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REVIEW

Mecillinam for the treatment of acute pyelonephritis and bacteremia caused by Enterobacteriaceae: a literature review

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Purpose: The pharmacokinetic properties of mecillinam (MEC) for urinary tract infections are excellent, and the resistance rate in Enterobacteriaceae is low compared to other recommended antibiotics. The oral prodrug pivmecillinam (P-MEC) has been used successfully as first choice for cystitis in the Nordic countries for many years. Norwegian and Danish guidelines also recommend P-MEC for acute uncomplicated pyelonephritis (AUP) and intravenous (IV) MEC for suspected urosepsis (only in Denmark). Here, we wish to present an updated investigation on the clinical data behind these recommendations together with sparse but more current clinical data.
Methods: Prospective clinical trials evaluating MEC as monotherapy or in polytherapy with one other beta-lactam (mostly ampicillin [AMP]) for pyelonephritis or bacteremia were reviewed. Outcomes of primary interest were clinical and bacteriological success and relapse, respectively. Search databases used were PubMed, Cochrane Library, and Embase.
Results: Twelve clinical studies (1979–2015) were included in this integrated literature review. Clinical success was seen in 38/51 (75%) patients treated with MEC as monotherapy and in 152/164 (93%) patients treated with MEC and one other beta-lactam. Bacteriological success was seen in 35/47 (74%) and 117/167 (70%) patients treated with MEC alone and with one other beta-lactam, respectively. In complicated infections, bacteriological success was much lower. Clinical relapse rate was not well described. Several uropathogenic bacteremia cases were treated successfully with MEC alone (ie, 10/15 [67%] and 13/15 [87%] for clinical and bacteriological success, respectively) or with one other beta-lactam (ie, 57/65 [88%] and 53/63 [84%] for clinical and bacteriological success, respectively). However, data on bacteremia are very sparse. Adverse reactions were few and mild (73/406 [18%]) and primarily seen when AMP was co-administered (69/73 [95%]). No serious adverse reactions were reported.
Conclusion: IV MEC or oral P-MEC for 14 days may be suitable for the treatment of AUP and pediatric pyelonephritis. Randomized controlled trials using a single standardized dose of P-MEC compared to other current recommendations are warranted. Similarly, more evidence is required before MEC should be recommended for bacteremia or sepsis due to Enterobacteriaceae.
Keywords: pyelonephritis, mecillinam, review, pivmecillinam, amdinocillin

Introduction

Mecillinam (MEC) (known as amdinocillin in the USA) is an antimicrobial drug from the amidinopenicillin group that was first introduced in 1972. MEC is selective and highly effective against Gram-negative bacteria, especially *Escherichia coli*.[1,2] The oral prodrug pivmecillinam (P-MEC) has high bioavailability (~70%), and 45% of the dose is secreted in the urine as MEC within 6 hours. Side effects are few and most commonly include mild gastrointestinal symptoms.[2,3] Community resistance rates are generally

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low (including in Scandinavia [5%–6%][4–6] where MEC has been used for several decades), with a low rate of collateral damage and a low risk of clonal spread of resistance.[7–12]

The international guideline for acute uncomplicated pyelonephritis (AUP) recommends that local resistance toward an empirical antibiotic should be <10%,[13] and as the rates of resistance to recommended antibiotics continue to rise,[8,11] the current recommendations are increasingly limited.[13] The resistance to ciprofloxacin is of particular concern because ciprofloxacin is generally the recommended first-line therapy for outpatient care of pyelonephritis.[13] The present pipeline of novel oral antimicrobials is very limited. Therefore, it is crucial to re-vitalize old antimicrobials for potential effectiveness against pyelonephritis. We believe that MEC has several interesting properties for this indication, including high efficacy for the treatment of lower urinary tract infections (UTI),[3,14–16] high renal tissue concentration compared to serum,[17] low rates and spread of resistance even in countries with high consumption,[7–11] and few side effects and synergism with other antibiotics.[2] MEC also exhibits good in vitro activity against extended spectrum beta-lactamase (ESBL) and carbapenemase producing Enterobacteriaceae;[18–22] however, clinical utility is still not well established in the literature.[23,24]

Nevertheless, the potential use of MEC for the treatment of pyelonephritis and urosepsis is not internationally acknowledged. The oral prodrug is however recommended empirically against AUP in Denmark and Norway (400 mg three times daily [tid], for 7–14 days),[25–27] or intravenously (IV) as MEC (1 g tid) for the treatment of urosepsis,[28] but the evidence behind these recommendations is not specified in the guidelines.

Aim

With this study, we wanted to present an updated investigation of the clinical trials underlying these recommendations. We believe that this could enlighten the medical community outside Scandinavia of this old alternative antimicrobial drug for especially acute pyelonephritis, where the causative bacteria increasingly are resistant to the currently recommended therapies.

Methods

Inclusion criteria

We included prospective clinical trials in children (excluding neonates) and adults of MEC/P-MEC as monotherapy or in combination with another antibiotic for acute pyelonephritis and/or urosepsis/bacteremia. Bacteriological and/or clinical effects had to have been evaluated. We did not limit our inclusion to randomized controlled trials since there were few studies on the subject.

Search strategy

We conducted a widespread search for relevant studies in English regardless of age of the studies. We performed an unfiltered PubMed search combining the following terms: (“pyelonephritis” OR “upper urinary tract infection” OR “urinary tract infection” OR “UTI” OR “Sepsis” OR “Septic” OR “SIRS” OR “bacteraemia” OR “fever” OR “Febrile”) AND (“mecillinam” OR “pivmecillinam” OR “amdinocillin” OR “amidinopenicillin”) (N=317). A MeSH database search was done with the following mesh words in combination: (“Fever” OR “Sepsis” OR “Pyelonephritis” OR “Urinary Tract Infections” OR “Systemic Inflammatory Response Syndrome” OR “Bacteraemia”) AND (“Amdinocillin” OR “Amdinocillin Pivoxil”) (N=169). After removing duplications, the searches yielded 317 articles. The last search was conducted on February 17, 2017. Similar searches in the Cochrane Library (N=61) and Embase (N=218) were performed. The reference lists of the included studies and relevant reviews were additionally scanned for relevant clinical trials not found in the PubMed and MeSH database search.

Trial selection and data extraction

The primary reviewer selected studies according to inclusion criteria and extracted data. Outcomes of interest were clinical success and relapse, as well as bacteriological success and relapses. Senior reviewers controlled justifications for excluded studies and data extractions. All reviewers evaluated the scientific context and relevance of the selected studies and data extraction. We extracted data on characteristics such as trial design, patients (ie, sex, age, and comorbidities), type of infections (ie, pyelonephritis, bacteremia, acute, and complicated), pathogens and sensibility, and intervention (ie, antibiotics, doses, intervals, and durations). The data were analyzed by per-protocol, since majority of the studies used this methodology.

Results

Results from the literature search are summarized in Figure 1. We identified 317 articles in the PubMed and MeSH database search, which yielded the included clinical trials.[29–38] The following two clinical trials were further included: one from Embase and reference lists[39] and one recent quality control study on the Danish guidelines by our own research group.[40] We identified the following 12 prospective clinical studies[29–40] that met our criteria: two studies on MEC’s effect

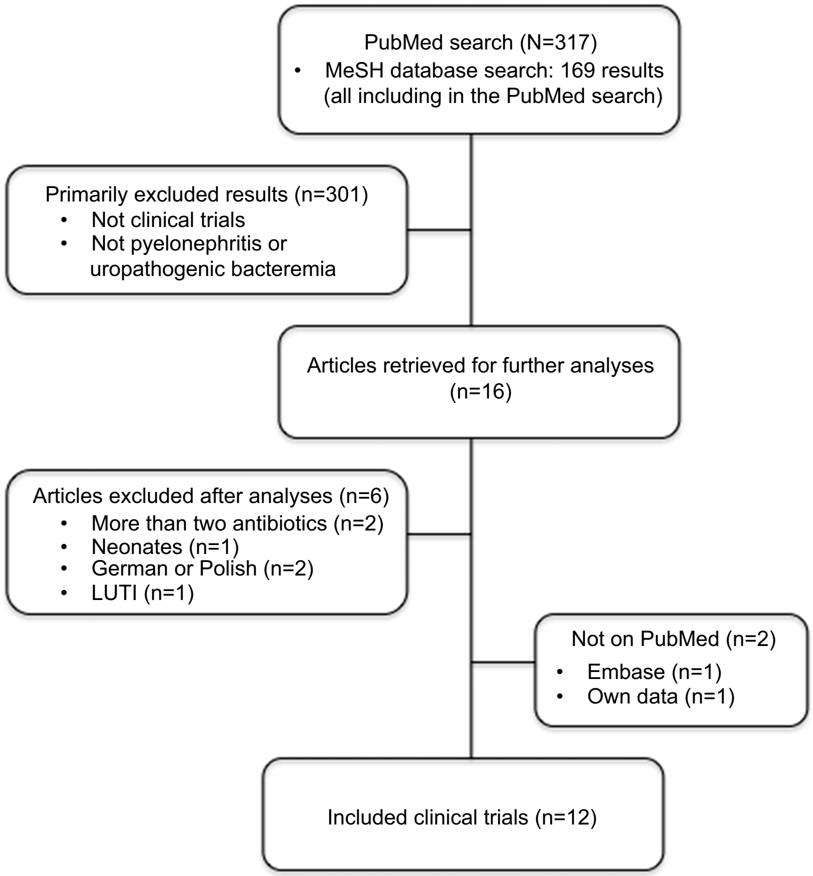

Figure 1 Literature search.
Abbreviation: LUTI, lower urinary tract infections.

on uropathogenic bacteremia,[30,32] one study on MEC's effect on pediatric pyelonephritis,[33] four studies on MEC's effect on pyelonephritis with or without bacteremia,[36,38–40] and five studies on concomitant MEC and ampicillin (AMP) therapy on pyelonephritis with or without bacteremia.[31,34,35,37] Three studies were prospective noncomparative,[32,33,36,40] and eight studies were prospective comparative;[29–31,34,35,37–39] of these studies, six were randomized,[29–31,34,38,39] of which only three studies were double blinded.[29,31,34]

Definitions of outcomes

As shown in Table 1, the definitions on treatment effect parameters were heterogeneous among the trials. Clinical success was defined as relief of symptoms and fever during the first 3–7 days.

Bacteriological success was heterogeneously defined; it was mainly defined as eradication of bacteria during or after therapy, although some studies included "no relapse or reinfection" in the definition and some studies defined bacteriological relapse separately (range 2–24 weeks). Therefore, to make the definition more homogenous in this review, we chose a wide definition of bacteriological success: bacteriologically cured without relapse or reinfection. This lowered the bacteriological success rate in the studies that did not include bacteriological relapse or reinfection in the definition for bacteriological success. Very few studies described whether a bacteriological failure, relapse, or reinfection was symptomatic.

Outcomes

The 12 included clinical trials are described in Table 1. The trials were published from 1979 to 2015. They included a total of 296 adult patients with pyelonephritis and/or bacteremia; 57 patients were treated with P-MEC alone and 239 patients were treated with P-MEC and one other beta-lactam. The 20 pediatric patients with acute pyelonephritis were treated with P-MEC alone.

MEC in pyelonephritis

The summarized results for P-MEC for the treatment of pyelonephritis are shown in Table 2.[38–40] The cumulative clinical success and the bacteriological success were 75% and

Table 1 Prospective studies of mecillinam for the treatment of pyelonephritis and Enterobacteriaceae bacteremia

Pyelonephritis

Study	Design	Intervention	Patients (N)	Age (mean) (years)	Temperature (°C)	Male: female	Bacteremia (N)
Trollfors et al (1982)[38]	Randomized, open label, comparative	IV: mecillinam 800 mg tid 5 days Oral: P-MEC 400 mg tid 5 days Duration: 10 days	25	19–76 (48)	≥38.5	6:19	7
		IV: cephaloridine 1 g tid 5 days Oral: cephalexin 500 mg tid 5 days Duration: 10 days	26	18–83 (55)		6:20	10
Ode et al (1983)[39]	Randomized, open label, comparative	IV: mecillinam 1.2 g qid ≥3 days Oral: P-MEC 400 mg tid Duration: 28 days	20	19–88 (56)	>37.5	4:16	4
		IV: trimetoprim 160 mg bid ≥3 days Oral: trimetoprim 160 mg bid Duration: 28 days	22	32–86 (56)		8:14	5
		IV: AMP 2 g qid ≥3 days Oral: P-AMP 600 mg tid Duration: 28 days	21	20–86 (58)		2:19	6
Helin (1983)[33]	Open label, noncomparative (pediatric)	Oral: P-MEC 25–40 mg/kg/day bid or tid Duration: 10 days	20	0.5–14 (4)	>38.5	4:16	–
Rotstein and Farrar (1983)[37]	Open label, comparative	IV: mecillinam 10 mg/kg + AMP nd qid Duration: 4–10 days	11	18–80 (39)[a]	nd	~1/3 male	4
		IV: mecillinam 10 mg/kg + CCC nd qid Duration: 4–10 days	9				3
King et al (1983)[35]	Open label, comparative	IV: mecillinam 10 mg/kg + AMP nd qid Duration: nd	14	nd	nd	~50% male	nd
		IV: mecillinam 10 mg/kg + CCC nd qid Duration: nd	14				
Eriksson et al (1986)[31]	Randomized, open label, comparative	IV: mecillinam 400 mg/AMP 500 mg tid (N=15) ∼4 days Oral: P-MEC 200 mg/P-AMP 250 mg tid Duration: 14 days	27 (IV: 15)	15–86 (55)	≥38	6:21	5
		IV: AMP 1.4 g or tid ∼4 days Oral: P-AMP 700 mg bid Duration: 14 days	30 (IV: 17)	16–82 (57)		8:22	9
Jernelius et al (1988)[34]	Randomized, double blinded, placebo controlled	Oral: P-MEC /P-AMP 400/500 mg tid 7 days + placebo tid 14 days Duration: 7 days	32	18–81 (59)	≥38	12:20	5
		Oral: P-MEC /P-AMP 400/500 mg tid 7 days + 200/250 mg tid 14 days Duration: 21 days	29	16–78 (61)		7:22	4
Cronberg et al (1995)[29]	Randomized, double blinded, comparative	IV: mecillinam 600 mg/AMP 1.2 g bid ∼3 days Oral: P-MEC 400 mg/P-AMP 500 mg bid Duration: 14 days	65	(61)	≥38.5	Estimated <50% male	12
		IV: cefotaxime 2 g bid ∼3 days Oral: cefadroxil 800 mg bid Duration: 14 days	71	(61)		Estimated <50% male	20

Complicating factors (N)	Estimated AUP (N)	Pathogens (S to mecillinam) (N)	Clinical success	Bacteriological		Comment
				Success	Without relapse/ reinfection	
8	≤17	*E. coli* (S) (22) *K. pneumoniae* (S) (1) *P. mirabilis* (S) (2)	15/25	24/25	18/23 (2 lower UTI)	The clinical outcome was significantly poorer ($P<0.05$) in patients with mecillinam. The study excluded resistant strains and negative culture
10	≤16	*E. coli* (S) (24) *K. pneumoniae* (S) (2) *P. mirabilis* (S) (1)	25/26	26/26	18/24 (3 lower UTI)	
6	14	*E. coli* (S) (17) *E. coli* (R) (1) *P. mirabilis* (S) (1) *K. pneumoniae* (R) (1)	17/20 AUP: 12/14	12/18 AUP: 11/13		The resistant isolates were not evaluable for bacteriological evaluation because of change in therapy
10	12	*E. coli* (17) *P. mirabilis* (1) *K. pneumoniae* (1) Others (3)	18/22	12/21		
5	15	*E. coli* (18) *K. pneumoniae* (1) Others (2)	16/21	13/20		
1	–	*E. coli* (S) (16) *K. pneumoniae* (S) (2) *S. saphropyticus* (R) (1) Others (R) (1)	nd	19/20	18/19	Failure was seen in the patient with mixed Gram-positive bacteriuria. Relapse was seen in the patient with ureteral stenosis (*K. pneumoniae*)
–	–	*E. coli* (S) (16) *E. coli* (R) (5)	11/11	11/11	nd	3/10 had clinical relapse (intervention group nd). In vitro synergism between mecillinam and other beta-lactam ($P<0.025$)
2	–	*K. pneumoniae* (S) (5)	8/9	9/9		
nd	nd	Gram-negative bacteria (31)	26/28	21/31		Low bacteriological cure rate in subgroup with complicated UTI
7	20	*E. coli* (25) *S. saphropyticus* (1) Others (2)	25/27 (including no relapse)	27/27	15/27 (only two clinical relapses)	Better clinical outcome in the combination group ($P=0.002$). With only S strains ($P=0.06$). Better bacteriological outcome in the combination group ($P=0.007$). Males and complicated infections ($P=0.06$) and high age ($P<0.01$) were more common in the unsuccessful treatment group
9	21	*E. coli* (24) *K. pneumoniae* (4) *P. mirabilis* (3) Others (2)	16/30 (including no relapse)	22/30	10/21 (only two clinical relapses)	
14	18	*E. coli* (S) (28) *K. pneumoniae* (S) (2) *P. mirabilis* (S) (1) *S. saphropyticus* (R) (2) Others (R) (1) Others (S) (2)	29/32 Relapse: 3/32	9/32	14/32	Significantly better bacteriological success ($P=0.004$) and lower relapse rate in the 3-week group, ($P=0.02$). Of the nine patients without bacteriological success in the 3-week group, seven had complicating factors. All bacteria had clinical success
13	16	*E. coli* (S) (29) *S. saphropyticus* (R) (1) Others (R) (2)	28/29 Relapse: 1/29	20/29	23/29	
nd	nd	*E. coli* (49) *K. pneumoniae* (5) *P. mirabilis* (2) Others (12)	41/60		44/60	Therapeutic outcomes, parameters adherence rate, and adverse effects were similar in both groups. More severe adverse reactions in cephalosporin group (ie, diarrhea, *Clostridium difficile*. and fungal superinfection). The study used ITT analyses, however, since the majority of the studies used PP analysis we decided to use that
nd	nd	*E. coli* (58) *K. pneumoniae* (3) *P. mirabilis* (6) Others (16)	45/70		50/70	

(*Continued*)

Table 1 (*Continued*)

Pyelonephritis

Study	Design	Intervention	Patients (N)	Age (mean) (years)	Temperature (°C)	Male: female	Bacteremia (N)
Nicolle and Mulvey (2007)[36]	Case report	Oral: P-MEC 400 mg bid Duration: 2 years	1	47	nd	0:1	–
Jansåker et al (2015)[40]	Observational noncomparative	Oral: P-MEC 400 mg tid Duration: 14 days	6	23–78 (47)	nd	0:6	–

Enterobacteriaceae bacteremia

Study	Design	Intervention	Number of patients	Age (median) (years)	Male:female	Complicating factors
Frimodt-Møller and Ravn (1979)[32]	Observational noncomparative	IV: mecillinam 10 mg/kg qid with/without one other antibiotics Duration: 4–10 days (median 7)	5	47–85 (78)	1:4	All patients had serious comorbidities and impaired renal function
Ekwall et al (1980)[30]	Randomized, open label, comparative	IV: mecillinam 10 mg/kg qid 7–14 days Oral: P-MEC 400 mg tid Duration: 21 days	3	56–86 (57)	1:2	nd
		IV: mecillinam 5 mg/kg + AMP 15 mg/kg qid 7–14 days Oral: P-MEC 200 mg + P-AMP 350 mg tid Duration: 21 days	5	21–73 (45)	3:2	nd
	Nonrandomized	IV: mecillinam 10 mg/kg + AMP 30 mg/kg qid 7–14 days Oral: P-MEC 400 mg + P-AMP 700 mg tid Duration: 21 days	5	52–87 (65)	3:2	Patients with serious comorbidities
King et al (1983)[35]	Open-label comparative (stratified cases)	IV: mecillinam 10 mg/kg + AMP nd qid Duration: nd	11	[b]	~50% male	[b]
		IV: mecillinam 10 mg/kg + CCC nd qid Duration: nd	14			

Notes: [a]Including five cases with other infections. [b]Stratified cases of bacteremia caused by pyelonephritis (for detailed data refer Table 2).
Abbreviations: AMP, ampicillin; AUP, acute uncomplicated pyelonephritis; bid, two times daily; CCC, cephalosporin or carbenicillin; *E. coli*, *Escherichia coli*; ESBL, extended spectrum beta-lactamase; GI, gastrointestinal; ITT, intention to treat; IV, intravenous; *K. oxytoca*, *Klebsiella oxytoca*; *K. pneumoniae*, *Klebsiella pneumoniae*; nd, no data/not described; *P. mirabilis*, *Proteus mirabilis*; P-AMP, pivampicillin; P-MEC, pivmecillinam; PP, per protocol; qid, four times daily; SAR, severe adverse reaction; S, sensitive; *S. saphropyticus*, *Staphylococcus saphropyticus*; tid, three times daily; UTI, urinary tract infections.

74%, respectively. Considerably higher treatment failure was found in complicated infections (ie, high age, males, bacteremia, and females with predisposing factors),[38,39] and high treatment success was seen in the studies where AUP could be stratified.[38,40] There are two cases with treatment success with P-MEC in pyelonephritis caused by ESBL producing *E. coli*.[36,40] In a comparative study, MEC (800 mg tid) had significantly lower clinical success than cephaloridine 1 g tid ($P<0.05$).[38] With a higher initial MEC dose of 1200 mg four times daily (qid), an overall superior treatment success was achieved compared to MEC 800 mg tid and with no difference compared to AMP and trimethoprim.[39]

To our knowledge, there is only one pediatric clinical study on P-MEC.[33] The author found an excellent bacteriological success (19/20) of P-MEC in children (0.5–14 years) with pyelonephritis, when administered as 25–40 mg/kg/day two times daily (bid)/tid for 10 days.

The summarized results for P-MEC combined with another beta-lactam (pivampicillin [P-AMP] in 141/163) for pyelonephritis are listed in Table 2. The clinical success and the bacteriological success were 93% and 70%, respectively. The combination of P-AMP/P-MEC had excellent clinical success within the first week of treatment. However, Jernelius et al found that the bacteriological success was 39% and 88% for AUP, with 1- and 3-week therapies, respectively ($P=0.02$). Symptomatic relapses were mainly lower UTI in both groups, and the few relapses found in the 3-week therapy were asymptomatic in >80% of the cases.[34] The 2-week therapy demonstrated intermediate results as compared to the 1- and 3-week therapies.[29,31] One study used

Complicating factors (N)	Estimated AUP (N)	Pathogens (S to mecillinam) (N)	Clinical success	Bacteriological		Comment
				Success	Without relapse/ reinfection	
1	0	ESBL – *E. coli* (S) (1)				Bacteriological and clinical success was seen over the following weeks after initiating the therapy, no relapse of ESBL producing *E. coli* over following 2 years
0	6	*E. coli* (S) (6) *K. pneumoniae* (S) (1)	6/6	6/6	4/5 (relapse: asymptomatic)	Including retrospective cases: bacteriological and clinical success 17/22 (77%). Bacteriological relapse 7/22 (32%). One ESBL producing *E. coli* infection with treatment success

Pathogens	Results and comments
E. coli (S) (2) *K. pneumoniae* (S) (2) *K. oxytoca* (S) (1)	2/2 with monotherapy had clinical and bacteriological success 3/3 with concomitant therapy had clinical and bacteriological success
E. coli (S) *Citrobacter* sp (S) *K. pneumoniae* (S)	2/3 had clinical and bacteriological success 1/3 had clinical and bacteriological failure (female with *K. pneumoniae*)
E. coli (S) (4) *K. pneumoniae* (S)	4/5 had clinical and bacteriological success 1/5 had clinical and bacteriological failure (male with *E. coli*)
E. coli (S) (3) *Citrobacter* sp (S) *P. mirabilis* (S) (2)	4/5 had clinical and bacteriological success 1/5 had clinical and bacteriological failure (male with Ec and *Citrobacter* sp)
Gram-negative bacteria	11/11 had clinical and bacteriological success
	13/14 had clinical and bacteriological success

a lower dose of P-MEC/P-AMP (0.2/0.25 g tid)[31] compared to similar trials.[29,34] The bacteriological success (56%) and overall success (ie, both clinical success and bacteriological success without relapse) in AUP (55%) were much lower in this study[31] compared to the other studies, where the bacteriological success was ~69%[29,34] and the overall success in AUP was 81%.[34] In the two studies that cases could be stratified into uncomplicated or complicated pyelonephritis, the overall success rates were 67% and 25%, respectively. It was found that patients of high age, males, and females with predisposing factors demonstrated a considerably lower and insufficient treatment success, mostly because of bacteriological failure.[31,34] Eriksson et al[31] found that MEC combined with AMP was superior both clinically and bacteriologically to AMP alone, in spite of a lower dosage in the combination therapy. AMP monotherapy was associated with higher selection of resistant strains to both AMP (P=0.02) and MEC (P=0.06) compared to combination therapy, which was not associated with the selection of resistant strains. Cronberg et al[29] found that MEC combined with AMP for 14 days (IV followed by oral administration) had similar rates for treatment success, treatment discontinuation, and bacteriological relapses for acute pyelonephritis as treatment with a cephalosporin (IV followed by an oral administration). The relapse rate was similar to other studies on the MEC/AMP combination.[30,34,39] Two studies compared MEC (10 mg/kg qid) combined with either AMP or cephalosporines (doses not defined).[45,46] One of these studies found that both combinations had equal excellent outcome after a 4- to 10-day therapy.[37] The second study found that the AMP combination had an inferior bacteriological success (duration not defined); yet, there was no difference in the bacteremia group.[35]

Table 2 Effect of mecillinam and mecillinam in combination with other beta-lactams for the treatment of pyelonephritis with and without bacteremia

Mecillinam						
Reference	**Without predisposing factors (AUP)**		**With predisposing factors**		**All pyelonephritis**	
	Clinical success	**Bacteriological success (without relapse/reinfections)**	**Clinical success**	**Bacteriological success (without relapse/reinfections)**	**Clinical success**	**Bacteriological success (without relapse/reinfections)**
Ode et al[39]	12/14	11/13[a]	5/6	1/5[b]	17/20	12/18[a,b]
Trollfors et al[38]	Not possible to determine				15/25	18/23[c]
Jansåker et al[40]	6/6	5/6	–	–	6/6	5/6
Total	18/20 (90%)	16/19 (84%)	5/6 (83%)	1/5 (20%)	38/51 (75%)	35/47 (74%)
Mecillinam in combination with other beta-lactams						
Reference	**Without predisposing factors (AUP) (overall success[d])**		**With predisposing factors (overall success[d])**		**All acute pyelonephritis**	
					Clinical success	**Bacteriological success (without relapse/reinfections)**
Rotstein and Farrar[37]	Not possible to determine		Not possible to determine		16/20	20/20
King et al[35]	Not possible to determine		Not possible to determine		26/28	21/31
Eriksson et al[31]	11/20		4/7		25/27	15/27
Jernelius et al[34,e]	13/16		1/13		28/29	20/29
Cronberg et al[29]	Not possible to determine		Not possible to determine		57/60	41/60
Total	24/36 (67%)		5/20 (25%)		152/164 (93%)	117/167 (70%)

Notes: [a]Resistant *E. coli* was not evaluable because change in therapy. [b]Resistant *K. pneumoniae* was not evaluable because change in therapy. [c]Two dropouts, three asymptomatic bacteriuria (different strains), and two bacteriuria with symptoms of LUTI. [d]Defined as both clinical success and bacteriological success, without bacteriological relapse. [e]Since it was significantly inferior, the 1-week therapy was not included.
Abbreviations: AUP, acute uncomplicated pyelonephritis; *K. pneumoniae*, *Klebsiella pneumoniae*; *E. coli*, *Escherichia coli*.

MEC in bacteremia

The data are very sparse on MEC given as monotherapy for bacteremia caused by Enterobacteriaceae. The results from the studies we found are listed in Table 3. Cumulatively, the clinical success and the bacteriological success were 67% (10/15) and 87% (13/15), respectively. The results for MEC combined with another beta-lactam (mostly AMP) on bacteremia caused by Enterobacteriaceae are listed in Table 3. Cumulatively, the clinical success and the bacteriological success were 88% (57/65) and 84% (53/63).

Adverse reactions

The cumulative results of adverse reactions with MEC with/without AMP for pyelonephritis and/or uropathogenic bacteremia are shown in Table 4. There was no serious adverse reaction, but approximately one of the five patients had an adverse reaction, which was mainly seen in the concomitant therapy groups.

Discussion

MEC has been used for AUP for several years in parts of Scandinavia. We found no evidence that MEC should be an insufficient alternative against AUP, but insufficient for patients with acute complicated pyelonephritis on bacteriological outcome, even when combined with AMP.

Table 3 Effect of mecillinam and mecillinam in combination with other beta-lactams for the treatment of bacteremia caused by Enterobacteriaceae

Reference	**Cases**	**Clinical success**	**Bacteriological success (without relapse/reinfections)**
Mecillinam			
Frimodt-Møller and Ravn[32]	2	2/2	2/2
Ekwall et al[30]	3	2/3	2/3
Ode et al[39]	3	3/3	3/3
Trollfors et al[38]	7	3/7	6/7
Total	15	10/15 (67%)	13/15 (87%)
Mecillinam in combination with other beta-lactams			
Frimodt-Møller and Ravn[32]	3	3/3	3/3
Ekwall et al[30,a]	10	8/10	8/10
Rotstein and Farrar[37]	7	7/7	7/7
King et al[35]	25	24/25	24/25
Eriksson et al[31]	4	4/4	2/2
Jernelius et al[34,b]	4	4/4	2–3/4
Cronberg et al[29]	12	7/12	7/12
Total	64	57/65 (88%)	53/63 (84%)

Notes: [a]Twofold doses in 50% of the patients. [b]Since the 1-week therapy was significantly inferior, it is not included in this table.

From the published results, it seems that the regimen for AUP in adults should be P-MEC ≥400 mg tid (adjusted for weight) for at least 14 days in adults with/without initially IV MEC. Both clinical[33] and retrospective data on resistance

Table 4 ARs of mecillinam as monotherapy or combined with AMP

Reference	Therapy	Exanthema	GI	Others	Total AR	Total SAR
Frimodt-Møller and Ravn[32]	MEC or MEC/AMP	0	0	0	0/5	0/5
Ekwall et al[30,a]	MEC/AMP, P-MEC/P-AMP	4	0	0	5/73	0/73
Ekwall et al[30]	MEC/P-MEC	1	0	0		
Ode et al[39]	MEC/P-MEC	1	2	0	3/20	0/20
Trollfors et al[38]	MEC/P-MEC	0	0	0	0/25	0/25
Helin[33] (pediatric)	P-MEC	0	0	0	0/19	0/19
Eriksson et al[31]	MEC/AMP	7	4	5	16/43	0/43
Jernelius et al[34]	P-MEC/P-AMP	1	2	2	5/38	0/38
Jernelius et al[34] (21 days)	P-MEC/P-AMP	0	11	1	12/39	0/39
Cronberg et al[29]	MEC/AMP, P-MEC/P-AMP	12	15	5	32/144	0/144
Total	Cumulative	26	34	13	73/406[b] (18%)	0/406 (0%)
Total	MEC	2	2	0	4	0
Total	MEC/AMP	24	32	13	69	0

Notes: We did not include the studies that did not report, specify, and/or categorize the side effects. [a]Half had double dose. [b]Some patients had more than one AR.
Abbreviations: AMP, ampicillin; AR, adverse reaction; GI, gastrointestinal; MEC, mecillinam; P-AMP, pivampicillin; P-MEC, pivmecillinam; SAR, serious adverse reaction.

rates[41] support a recommendation of P-MEC in pediatric pyelonephritis, administered as 25–40 mg/kg/day bid/tid for 10 days.[33]

The low bacteriological success rates in pyelonephritis[31] and lower UTI caused by ESBL producing bacteria[24] can largely be explained by suboptimal dosing with P-MEC 200 mg tid. Higher dosage and shorter dosing interval of MEC for UTI are suggested to attain sufficient time above minimal inhibitory concentration (MIC),[42] especially for ESBL producing *E. coli* (manuscript in preparation). Studies similar to Eriksson et al[31] that administered P-MEC as 400 mg instead of 200 mg demonstrated a higher bacteriological success rate.[29,34] Similarly, the lesser clinical effect of MEC compared to cephaloridine for pyelonephritis[38] could also be explained by the lower dosage of 800 mg tid, since no difference was found when dosing MEC 1.2 g qid compared to AMP and trimethoprim.[39] Hence, a higher dose of P-MEC, eg, 1000 mg tid, could be more beneficial in pyelonephritis than the currently recommended doses, which should also be sufficient for ESBL producing strains. The duration should be 14 days in pyelonephritis as the bacteriological effect seems to increase with duration,[29,31,34] and since there is still missing solid evidence that a short (eg, 7 days) course is sufficient for P-MEC.

Interestingly, MEC with or without AMP demonstrated satisfactory success on bacteremia caused by Enterobacteriaceae.[29–32,34,35,37–39] A Danish retrospective study reported a favorable 30-day mortality outcome of MEC (23%) compared to other antibiotics (43%) for *Klebsiella pneumoniae* bacteremia (OR 0.4, 95% CI 0.2–0.9).[43] Although MEC seems to be effective against selected cases of uropathogenic bacteremia, we do not recommend MEC to be used alone when urosepsis is suspected but administered together with an aminoglycoside to broaden the antimicrobial spectra for empirical treatments.

Synergism with MEC and other beta-lactams occurs because MEC is an amidinopenicillin, with more selective affinity to penicillin-binding protein 2, as compared with aminopenicillins or cephalosporines.[44] This synergism has been investigated clinically in a few studies,[29–31,34,37] but only one study found a significant difference ($P<0.025$).[37] Cumulatively, there seems to be a difference in outcomes between monotherapy and combination therapy (75% and 93% clinical success, respectively), which could be explained by the synergistic effect. MEC alone was also seen bacteriologically inferior in pyelonephritis compared to a cephalosporin,[38] but not when combined with AMP.[29] Synergism and higher bactericidal activity have also been demonstrated in vitro between MEC and clavulanic acid.[18,45]

The side effects of monotherapy with P-MEC are described as few and mild.[2] This is similar to the findings of this study (Table 4). However, concomitant therapy of MEC and AMP was associated with mild adverse reactions in one of the five patients treated.

A major limitation with these old studies is that they fail to describe the clinical details in the cases of bacteriological failures/relapses, which was frequently seen in many papers regarding complicated infections. This is of major importance since asymptomatic bacteriuria is much less worrisome than a symptomatic bacteriological failure/relapse. Thus, we believe that clinical success represents the major outcome, which was excellent in the majority of the studies.

Although the reviewed studies were well designed and conducted at the time, they were conducted several decades ago, comparator drugs are uncommon today, the included sample sizes were generally small, the clinical picture on bacteriological failure/relapse was limited, and many used definitions of disease and outcome that vary from current standards. This severely limits the possibility to provide sufficient evidence-based recommendations to treat AUP with MEC. Therefore, there is an urgent need of clinical controlled trials comparing a single, standardized dose of P-MEC/MEC with other currently recommended antimicrobial treatments of uncomplicated and complicated pyelonephritis and sepsis.

A recent meta-analysis on the duration of antibiotic therapy for pyelonephritis with or without bacteremia concluded that 7 days of treatment is equivalent to longer therapies (including beta-lactams).[46] However, the analysis only included one study with MEC,[34] in which 7 days was found to be significantly bacteriologically inferior to 21 days of treatment. With this in consideration, we believe that the first randomized control study on the subject preferably should be a noninferiority trail comparing MEC in a higher dosage of 1000 mg tid with ciprofloxacin in currently recommended dosage[13] for 7 days.

Conclusion

MEC is an important older antimicrobial drug, which based on limited number of studies may be considered as an alternative in AUP, especially in patients with high predicted probability of bacteria with resistance to fluoroquinolone and other first-line agents. MEC may also be considered for pediatric pyelonephritis. Randomized clinical trial comparing the drug with standard of care regimens is warranted. There are currently no sufficient data to support the use of MEC in patients with bacteremia or sepsis due to Enterobacteriaceae.

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Author contributions

FJ came up with the idea, designed and conducted the study and wrote the review. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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