

## Route and duration of antibiotic therapy in acute cellulitis: a systematic review and meta-analysis of the effectiveness and harms of antibiotic treatment

Article (Supplemental Material)

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Figure 1. Study selection

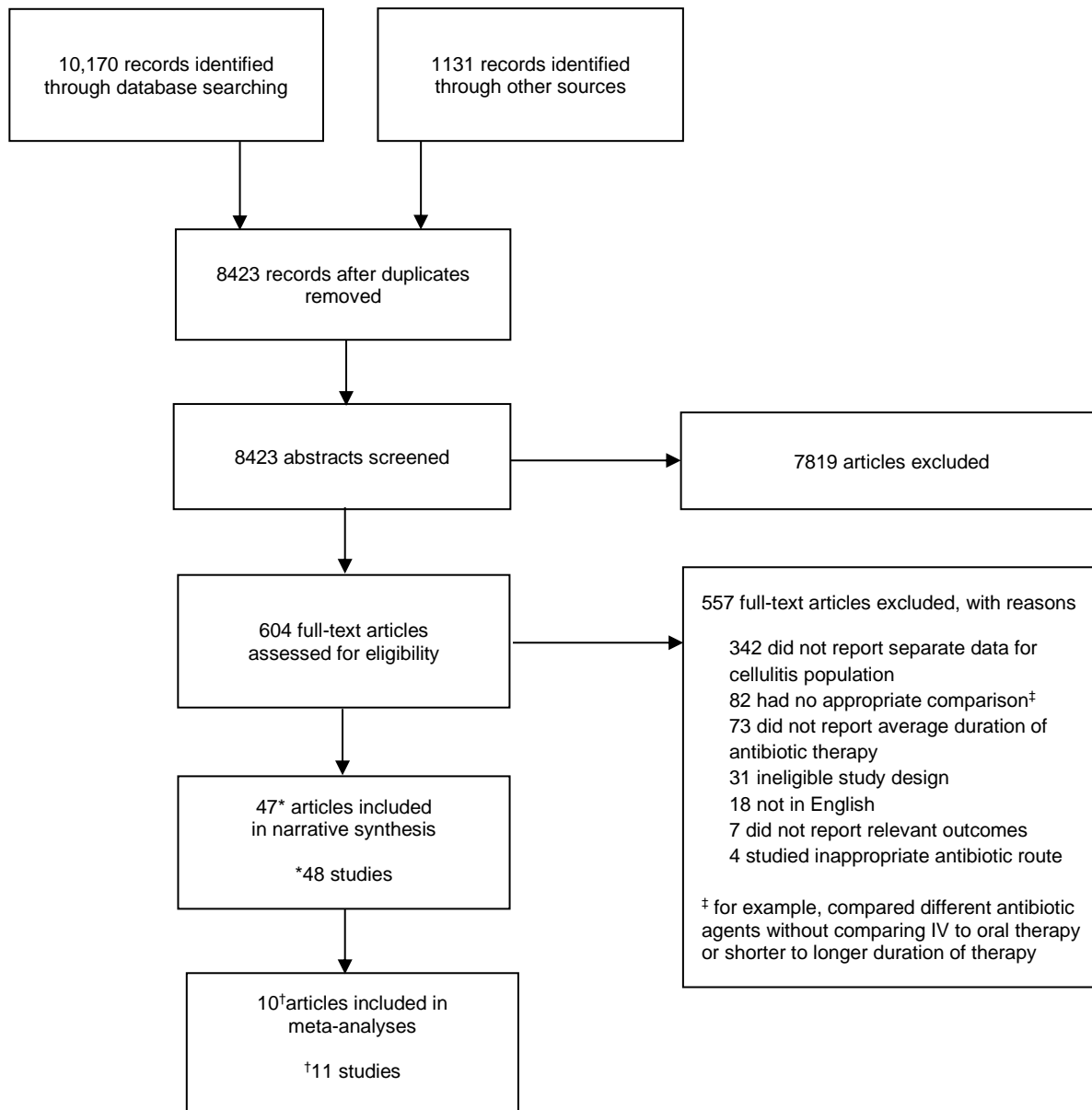
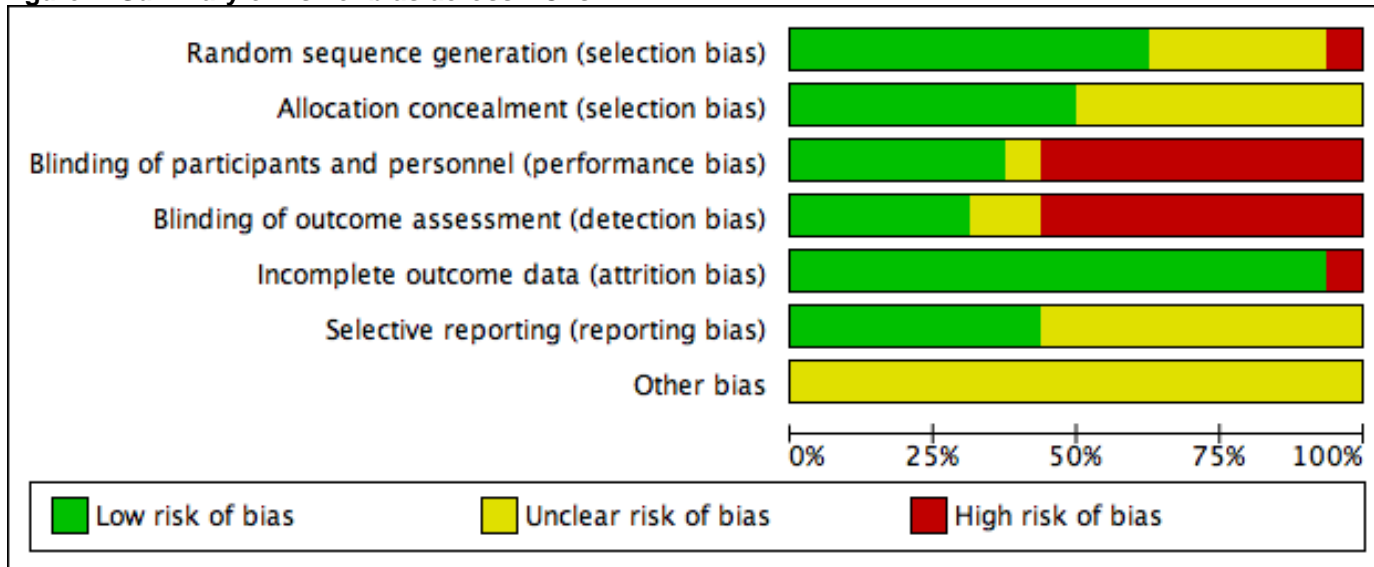


Figure 2. Summary of risk of bias across RCTs.

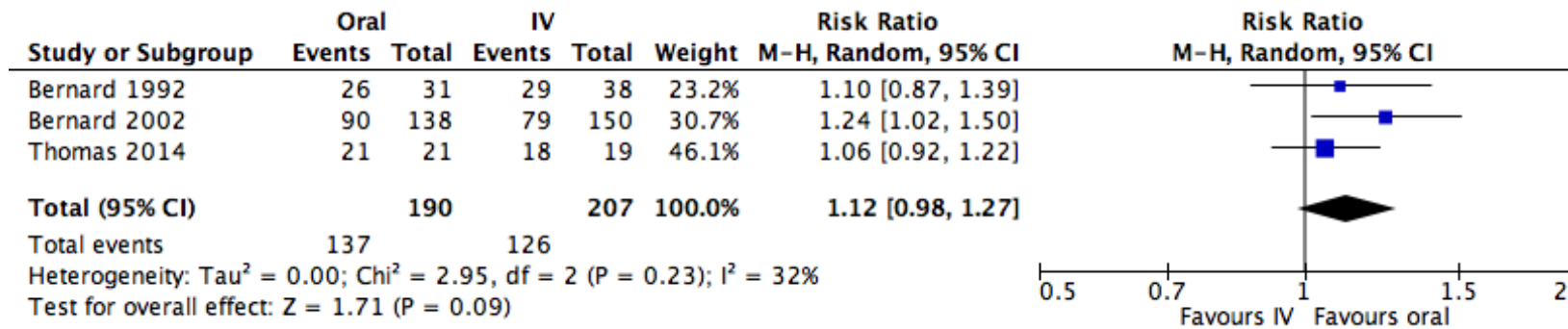


**Table 1. Characteristics of studies comparing oral versus IV with step down to oral treatment**

Author & year	Study design	Setting	Population	Severity & site	Oral antibiotic arm	IV antibiotic arm	Primary outcome	Findings	
								Oral arm	IV arm
Aboltins 2015	RCT	Single tertiary teaching hospital, Australia Inpatients & OPAT	47 adults with cellulitis	Uncomplicated (not mild) - 87% lower limb - 13% upper limb	Oral cephalexin*  10 days	IV-to-oral cefazolin to cephalexin *  10 days	Mean days until no advancement of the area of cellulitis	1.29 (SD 0.62) days (n=24)	1.78 (SD 1.13) days (n=23)
								Mean difference -0.49 (95% CI, -1.02 to +0.04)	
Bernard 1992	RCT	6 dermatological departments, France Inpatients	69 adults with erysipelas	Non-gangrenous erysipelas  - Site NR	Oral roxithromycin  Average duration (range) 13 days (2 to 29)	IV-to-oral penicillin  Average IV duration (range) 6 days (2 to 17)  Average oral duration 7 days (0 to 21)	Efficacy rate  Timing NR (some point within 30 days)	26/31 (84%)	29/38 (76%) (P=0.43)
Bernard 2002	RCT	22 dermatology centres, France Inpatients	289 adults with erysipelas	Superficial, non-necrotising  - 94% lower limb	Oral pristinamycin  14 days	IV-to-oral benzylpenicillin to phenoxymethylpenicillin  14 days	Clinical cure rate Day 25 to 45	90/138 (65%) <sup>†</sup>	79/150 (53%) <sup>†</sup>
Thomas 2014	RCT	Single hospital, New Zealand Inpatients	40 adults with cellulitis	Severity NR  - 78% lower limb - 10% upper limb	Oral clindamycin  Median no. of doses of IV 'treatment' <sup>‡</sup> (range) 11 (0 to 15)	IV-to-oral flucloxacillin  Median no. of doses of IV treatment (range) 8 (0 to 21), (P=0.23)	Clinical efficacy  Daily review at 'completion of treatment'	21/21 (100%) Cured 18/21 (86%) Improved 3/21 (14%)	18/19 (95%) Cured 7/19 (37%) Improved 11/19 (58%)
					Median oral duration (range) 9 days (0 to 21)	Median oral duration 8 (0 to 18), (P=0.81)			
Jorup-Rönström 1984	Quasi-RCT	Single hospital, Sweden Inpatients	73 adults with erysipelas	'severe local findings'  - Site NR	Oral phenoxymethylpenicillin ± flucloxacillin  For at least 10 days	IV-to-oral Benzylpenicillin ± cloxacillin  For at least 10 days	Time to temperature fall to ≤37.5°C (median fever duration)	2 days	3 days

NR = Not reported. Primary outcome defined by study authors, where not defined the first outcome measure of clinical response to be reported was selected. \*Clindamycin if penicillin allergic. <sup>†</sup>In the intention-to-treat (ITT) analysis. <sup>‡</sup>Placebo IV treatment given in the oral clindamycin arm.

Figure 3. Forest plot of comparison: Oral versus IV antibiotics, outcome clinical response



**Table 2. Summary of studies reporting on timing of IV-to-oral switch**

Study	Design	Setting	Population	Relevant Outcome	Finding
Clarke 2019 Switch Trial	RCT comparing early (24h) vs later ( $\geq 72$ h) oral switch	10 sites, Australia & New Zealand  Inpatients & OPAT	80 adults with cellulitis requiring IV therapy (39 in shorter, 41 in longer group)	Resolution of cellulitis at the end of therapy (10 days after randomisation)	Cellulitis resolution achieved in 31 (79%) in shorter group and 35 (85%) in longer group (difference of -5.8% (95%CI, -22.5% to 10.7%)
Bogner 2013	Prospective, multicentre cohort study describing outcomes among patients treated with moxifloxacin	>600 sites, Europe, the Middle East and Asia-Pacific region  Inpatients	5444 adults and children with complicated SSTIs, 820 with cellulitis	Effectiveness (improvement and resolution of cellulitis) at follow-up	Mean IV-to-oral switch time of 3.4 days associated with 'very good' (68%), 'good' (26%) and 'sufficient' (3%) effectiveness ratings
Lipsky 2012	Prospective, multicentre cohort study describing patient characteristics and treatment outcomes in cellulitis	56 hospitals, USA  Inpatients	1033 adults with complicated SSTIs, 278 with cellulitis	Clinical response at the end of IV treatment	Mean IV duration of 2 to 3 days associated with cure in 11.9% and improvement in 78.4%
Morpeth 2005	Prospective cohort study assessing determinants of LOS, length of IV antibiotic therapy and outcomes in cellulitis	Single hospital, New Zealand  Inpatients	51 adults with cellulitis	Recurrence of cellulitis within six weeks of discharge	Median IV duration of 3 days, 12% were readmitted to hospital for recurrence
McNamara 2007	Retrospective cohort to examine risk factors and develop a predictive model for recurrent lower limb cellulitis	Multicentre, USA  Inpatients and outpatients	209 adults with cellulitis	Recurrence of cellulitis within 2 years	Mean IV duration of 1.1 days, 35 (16.7%) experienced a recurrence within 2 years
Gouin 2008	Prospective cohort study assessing outcomes of children with cellulitis managed at a day treatment centre	Single hospital, Canada  OPAT/day treatment centre	92 children with cellulitis	Relapse of cellulitis within 14 days	Mean IV duration of 2.5 days at which point 19 children received further 4.5 days IV therapy and 73 were discharged on oral therapy. 1/73 relapsed
Ibrahim 2017	Prospective cohort study describing outcomes of children with cellulitis treated on an admission avoidance pathway	Single hospital, Australia  OPAT & inpatients	115 children with cellulitis (47 OPAT, 68 inpatients)	Treatment failure within 48 hours	Median duration of IV therapy similar between OPAT and inpatient groups (1.9 vs. 1.8 days, P=0.31) as was treatment failure (4% vs. 14%, P=0.10)

**Table 3. Characteristics of RCTs comparing shorter versus longer duration antibiotics**

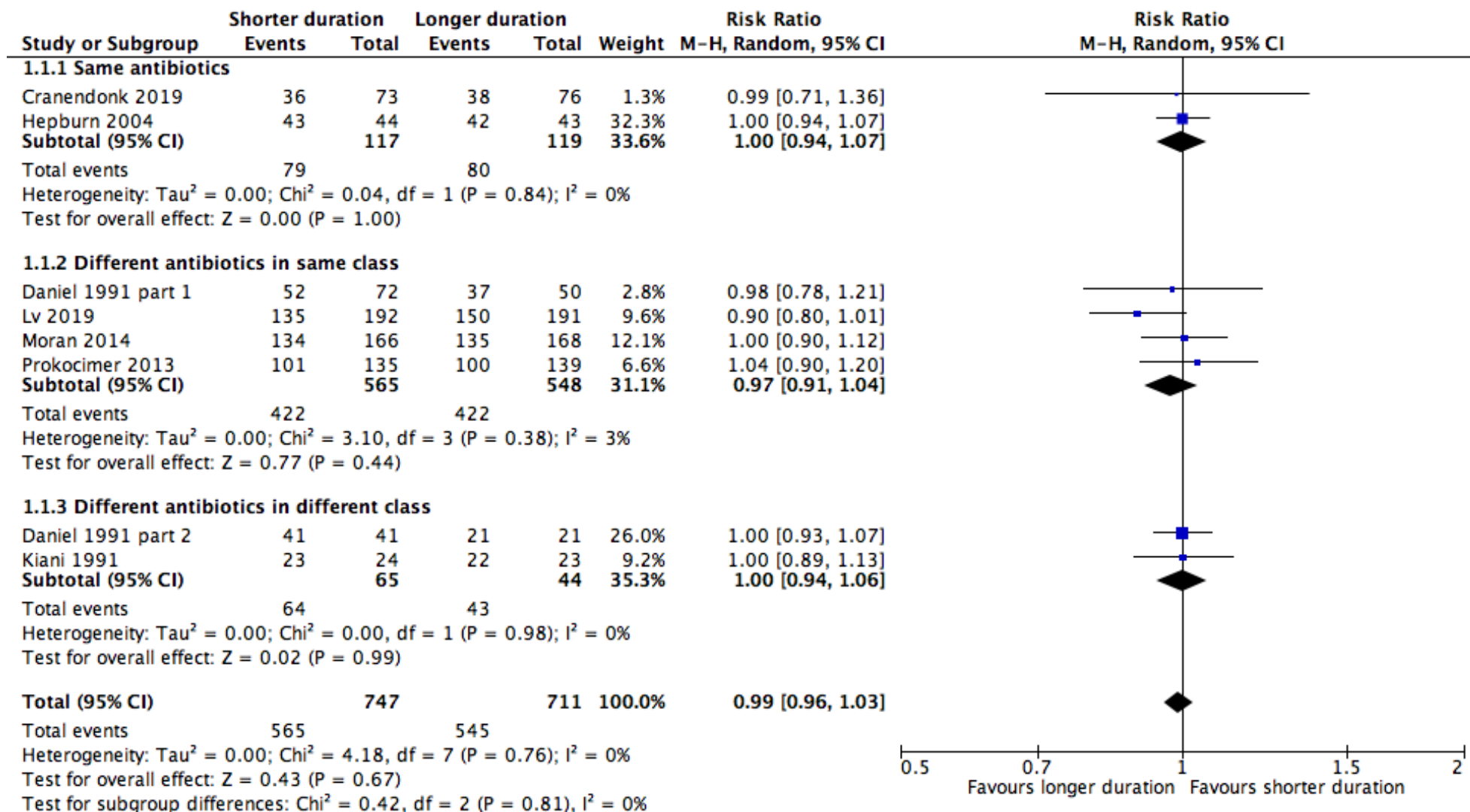
Author & year	Setting	Population	Severity & site	Shorter arm	Longer arm	Primary outcome	Findings	
							Shorter arm	Longer arm
Daniel 1991 part 1	29 centres, 6 European countries In-/outpatient, unclear	122 adults with cellulitis (308 SSTIs)	Severity & site NR	5 days of oral azithromycin	7 days of oral erythromycin	Clinical cure 7-10 days after treatment completion	52/72 (72%)	37/50 (74%)
Daniel 1991 part 2	15 centres, 4 European countries In-/outpatient, unclear	62 adults with cellulitis (323 SSTIs)	Severity & site NR	5 days of oral azithromycin	7 days of oral cloxacillin	Clinical response 4-9 days post treatment completion	41/41 (100%) Cured 27/41 (66%) Improved 14/41 (34%)	21/21 (100%) Cured 11/21 (52%) Improved 10/ 21 (48%)
Kiani 1991	22 centres, USA Inpatients & outpatients	47 adults with cellulitis (366 SSTIs)	Severity & site NR	5 days oral azithromycin	10 days of oral cephalexin	Clinical response Day 11 (10-13)	23/24 (96%) Cured 12/24 (50.0%) Improved 11/24 (45.8%)	22/23 (96%) Cured 14/23 (60.9%) Improved 8/23 (34.8%)
Hepburn 2004	Single tertiary care military hospital, USA Inpatients & outpatients	87 adults with cellulitis	Uncomplicated Face, trunk or extremity	5 days of levofloxacin*	10 days of levofloxacin*	Resolution of infection Day 14 (without symptom recurrence by day 28)	43/44 (98%)	42/43 (98%)
Prokocimer 2013 (ESTABLISH 1)	81 centres, North America, Latin America and Europe In-/outpatient, unclear	275 adults with cellulitis (667 SSTIs)	Complicated Site NR	6 days oral tedizolid	10 days oral linezolid	Early clinical response 48-72hrs after the start of treatment	101/135 (74.8%)	100/139 (71.9%)
Moran 2014 (ESTABLISH 2)	58 centres, various countries† In-/outpatient, unclear	334 adults & children (age range 15-89) with cellulitis (666 SSTIs)	Complicated Site NR	6 days IV-to-oral tedizolid	10 days IV-to-oral linezolid	Early clinical response 48-72hrs after the start of treatment	134/166 (81%)	135/168 (80%)
							Treatment difference 0.3% (95% CI, -8.2 to 8.9%)	
Lv 2019	Multicentre, USA, China, Taiwan and the Philippines In-/outpatient, unclear	383 adults with cellulitis (598 SSTIs)	Complicated - 59% lower limb - 12% upper limb	6 days IV-to-oral tedizolid	10 days IV-to-oral oral linezolid	Early clinical response 48-72hrs after the start of treatment	135/192 (70.3%)	150/191 (78.0%)
Cranendonk 2019	11 centres, the Netherlands Inpatients	149 adults with cellulitis	'High severity' - 84% lower limb - 9% upper limb	6 days IV-to-oral flucloxacillin	12 days IV-to-oral flucloxacillin	Cure by day 14 without relapse by day 28	36/73 (49%)	38/76 (50%)
<b>Paediatric studies</b>								
Rodriguez-Solares 1993	5 centres, Costa Rica, Guatemala, Panama, Venezuela Outpatients	16 children with cellulitis (118 with SSTIs)	Severity & site NR	Oral azithromycin for 3 days	Oral dicloxacillin or flucloxacillin for 7 days	Clinical response 7-10 days after the start of treatment	5/5 (100%) Cured 4/5 (80%) Improved 1/5 (20%)	11/11/ (100%) Cured 11/11 (100%) Improved 0/11 (0%)

Montero 1996	'Multicentre', Colombia, Guatemala, Panama, South Africa Inpatients	34 children with cellulitis (200 SSTIs)	Severity & site NR	Oral azithromycin for 3 days	Oral cefaclor for 10 days	Clinical efficacy (cured/improved) 10-14 days after the start of treatment	13/16 (81%)	16/18 (89%)
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NR = Not reported. Primary outcome defined by study authors, where not defined the first outcome measure of clinical response to be reported was selected. \*Mostly oral (12 IV-to-oral). †Argentina, Australia, Germany, New Zealand, Poland, Russia, South Africa, Spain, and the USA.



Figure 4. Forest plot of comparison: Shorter versus longer duration antibiotics, outcome clinical response



**Table 4. Summary of non-randomised studies reporting on shorter versus longer duration antibiotics**

Study	Design	Setting	Population	Relevant Outcome	Finding
Jenkins 2011	Retrospective pre- and post-intervention study evaluating a guideline for the inpatient management of cellulitis	Single hospital, USA Inpatients	148 adults with cellulitis (66 pre-, 82 post-intervention)	Composite endpoint of clinical failure within 30 days of discharge	From pre-to post-intervention, median antibiotic duration decreased from 13 to 10 days (P<0.001) and clinical failure rates remained similar 12.1% vs. 9.8% (P=0.65), respectively
Seaton 2005	Pre- and post-intervention study evaluating a new protocol for specialist nurse management of cellulitis through an OPAT service	Single centre, Glasgow OPAT	342 adults & children with cellulitis	Clinical response (cure/improved) at 'completion of treatment'	From pre-to post-intervention, median antibiotic duration decreased from 5 to 4 days (P=0.01) and clinical response rates remained similar 99% vs. 97%, respectively
Aly 1996	Retrospective observational study examining the management of cellulitis in a teaching hospital	Tertiary teaching hospital, Australia Inpatients	118 adults with cellulitis	Clinical response (not clearly defined) within 5 days	Most patients (93%) had a clinical response within 5 days. However, 40% of the cohort continued IV therapy for >5 days and in 10% for >10 days, with no evidence of difference in outcomes
Kam 2010	Retrospective observational study comparing emergency department short-course IV therapy vs. inpatient IV therapy or outpatient oral antibiotics	Single hospital, Canada Inpatients and outpatients	321 children with cellulitis	Treatment failure within 7 days of index visit	The odds of treatment failure were higher for short-course IV therapy compared to inpatient IV therapy (7.2, 95% CI 1.6 to 33.1) and outpatient oral antibiotics (3.2, 95% CI 1.3 to 8.3)