Ceftaroline:
a new generation of cephalosporin

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Dipresentasikan dalam:

Rapat Komite Farmasi dan Terapi RSK. St. Vincentius a Paulo

Jumat, 25 Oktober 2019

OUTLINE

INTRODUCTION

Generation of cephalosporin and spectrum of activity

Brief information about resistant bacteria

CEFTAROLINE

Chemical structure and approval information

Mechanism of action

PK profile

EVIDENCE & PLACE IN THERAPY

Ceftaroline for:
pneumonia & skin and soft tissue infection

Place in therapy

AVAILABILITY

Indonesia?

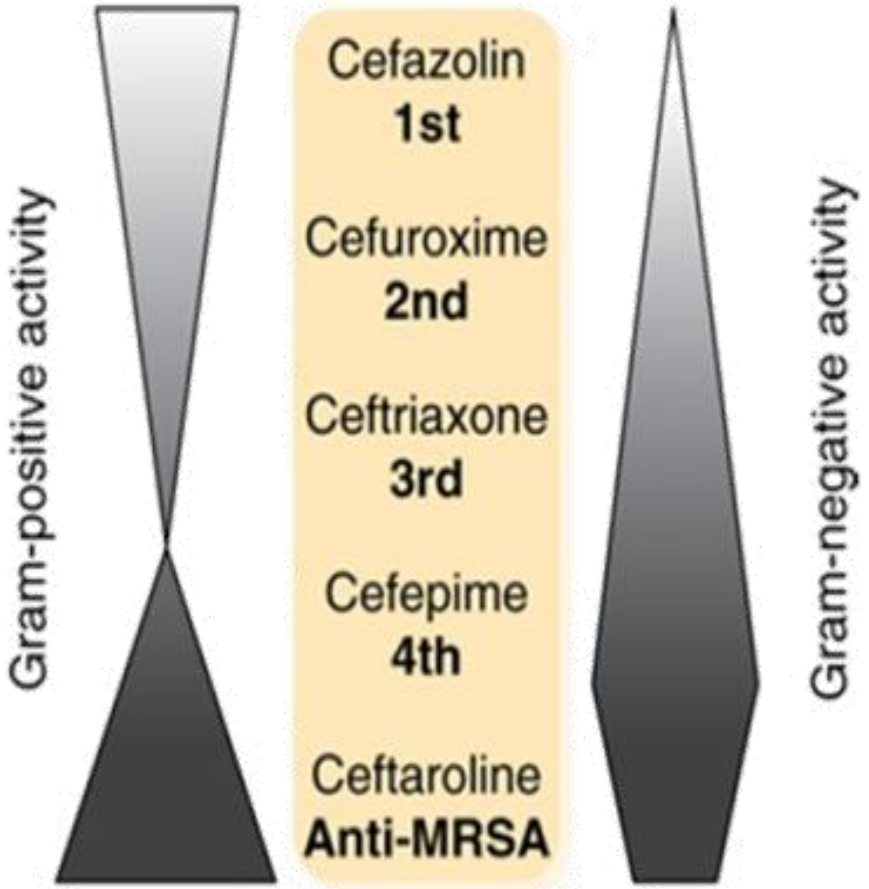
Prices?

CONCLUSION

Ceftaroline as a new generation of cephalosporin

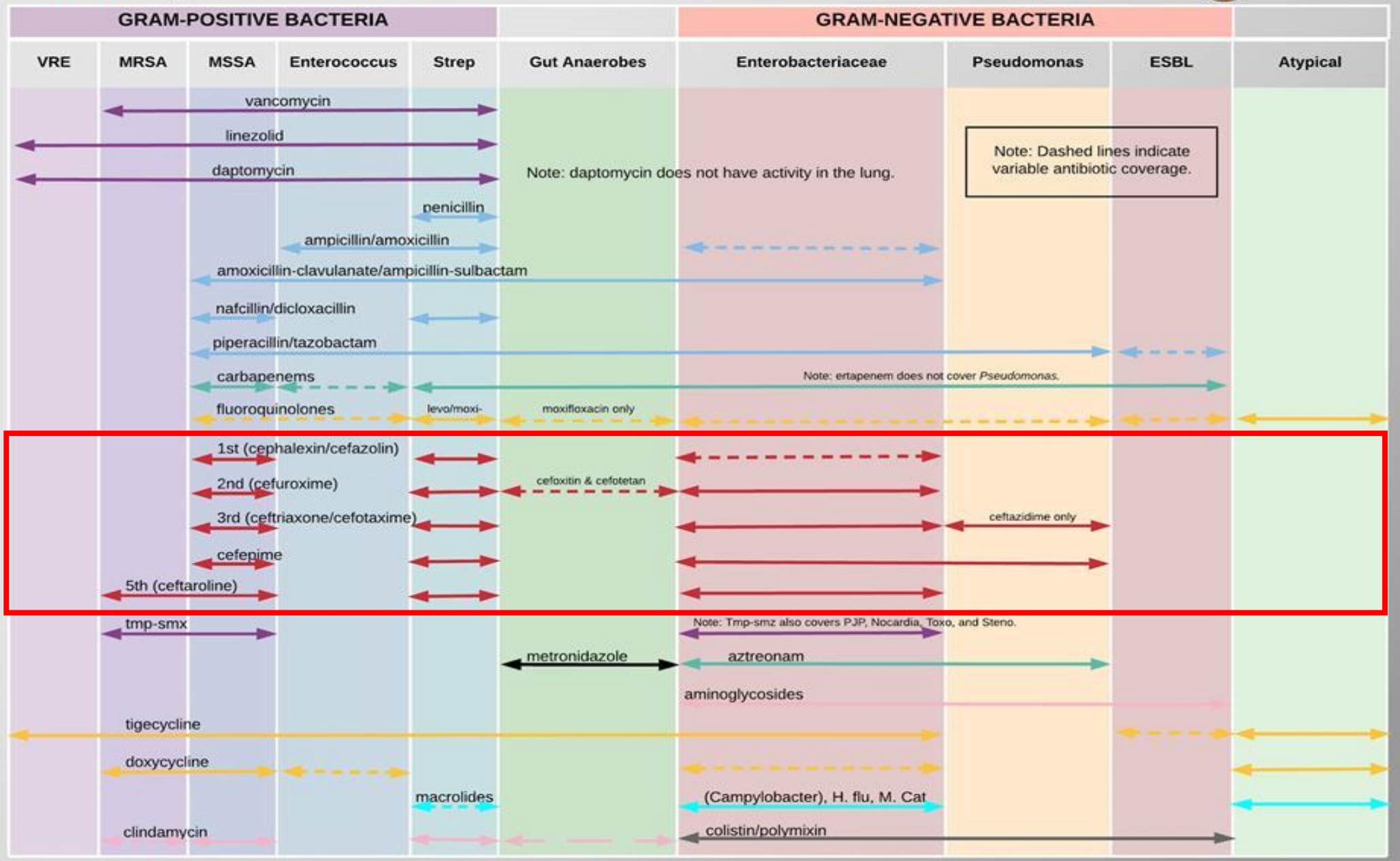
INTRODUCTION

Cephalosporin generation	Agents
1st generation	cefazolin, cephalexin, cefadroxil, cephalothin, cephapirin,cephradine
2nd generation	cefuroxime, cefoxitin, cefotetan, cefprozil, loracarbef, cefmetazole, cefonicid, cefamandole, cefaclor
3rd generation	ceftriaxone, cefotaxime, ceftazidime, cefdinir, cefpodoxime, cefixime, ceftibuten, cepoperazone, ceftizoxime, cefditoren
4th generation	cefepime
5th generation	**ceftaroline**, ceftofibrole



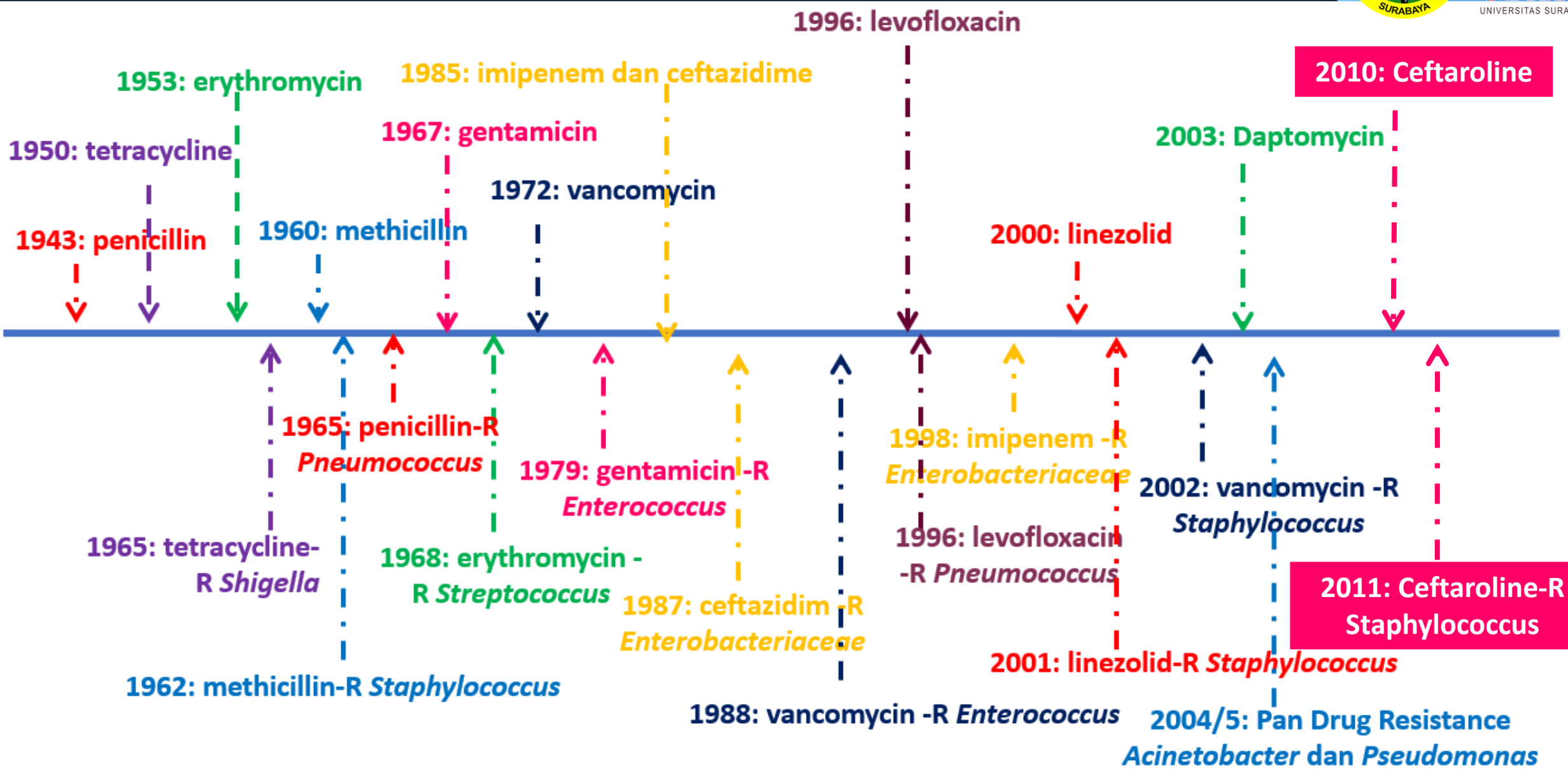
INTRODUCTION

General Spectrum of Antibiotics



Please also refer to patient-level culture susceptibilities, intitutional antibiogram, or the Antimicrobial Stewardship Intranet Site (http://vaww.salt-lake.med.va.gov/antibiotics/).
Contact Antimicrobial Stewardship or Infectious Diseases Consult Team for additional questions.

INTRODUCTION



CEFTAROLINE

Informasi mengenai perijinan

	FDA	EMA	TGA
Approval year	2010	2012	2013
Brand name	Teflaro®	Zinforo®	
Bentuk sediaan	600 mg atau 400 mg serbuk steril dalam 20 ml vial (IV)	600 mg serbuk steril untuk larutan injeksi (IV)	
Indikasi	*acute bacterial skin and skin structure infections* (ABSSSI) dan *community-acquired bacterial pneumonia* (CABP)‡		
Dosis	600 mg setiap 12 jam melalui infus selama 1 jam baik untuk ABSSSI (5-14 hari) dan CABP (5-7 hari) untuk pasien dewasa ≥ 18 tahun		

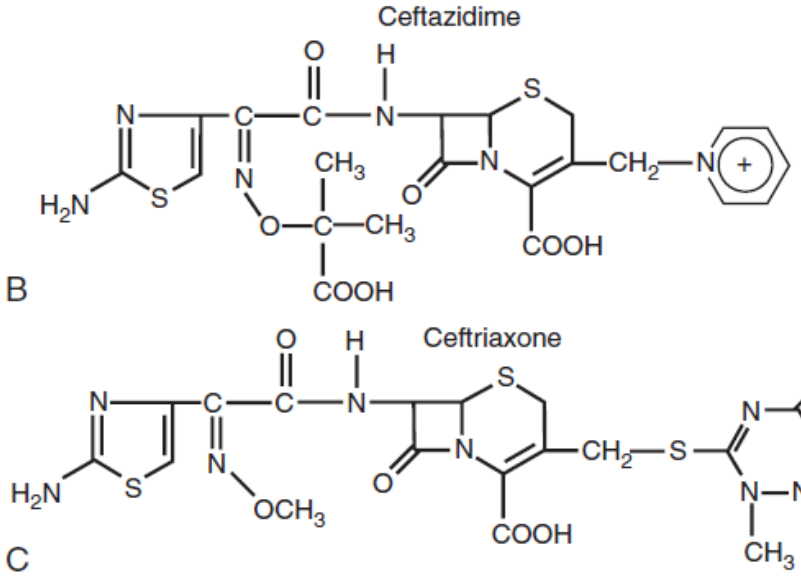
FDA: food and drug administration (USA) | **EMA:** european medicine agency | **TGA:** therapeutics goods administration (AUS)

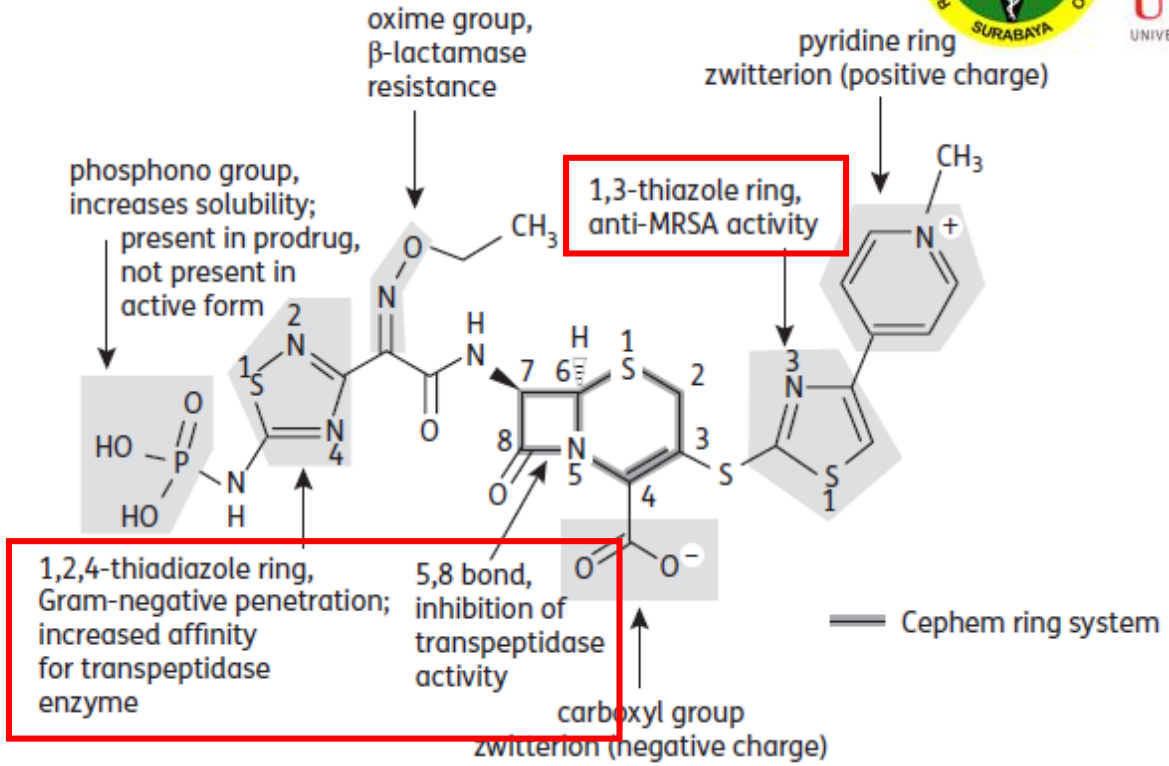
‡ **FDA, TGA:** untuk dewasa ≥ 18 tahun

EMA: neonate, infants, children, adolescent, adult

CEFTAROLINE

Struktur dan aktivitas





Kelas terapi dan mekanisme aksi

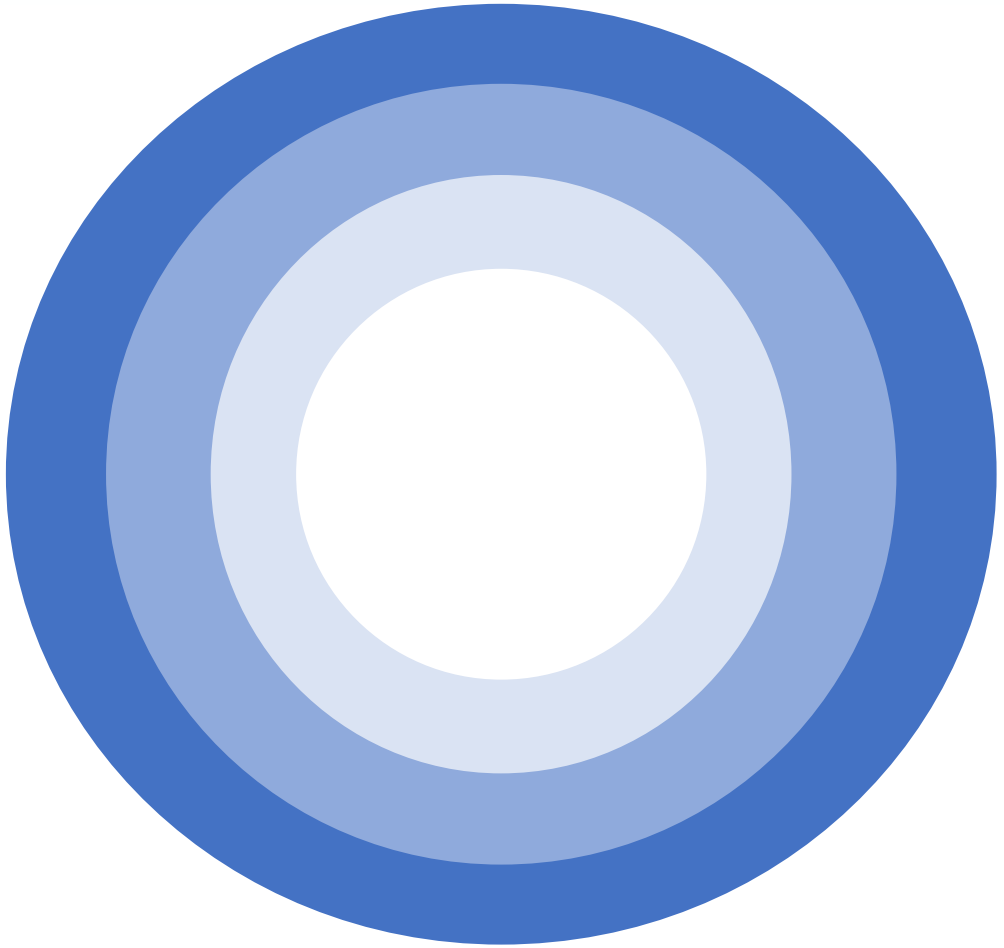
- Merupakan antibiotik golongan **beta-laktam (sefalosporin generasi 5)**
- Ceftaroline bekerja dengan **menghambat** pembentukan **dinding sel** (peptidoglikan) melalui PBP **1a**, 1b, **2a**, **2b, 2x**, 3 (enzim transpeptidase) yang menghubungkan D-ala (pada NAG) dan lisin (pada NAM), yang disebut ***cross-linking***.
- Memiliki aktivitas terhadap **MRSA**, namun **tidak** pada ***Pseudomonas aeruginosa*** → disebut ***anti*-MRSA *cephalosporins***

CEFTAROLINE

Farmakokinetik Ceftaroline Fosamil

FK	Keterangan
A	C_{max}: • 21,3 mcg/ml saat diberikan 600 mg secara IV infus setiap 12 jam selama 1 jam pada subyek sehat dalam 14 hari → t_{max}: 0,9 jam • 32,5 mcg/ml saat diberikan 600 mg secara IV infus (50 ml) setiap 8 jam selama 5 menit dan 17,4 mcg/ml diberikan dalam 60 menit selama 5 hari
D	V_{dss}: 20,3 L (pada pasien dewasa sehat) ***Binding protein***: 20%, ikatan O-P bisa menurun sedikit pada konsentrasi >50 mcg/ml
M	Ceftaroline fosamil merupakan **pro-drug**, namun **bukan substrat** CYP P450 Ceftaroline fosamil diubah menjadi **ceftaroline (aktif)** oleh **fosfatase di plasma**. Cincin beta laktam **dihidrolisis** menjadi **ceftaroline M-1 (inaktif)**.
E	Ceftaroline dan metabolitnya diekskresi melalui **ginjal** (filtrasi glomerulus) dalam bentuk urin (64% *as unchanged*, 2% ceftaroline M-1) dan 6% diekskresi melalui feses $t_{1/2}$: 2,7 jam

EVIDENCE - PNEUMONIA



	Modified intention to treat (MITT)
	Clinical modified intention to treat (cMITT)
	Clinically evaluable (CE)
	Microbiologically evaluable (ME)

MITT

- Seluruh pasien yang memenuhi **protokol penelitian** dan ter**diagnosis** penyakit (CAP/SSTI) dengan/tanpa gejala klinis yang memperoleh terapi antibiotik

cMITT

- Seluruh pasien pada MITT yang memiliki **tanda dan gejala klinis** penyakit (CAP/SSTI) yang memperoleh terapi antibiotik dengan/tanpa *confounding factor* dan *test of cure* (TOC)

CE

- Pasien dalam cMITT **tanpa *confounding factor*,** dengan/ tanpa test mikrobiologi

ME

- Pasien dalam CE dengan **test mikrobiologi**

EVIDENCE - PNEUMONIA (1)

Journal of
Clinical Medicine

MDPI

Article

Efficacy and Safety of Ceftaroline for the Treatment of Community-Acquired Pneumonia: A Systemic Review and Meta-Analysis of Randomized Controlled Trials

Shao-Huan Lan [1], Shen-Peng Chang [2], Chih-Cheng Lai [3], Li-Chin Lu [4] and Chien-Ming Chao [3,*]

Received: 15 May 2019; Accepted: 7 June 2019; Published: 9 June 2019

EVIDENCE - PNEUMONIA (1)

Table 1. Characteristics of included studies.

Study, Published Year	Study Design	Study Period	Study Population	No of Patients		Dose Regimen	
				Ceftaroline	Comparator	Ceftaroline	Comparator
File et al., 2011 [20]	Multicenter, multinational, double-blinded, randomized trial	January 2008 to December 2008	Adult patients with PORT risk class III or IV CAP requiring hospitalization and IV therapy	304	309	600 mg q12 h	Ceftriaxone 1 g q24 h
Low et al., 2011 [21]	Multicenter, multinational, double-blinded, randomized trial	2007–2009	Patients (aged ≥18 years) with PORT risk class III or IV CAP requiring hospitalization and IV therapy	317	310	600 mg q12 h	Ceftriaxone 1 g q24 h
Zhong et al., 2015 [22]	Multicenter, multinational, double-blinded, randomized trial	2011–2013	Adult Asian patients with PORT risk class III–IV CAP	381	382	600 mg q12 h	Ceftriaxone 2 g q24 h
Cannavino et al., 2016 [23]	Multicenter, multinational, randomized	2012–2014	Ages of 2 months and <18 years with CAP requiring hospitalization and IV antibacterial therapy	121	39	Age < 6 m, 8 mg/kg q8 h; aged ≥ 6 m, 12 mg/kg q8 h for those weighing ≤ 33 kg or 400 mg q8 h for those weighing >33 kg	Ceftriaxone 75 mg/kg/d to a maximum 4g/d q12 h
Blumer et al., 2016 [24]	Multicenter, multinational randomized, observe-blinded	2012–2014	Pediatric patients between 2 months and 17 years of age with complicated CAP	30	10	15 mg/kg or 600 mg q8 h if weight > 40 kg if ≥6 m or 10 mg/kg q8 h if <6 m	Ceftriaxone, 75 mg/kg/d q12 h, and vancomycin 15 mg/kg q6 h

Primary outcome:

- *Overall clinical cure* – tanda dan gejala klinis pneumonia **atau** perbaikan kondisi pada saat berhenti menggunakan antibiotik. Dinilai pada saat *end of test* (EOT) dan *test of cure* (TOC)

Secondary outcome:

- Risiko kejadian *adverse effect* (ringan, sedang, dan berat), *discontinuation* karena AE, *relapse rate*, mortalitas

EVIDENCE - PNEUMONIA (1)

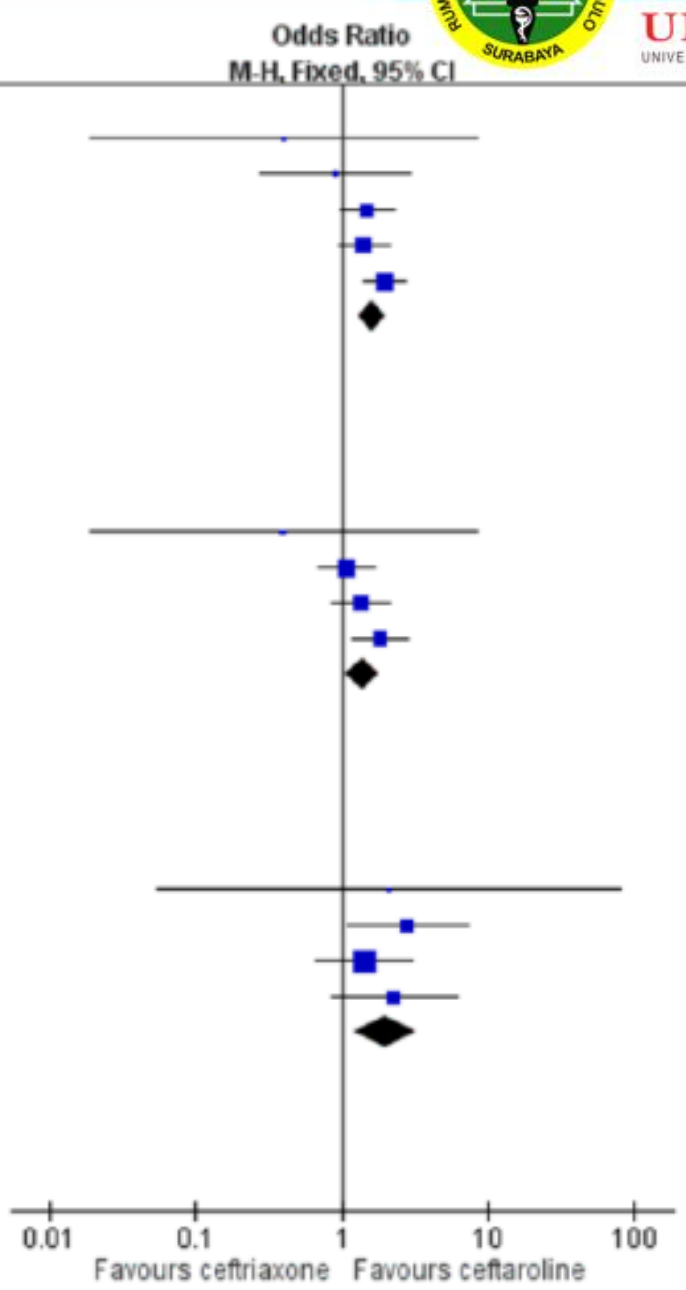
***OUTCOME* 1:**

overall clinical cure rates

based on patient population

Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 MITT population						
Blumer et al, 2016 [24]	26	29	9	9	1.2%	0.40 [0.02, 8.45]
Cannavino et al, 2016 [23]	94	107	32	36	4.3%	0.90 [0.27, 2.97]
File et al, 2011 [20]	244	291	233	300	27.4%	1.49 [0.99, 2.26]
Low et al, 2011 [21]	235	289	206	273	29.3%	1.42 [0.94, 2.12]
Zhong et al, 2015 [22]	305	381	256	382	37.7%	1.98 [1.42, 2.75]
Subtotal (95% CI)		**1097**		**1000**	**100.0%**	**1.61 [1.31, 1.99]**
Total events	904		736			
Heterogeneity: Chi² = 3.70, df = 4 (P = 0.45); I² = 0%						
Test for overall effect: Z = 4.42 (P < 0.00001)						
1.1.2 CE population						
Blumer et al, 2016 [24]	26	29	9	9	1.7%	0.40 [0.02, 8.45]
File et al, 2011 [20]	194	244	183	234	38.2%	1.08 [0.70, 1.68]
Low et al, 2011 [21]	193	235	166	215	30.9%	1.36 [0.86, 2.15]
Zhong et al, 2015 [22]	217	258	178	240	29.2%	1.84 [1.19, 2.87]
Subtotal (95% CI)		**766**		**698**	**100.0%**	**1.38 [1.07, 1.78]**
Total events	630		536			
Heterogeneity: Chi² = 3.48, df = 3 (P = 0.32); I² = 14%						
Test for overall effect: Z = 2.46 (P = 0.01)						
1.1.3 ME population						
Blumer et al, 2016 [24]	9	10	1	1	1.5%	2.11 [0.06, 79.97]
File et al, 2011 [20]	62	69	54	71	23.9%	2.79 [1.08, 7.23]
Low et al, 2011 [21]	69	85	57	76	50.1%	1.44 [0.68, 3.05]
Zhong et al, 2015 [22]	50	57	47	62	24.5%	2.28 [0.85, 6.08]
Subtotal (95% CI)		**221**		**210**	**100.0%**	**1.98 [1.20, 3.25]**
Total events	190		159			
Heterogeneity: Chi² = 1.27, df = 3 (P = 0.74); I² = 0%						
Test for overall effect: Z = 2.69 (P = 0.007)						

Test for subgroup differences: Chi² = 1.87, df = 2 (p = 0.39), I² = 0%



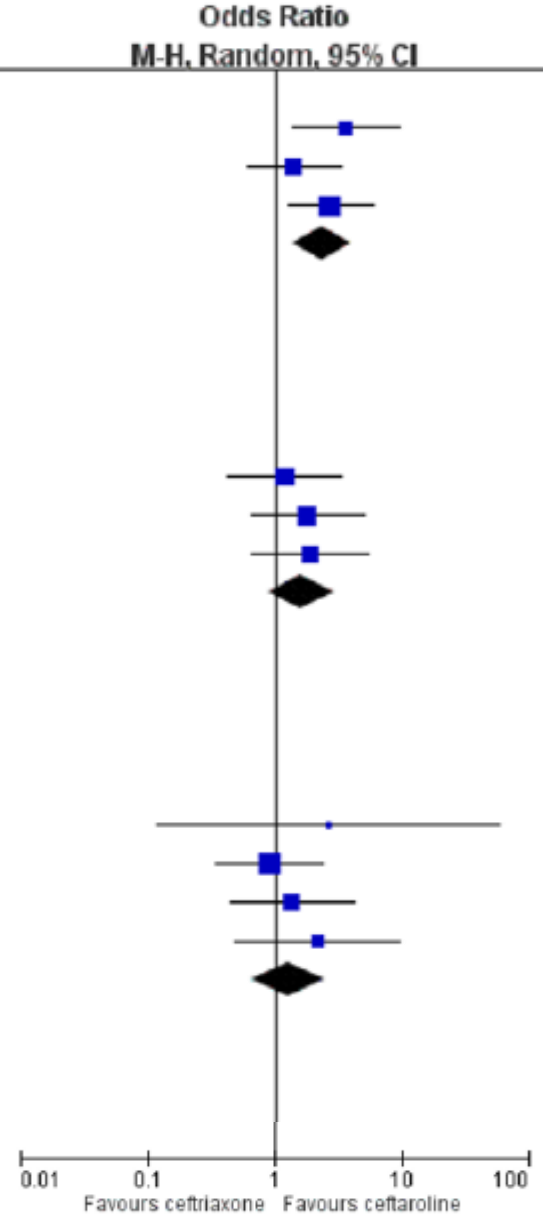
EVIDENCE - PNEUMONIA (1)

***OUTCOME* 1:**

overall clinical cure rates

based on patient group

Study or Subgroup	Ceftaroline Events	Total	Ceftriaxone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.3.1 PORT risk III						
File et al, 2011 [20]	136	150	113	142	27.0%	2.49 [1.26, 4.95]
Low et al, 2011 [21]	113	137	104	132	33.3%	1.27 [0.69, 2.33]
Zhong et al, 2015 [22]	148	173	126	169	39.7%	2.02 [1.17, 3.49]
Subtotal (95% CI)		**460**		**443**	**100.0%**	**1.83 [1.26, 2.67]**
Total events	397		343			
Heterogeneity: Tau² = 0.02; Chi² = 2.32, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 3.14 (P = 0.002)						
1.3.2 PORT risk IV						
File et al, 2011 [20]	58	74	70	92	33.4%	1.14 [0.55, 2.37]
Low et al, 2011 [21]	80	98	62	83	35.3%	1.51 [0.74, 3.07]
Zhong et al, 2015 [22]	69	85	52	71	31.3%	1.58 [0.74, 3.36]
Subtotal (95% CI)		**257**		**246**	**100.0%**	**1.39 [0.91, 2.12]**
Total events	207		184			
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 2 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.53 (P = 0.13)						
1.3.3 Prior antibiotic use						
Cannavino et al, 2016 [23]	12	18	2	4	4.4%	2.00 [0.22, 17.89]
File et al, 2011 [20]	85	105	87	106	43.6%	0.93 [0.46, 1.86]
Low et al, 2011 [21]	67	80	71	88	33.3%	1.23 [0.56, 2.73]
Zhong et al, 2015 [22]	42	49	35	45	18.6%	1.71 [0.59, 4.97]
Subtotal (95% CI)		**252**		**243**	**100.0%**	**1.18 [0.75, 1.87]**
Total events	206		195			
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 3 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.72 (P = 0.47)						



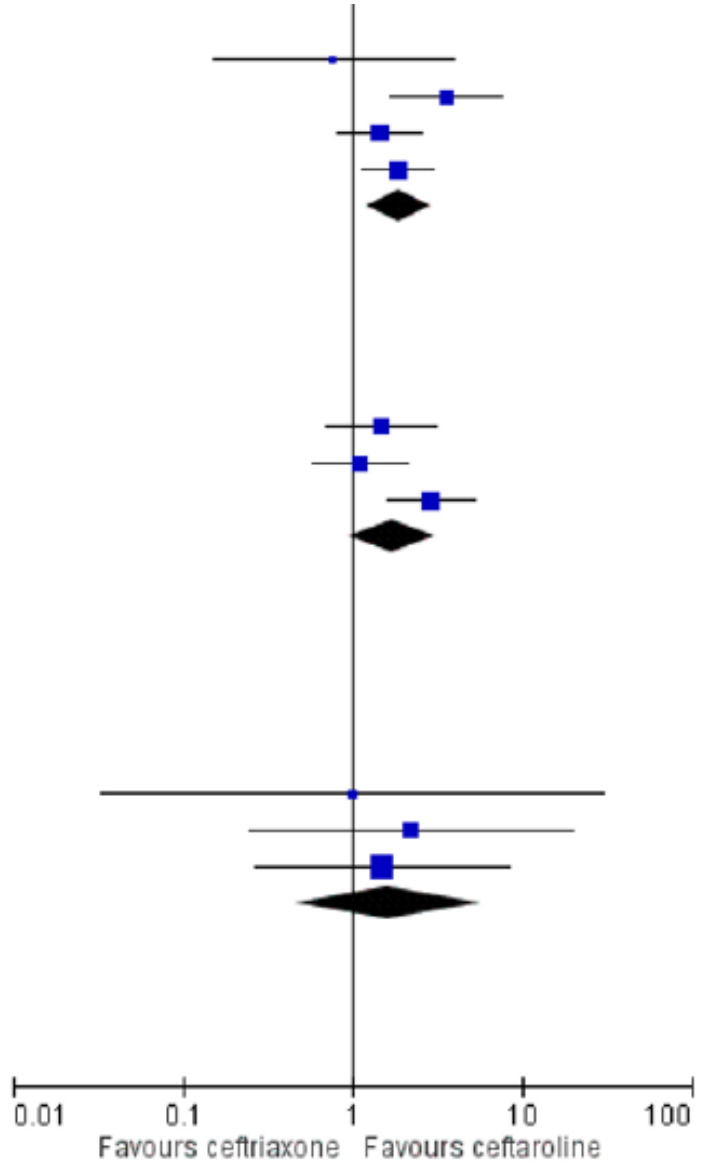
EVIDENCE - PNEUMONIA (1)

***OUTCOME* 1:**

overall clinical cure rates

based on patient group

1.3.4 No prior antibiotic use						
Cannavino et al, 2016 [23]	82	89	30	32	6.7%	0.78 [0.15, 3.97]
File et al, 2011 [20]	109	119	96	128	22.8%	3.63 [1.70, 7.78]
Low et al, 2011 [21]	126	155	95	127	32.5%	1.46 [0.83, 2.58]
Zhong et al, 2015 [22]	175	209	143	195	38.0%	1.87 [1.15, 3.04]
Subtotal (95% CI)		**572**		**482**	**100.0%**	**1.90 [1.22, 2.95]**
Total events	492		364			
Heterogeneity: Tau² = 0.07; Chi² = 4.75, df = 3 (P = 0.19); I² = 37%						
Test for overall effect: Z = 2.83 (P = 0.005)						
1.3.5 Elderly						
File et al, 2011 [20]	105	119	97	116	30.2%	1.47 [0.70, 3.09]
Low et al, 2011 [21]	90	113	80	103	33.9%	1.13 [0.59, 2.16]
Zhong et al, 2015 [22]	133	151	111	155	36.0%	2.93 [1.60, 5.36]
Subtotal (95% CI)		**383**		**374**	**100.0%**	**1.72 [0.95, 3.11]**
Total events	328		288			
Heterogeneity: Tau² = 0.16; Chi² = 4.78, df = 2 (P = 0.09); I² = 58%						
Test for overall effect: Z = 1.79 (P = 0.07)						
1.3.6 Bacteremia						
Blumer et al, 2016 [24]	1	2	0	0		Not estimable
Cannavino et al, 2016 [23]	2	4	1	2	13.8%	1.00 [0.03, 29.81]
File et al, 2011 [20]	6	8	4	7	33.1%	2.25 [0.25, 20.13]
Low et al, 2011 [21]	9	13	6	10	53.1%	1.50 [0.27, 8.45]
Subtotal (95% CI)		**27**		**19**	**100.0%**	**1.62 [0.46, 5.72]**
Total events	18		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 2 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.75 (P = 0.45)						



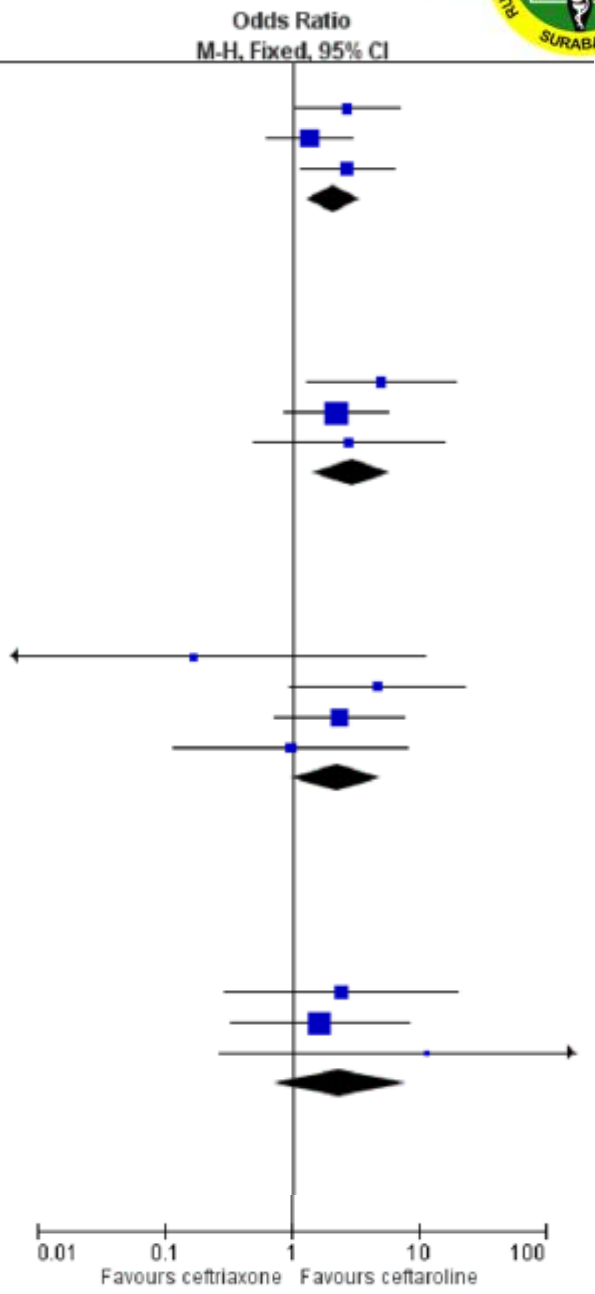
EVIDENCE - PNEUMONIA (1)

***OUTCOME* 1:**

overall clinical cure rates

based on patogens

Study or Subgroup	Ceftaroline Events	Total	Ceftriaxone Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 All						
File et al, 2011 [20]	66	75	60	80	23.7%	2.44 [1.03, 5.78]
Low et al, 2011 [21]	72	90	66	88	45.3%	1.33 [0.66, 2.70]
Zhong et al, 2015 [22]	68	80	67	96	31.0%	2.45 [1.16, 5.21]
Subtotal (95% CI)		**245**		**264**	**100.0%**	**1.94 [1.25, 3.01]**
Total events	206		193			
Heterogeneity: Chi² = 1.73, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 2.97 (P = 0.003)						
1.5.2 GPC						
File et al, 2011 [20]	32	36	28	43	23.6%	4.29 [1.27, 14.43]
Low et al, 2011 [21]	45	56	36	54	59.8%	2.05 [0.86, 4.88]
Zhong et al, 2015 [22]	24	27	16	21	16.6%	2.50 [0.52, 11.96]
Subtotal (95% CI)		**119**		**118**	**100.0%**	**2.65 [1.40, 5.01]**
Total events	101		80			
Heterogeneity: Chi² = 0.95, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 3.00 (P = 0.003)						
1.5.3 S. pneumoniae						
Cannavino et al, 2016 [23]	0	2	1	2	12.2%	0.20 [0.00, 8.82]
File et al, 2011 [20]	24	27	20	30	20.6%	4.00 [0.97, 16.55]
Low et al, 2011 [21]	35	42	28	40	46.7%	2.14 [0.75, 6.16]
Zhong et al, 2015 [22]	19	22	13	15	20.6%	0.97 [0.14, 6.67]
Subtotal (95% CI)		**93**		**87**	**100.0%**	**2.05 [0.99, 4.25]**
Total events	78		62			
Heterogeneity: Chi² = 2.88, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.92 (P = 0.05)						
1.5.4 S. aureus						
Blumer et al, 2016 [24]	4	4	1	1		Not estimable
File et al, 2011 [20]	8	10	9	14	32.2%	2.22 [0.33, 14.80]
Low et al, 2011 [21]	10	15	9	16	62.4%	1.56 [0.36, 6.69]
Zhong et al, 2015 [22]	4	4	2	4	5.4%	9.00 [0.30, 271.65]
Subtotal (95% CI)		**33**		**35**	**100.0%**	**2.17 [0.74, 6.33]**
Total events	26		21			
Heterogeneity: Chi² = 0.87, df = 2 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						



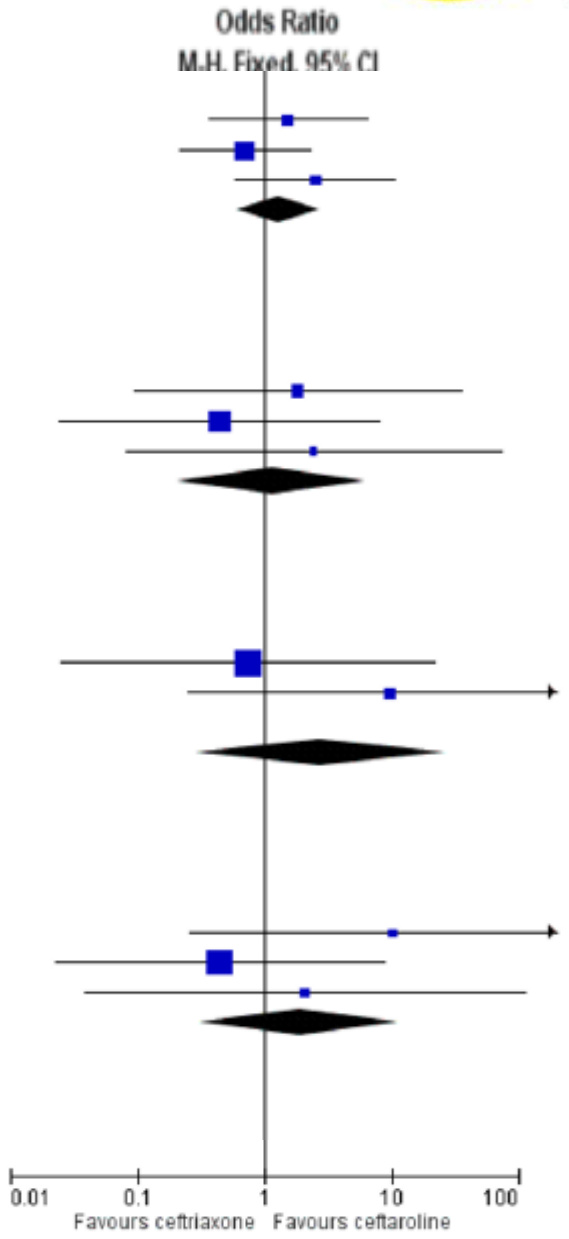
EVIDENCE - PNEUMONIA (1)

***OUTCOME* 1:**

overall clinical cure rates

based on patogens

Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.5 GNB						
File et al, 2011 [20]	39	44	37	44	26.3%	1.48 [0.43, 5.06]
Low et al, 2011 [21]	36	46	39	47	52.5%	0.74 [0.26, 2.08]
Zhong et al, 2015 [22]	28	32	31	41	21.2%	2.26 [0.64, 8.02]
Subtotal (95% CI)		**122**		**132**	**100.0%**	**1.26 [0.65, 2.42]**
Total events	103		107			
Heterogeneity: Chi² = 1.90, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.5.6 H. influenzae						
File et al, 2011 [20]	4	5	7	10	28.4%	1.71 [0.13, 22.51]
Low et al, 2011 [21]	13	15	13	14	54.6%	0.50 [0.04, 6.22]
Zhong et al, 2015 [22]	11	12	5	6	16.9%	2.20 [0.11, 42.73]
Subtotal (95% CI)		**32**		**30**	**100.0%**	**1.13 [0.26, 4.99]**
Total events	28		25			
Heterogeneity: Chi² = 0.70, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.87)						
1.5.7 H. parainfluenzae						
File et al, 2011 [20]	7	8	9	10	74.5%	0.78 [0.04, 14.75]
Low et al, 2011 [21]	9	9	6	8	25.5%	7.31 [0.30, 178.57]
Zhong et al, 2015 [22]	0	0	4	6		Not estimable
Subtotal (95% CI)		**17**		**24**	**100.0%**	**2.44 [0.34, 17.60]**
Total events	16		19			
Heterogeneity: Chi² = 1.03, df = 1 (P = 0.31); I² = 3%						
Test for overall effect: Z = 0.89 (P = 0.38)						
1.5.8 E. coli						
File et al, 2011 [20]	8	8	5	7	13.3%	7.73 [0.31, 193.44]
Low et al, 2011 [21]	2	4	4	6	66.0%	0.50 [0.04, 6.68]
Zhong et al, 2015 [22]	3	3	5	6	20.6%	1.91 [0.06, 61.34]
Subtotal (95% CI)		**15**		**19**	**100.0%**	**1.76 [0.36, 8.50]**
Total events	13		14			
Heterogeneity: Chi² = 1.72, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						



EVIDENCE - PNEUMONIA (1)

OUTCOME 1:

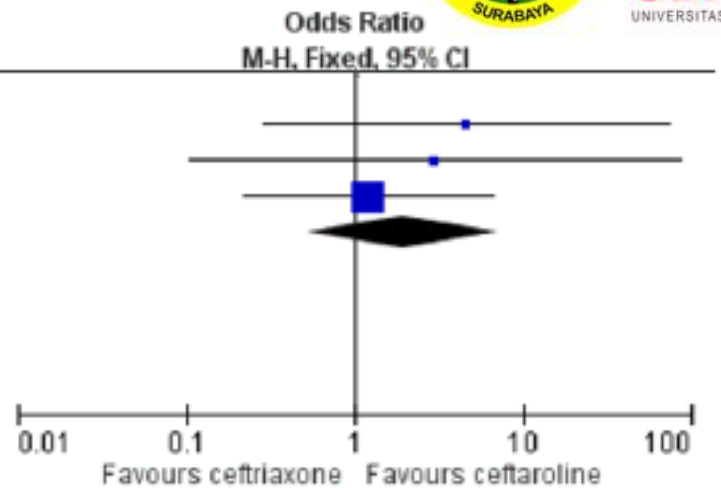
overall clinical cure rates

based on patogens

Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.9 K. pneumoniae						
File et al, 2011 [20]	7	8	3	5	14.0%	4.67 [0.30, 73.38]
Low et al, 2011 [21]	7	7	7	8	13.4%	3.00 [0.10, 86.09]
Zhong et al, 2015 [22]	11	14	12	16	72.7%	1.22 [0.22, 6.73]
Subtotal (95% CI)		**29**		**29**	**100.0%**	**1.94 [0.53, 7.16]**
Total events	25		22			

Heterogeneity: Chi² = 0.74, df = 2 (P = 0.69); I² = 0%

Test for overall effect: Z = 1.00 (P = 0.32)



Test for subgroup differences: Chi² = 3.22, df = 8 (p = 0.92), I² = 0%

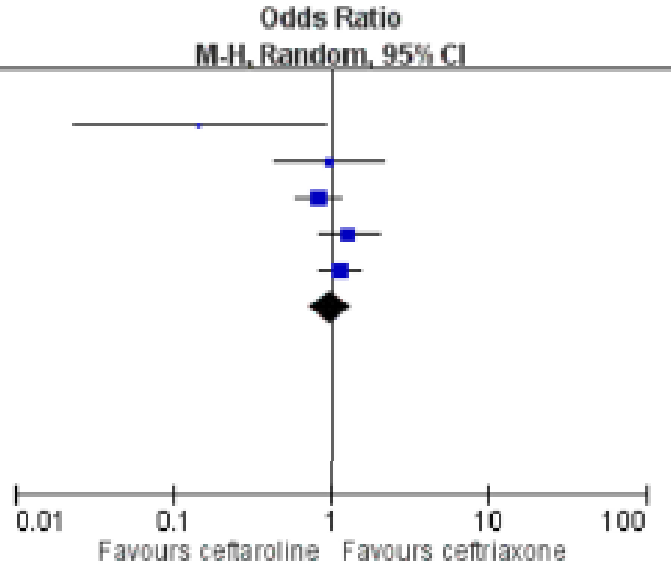
OUTCOME 2:

Risk of adverse effect

Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Odds Ratio M-H, Random, 95% CI
2.1.1 TEAE						
Blumer et al, 2016 [24]	12	30	8	10	2.4%	0.17 [0.03, 0.92]
Cannavino et al, 2016 [23]	55	121	18	39	11.1%	0.97 [0.47, 2.01]
File et al, 2011 [20]	119	298	136	308	29.8%	0.84 [0.61, 1.16]
Low et al, 2011 [21]	64	315	52	307	24.0%	1.25 [0.83, 1.88]
Zhong et al, 2015 [22]	172	381	163	383	32.8%	1.11 [0.83, 1.48]
Subtotal (95% CI)		**1145**		**1047**	**100.0%**	**0.99 [0.75, 1.30]**
Total events	422		377			

Heterogeneity: Tau² = 0.04; Chi² = 6.99, df = 4 (P = 0.14); I² = 43%

Test for overall effect: Z = 0.07 (P = 0.94)



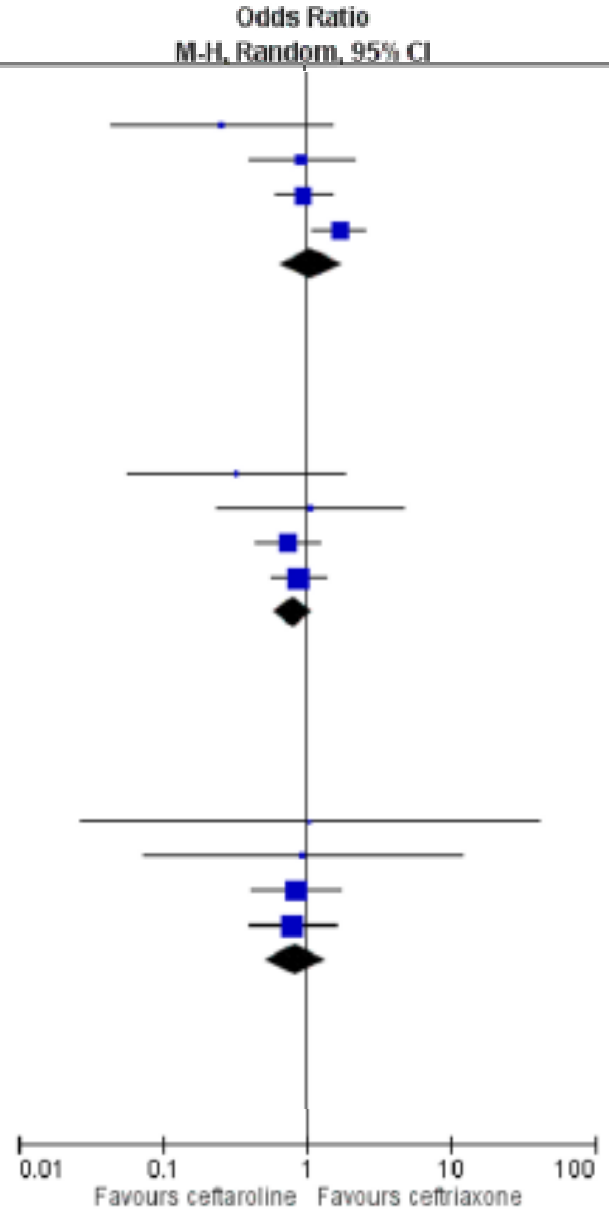
TEAE: *treatment-emergent adverse events*

EVIDENCE - PNEUMONIA (1)

***OUTCOME* 2:**

Risk of adverse effect

Study or Subgroup	Ceftaroline Events	Total	Ceftriaxone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2.1.2 mild AE						
Blumer et al, 2016 [24]	5	30	4	10	6.9%	0.30 [0.06, 1.47]
Cannavino et al, 2016 [23]	42	121	14	39	20.7%	0.95 [0.45, 2.02]
File et al, 2011 [20]	59	298	62	308	35.5%	0.98 [0.66, 1.46]
Low et al, 2011 [21]	91	315	61	307	36.8%	1.64 [1.13, 2.38]
Subtotal (95% CI)		**764**		**664**	**100.0%**	**1.08 [0.69, 1.70]**
Total events	197		141			
Heterogeneity: Tau² = 0.11; Chi² = 7.00, df = 3 (P = 0.07); I² = 57%						
Test for overall effect: Z = 0.35 (P = 0.73)						
2.1.3 moderate AE						
Blumer et al, 2016 [24]	6	30	4	10	3.4%	0.38 [0.08, 1.77]
Cannavino et al, 2016 [23]	10	121	3	39	4.5%	1.08 [0.28, 4.14]
File et al, 2011 [20]	41	298	52	308	41.2%	0.79 [0.50, 1.22]
Low et al, 2011 [21]	58	315	61	307	50.9%	0.91 [0.61, 1.36]
Subtotal (95% CI)		**764**		**664**	**100.0%**	**0.84 [0.63, 1.11]**
Total events	115		120			
Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 3 (P = 0.70); I² = 0%						
Test for overall effect: Z = 1.22 (P = 0.22)						
2.1.4 Severe AE						
Blumer et al, 2016 [24]	1	30	0	10	1.7%	1.07 [0.04, 28.30]
Cannavino et al, 2016 [23]	3	121	1	39	3.6%	0.97 [0.10, 9.56]
File et al, 2011 [20]	19	298	22	308	46.3%	0.89 [0.47, 1.67]
Low et al, 2011 [21]	20	315	23	307	48.5%	0.84 [0.45, 1.56]
Subtotal (95% CI)		**764**		**664**	**100.0%**	**0.87 [0.56, 1.34]**
Total events	43		46			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 3 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						

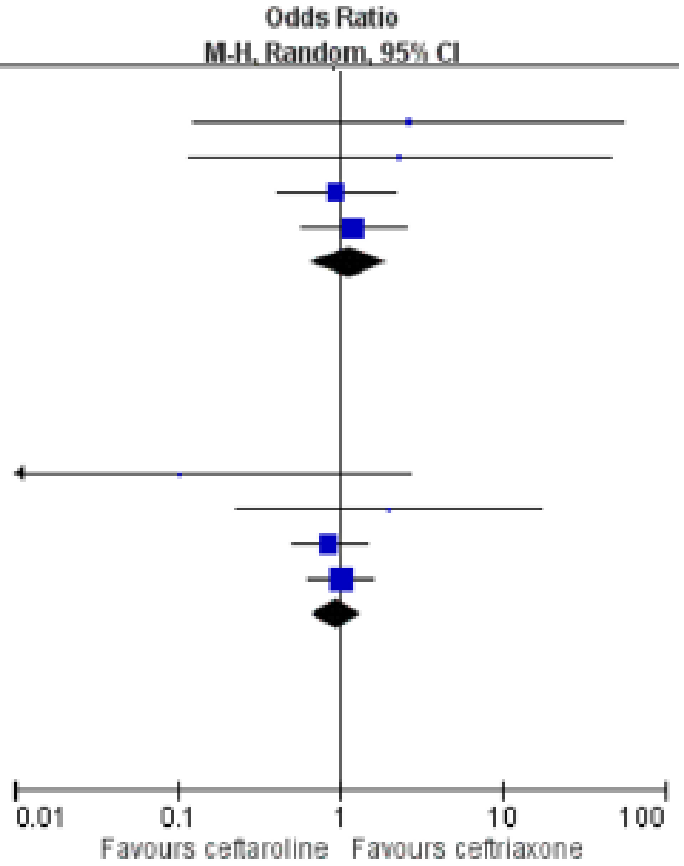


EVIDENCE - PNEUMONIA (1)

OUTCOME 2:

Risk of adverse effect

Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Odds Ratio M-H, Random, 95% CI
2.1.5 DC drug due to AE						
Blumer et al, 2016 [24]	3	30	0	10	3.1%	2.67 [0.13, 56.28]
Cannavino et al, 2016 [23]	3	121	0	39	3.3%	2.33 [0.12, 46.17]
File et al, 2011 [20]	11	298	12	308	41.8%	0.95 [0.41, 2.18]
Low et al, 2011 [21]	16	315	13	307	51.8%	1.21 [0.57, 2.56]
Subtotal (95% CI)		**764**		**664**	**100.0%**	**1.14 [0.67, 1.96]**
Total events	33		25			
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 3 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.63)						
2.1.6 SAE						
Blumer et al, 2016 [24]	0	30	1	10	1.1%	0.10 [0.00, 2.77]
Cannavino et al, 2016 [23]	6	121	1	39	2.6%	1.98 [0.23, 17.00]
File et al, 2011 [20]	28	298	33	308	42.3%	0.86 [0.51, 1.47]
Low et al, 2011 [21]	41	315	39	307	54.0%	1.03 [0.64, 1.64]
Subtotal (95% CI)		**764**		**664**	**100.0%**	**0.95 [0.67, 1.34]**
Total events	75		74			
Heterogeneity: Tau² = 0.00; Chi² = 2.43, df = 3 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						



Test for subgroup differences: $Chi^2 = 1.78$, df = 5 (p = 0.88), $I^2 = 0\%$

DC: *discontinue* | **SAE:** *serious adverse events*

EVIDENCE – PNEUMONIA (2)

Sotgiu *et al. Respiratory Research* (2018) 19:205
https://doi.org/10.1186/s12931-018-0905-x

RESEARCH Open Access

Efficacy and effectiveness of Ceftaroline Fosamil in patients with pneumonia: a systematic review and meta-analysis

14 studies

Giovanni Sotgiu[1], Stefano Aliberti[2,3*], Andrea Gramegna[2,3], Marco Mantero[2,3], Marta Di Pasquale[2,3], Federica Trogu[1], Laura Saderi[1] and Francesco Blasi[2,3]

CEFTAROLINE vs **CEFTRIAXONE** / **VANCO/LINZ** / **OTHERS**

CAP, HAP, VAP, HCAP / *adult, elderly* vs *younger*, MRSA (van/linz)

EVIDENCE – PNEUMONIA (2)

14 studies

CEFTAROLINE **VS** **CEFTRIAXONE** / **VANCO/LINZ** / **OTHERS**

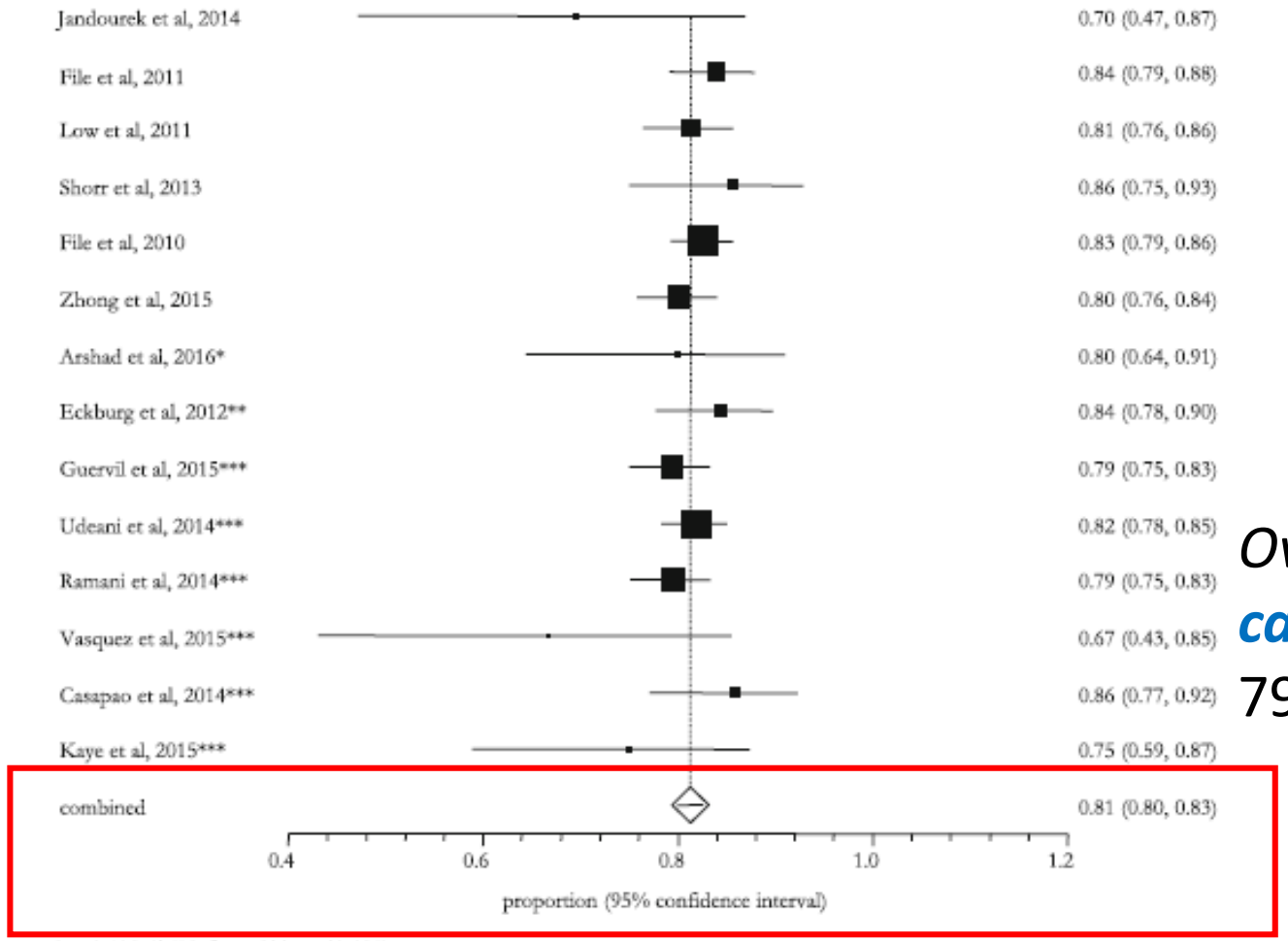
CAP, HAP, VAP, HCAP / *adult, elderly* vs *younger*, MRSA (van/linz)

Outcome:

- ***Efficacy/effectiveness*** dari Ceftaroline fosamil pada pasien **pneumonia** (CAP, HAP, VAP, HCAP) yang terukur pada **salah satu *outcome*** berikut:
  - ❑ Respon pada hari ke 4 terapi
  - ❑ Tingkat kesembuhan pada *end of therapy* (EOT)
  - ❑ Tingkat kesembuhan pada *test of cure* (TOC)
  - ❑ Keberhasilan klinis hari ke 14 dari diagnosis pneumonia
- Keamanan – ***adverse effect***

EVIDENCE – PNEUMONIA (2)

OUTCOME 1: *Efficacy/efffectiveness*



I^2 = 1.2% (95% CI = 0% to 48.1%)
Pooled proportion = 0.812421 (95% CI = 0.798956 to 0.825524)

*Evaluated 14 days from diagnosis of pneumonia
** Evaluated at EOT
*** Not specified

Fig. 2 Efficacy of ceftaroline in the overall pneumonia (including CAP, VAP, HCAP, HAP)

*Overall **efficacy/effectiveness** in **all case** of pneumonia* 81.2% (95% CI: 79.9–82.6; I2: 1.2%)

EVIDENCE – PNEUMONIA (2)

OUTCOME 1: *Efficacy/efffectiveness*

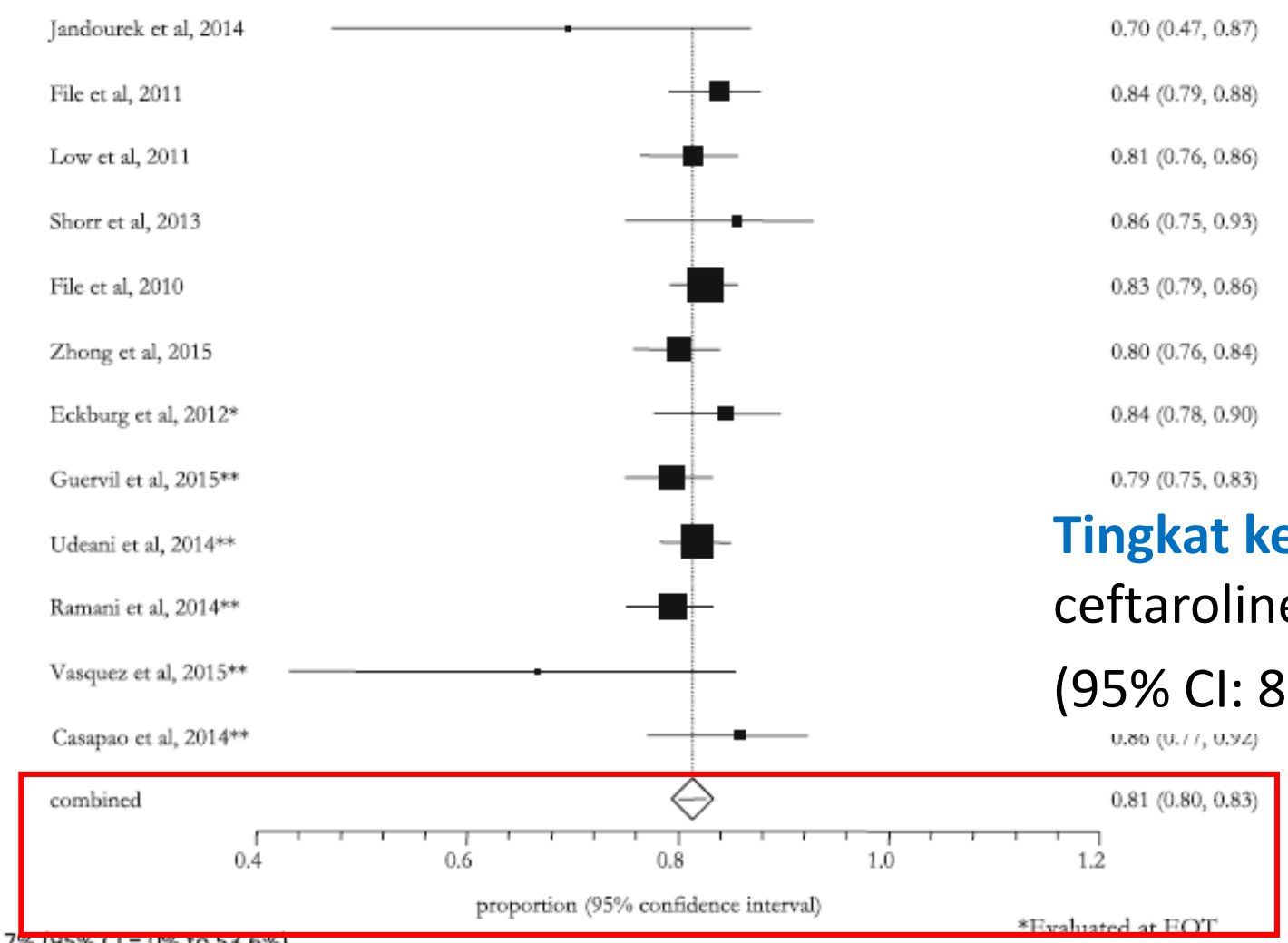
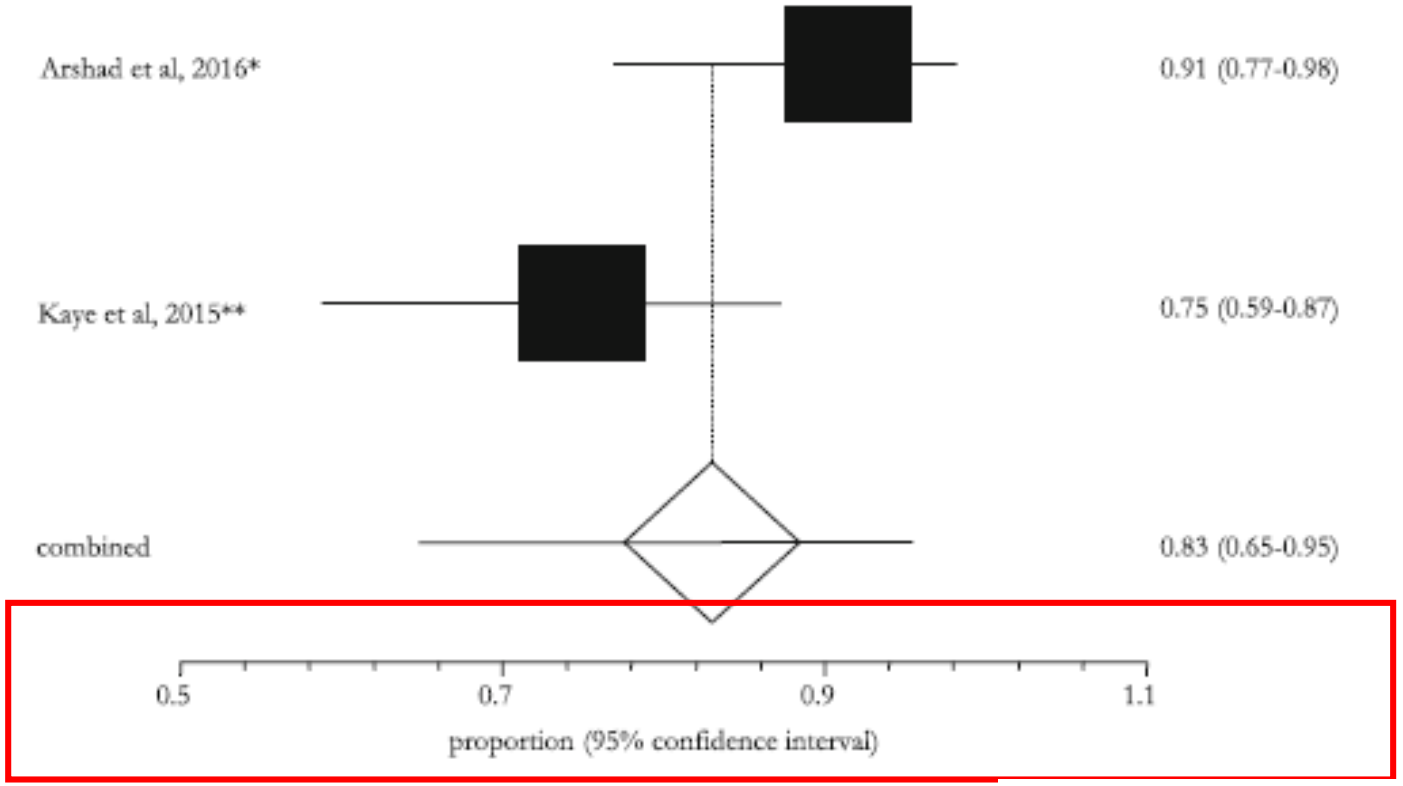


Fig. 3 Clinical success in CAP subjects treated with ceftaroline

Tingkat keberhasilan terapi ceftaroline pada **CAP** adalah **81.3%** (95% CI: 80.0–82.7; I2: 7.7%)

EVIDENCE – PNEUMONIA (2)

OUTCOME 1: *Efficacy/efffectiveness*



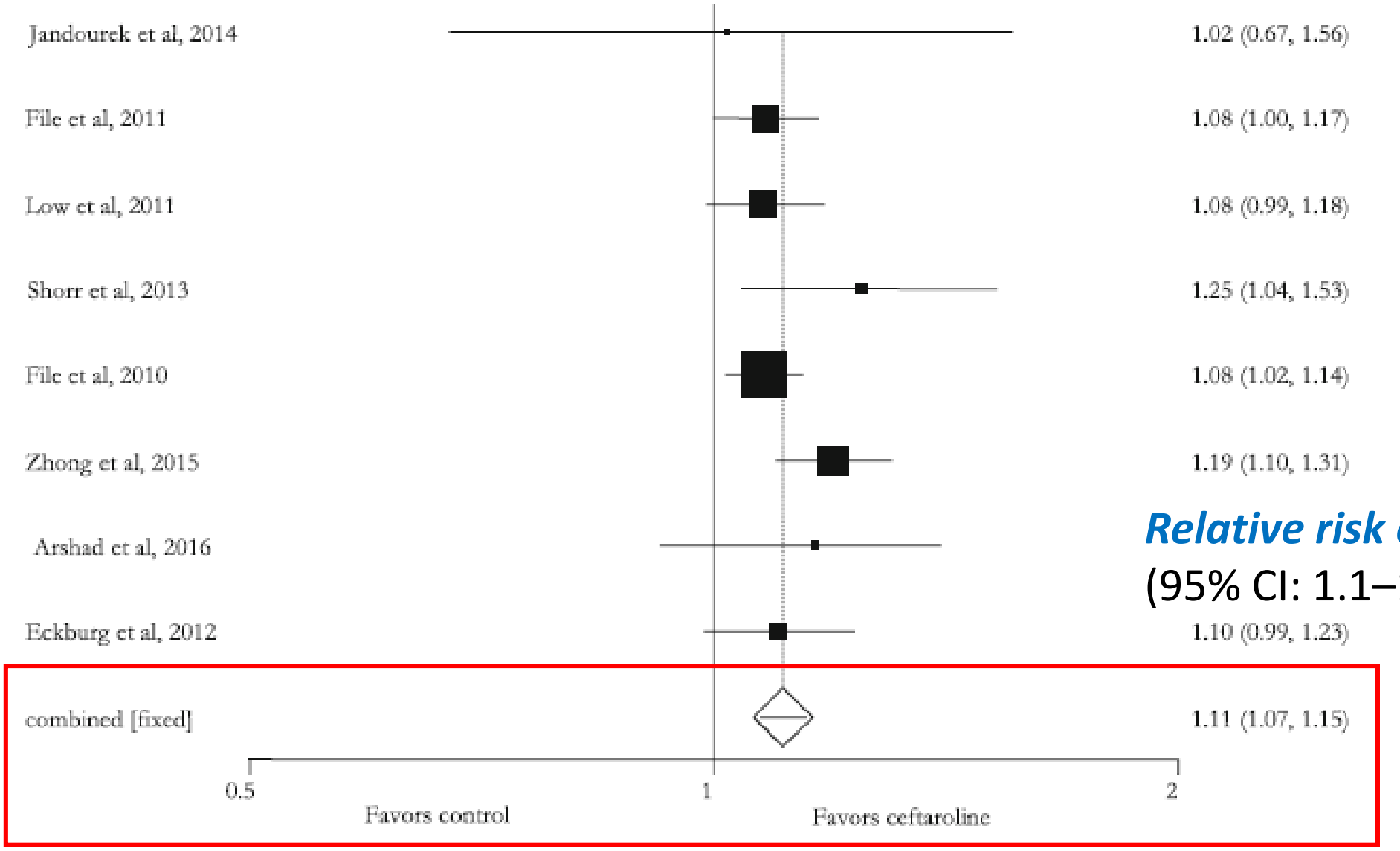
I^2 = *% (95% CI = *% to *%)
Pooled proportion = 0.83 (95% CI = 0.65 to 0.95)

Fig. 4 Clinical success in HAP/VAP/HCAP subjects treated with ceftaroline

Keberhasilan klinis terapi ceftaroline pada **HAP/VAP/HCAP** adalah (83.0%, 95% CI: 65.0–95.0; I2: -)

EVIDENCE – PNEUMONIA (2)

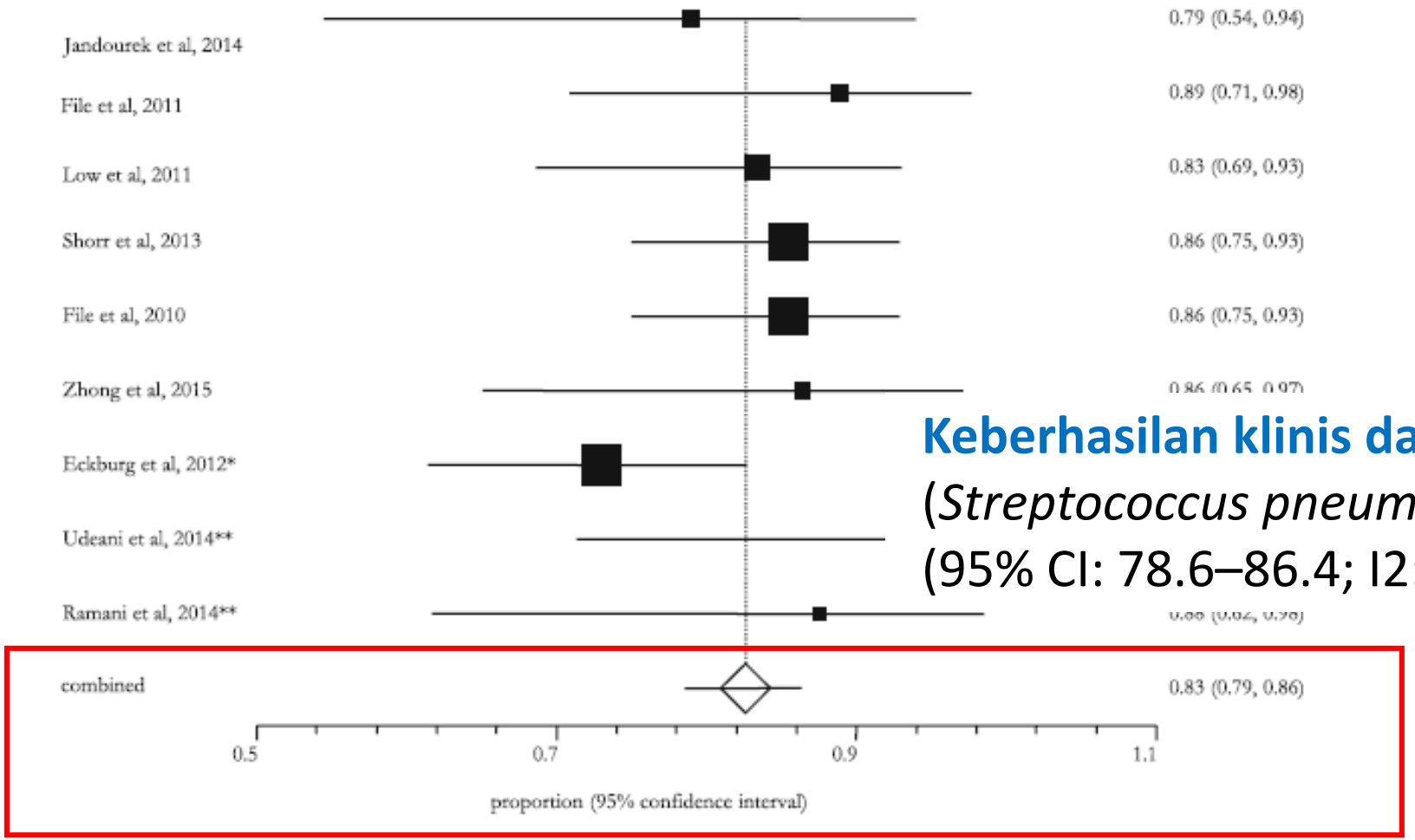
OUTCOME 1: *Efficacy/efffectiveness*



Relative risk of clinical cure was 1.1 (95% CI: 1.1–1.2; I2: 0.0%)

EVIDENCE – PNEUMONIA (2)

OUTCOME 1: *Efficacy/efffectiveness*



Keberhasilan klinis dan mikrobiologi (*Streptococcus pneumoniae*) 82.6% (95% CI: 78.6–86.4; I2: 0.0%)

*Evaluated at EOT
** Not specified

I^2 = 0% (95% CI = 0% to 54.4%)
Pooled proportion = 0.826333 (95% CI = 0.785764 to 0.86346)

Fig. 6 Clinical and microbiological response rates in subjects with *Streptococcus pneumoniae* treated with ceftaroline

EVIDENCE – PNEUMONIA (2)

OUTCOME 1: *Efficacy/efffectiveness*

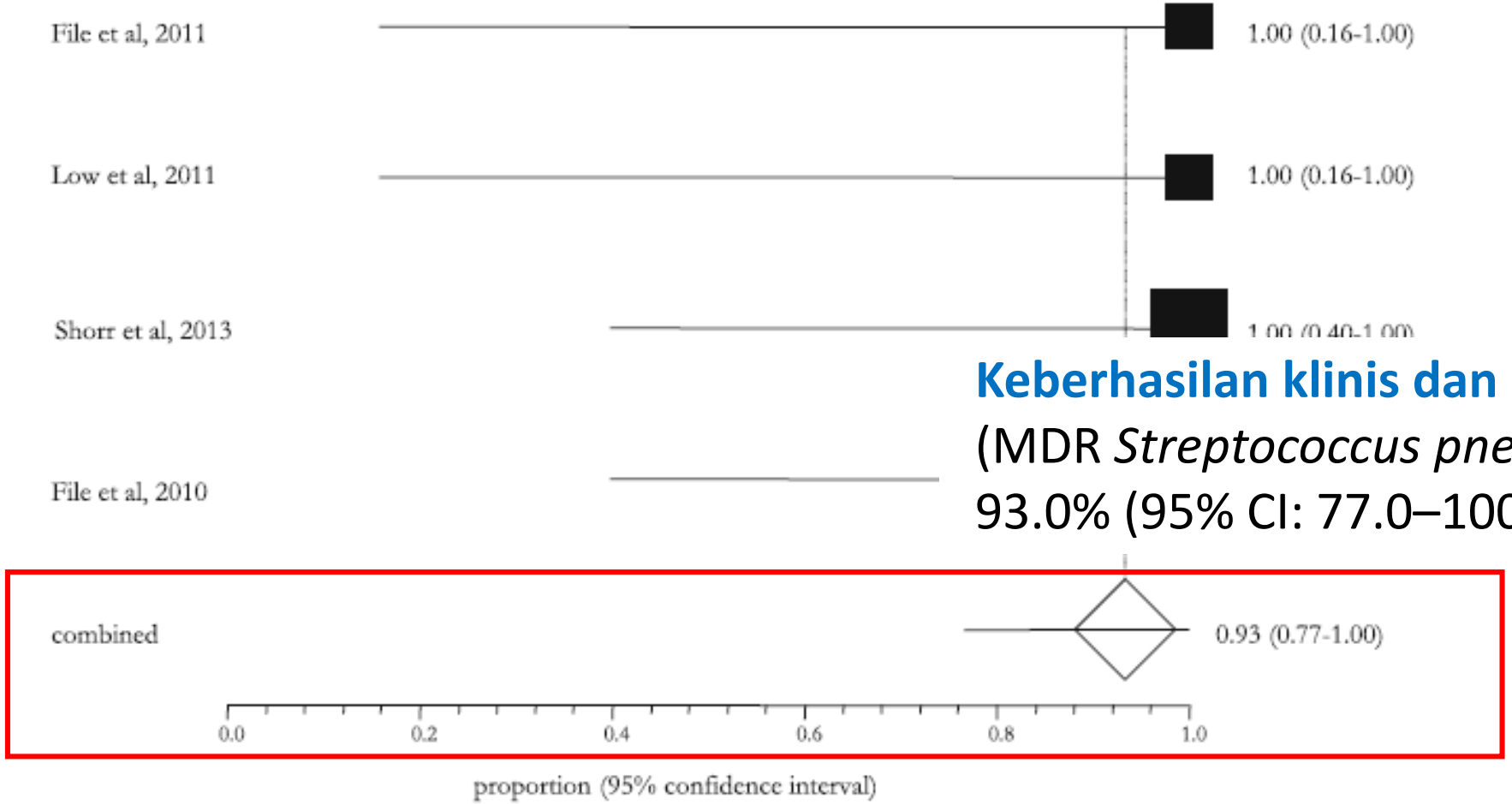
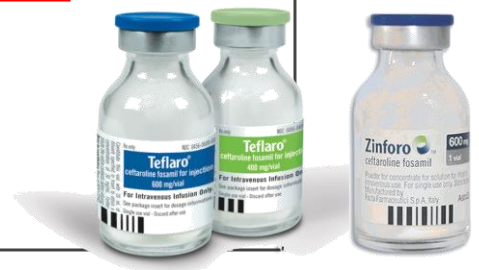


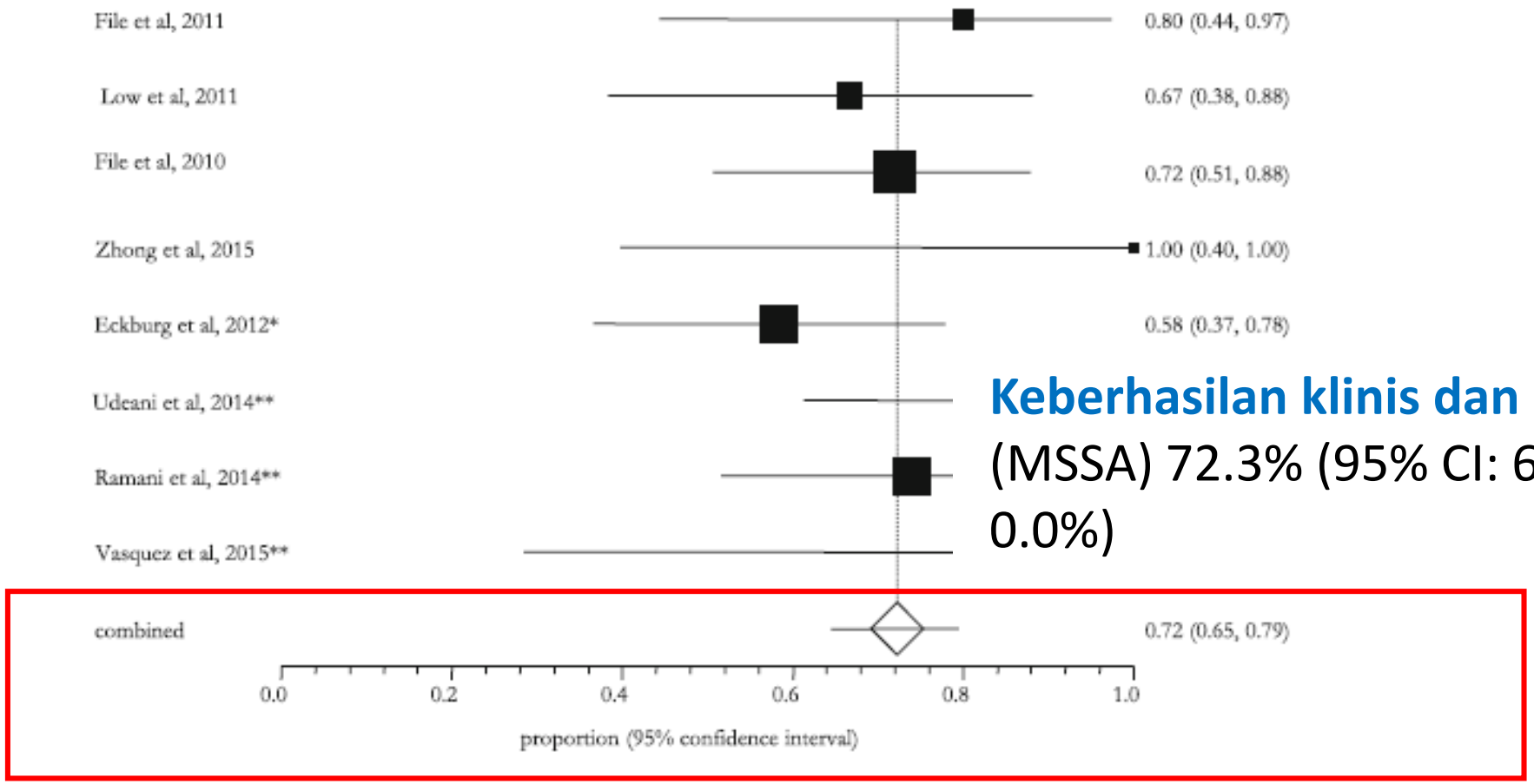
Fig. 7 Clinical cure rates in subjects with *MDR Streptococcus pneumoniae* treated with ceftaroline at TOC visit

Keberhasilan klinis dan mikrobiologi
(MDR *Streptococcus pneumoniae*)
93.0% (95% CI: 77.0–100.0; I2: 0.0%)



EVIDENCE – PNEUMONIA (2)

OUTCOME 1: *Efficacy/efffectiveness*



Keberhasilan klinis dan mikrobiologi (MSSA) 72.3% (95% CI: 64.5–79.4; I2: 0.0%)

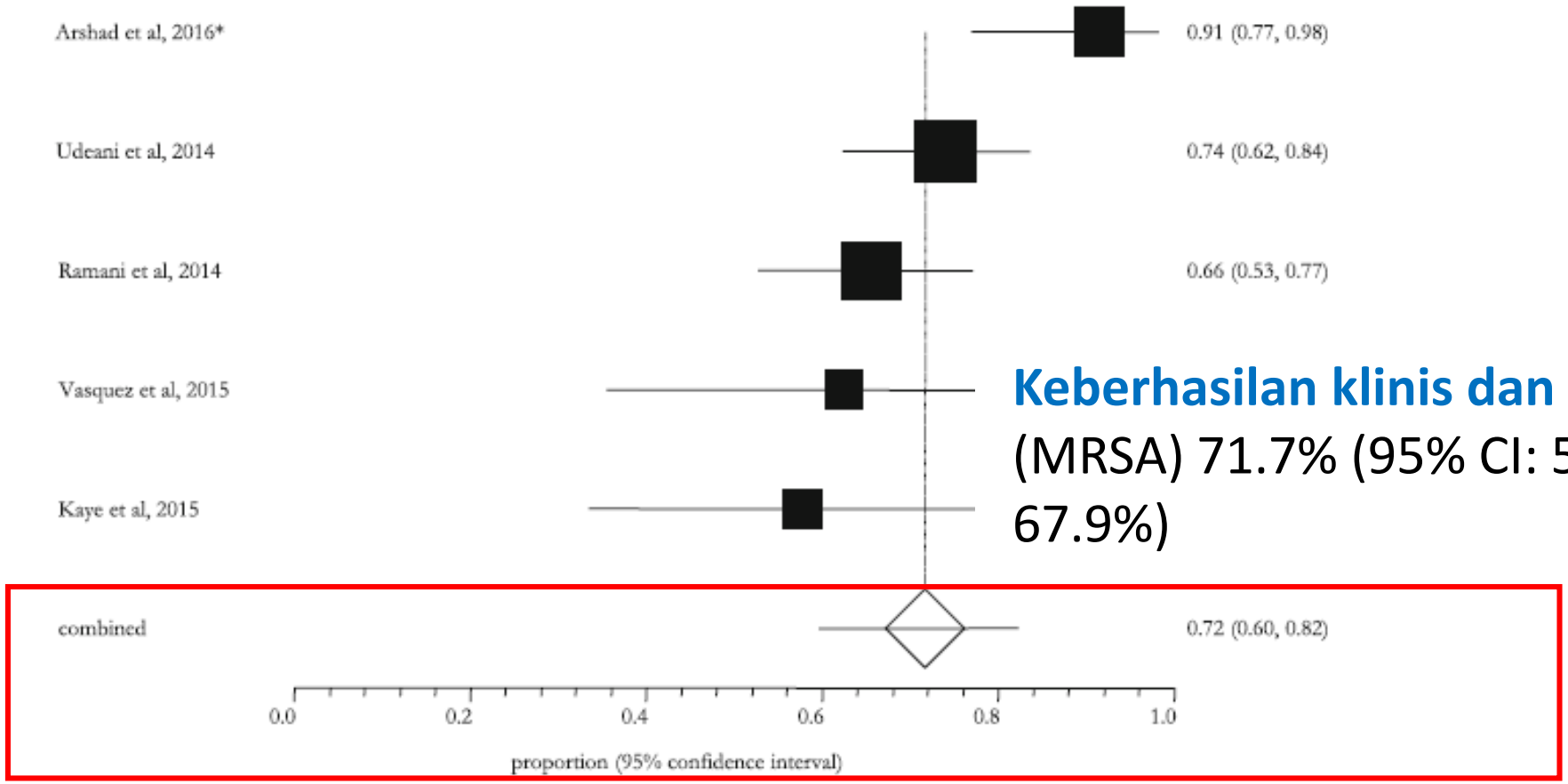
*Evaluated at EOT
** Not specified

I^2 = 0% (95% CI = 0% to 56.3%)
Pooled proportion = 0.722858 (95% CI = 0.645142 to 0.79434)

Fig. 8 Clinical and microbiological response rates in subjects with *MSSA* treated with ceftaroline

EVIDENCE – PNEUMONIA (2)

OUTCOME 1: *Efficacy/efffectiveness*

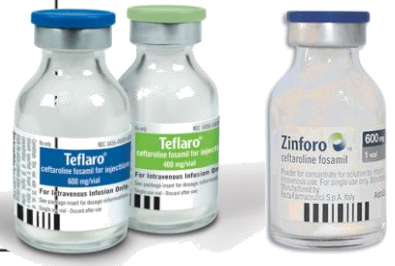


Keberhasilan klinis dan mikrobiologi (MRSA) 71.7% (95% CI: 59.7–82.3; I2: 67.9%)

*Evaluated at TOC

I^2 = 67.9% (95% CI = 0% to 85.5%)
Pooled proportion = 0.716491 (95% CI = 0.596717 to 0.822466)

Fig. 9 Clinical and microbiological response rates in subjects with *MRSA* treated with ceftaroline



EVIDENCE – PNEUMONIA (2)

OUTCOME 2: *Safety due to adverse effect*

Table 6 Adverse events (safety population)

Study	Ceftaroline group	Control group	Ceftaroline group	Control group	Ceftaroline group	Control group	Ceftaroline group	Control group
	Any adverse events, n (%)		Diarrhea, n (%)		Headache, n (%)		Insomnia, n (%)	
File et al., *2011* [10]	119/298 (39.9)	136/308 (44.2)	14/298 (4.7)	7/308 (2.3)	10/298 (3.4)	4/308 (1.3)	9/298 (3.0)	6/308 (1.9)
Low et al., *2011* [11]	196/315 (53.7)	145/307 (47.2)	12/315 (3.8)	9/307 (2.9)	11/315 (3.5)	5/307 (1.6)	10/315 (3.2)	8/307 (2.6)
File et al, *2010* [13]	288/613 (47.0)	281/615 (45.7)	26/613 (4.2)	16/615 (2.6)	21 /613 (3.4)	9/615 (1.5)	19/613 (3.1)	14/615 (2.3)
Zhong et al., *2015* [14]	172/381 (45.1)	163/383 (42.7)	24/381 (6.3)	13/383 (3.4)	6/381 (1.6)	9/383 (2.4)	–	–
	Nausea, n (%)		Phlebitis, n (%)		Hypertension, n (%)		Hypokalaemia, n (%)	
File et al, *2011* [10]	8/298 (2.7)	8/308 (2.6)	7/298 (2.3)	5/308 (1.6)	6/298 (2.0)	8/308 (2.6)	4/298 (1.3)	10/308 (3.2)
Low et al, *2011* [11]	6/315 (1.9)	6/307 (2.0)	10/315 (3.2)	8/307 (2.6)	8/315 (2.5)	8/307 (2.6)	10/315 (3.2)	5/307 (1.6)
File et al, *2010* [13]	14/613 (2.3)	14/615 (2.3)	17/613 (2.8)	13/615 (2.1)	14/613 (2.3)	16/615 (2.6)	14/613 (2.3)	15/615 (2.4)
Zhong et al, *2015* [14]	8/381 (2.1)	3/383 (0.8)	–	–	–	–	5/381 (1.3)	4/383 (1.1)

EVIDENCE – PNEUMONIA (2)

OUTCOME 2: *Safety due to adverse effect*

Table 7 Mortality rate in the ceftaroline and control groups

Study	Mortality rate, n (%)	
	Ceftaroline group	Control group
Jandourek et al, *2014*	–	–
File et al, *2011*	6/298 (2.0)	6/308 (1.9)
Low et al, *2011*	9/315 (2.9)	6/307 (2.0)
Shorr et al, *2013*	–	1/70 (1.4)
File et al, *2010*	15/613 (2.4)	12/615 (2.0)
Zhong et al, *2015*	3/381 (0.8)	4/383 (1.0)
Arshad et al, *2016 28-day mortality*	4/40 (10.0)[a]	16/109 (14.7)[a]
Eckburg et al, *2012*	–	–
Ramani et al, *2014*	8/398 (2.0)[b]	–
Casapao et al, *2014*	13/92 (14.1)[b]	–
Vasquez et al, *2015*	1/21 (4.8)	–
Guervil et al, *2015*	8/396 (2.0)[b]	–
Kaye et al, *2015*	5/40 (12.5)	–
Udeani et al, *2014*	15/528 (2.8)	–

[a] 28-day mortality
[b] Hospital mortality

EVIDENCE - SSTI

Journal of *Clinical Medicine*

MDPI

Article

Ceftaroline Efficacy and Safety in Treatment of Complicated Skin and Soft Tissue Infection: A Systemic Review and Meta-Analysis of Randomized Controlled Trials

Shao-Huan Lan [1], Shen-Peng Chang [2], Chih-Cheng Lai [3], Li-Chin Lu [4] and Chien-Ming Chao [3,*]

Received: 3 May 2019; Accepted: 28 May 2019; Published: 31 May 2019

EVIDENCE – SSTI (1)

Table 1. Clinical trial summary.

Study, Published Year	Study Design	Study Site	No (Male Ratio, %) of Patients		Mean Age of Patients		Dose Regimen	
			Ceftaroline	Comparator	Ceftaroline	Comparator	Ceftaroline	Comparator
Talbot et al., 2007 [18]	Multicenter, randomized, observe-blinded (2:1)	15 clinical sites in USA, South America, South Africa, Russia	67 (55.2)	33 (59.4)	41.6	44.0	600 mg q12h	Vancomycin 1 g q12h ± aztreonam 1 g q8h
Corey et al., 2010 [16]	Multicenter, randomized, double-blind (1:1)	55 sites in 10 countries	351 (62.7)	347 (62.8)	47.2	49.2	600 mg q12h	Vancomycin 1 g q12h + aztreonam 1 g q12h
Wilcox et al., 2010 [19]	Multicenter, randomized, double-blind (1:1)	56 sites in 12 countries	348 (65.5)	346 (59.5)	47.8	47.5	600 mg q12h	Vancomycin 1 g q12h + aztreonam 1 g q12h
Dryden et al., 2016 [17]	Multicenter, randomized, double-blind (2:1)	111 sites in 28 countries	506 (61.3)	255 (58.0)	52.6	53.6	600 mg q8h	Vancomycin 15 mg/kg q12h + aztreonam 1 g q8h
Claeys et al., 2019 [15]	Multicenter, randomized, double-blind (1:1)	3 sites in USA	54 (NA)	54 (NA)	54.8	48.1	± metronidazole *	Vancomycin ± ceftriaxone ± metronidazole or ampicillin/sulbactam *

* dosed based on renal function or per site protocol; NA: not available.

EVIDENCE – SSTI (1)

Primary outcome:

- *Overall clinical cure* – tanda dan gejala klinis cSSSI **atau** perbaikan kondisi pada saat berhenti menggunakan antibiotik. Dinilai pada saat *test of cure* (TOC) → 8-15 hari setelah dosis terakhir

Secondary outcome:

- Tingkat kegagalan terapi dari segi klinis
- Risiko kejadian *adverse effect* → treatment-emergent AEs (TEAEs), AE serius, dan penghentian terapi karena AE

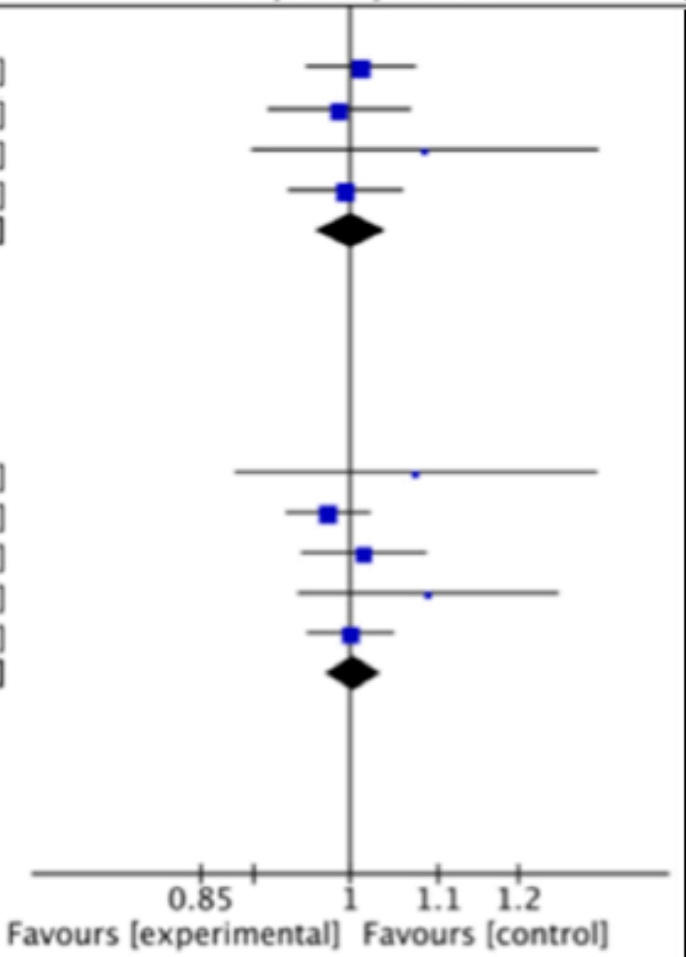
EVIDENCE – SSTI (1)

***OUTCOME* 1:**

overall clinical cure rates

Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 MITT						
Corey et al, 2010 [16]	304	351	297	347	33.4%	1.01 [0.95, 1.07]
Dryden et al, 2016 [17]	396	506	202	255	30.1%	0.99 [0.91, 1.07]
Talbot et al, 2007 [18]	59	67	26	32	3.9%	1.08 [0.90, 1.31]
Wilcox et al, 2010 [19]	291	342	289	338	32.5%	1.00 [0.93, 1.06]
Subtotal (95% CI)		**1266**		**972**	**100.0%**	**1.00 [0.97, 1.04]**
Total events	1050		814			
Heterogeneity: $Chi^2 = 0.94$, df = 3 (P = 0.81); $I^2 = 0\%$						
Test for overall effect: Z = 0.11 (P = 0.91)						
1.1.2 CE						
Claeys et al, 2019 [15]	44	54	41	54	4.7%	1.07 [0.88, 1.31]
Corey et al, 2010 [16]	288	316	280	300	33.2%	0.98 [0.93, 1.02]
Dryden et al, 2016 [17]	342	395	180	211	27.1%	1.01 [0.95, 1.09]
Talbot et al, 2007 [18]	59	61	24	27	3.8%	1.09 [0.94, 1.25]
Wilcox et al, 2010 [19]	271	294	269	292	31.2%	1.00 [0.95, 1.05]
Subtotal (95% CI)		**1120**		**884**	**100.0%**	**1.00 [0.97, 1.03]**
Total events	1004		794			
Heterogeneity: $Chi^2 = 3.19$, df = 4 (P = 0.53); $I^2 = 0\%$						
Test for overall effect: Z = 0.21 (P = 0.83)						

Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.96), $I^2 = 0\%$



EVIDENCE – SSTI (1)

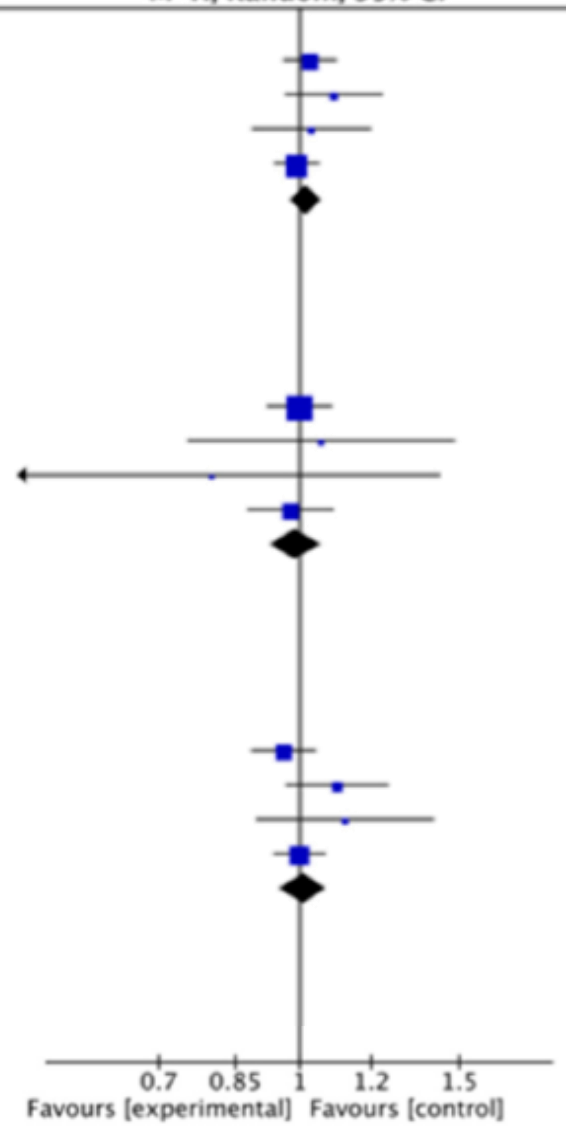
OUTCOME 2:

overall clinical failure rates

Based on different pathogen

Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 S. aureus						
Corey et al, 2010 [16]	172	185	158	174	34.6%	1.02 [0.96, 1.09]
Dryden et al, 2016 [17]	109	119	61	72	10.5%	1.08 [0.97, 1.21]
Talbot et al, 2007 [18]	29	30	16	17	7.1%	1.03 [0.90, 1.18]
Wilcox et al, 2010 [19]	182	195	172	183	47.9%	0.99 [0.94, 1.05]
Subtotal (95% CI)		**529**		**446**	**100.0%**	**1.01 [0.98, 1.05]**
Total events	492		407			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.11$, df = 3 (P = 0.55); $I^2 = 0\%$						
Test for overall effect: Z = 0.80 (P = 0.42)						
3.1.2 MRSA						
Corey et al, 2010 [16]	78	82	59	62	60.6%	1.00 [0.93, 1.08]
Dryden et al, 2016 [17]	21	25	12	15	3.6%	1.05 [0.77, 1.43]
Talbot et al, 2007 [18]	4	5	5	5	1.2%	0.82 [0.49, 1.38]
Wilcox et al, 2010 [19]	64	70	56	60	34.6%	0.98 [0.89, 1.08]
Subtotal (95% CI)		**182**		**142**	**100.0%**	**0.99 [0.94, 1.05]**
Total events	167		132			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.77$, df = 3 (P = 0.86); $I^2 = 0\%$						
Test for overall effect: Z = 0.27 (P = 0.78)						
3.1.3 MSSA						
Corey et al, 2010 [16]	94	103	106	112	33.5%	0.96 [0.90, 1.04]
Dryden et al, 2016 [17]	88	94	49	57	17.0%	1.09 [0.97, 1.22]
Talbot et al, 2007 [18]	25	25	11	12	6.4%	1.11 [0.90, 1.36]
Wilcox et al, 2010 [19]	118	125	119	126	43.1%	1.00 [0.94, 1.06]
Subtotal (95% CI)		**347**		**307**	**100.0%**	**1.01 [0.96, 1.06]**
Total events	325		285			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.04$, df = 3 (P = 0.26); $I^2 = 26\%$						
Test for overall effect: Z = 0.32 (P = 0.75)						

Test for subgroup differences: $Chi^2 = 2.00$, df = 4 (P = 0.74), $I^2 = 0\%$



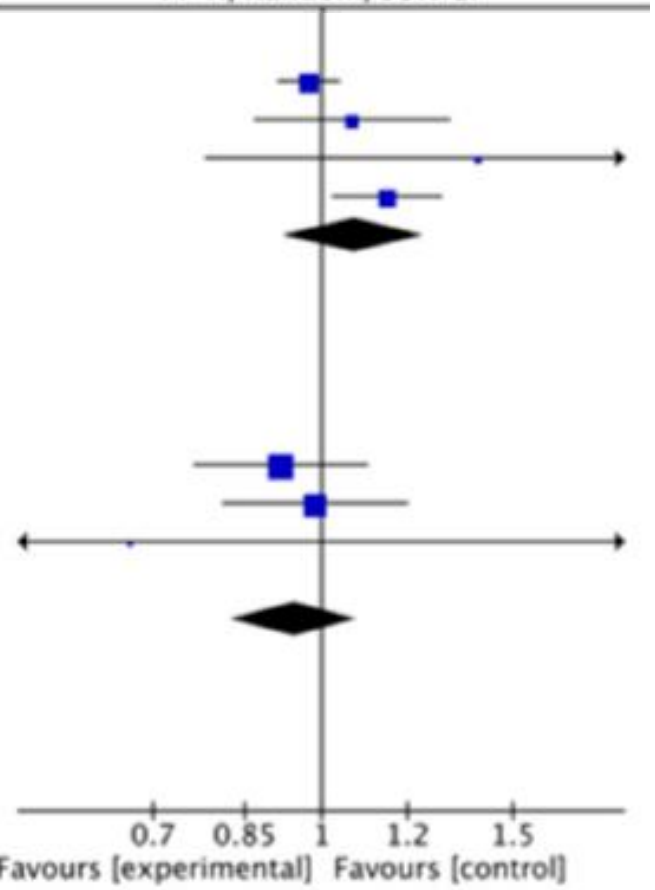
EVIDENCE – SSTI (1)

OUTCOME 2:

overall clinical failure rates

Based on different pathogen

Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.4 Streptococcus spp.						
Corey et al, 2010 [16]	39	40	45	45	38.3%	0.97 [0.91, 1.04]
Dryden et al, 2016 [17]	28	30	14	16	22.9%	1.07 [0.87, 1.31]
Talbot et al, 2007 [18]	19	19	3	4	5.7%	1.39 [0.78, 2.48]
Wilcox et al, 2010 [19]	52	52	40	46	33.0%	1.15 [1.02, 1.29]
Subtotal (95% CI)		**141**		**111**	**100.0%**	**1.07 [0.92, 1.24]**
Total events	138		102			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 10.94$, df = 3 (P = 0.01); $I^2 = 73\%$						
Test for overall effect: Z = 0.92 (P = 0.36)						
3.1.5 Gram-negative bacteria						
Corey et al, 2010 [16]	26	31	32	35	52.6%	0.92 [0.76, 1.10]
Dryden et al, 2016 [17]	30	34	17	19	46.2%	0.99 [0.81, 1.20]
Talbot et al, 2007 [18]	2	4	1	1	1.3%	0.67 [0.20, 2.18]
Wilcox et al, 2010 [19]	15	0	16	9		Not estimable
Subtotal (95% CI)		**69**		**64**	**100.0%**	**0.94 [0.83, 1.08]**
Total events	73		66			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.63$, df = 2 (P = 0.73); $I^2 = 0\%$						
Test for overall effect: Z = 0.83 (P = 0.40)						
Test for subgroup differences: $Chi^2 = 2.00$, df = 4 (P = 0.74), $I^2 = 0\%$						



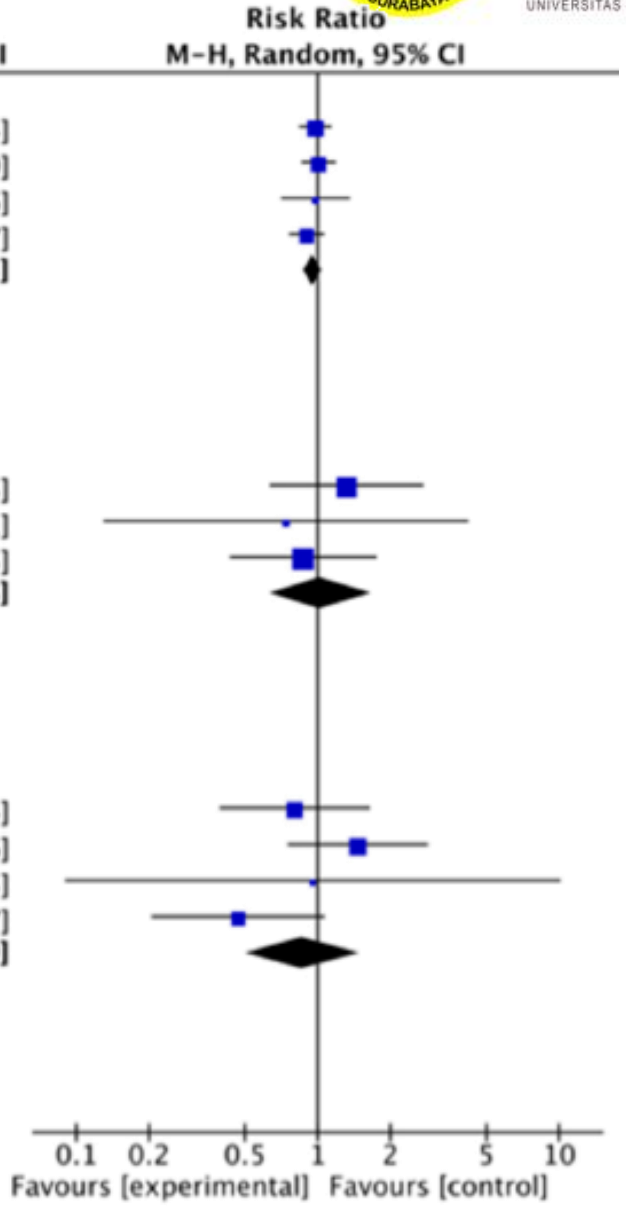
EVIDENCE – SSTI (1)

***OUTCOME* 3:**

Risiko *adverse effects*

Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Treatment emergent adverse event						
Corey et al, 2010 [16]	165	351	167	347	33.5%	0.98 [0.84, 1.14]
Dryden et al, 2016 [17]	232	506	116	255	30.1%	1.01 [0.86, 1.19]
Talbot et al, 2007 [18]	41	67	20	32	7.5%	0.98 [0.70, 1.36]
Wilcox et al, 2010 [19]	144	341	159	339	28.8%	0.90 [0.76, 1.07]
Subtotal (95% CI)		**1265**		**973**	**100.0%**	**0.96 [0.88, 1.05]**
Total events	582		462			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.95$, df = 3 (P = 0.81); $I^2 = 0\%$						
Test for overall effect: Z = 0.81 (P = 0.42)						
5.1.2 Serious adverse event						
Corey et al, 2010 [16]	16	351	12	347	44.0%	1.32 [0.63, 2.75]
Talbot et al, 2007 [18]	3	67	2	33	7.8%	0.74 [0.13, 4.21]
Wilcox et al, 2010 [19]	14	341	16	339	48.2%	0.87 [0.43, 1.75]
Subtotal (95% CI)		**759**		**719**	**100.0%**	**1.03 [0.63, 1.68]**
Total events	33		30			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.80$, df = 2 (P = 0.67); $I^2 = 0\%$						
Test for overall effect: Z = 0.12 (P = 0.90)						
5.1.3 Discontinuation of drug treatment due to adverse effects						
Corey et al, 2010 [16]	13	351	16	347	32.5%	0.80 [0.39, 1.64]
Dryden et al, 2016 [17]	32	506	11	255	35.1%	1.47 [0.75, 2.86]
Talbot et al, 2007 [18]	2	67	1	32	4.9%	0.96 [0.09, 10.15]
Wilcox et al, 2010 [19]	8	341	17	339	27.4%	0.47 [0.20, 1.07]
Subtotal (95% CI)		**1265**		**973**	**100.0%**	**0.86 [0.50, 1.49]**
Total events	55		45			
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 4.55$, df = 3 (P = 0.21); $I^2 = 34\%$						
Test for overall effect: Z = 0.53 (P = 0.60)						

Test for subgroup differences: $Chi^2 = 0.23$, df = 2 (P = 0.89), $I^2 = 0\%$



EVIDENCE – PNEUMONIA/SSTI (1)

Ceftaroline fosamil for community-acquired pneumonia and skin and skin structure infections: a systematic review

Maguy Saffouh El Hajj[1] · Ricky D. Turgeon[2] · Kyle John Wilby[1]

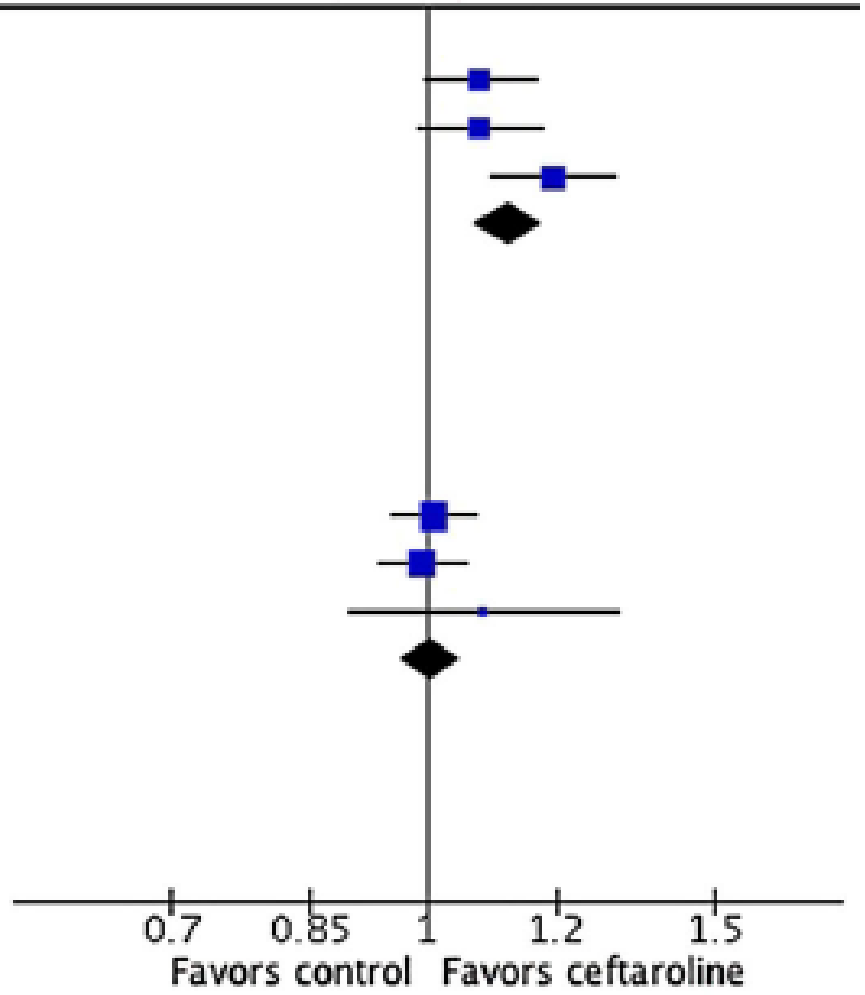
Received: 8 September 2016 / Accepted: 15 December 2016

Pengarang	Diagnosis pasien	Terapi	Outcome
FOCUS 1	*Community acquired pneumonia* (CAP)	Ceftaroline vs ceftriaxone	***Primary outcome:*** • *clinical cure* ***Secondary outcome:*** • mortalitas • *adverse effect*
FOCUS 2			
ZHONG 2014			
CANVAS 1	*Complicated skin and skin structure infections* (cSSSI)	Ceftaroline vs vancomycin+aztreonam	
CANVAS 2			
TALBOT 2007		Ceftaroline vs vancomycin with/without aztreonam	

EVIDENCE – PNEUMONIA/SSTI (1)

OUTCOME 1: *clinical cure*

Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 CAP						
FOCUS 1	244	291	233	300	32.9%	1.08 [1.00, 1.17]
FOCUS 2	235	289	206	273	30.4%	1.08 [0.99, 1.18]
Zhong et al	305	381	256	382	36.7%	1.19 [1.10, 1.30]
Subtotal (95% CI)		**961**		**955**	**100.0%**	**1.12 [1.07, 1.18]**
Total events	784		695			
Heterogeneity: $Chi^2 = 3.74$, df = 2 (P = 0.15); $I^2 = 47\%$						
Test for overall effect: Z = 4.58 (P < 0.00001)						
1.1.2 cSSSI						
CANVAS 1	304	351	297	347	47.8%	1.01 [0.95, 1.07]
CANVAS 2	291	342	289	338	46.5%	1.00 [0.93, 1.06]
Talbot et al	59	67	26	32	5.6%	1.08 [0.90, 1.31]
Subtotal (95% CI)		**760**		**717**	**100.0%**	**1.01 [0.97, 1.05]**
Total events	654		612			
Heterogeneity: $Chi^2 = 0.75$, df = 2 (P = 0.69); $I^2 = 0\%$						
Test for overall effect: Z = 0.38 (P = 0.71)						

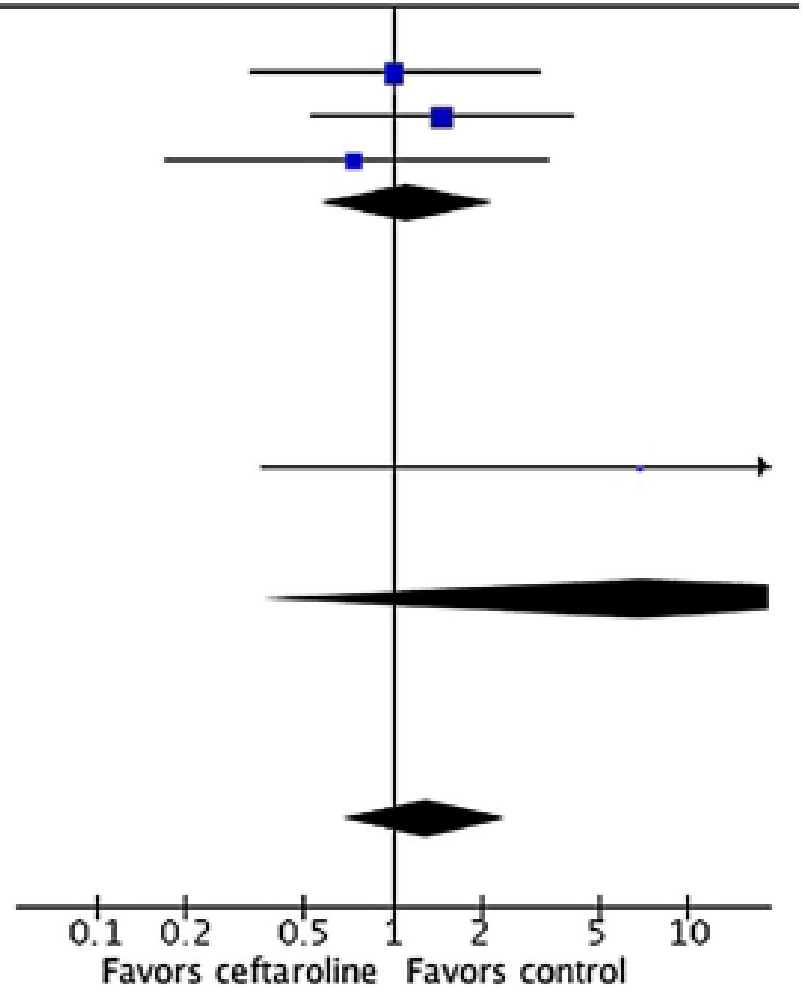


Test for subgroup differences: $Chi^2 = 10.40$, df = 1 (P = 0.001), $I^2 = 90.4\%$

EVIDENCE – PNEUMONIA/SSTI (1)

OUTCOME 2: mortalitas

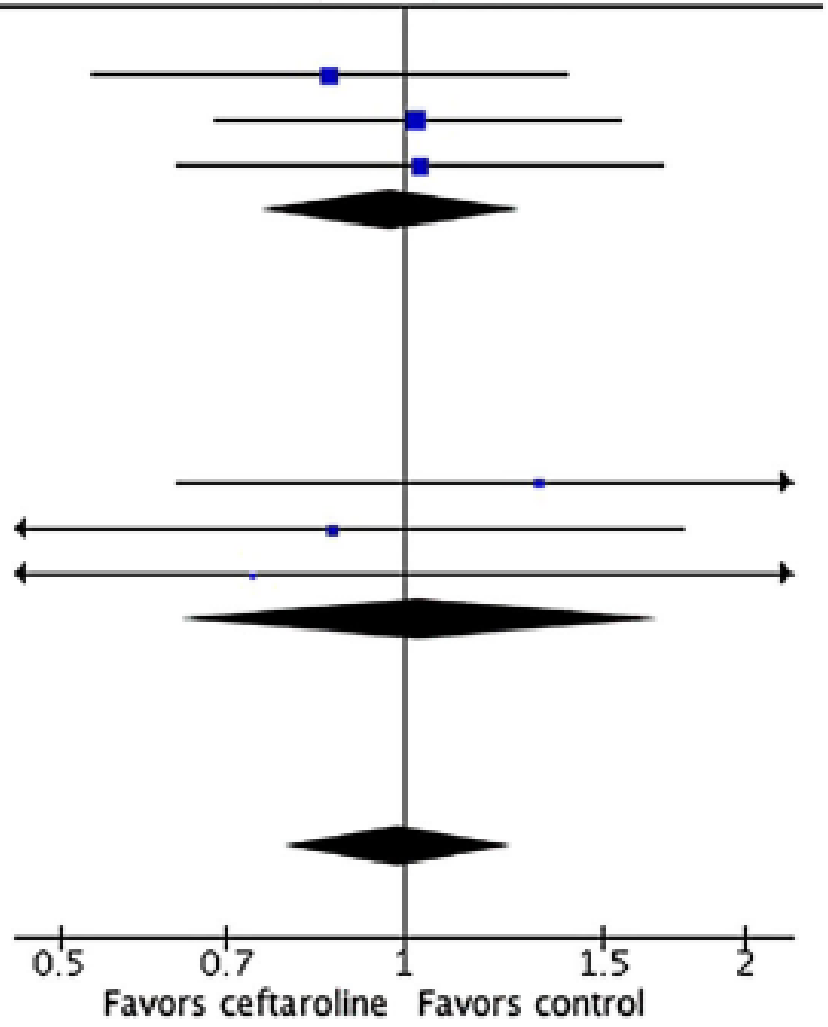
Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 CAP						
FOCUS 1	6	304	6	309	36.0%	1.02 [0.33, 3.12]
FOCUS 2	9	317	6	310	36.7%	1.47 [0.53, 4.07]
Zhong et al	3	385	4	386	24.2%	0.75 [0.17, 3.34]
Subtotal (95% CI)		**1006**		**1005**	**97.0%**	**1.12 [0.58, 2.19]**
Total events	18		16			
Heterogeneity: $Chi^2 = 0.57$, df = 2 (P = 0.75); $I^2 = 0\%$						
Test for overall effect: Z = 0.34 (P = 0.74)						
2.1.2 cSSSI						
CANVAS 1	3	353	0	349	3.0%	6.92 [0.36, 133.49]
CANVAS 2	0	348	0	346		Not estimable
Talbot et al	0	67	0	33		Not estimable
Subtotal (95% CI)		**768**		**728**	**3.0%**	**6.92 [0.36, 133.49]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.28 (P = 0.20)						
Total (95% CI)		**1774**		**1733**	**100.0%**	**1.30 [0.69, 2.45]**
Total events	21		16			
Heterogeneity: $Chi^2 = 1.98$, df = 3 (P = 0.58); $I^2 = 0\%$						
Test for overall effect: Z = 0.80 (P = 0.42)						
Test for subgroup differences: $Chi^2 = 1.38$, df = 1 (P = 0.24), $I^2 = 27.7\%$						



EVIDENCE – PNEUMONIA/SSTI (1)

OUTCOME 3: *adverse effect*

Study or Subgroup	Ceftaroline Events	Ceftaroline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 CAP						
FOCUS 1	28	304	33	309	24.8%	0.86 [0.53, 1.39]
FOCUS 2	41	317	39	310	29.9%	1.03 [0.68, 1.55]
Zhong et al	30	385	29	386	22.0%	1.04 [0.64, 1.69]
Subtotal (95% CI)		**1006**		**1005**	**76.7%**	**0.98 [0.75, 1.27]**
Total events	99		101			
Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.86)						
2.2.2 cSSSI						
CANVAS 1	16	353	12	349	9.1%	1.32 [0.63, 2.75]
CANVAS 2	14	348	16	346	12.2%	0.87 [0.43, 1.75]
Talbot et al	3	67	2	33	2.0%	0.74 [0.13, 4.21]
Subtotal (95% CI)		**768**		**728**	**23.3%**	**1.03 [0.64, 1.68]**
Total events	33		30			
Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
Total (95% CI)		**1774**		**1733**	**100.0%**	**0.99 [0.79, 1.25]**
Total events	132		131			
Heterogeneity: Chi² = 1.21, df = 5 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.93)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						



EVIDENCE – PNEUMONIA/SSTI in PEDIATRIC (1)

The efficacy and safety of ceftaroline in the treatment of acute bacterial infection in pediatric patients – a systemic review and meta-analysis of randomized controlled trials

Chih-Wei Chen[1,2]
Shen-Peng Chang[3]
Hui-Ting Huang[4]
Hung-Jen Tang[5]
Chih-Cheng Lai[6]

Infection and Drug Resistance 2019:12 1303–1310

Table 1 Characteristics of included studies

Study, published year	Study design	Study site	Study period	Study population	No. of patients		Dose regimen	
					Ceftaroline	Comparator	Ceftaroline	Comparator
Blumer et al,[14] 2016	Multicenter, randomized, observe-blinded	20 centers in 4 countries	2012–2014	Complicated community-acquired bacterial pneumonia	30	10	15 mg/kg or 600 mg q8h if weight >40 kg if ≥6 m or 10 mg/kg q8h if <6m	Ceftriaxone, 75 mg/kg/d q12h, and vancomycin 15 mg/kg q6h
Cannavino et al,[13] 2016	Multicenter, randomized	34 centers in 8 countries	2012–2014	Community-acquired bacterial pneumonia requiring hospitalization	121	39	Age <6 m, 8 mg/kg q8h; aged ≥6 m, 12 mg/kg q8h for those weighing ≤33 kg or 400 mg q8h for those weighing >33 kg	Ceftriaxone 75 mg/kg/d to a maximum 4g/d q12h
Korczowski et al,[15] 2016	Multicenter, randomized, observe-blinded	10 countries	2012–2014	Acute bacterial skin and skin structure infection	110	53	Age <6 m, 8 mg/kg q8h if <6 m; aged ≥6 m, 12 mg/kg q8h for those weighing ≤33 kg or 400 mg q8h for those weighing >33 kg	Vancomycin 15 mg/kg q6h or cefazolin 75 mg/kg/d q8h

EVIDENCE – PNEUMONIA/SSTI in PEDIATRIC (1)

Study or subgroup	Ceftaroline Events	Total	Comparator Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
1.1.1 at EOT						
Blumer et al, 2016	24	29	7	9	22.5%	1.37 [0.22, 8.66]
Cannavino et al, 2016	103	107	46	52	28.3%	3.36 [0.90, 12.47]
Korczowski et al, 2016	98	107	32	36	49.2%	1.36 [0.39, 4.72]
Subtotal (95% CI)		**243**		**97**	**100.0%**	**1.93 [0.88, 4.25]**
Total events	225		85			
Heterogeneity: Chi^2=1.12, df=2 (P=0.57); I^2=0%						
Test for overall effect: Z=1.63 (P=0.10)						
1.1.2 at TOC						
Blumer et al, 2016	26	29	9	9	15.3%	0.40 [0.02, 8.45]
Cannavino et al, 2016	101	107	45	52	31.2%	2.62 [0.83, 8.23]
Korczowski et al, 2016	94	107	32	36	53.5%	0.90 [0.27, 2.97]
Subtotal (95% CI)		**243**		**97**	**100.0%**	**1.36 [0.64, 2.91]**
Total events	221		86			
Heterogeneity: Chi^2=2.33, df=2 (P=0.31); I^2=14%						
Test for overall effect: Z=0.80 (P=0.43)						

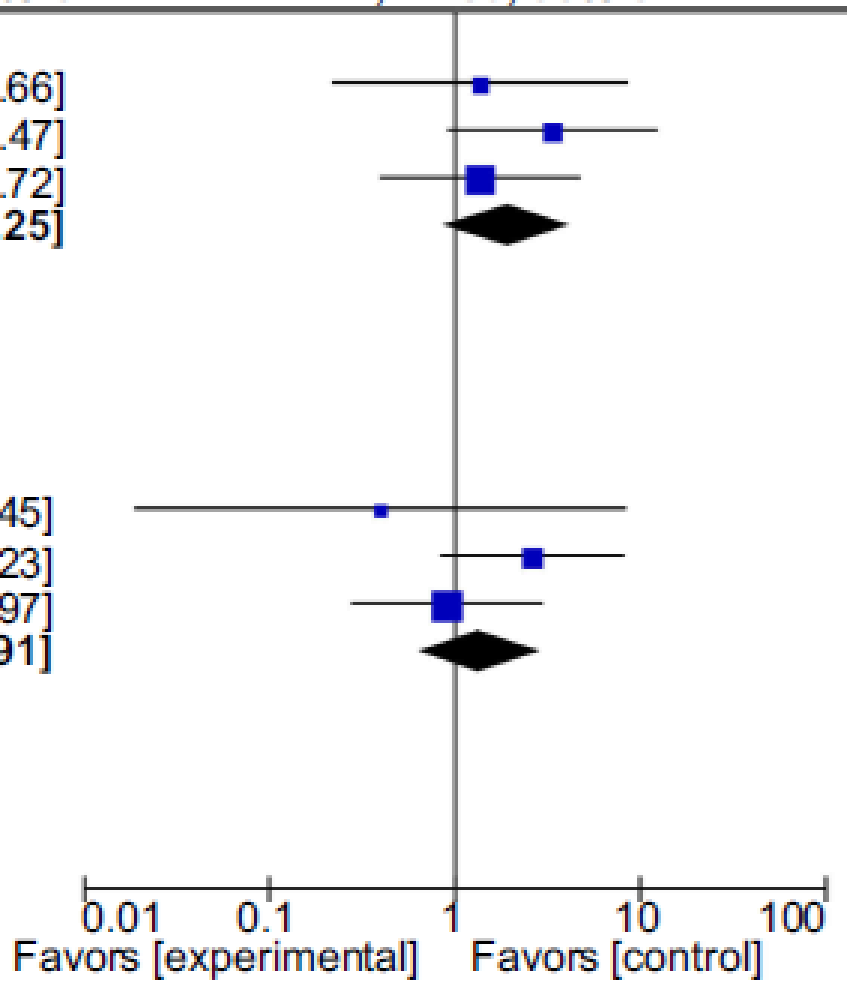


Figure 3 The overall clinical cure rates of ceftaroline and comparators in the treatment of acute bacterial infections.

EVIDENCE – PNEUMONIA/SSTI in PEDIATRIC (1)

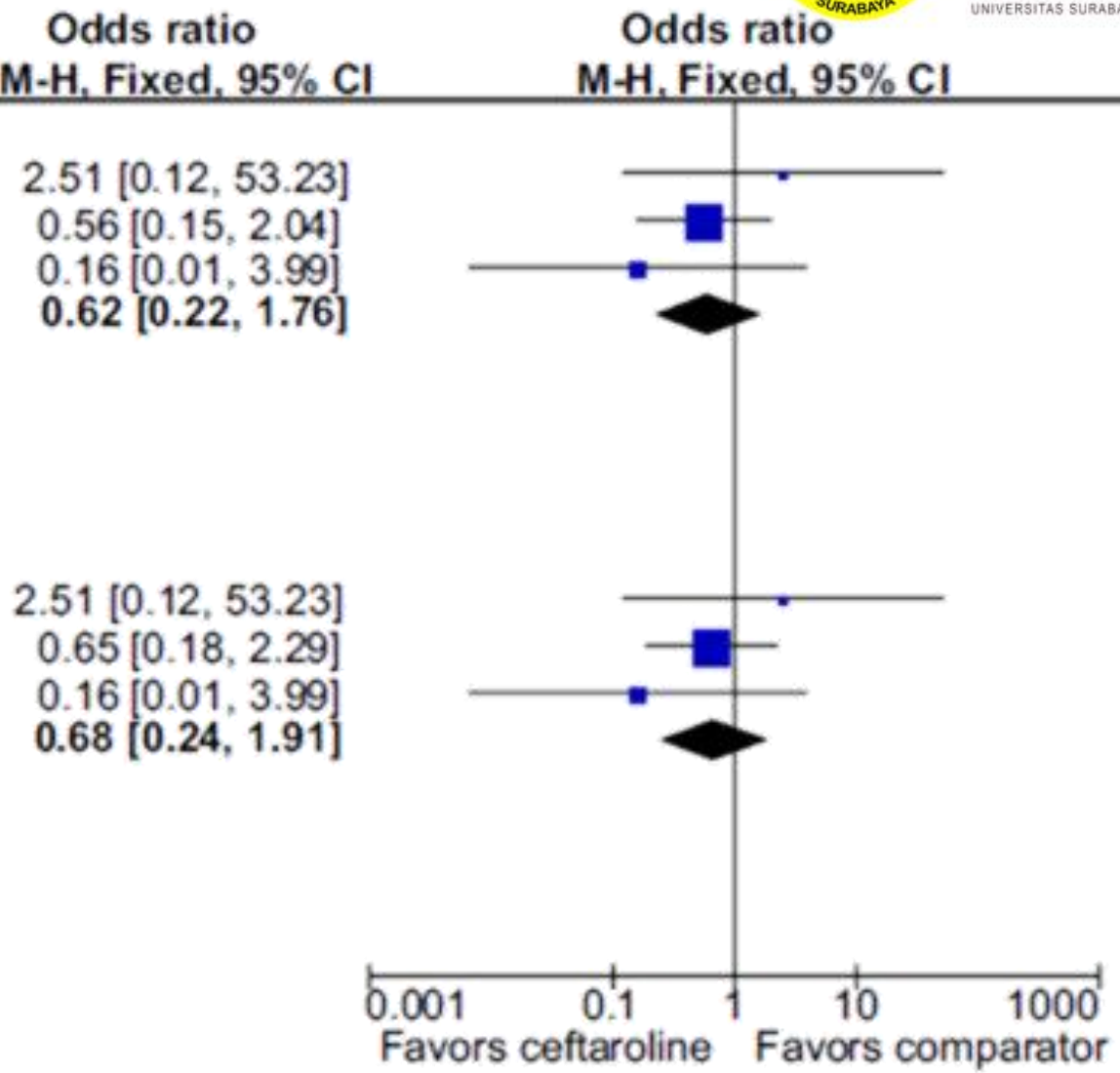


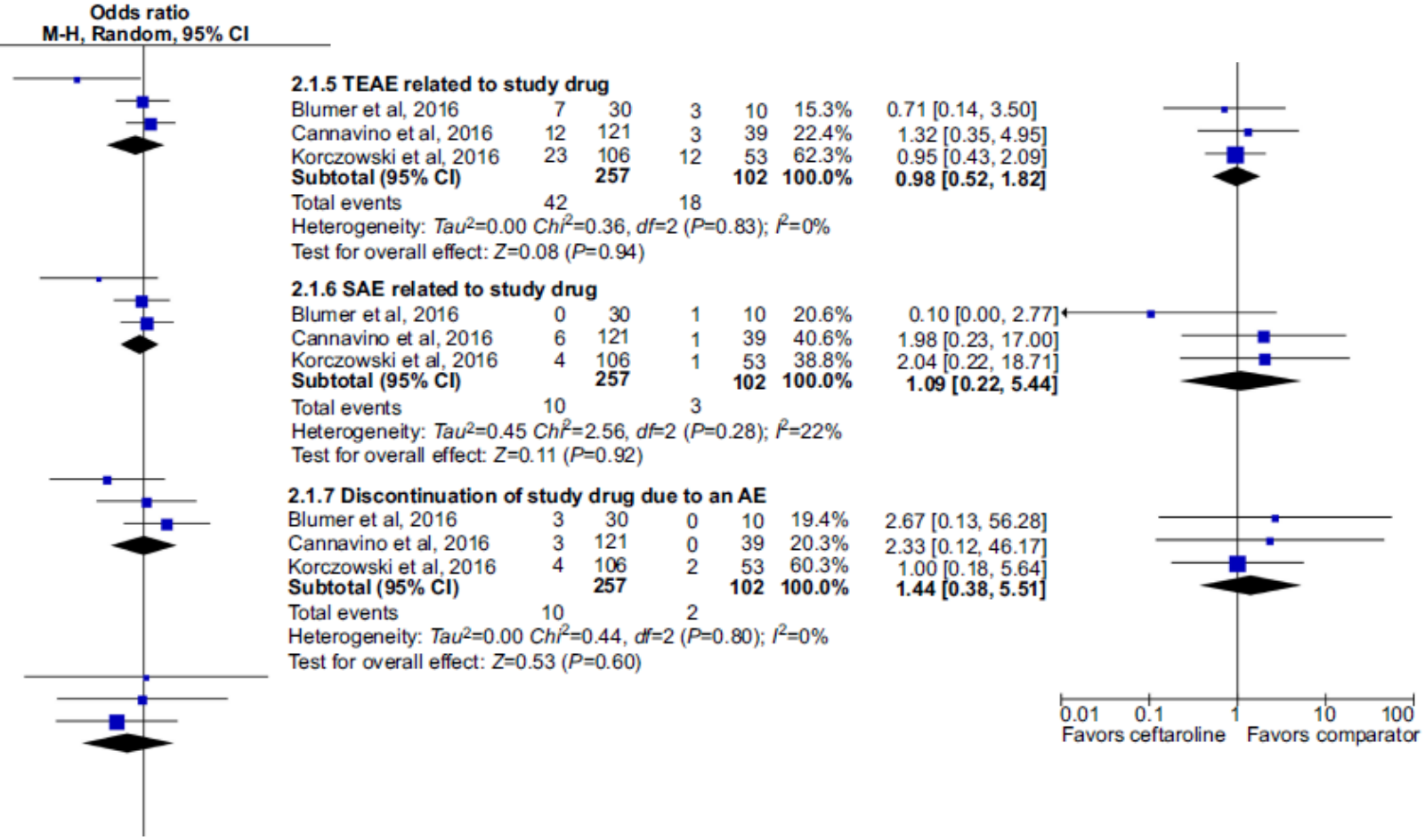
Figure 4 The overall clinical failure rates of ceftaroline and comparators in the treatment of acute bacterial infections.

EVIDENCE – PNEUMONIA/SSTI in PEDIATRIC (1)

OUTCOME: *adverse effect*

Study or subgroup	Ceftaroline Events	Ceftaroline Total	Comparator Events	Comparator Total	Weight	Odds ratio M-H, Random, 95% CI
2.1.1 TEAE						
Blumer et al, 2016	12	30	8	10	15.7%	0.17 [0.03, 0.92]
Cannavino et al, 2016	55	121	18	39	40.9%	0.97 [0.47, 2.01]
Korczowski et al, 2016	51	106	23	53	43.3%	1.21 [0.62, 2.35]
Subtotal (95% CI)		**257**		**102**	**100.0%**	**0.81 [0.37, 1.78]**
Total events	118		49			
Heterogeneity: Tau^2=0.26 Chi^2=4.50, df=2 (P=0.11); I^2=56%						
Test for overall effect: Z=0.53 (P=0.60)						
2.1.2 mild TEAE						
Blumer et al, 2016	5	30	4	10	10.3%	0.30 [0.06, 1.47]
Cannavino et al, 2016	42	121	14	39	42.7%	0.95 [0.45, 2.02]
Korczowski et al, 2016	34	106	16	53	47.0%	1.09 [0.53, 2.23]
Subtotal (95% CI)		**257**		**102**	**100.0%**	**0.90 [0.54, 1.51]**
Total events	81		34			
Heterogeneity: Tau^2=0.02 Chi^2=2.14, df=2 (P=0.34); I^2=6%						
Test for overall effect: Z=0.40 (P=0.69)						
2.1.3 moderate TEAE						
Blumer et al, 2016	6	30	4	10	26.4%	0.38 [0.08, 1.77]
Cannavino et al, 2016	10	121	3	39	33.0%	1.08 [0.28, 4.14]
Korczowski et al, 2016	14	106	4	53	47.0%	1.86 [0.58, 5.97]
Subtotal (95% CI)		**257**		**102**	**100.0%**	**1.02 [0.42, 2.48]**
Total events	30		11			
Heterogeneity: Tau^2=0.15 Chi^2=2.64, df=2 (P=0.27); I^2=24%						
Test for overall effect: Z=0.04 (P=0.96)						
2.1.4 secere TEAE						
Blumer et al, 2016	1	30	0	10	14.2%	1.07 [0.04, 28.30]
Cannavino et al, 2016	3	121	1	39	29.0%	0.97 [0.10, 9.56]
Korczowski et al, 2016	3	106	3	53	56.9%	0.49 [0.09, 2.49]
Subtotal (95% CI)		**257**		**102**	**100.0%**	**0.66 [0.19, 2.27]**
Total events	7		4			
Heterogeneity: Tau^2=0.00 Chi^2=0.32, df=2 (P=0.85); I^2=0%						
Test for overall effect: Z=0.65 (P=0.51)						

2.1.5 TEAE related to study drug						
Blumer et al, 2016	7	30	3	10	15.3%	0.71 [0.14, 3.50]
Cannavino et al, 2016	12	121	3	39	22.4%	1.32 [0.35, 4.95]
Korczowski et al, 2016	23	106	12	53	62.3%	0.95 [0.43, 2.09]
Subtotal (95% CI)		**257**		**102**	**100.0%**	**0.98 [0.52, 1.82]**
Total events	42		18			
Heterogeneity: Tau^2=0.00 Chi^2=0.36, df=2 (P=0.83); I^2=0%						
Test for overall effect: Z=0.08 (P=0.94)						
2.1.6 SAE related to study drug						
Blumer et al, 2016	0	30	1	10	20.6%	0.10 [0.00, 2.77]
Cannavino et al, 2016	6	121	1	39	40.6%	1.98 [0.23, 17.00]
Korczowski et al, 2016	4	106	1	53	38.8%	2.04 [0.22, 18.71]
Subtotal (95% CI)		**257**		**102**	**100.0%**	**1.09 [0.22, 5.44]**
Total events	10		3			
Heterogeneity: Tau^2=0.45 Chi^2=2.56, df=2 (P=0.28); I^2=22%						
Test for overall effect: Z=0.11 (P=0.92)						
2.1.7 Discontinuation of study drug due to an AE						
Blumer et al, 2016	3	30	0	10	19.4%	2.67 [0.13, 56.28]
Cannavino et al, 2016	3	121	0	39	20.3%	2.33 [0.12, 46.17]
Korczowski et al, 2016	4	106	2	53	60.3%	1.00 [0.18, 5.64]
Subtotal (95% CI)		**257**		**102**	**100.0%**	**1.44 [0.38, 5.51]**
Total events	10		2			
Heterogeneity: Tau^2=0.00 Chi^2=0.44, df=2 (P=0.80); I^2=0%						
Test for overall effect: Z=0.53 (P=0.60)						



GUIDELINE CAP – ATS/IDSA 2019

Table 4. Initial Treatment Strategies for Inpatients with Community-acquired Pneumonia by Level of Severity and Risk for Drug Resistance

	Standard Regimen	Prior Respiratory Isolation of MRSA	Prior Respiratory Isolation of *Pseudomonas aeruginosa*	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for MRSA	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for *P. aeruginosa*
Nonsevere inpatient pneumonia*	β-Lactam + macrolide† or respiratory fluroquinolone‡	Add MRSA coverage§ and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*‖ and obtain cultures to allow deescalation or confirmation of need for continued therapy	Obtain cultures but withhold MRSA coverage unless culture results are positive. If rapid nasal PCR is available, withhold additional empiric therapy against MRSA if rapid testing is negative or add coverage if PCR is positive and obtain cultures	Obtain cultures but initiate coverage for *P. aeruginosa* only if culture results are positive
Severe inpatient pneumonia*	β-Lactam + macrolide† or β-lactam + fluroquinolone‡	Add MRSA coverage§ and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*‖ and obtain cultures to allow deescalation or confirmation of need for continued therapy	Add MRSA coverage§ and obtain nasal PCR and cultures to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*‖ and obtain cultures to allow deescalation or confirmation of need for continued therapy

Definition of abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.

*As defined by 2007 ATS/IDSA CAP severity criteria guidelines (see Table 1).

†Ampicillin + sulbactam 1.5–3 g every 6 hours, cefotaxime 1–2 g every 8 hours, ceftriaxone 1–2 g daily, or ceftaroline 600 mg every 12 hours AND azithromycin 500 mg daily or clarithromycin 500 mg twice daily.

‡Levofloxacin 750 mg daily or moxifloxacin 400 mg daily.

§Per the 2016 ATS/IDSA HAP/VAP guidelines: vancomycin (15 mg/kg every 12 h, adjust based on levels) or linezolid (600 mg every 12 h).

‖Per the 2016 ATS/IDSA HAP/VAP guidelines: piperacillin-tazobactam (4.5 g every 6 h), cefepime (2 g every 8 h), ceftazidime (2 g every 8 h), imipenem (500 mg every 6 h), meropenem (1 g every 8 h), or aztreonam (2 g every 8 h). Does not include coverage for extended-spectrum β-lactamase–producing Enterobacteriaceae, which should be considered only on the basis of patient or local microbiological data.

GUIDELINE VAP – IDSA 2016

Table 3. Suggested Empiric Treatment Options for Clinically Suspected Ventilator-Associated Pneumonia in Units Where Empiric Methicillin-Resistant *Staphylococcus aureus* Coverage and Double Antipseudomonal/Gram-Negative Coverage Are Appropriate

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

Choose one gram-positive option from column A, one gram-negative option from column B, and one gram-negative option from column C. Note that the initial doses suggested in this table may need to be modified for patients with hepatic or renal dysfunction.

Abbreviations: CrCl, creatinine clearance; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] Drug levels and adjustment of doses and/or intervals required.

[b] Extended infusions may be appropriate. Please see section XIII on pharmacokinetic/pharmacodynamic optimization of antibiotic therapy.

[c] On meta-analysis, aminoglycoside regimens were associated with lower clinical response rates with no differences in mortality.

[d] The dose may need to be lowered in patients weighing <70 kg to prevent seizures.

[e] Polymyxins should be reserved for settings where there is a high prevalence of multidrug resistance and local expertise in using this medication. Dosing is based on colistin-base activity (CBA); for example, One million IU of colistin is equivalent to about 30 mg of CBA, which corresponds to about 80 mg of the prodrug colistimethate. Polymyxin B (1 mg = 10 000 units) [136].

[f] In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam–based agent because it has different targets within the bacterial cell wall [137].

Ceftaroline?

GUIDELINE HAP – IDSA 2016

Table 4. Recommended Initial Empiric Antibiotic Therapy for Hospital-Acquired Pneumonia (Non-Ventilator-Associated Pneumonia)

Not at High Risk of Mortality[a] and no Factors Increasing the Likelihood of MRSA[b,c]	Not at High Risk of Mortality[a] but With Factors Increasing the Likelihood of MRSA[b,c]	High Risk of Mortality or Receipt of Intravenous Antibiotics During the Prior 90 d[a,c]
One of the following:	One of the following:	Two of the following, avoid 2 β-lactams:
Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h
OR	OR	OR
Cefepime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h
OR	OR	OR
Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily
	Ciprofloxacin 400 mg IV q8h	Ciprofloxacin 400 mg IV q8h
	OR	OR
Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h
Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h
	OR	OR
	Aztreonam 2 g IV q8h	Amikacin 15–20 mg/kg IV daily
		Gentamicin 5–7 mg/kg IV daily
		Tobramycin 5–7 mg/kg IV daily
		OR
		Aztreonam[e] 2 g IV q8h
	Plus: Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Plus: Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg IV × 1 for severe illness)
	OR	OR
	Linezolid 600 mg IV q12h	Linezolid 600 mg IV q12h
		If MRSA coverage is not going to be used, include coverage for MSSA. Options include: Piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem. Oxacillin, nafcillin, and cefazolin are preferred for the treatment of proven MSSA, but would ordinarily not be used in an empiric regimen for HAP.
If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam–based antibiotic, include coverage for MSSA.		

Ceftaroline?

GUIDELINE CAP - TAIWAN 2019

Table 1 Empiric therapy for community-acquired pneumonia in adults.

Disease severity	Disposition	Preferred	Alternative	Treatment duration
Low severity	Outpatient	Amoxicillin 500 mg-1g PO q8h		5–7 days[e]
CRB-65=0–1[a]		Amoxicillin/clavulanate 1–2 g PO q12h		
No comorbidities, no history of antibiotic treatment in recent 3 months		Ampicillin/sulbactam 375–750 mg PO q12h		
		Cefaclor 500 mg PO q8h[b]		
		Presumed atypical pathogen		
		Azithromycin 500 mg PO qd		3–5 days[f]
		Clarithromycin 500 mg PO q12h		
		Doxycycline 100 mg PO q12h		
		Minocycline 100 mg PO q12h		
With comorbidities, or history of antibiotic treatment in recent 3 months		Amoxicillin 500 mg -1 g PO q8h	Moxifloxacin 400 mg PO qd[c]	5–7 days[e]
		Amoxicillin/clavulanate 1–2 g PO q12h	Levofloxacin 500–750 mg PO qd[c]	
		Ampicillin/sulbactam 375–750 mg PO q12h	Gemifloxacin 320 mg PO qd	
		Cefaclor 500 mg PO q8h[b]	Nemonoxacin 500 mg PO qd[d]	
		+/–		3–5 days[f]
		Azithromycin 500 mg PO qd		
		Clarithromycin 500 mg PO q12h		
Low severity	Non-ICU	Amoxicillin 500 mg-1 g PO q8h	Moxifloxacin 400 mg PO/IV qd[c]	5–7 days[e]
CURB-65 = 0–1[a]		Amoxicillin/clavulanate 1–2 g PO q12h	Levofloxacin 500–750 mg PO/IV qd[c]	
Hospitalized due to reasons other than disease severity (e.g. living alone, difficult to follow up, or accompanied with other clinical conditions requiring hospitalization.)		Ampicillin/sulbactam 375–750 mg PO q12h		
		Cefaclor 500 mg PO q8h[b]	Gemifloxacin 320 mg PO qd	
		Penicillin G 1–2 MU IV q6h-q4h	Nemonoxacin 500 mg PO qd[d]	
		Ampicillin 1–2 g IV q6h		
		Amoxicillin/clavulanate 1.2 g IV q8h		
		Ampicillin/sulbactam 1.5–3 g IV q6h		
		Cefuroxime 1.5 g IV q8h[g]		
		+/–		
		Azithromycin 500 mg PO QD		
		Clarithromycin 500 mg PO q12h		3–5 days[f]
Moderate severity	Non-ICU	Amoxicillin/clavulanate 1.2 g IV q8h	Moxifloxacin 400 mg IV qd[c]	5–7 days[e]
CURB-65 = 2–3[a]		Ampicillin/sulbactam 1.5–3 g IV q6h	Levofloxacin 500–750 mg IV qd	
		Cefuroxime 1.5 g IV q8h[g]	Tigecycline[i] 100 mg loading, then 50mg IV q12h	
		Ceftriaxone 2 g IV qd	Ceftaroline 500mg IV q12h	
		Cefotaxime 1–2 g IV q8h		
		Ertapenem 1 g IV qd[h]		
		+		
		Azithromycin 500 mg PO qd		
		Clarithromycin 500 mg IV/PO q12h		3–5 days[f]

GUIDELINE CAP – NICE 2019

Antibiotic[1]	Dosage and course length[2]
First choice antibiotic if low-severity (based on clinical judgement and CRB65 score 0, or CURB65 score 0 or 1)[3]	
Amoxicillin	500 mg three times a day orally or IV[4] for 5 days in total[5]
Alternative antibiotics if low-severity, for penicillin allergy or if amoxicillin unsuitable (for example, atypical pneumonia suspected)[3]	
Clarithromycin	500 mg twice a day orally or IV[4] for 5 days in total[5]
Erythromycin (in pregnancy)	500 mg four times a day orally for 5 days[5]
Doxycycline	200 mg on first day, then 100 mg once a day orally for 5 days[5]
First choice antibiotics if moderate-severity (based on clinical judgement and CRB65 score 1 or 2, or CURB65 score 2); guided by microbiological results when available[3]	
Amoxicillin ***with (if atypical pneumonia suspected):***	500 mg three times a day orally or IV[4] (higher doses can be used – see BNF) for 5 days in total[5]
Clarithromycin[6] ***or***	500 mg twice a day orally or IV[4] for 5 days in total[5]
Erythromycin[6] (in pregnancy)	500 mg four times a day orally for 5 days[5]
Alternative antibiotics if moderate-severity, for penicillin allergy; guided by microbiological results when available[3]	
Clarithromycin	500 mg twice a day orally or IV[4] for 5 days in total[5]
Azithromycin	500 mg once a day orally for 3 days[5]
First choice antibiotics if high-severity (based on clinical judgement and CRB65 score 3 or 4, or CURB65 score 3 to 5); guided by microbiological results when available[3]	
Co-amoxiclav ***with***	500/125 mg three times a day orally or 1.2 g three times a day IV[4] for 5 days in total[5]
Clarithromycin ***or***	500 mg twice a day orally or IV[4] for 5 days in total[5]
Erythromycin (in pregnancy)	500 mg four times a day orally for 5 days[5]
Alternative antibiotics if high-severity, for penicillin allergy; guided by microbiological results when available[3]	
Levofloxacin	500 mg twice a day orally or IV[4] for 5 days in total[5]

[1]See BNF and MHRA advice for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding, and administering intravenous antibiotics.

[2]Oral doses are for immediate-release medicines.

Ceftaroline?

GUIDELINE HAP – NICE 2019

Antibiotic[1]	Dosage and course length[2]
First-choice oral antibiotic for non-severe symptoms or signs and not at higher risk of resistance[3] (guided by microbiological results when available)	
Co-amoxiclav	500/125 mg 3 times a day for 5 days then review[4]
Alternative oral antibiotics for non-severe symptoms or signs and not at higher risk of resistance[3], if penicillin allergy or if co-amoxiclav unsuitable	
Antibiotic choice should be based on specialist microbiological advice and local resistance data. Options include:	
Doxycycline	200 mg on first day, then 100 mg once a day for 4 days (5-day course) then review[4]
Cefalexin (caution in penicillin allergy)	500 mg twice or 3 times a day (can be increased to 1 g to 1.5 g 3 or 4 times a day) for 5 days then review[4]
Co-trimoxazole[5,6]	960 mg twice a day for 5 days then review[4]
Levofloxacin[6] (only if switching from IV levofloxacin with specialist advice; consider safety issues[7])	500 mg once or twice a day for 5 days then review[4]
First-choice intravenous antibiotics if severe symptoms or signs (for example, symptoms or signs of sepsis) or at higher risk of resistance[3]. Review IV antibiotics by 48 hoursand consider switching to oral antibiotics as above for a total of 5 days then review[4]	
Antibiotic choice should be based on specialist microbiological advice and local resistance data. Options include:	
Piperacillin with tazobactam	4.5 g 3 times a day (increased to 4.5 g 4 times a day if severe infection)
Ceftazidime	2 g 3 times a day
Ceftriaxone	2 g once a day
Cefuroxime	750 mg 3 or 4 times a day (increased to 1.5 g 3 or 4 times a day if severe infection)
Meropenem	0.5 g to 1 g 3 times a day
Ceftazidime with avibactam	2/0.5 g 3 times a day
Levofloxacin[6] (consider safety issues[7])	500 mg once or twice a day (use higher dosage if severe infection)
Antibiotics to be added if suspected or confirmed MRSA infection (dual therapy with an IV antibiotic listed above)	
Vancomycin[5,8]	15 mg/kg to 20 mg/kg 2 or 3 times a day IV, adjusted according to serum vancomycin concentration (a loading dose of 25 mg/kg to 30 mg/kg can be used in seriously ill people); maximum 2 g per dose
Teicoplanin[5,8]	Initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once a day
Linezolid[5] (if vancomycin cannot be used; specialist advice only)	600 mg twice a day orally or IV

Ceftaroline?

GUIDELINE SSTI – IDSA 2014

Table 2. Antimicrobial Therapy for Staphylococcal and Streptococcal Skin and Soft Tissue Infections

Disease Entity	Antibiotic	Dosage, Adults	Dosage, Children[a]	Comment
Impetigo[b] (*Staphylococcus* and *Streptococcus*)	Dicloxacillin	250 mg qid po	N/A	N/A
	Cephalexin	250 mg qid po	25–50 mg/kg/d in 3–4 divided doses po	N/A
	Erythromycin	250 mg qid po[c]	40 mg/kg/d in 3–4 divided doses po	Some strains of *Staphylococcus aureus* and *Streptococcus pyogenes* may be resistant.
	Clindamycin	300–400 mg qid po	20 mg/kg/d in 3 divided doses po	N/A
	Amoxicillin-clavulanate	875/125 mg bid po	25 mg/kg/d of the amoxicillin component in 2 divided doses po	N/A
	Retapamulin ointment	Apply to lesions bid	Apply to lesions bid	For patients with limited number of lesions
	Mupirocin ointment	Apply to lesions bid	Apply to lesions bid	For patients with limited number of lesions
MSSA SSTI	Nafcillin or oxacillin	1-2 g every 4 h IV	100–150 mg/kg/d in 4 divided doses	Parental drug of choice; inactive against MRSA
	Cefazolin	1 g every 8 h IV	50 mg/kg/d in 3 divided doses	For penicillin-allergic patients except those with immediate hypersensitivity reactions. More convenient than nafcillin with less bone marrow suppression
	Clindamycin	600 mg every 8 h IV or 300–450 mg qid po	25–40 mg/kg/d in 3 divided doses IV or 25–30 mg/kg/d in 3 divided doses po	Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA
	Dicloxacillin	500 mg qid po	25–50 mg/kg/d in 4 divided doses po	Oral agent of choice for methicillin-susceptible strains in adults. Not used much in pediatrics
	Cephalexin	500 mg qid po	25–50 mg/kg/d 4 divided doses po	For penicillin-allergic patients except those with immediate hypersensitivity reactions. The availability of a suspension and requirement for less frequent dosing
	Doxycycline, minocycline	100 mg bid po	Not recommended for age <8 y[d]	Bacteriostatic; limited recent clinical experience
	Trimethoprim-sulfamethoxazole	1–2 double-strength tablets bid po	8–12 mg/kg (based on trimethoprim component) in either 4 divided doses IV or 2 divided doses po	Bactericidal; efficacy poorly documented
MRSA SSTI	Vancomycin	30 mg/kg/d in 2 divided doses IV	40 mg/kg/d in 4 divided doses IV	For penicillin allergic patients; parenteral drug of choice for treatment of infections caused by MRSA
	Linezolid	600 mg every 12 h IV or 600 mg bid po	10 mg/kg every 12 h IV or po for children <12 y	Bacteriostatic; limited clinical experience; no cross-resistance with other antibiotic classes; expensive
	Clindamycin	600 mg every 8 h IV or 300–450 mg qid po	25–40 mg/kg/d in 3 divided doses IV or 30–40 mg/kg/d in 3 divided doses po	Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA. Important option for children
	Daptomycin	4 mg/kg every 24 h IV	N/A	Bactericidal; possible myopathy
	Ceftaroline	600 mg bid IV	N/A	Bactericidal
	Doxycycline, minocycline	100 mg bid po	Not recommended for age <8 y[d]	Bacteriostatic; limited recent clinical experience
	Trimethoprim-sulfamethoxazole	1–2 double-strength tablets bid po	8–12 mg/kg/d (based on trimethoprim component) in either 4 divided doses IV or 2 divided doses po	Bactericidal; limited published efficacy data

GUIDELINE ABSSi – IDSA 2019

Table 3. 2014 Infectious Diseases Society of America Recommendations for Antibiotic Treatment of Acute Bacterial Skin and Structure Infection Caused by Methicillin-resistant *Staphylococcus aureus* [6]

Antibiotic	Route	Recommended Dosing in Adults
Vancomycin	IV	15 mg/kg every 12 hours
Linezolid	IV/oral	IV: 600 mg every 12 hours Oral: 600 mg twice a day
Clindamycin	IV/oral	IV: 600 mg every 8 hours Oral: 300–450 mg 4 times a day
Daptomycin	IV	4 mg/kg daily
Ceftaroline	IV	600 mg every 12 hours
Doxycycline, minocycline	Oral	100 mg twice a day
Trimethoprim-sulfamethoxazole	Oral	1–2 double strength tablets twice a day

Abbreviations: IV, intravenous.

ANTIBIOTIC TREATMENT OPTIONS FOR ABSSSI

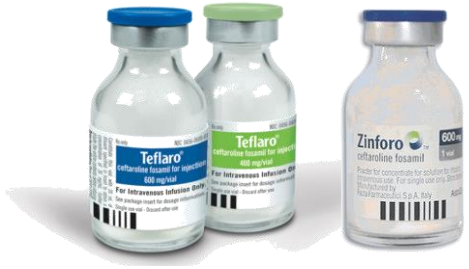
Beta-lactams

Among the beta-lactams, ceftaroline fosamil is an option for the initial empirical treatment of patients hospitalized with ABSSSIs, including those with suspected MRSA infection. Ceftaroline, administered twice daily, is an advanced-generation, intravenous (IV), bactericidal cephalosporin with broad-spectrum activity against gram-positive bacteria, including MRSA and some gram-negative bacteria, with the exception of *Pseudomonas aeruginosa* [17]. In 2 phase 3 studies [18, 19], ceftaroline showed noninferiority to vancomycin plus aztreonam in hospitalized patients with ABSSSI. Diarrhea was the most commonly reported adverse event (AE), and there was a low incidence of *Clostridium difficile*-associated diarrhea [18, 19]. Ceftaroline has

GUIDELINE SUMMARY

Indication	IDSA		Taiwan 2019	NICE 2019 (CAP/HAP)
	CAP 2019	HAP/VAP 2016		
Ceftaroline for pneumonia	Recommended as standard regimen	Not recommended	Recommended as alternative therapy for moderate to severe CAP	Not recommended

Indication	IDSA	
	2014	2019
Ceftaroline for ABSSSi	Recommended for MRSA SSTI	



RESTRICTION – WHO AWaRe CLASSIFICATION

A
access

Amikacin
Amoxicillin
Amoxicillin/Clav
Ampicillin
Ampicillin/Sulbac
Benzathine benzylP
Cefadroxile
Cefalexin
Cefalotin
Cefazoline
Cefradine
Chloramphenicol
Clindamycin
Cloxacillin
Dicloxacillin
Doxycycline
Flucloxacillin
Gentamicin
Metronidazole (IV/O)
Nitrofurantoin
Oxacillin
SMX/TMP
Tetracycline
Thiamphenicol
TMP

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watch

Azithromycin
Cefaclor
Cefamandole
Cefepime
Cefixime
Cefoperazone
Cefotaxime
Cefoxitin
Cefpodoxime
Ceftibuten
Ceftriaxone
Cefuroxime
Ciprofloxacin
Clarithromycin
Doripenem
Ertapenem
Erythromycin
Fosfomycin (oral)
Gatifloxacin
Gemifloxacin
Imipenem/Cil
Kanamycin
Levofloxacin
Lincomycin
Meropenem
Moxifloxacin
Neomycin
Norfloxacin
Oxytetracycline
Piperacillin
Piperacillin/tazo
Rifampicin
Spiramycin
Streptomycin
Tobramycin
Vancomycin (IV/Oral)

Re
reserve

Aztreonam
Ceftaroline fosamil
Ceftazidime/avibac
Ceftobiprole med
Ceftolozane
Colistin
Daptomycin
Fosfomycin (IV)
Linezolid
Meropenem/Vabor
Minocycline (IV)
Polymixin B
Televacin
Tigecycline

OFF LABEL USE OF CEFTAROLINE

Disease	Efficacy/Effectiveness	Mean time to eradication (days)	Concomitant antimicrobial therapy (no. of patients)	AEs (No. of events)	Treatment discontinuation because of AEs (No. of patients)	Reference (Year)
Bacteremia, pneumonia, bone and joint infection and other	Clinical success 88% (426/527); Hospital mortality 7.6% (40/527); 30-day readmission rate for same infection 9.1% (28/307); hosp. LOS median 12 days [IQR 7-21]	NR	29.2% (154/527) concomitant therapy; 42% metronidazole, 42% other anti-Staph agent	7.8% (41/527) Nausea, vomiting and diarrhea (9); rash (5); renal failure (6); CD associated diarrhea (3)	NR	2014 [28]
Bacteremia and sepsis, bone and joint infection, pneumonia, endocarditis, meningitis, device infections	Hosp. mortality 5%; hosp. LOS median 5 [IQR 3-12]; 30-day hosp. readmission rate 33%	NR	NR	Rates of eosinophilia, leukopenia, leukocytosis, fibromyalgia, myalgia, myositis < 1%	NR	2017 [17]
Bacteremia	Clinical success 74.2% (23/31); microbiological cure at EOT* 64.5% (20/31); mortality 6.5% (2/31)	(mean) 3.5 [1-8]	32.2% (10/31) concomitant therapy with additional anti-MRSA therapy (most frequently Daptomycin)	9.7% (3/31) Peripheral eosinophilia (3), rash (1), antibiotic associated diarrhea (2)	Eosinophilic pneumonia (1); eosinophilia (1); nausea, diarrhea, rash (1)	2013 [6]
Bacteremia	Overall survival 96% (25/26)	(median) 2 [1-6]	100% (26/26) in combination with daptomycin	NR	NR	2014 [14]
Bacteremia	Clinical success 88% (14/16); microbiological cure 100% (16/16); hosp. LOS median 37 [IQR 21.8-76.3]	(median) 4 [IQR 3-75]	19% (3/16) one each with rifampicin, daptomycin, vancomycin	NR	NR	2014 [10]
Bacteremia	Clinical success 4/5 (80%)	NR	Vancomycin (5)	NR	NR	2016 [18]
Bacteremia	Clinical success 68.3% (86/126[a]) Microbiological cure at EOT 91.3% (115/126 [a]); hosp. LOS median 12 [IQR 8-20]; hosp. mortality 22.2% (28/126 [a])	(median) 3 [IQR 1-4]	21.8% (46/211)	7% (16/211) CD infection (6), rash (7), neutropenia (3)	Unknown	2017 [11]
Bacteremia	Microbiological cure at EOT 29/30 (97%); 30-day readmission 7% (2/30); 30-day mortality 14% (4/30)	NR	No	NR	NR	2017 [11]
Bacteremia	Clinical success 83% (5/6)	(mean) 2 [1-5]	No	NR	NR	2012 [15]
Bacteremia	Clinical success at 6 months 31% (9/20 [β]) Microbiological success 90% (26/29);	(median) 3 [IQR 2-5]	In combination with trimethoprim-sulfamethoxazole 23/29, daptomycin 2/29	NR	Rash (1)	2014 [13]
Bacteremia,	Clinical success 60% (6/10) Microbiological cure 70% (7/10)	NR	1/10 concomitant therapy with daptomycin	NR	NR	2014 [39]
Endocarditis	Clinical success 62% (5/8)	NR	rifampicin (1) daptomycin (2)	0	0	2014 [20]

OFF LABEL USE OF CEFTAROLINE

Disease	Efficacy/Effectiveness	Mean time to eradication (days)	Concomitant antimicrobial therapy (no. of patients)	AEs (No. of events)	Treatment discontinuation because of AEs (No. of patients)	Reference (Year)
Endocarditis	Clinical success 70.9% (39/55)	NR	monotherapy 23/55 (41.8%) daptomycin 19/55 (34.5%), vancomycin 9/55 (16.4%) rifampin 7/55 (12.7%)	2	2	2019 [21]
Hospital acquired pneumonia	Clinical success 75% (30/40)	NR	18/40	NR	AE not recorded (1)	2015 [22]
Nosocomial Pneumonia	Clinical success 60% (6/10)	NR	NR	NR	NR	2015 [23]
Nosocomial pneumonia	Clinical success 91% (32/35^); mean hosp. LOS 27.7 (24.4)	NR	No	0	0	2016 [1]
Nosocomial pneumonia	Clinical success 62% (19/25); hosp. LOS mean 25; 30-day readmission 9%; death 6%	NR	7/25 (23%)	0	0	2017 [27]
Osteoarticular infections	Clinical success 58% (7/12); hosp. LOS median 25.5 [7-75]	NR	No	4/12 (33%) Pancytopenia (2) AST/ALT increase (1), pruritic rash (1)	AST/ALT increase (1), pruritic rash (1)	2017 [29]
Osteoarticular infections	180 day all cause readmission 42% (21/50); IRR 22% (11/50); time-to-IRR median 49 [IQR 30-88]	NR	36% non pseudomonal β-lactam, 10% metronidazole, 4% ciprofloxacin, 4% rifampicin	12/50 (24%) AKI (1), CD infection (2), nausea (3), rash (5)	(6)	2016 [28]
Osteoarticular	Clinical success 13/19 (68%)	NR	17 (89.5%)	4/19	Neutrope	2017 [27]
infections	Clinical success at 6-month FU 7/19 (37%) (5 NR)°		rifampicin (7/19), trimethoprim/sulfamethoxazole (3/19), fosfomycin (2/19), linezolid (2/19), vancomycin (1/19), daptomycin (1/19), metronidazole (2/19)	Neutropenia (2) Rash (2)	nia (2) Rash (2)	
Spinal infections	Clinical success 92% (34/37)	NR	0	3/37 eosinophilic pneumonia (1), drug fever (1), thrombocytopenia (1)	Eosinophilic pneumonia (1), drug fever (1)	2018 [26]
Meningitis	Clinical success 83% (5/6)	NR	NO	NR	NR	2015

Table 2. AEs adverse events; IRR infection related readmission; AKI acute kidney injury; LOT length of hospital stay; EOT end of treatment; NR not re

* Not assessed in all patients

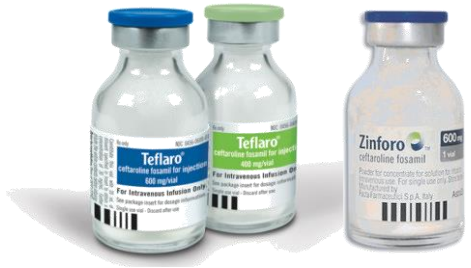
⊥ Composite failure outcome: 30-day mortality/42-day relapse/30-day readmission

^ 35 evaluable cases for the 14 days primary clinical outcome

° 14 evaluable cases for the 6-month FU

ª 126 patients included in the efficacy analysis

ᵝ 9 patients lost to follow-up



AVAILABILITY

INDONESIA: belum tersedia

Harga:

Merk	Harga	Total perkiraan biaya bila digunakan untuk CAP	Total perkiraan biaya bila digunakan untuk SSTi
Zinforo® (Pfizer Ltd)	£ 375.00 ~ Rp. 6.778.415 untuk 10 vial @600 mg (BNF; 2018) Maka 1 vial = ± Rp. 677.000,-	Pneumonia pengobatan 5-7 hari 2 x 600 mg 1 hari = Rp. 1.354.000,- Total biaya= ± Rp. 6.770.000 – Rp. 9.478.000	SSTi pengobatan 5-14 hari 2 x 600 mg 1 hari = Rp. 1.354.000,- Total biaya= ± Rp. 6.770.000 – Rp. 18.956.000
Teflaro® (Allergan plc)	$2,015.24 ~ Rp. 28.318.354 untuk 10 vial @400 mg atau 600 mg (drug.com) Maka 1 vial = ± Rp.2.831.000,-	Pneumonia pengobatan 5-7 hari 2 x 600 mg 1 hari = Rp. 5.662.000,- Total biaya= ± Rp. 28.310.000 – Rp. 39.634.000	SSTi pengobatan 5-14 hari 2 x 600 mg 1 hari = Rp. 1.354.000,- Total biaya= ± Rp. 6.770.000 – Rp. 18.956.000

The Scottish Medicines Consortium, has advised (Dec 2012) that ceftaroline fosamil (Zinforo ®) is accepted for **RESTRICTED** use within NHS Scotland when **meticillin– resistant S. aureus is suspected** in complicated skin and soft-tissue infection **and vancomycin cannot be used**. (BNF; 2018)

AVAILABILITY

Harga:

Zinforo (Ceftaroline)	Viccilin Sx (Ampicillin/ Sulbactam)	Broadced (Ceftriaxone)	Lancef (Cefotaxime)
1 hari 2 vial = Rp. 1.354.000,-	1,5 gram x 10 vial = Rp. 82.000 1 vial 8.200 Sehari 1,5-3 gram setiap 6 jam **4 vial 1,5 gram= Rp. 32.800** **8 vial 1,5 gram= 65.600**	1 gram/vial = Rp. 164.500 Dosis guideline: 1-2 gram/hari **Sehari= Rp. 164.500 – Rp. 329.000**	1 gram/vial = Rp. 126.000,- Dosis guideline: 1-2 gram setiap 8 jam (3x sehari) **3x1 gram = Rp. 378.000** **3x2 gram = Rp. Rp. 756.000**

The Scottish Medicines Consortium, has advised (Dec 2012) that ceftaroline fosamil (Zinforo ®) is accepted for **RESTRICTED** use within NHS Scotland when **meticillin– resistant S. aureus is suspected** in complicated skin and soft-tissue infection **and vancomycin cannot be used**. (BNF; 2018)

CONCLUSION

1. Berdasarkan **beberapa penelitian** Ceftaroline terbukti **efektif dan aman** bila digunakan untuk mengatasi CAP dan SSTi. Beberapa panduan terapi, salah satunya **IDSA merekomendasikan** penggunaan Ceftaroline untuk indikasi CAP dan SSTi. Hal tersebut dapat disebabkan oleh tingkat kejadian infeksi akibat ***community acquired*** **MRSA** (Ca-MRSA) relatif tinggi.

2. Dengan mempertimbangkan: 1) data prevalensi dan sensitivitas Ca-MRSA, khususnya di RKZ yang belum diketahui; 2) biaya pengobatan yang relatif tinggi; 3) Ceftaroline termasuk antibiotik kategori **RESERVED** berdasarkan kategori AWaRe dari WHO, maka Ceftaroline dapat digunakan sebagai "***LAST RESORT***" antibiotik untuk pengobatan CAP dan SSTi

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Thank you

"If we fail to act, we are looking at an almost unthinkable scenario where antibiotics no longer work and we are cast back into the dark ages of medicine" - David Cameron, former UK Prime Minister