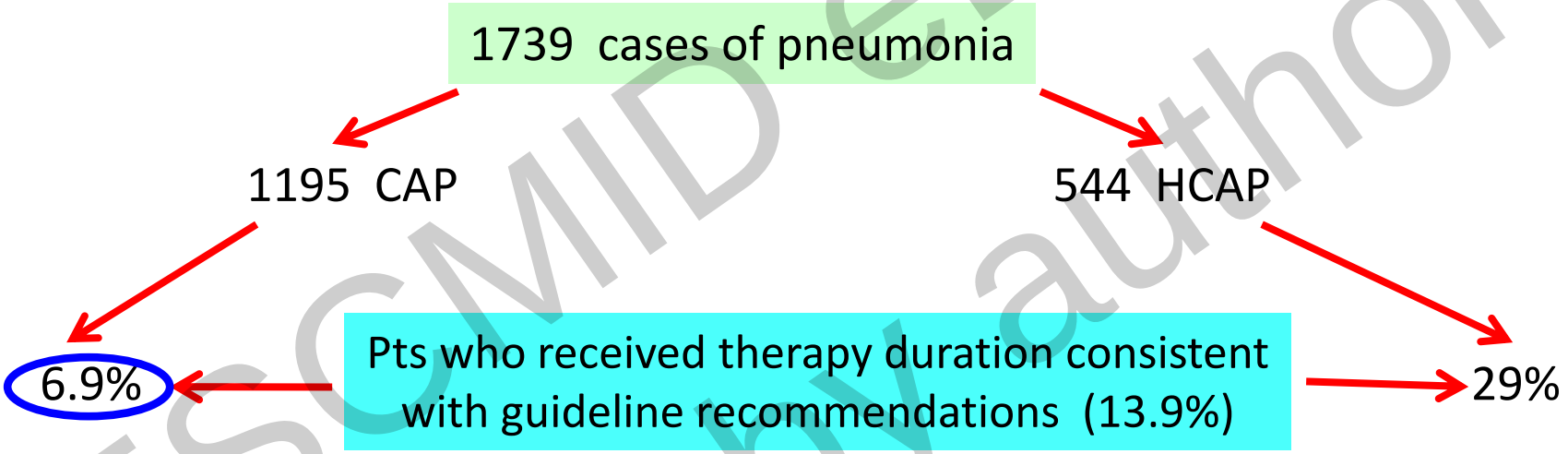
- 15 randomized controlled trials (1980-2006); mild/moderate CAP.
- Short-course (≤ 7 days) versus extended-course (>7 days).
- Short-course: azithro (10), β-lactams (2), FQ (2), ketolides (1).

Outcome	Relative risk, 95% CI
Clinical failure	0.89, 0.78 – 1.02
Mortality	0.81, 0.46 – 1.43
Bacteriologic eradication	1.11, 0.76 – 1.62

Li JZ. Am J Med 2007

Total duration of antimicrobial therapy in veterans hospitalized with uncomplicated pneumonia

- A national retrospective evaluation was conducted in thirty Veterans Affairs medical centers to assess the duration of antibiotic therapy

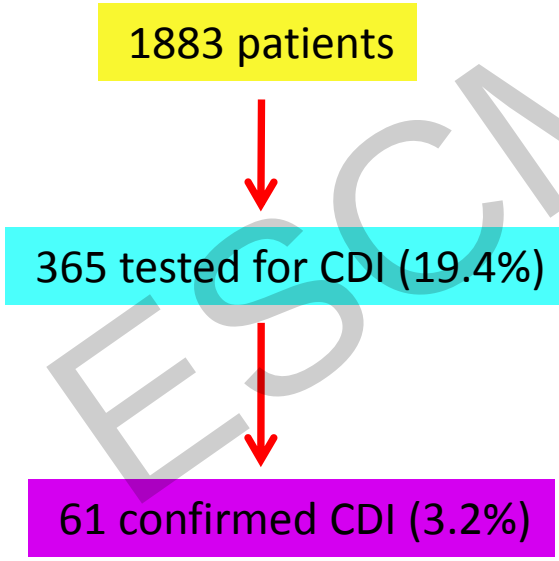


Antimicrobials were commonly prescribed for a longer duration that guidelines recommend. The majority of excessive therapy was completed after discharge

Madaras-Kelly KJ. J Hosp Med 2016

Risk factors for *Clostridium difficile* infection (CDI) in hospitalized patients with CAP

- Prospective, observational cohort of hospitalized patients with CAP.
- Patients with diarrhea were screened for CDI, and risk factors were determined through time-dependent survival analysis.



Variable	HR (95% CI)
Age	1.06 per year (1.03 – 1.08)
Total number of antibiotic classes received	3.01 per class (2.32 – 3.91)
Duration of antibiotic therapy	1.09 per day (1.00 – 1.19)
Hospitalization status	13.1 (6-0 – 28.7)

Chalmers JD. J Infect 2016

Impact of and antimicrobial stewardship intervention on shortening the duration of therapy for CAP

Intervention consisting of education and prospective feedback to teams regarding antibiotic (ATB) choice and duration

Variable	Preintervention (2008) (n= 56)	Intervention (2010) (n= 63)	*P*
Duration of ATB therapy, median (IQR), days	10 (8 – 13)	7 (7 – 8)	<.001
Excess ATB days, median (IQR), days	4 (2 – 6)	1 (0 – 3)	<.001

LOS, readmissions, and CDI were similar in the 2 groups

Avdic E. Clin Infect Dis 2012

Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections (ARIs)

Individual patient data meta-analysis of 4221 adults with ARIs in 14 trials

Variable	Procalcitonin (n= 2085)	Control (n= 2126)	Adjusted OR (95% CI)
Death	5.7%	6.3%	.94 (.71 – 1.23)
Treatment failure	19.1%	21.9%	.82 (.71 – 1.97)
Total antibiotic exposure per patient, median (IQR) d	4 (0 – 8)	8 (5 – 12)	-3.47 (-3.78 – -3.17)

Shuetz P. Clin Infect Dis 2012

Duration of antibiotic treatment in CAP
A multicenter randomized clinical trial

- Multicenter, noninferiority, RCT. Four spanish teaching hospitals (2012 - 2013)
- A total of 312 pts were randomized at day 5 to an intervention (ATBs for 5 days) or control group (duration of ATBs determined by physicians).

Outcome Intent-to-treat analysis	Control n= 150	Intervention n= 162	P value
Clinical success, n (%)			
At day 10	71 (49)	90 (56)	0.18
At day 30	132 (89)	147 (92)	0.33
CAP symptom questionnaire score, mean (SD)			
At day 5	24.7 (11)	27.2 (12)	0.10
At day 30	18.6 (9.0)	17.9 (8)	0.69

Uranga A. JAMA Intern Med 2016

The new antibiotic mantra "Shorter is Better"

Infections for which short-course therapy has been shown to be equivalent in efficacy to longer therapy

	Treatment, Days	
Disease	**Short**	**Long**
Community-acquired pneumonia[1-3]	3-5	7-10
Nosocomial pneumonia[6,7]	≤8	10-15
Pyelonephritis[10]	5-7	10-14
Intraabdominal infection[11]	4	10
Acute exacerbation of chronic bronchitis and COPD[12]	≤5	≥7
Acute bacterial sinusitis[13]	5	10
Cellulitis[14]	5-6	10
Chronic osteomyelitis[15]	42	84

Spellberg B. JAMA Intern Med 2016

Summary

- Antimicrobial stewardship principles and initiatives can be applied to optimize both the management and the outcomes of CAP.
- Elements of proper stewardship include antibiotic de-escalation, shortening the duration of antibiotic therapy, guaranteeing timely switches from IV to oral antibiotic therapy, and ensuring adherence to recommendations about empirical treatment.

Summary

- Antimicrobial stewardship strategies in CAP have improved antimicrobial use without adverse effects on patient outcomes.
- There is a limited number of randomized trials addressing antimicrobial stewardship strategies in CAP.
- Evaluation of combination approaches that incorporate many or all the most effective elements (i.e. bundles) should be performed in the future.