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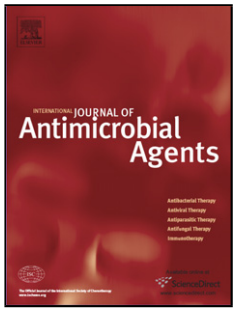

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Trimethoprim/sulfametrole: evaluation of the available clinical and pharmacokinetic/pharmacodynamic evidence

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ABSTRACT

Emergence of resistance to widely used trimethoprim/sulfamethoxazole (TMP/SMX) as well as common adverse events in human immunodeficiency virus (HIV)-infected patients casts interest on combinations of TMP with other sulfonamides. Sulfametrole (SMT) combined with TMP could provide a choice for difficult-to-treat infections, particularly when administered intravenously. The objective of this review was to evaluate the available clinical and pharmacokinetic/pharmacodynamic (PK/PD) evidence regarding TMP/SMT, particularly in comparison with TMP/SMX. We reviewed the available evidence retrieved from searches in PubMed/Scopus/Google Scholar and by bibliography hand-searching. In total, 46 eligible studies (most published before 1997) were identified, 7 regarding intravenous (i.v.) TMP/SMT, 24 regarding oral TMP/SMT and 15 providing comparative data for TMP/SMT versus TMP/SMX. The antimicrobial activity of TMP/SMT was similar to TMP/SMX for Gram-positive isolates, and a greater percentage of *Escherichia coli* and *Proteus* spp. were susceptible to TMP/SMT compared with TMP/SMX. PK/PD data suggest a dosage adjustment of i.v. TMP/SMT in patients with seriously impaired renal function. Four randomised controlled trials and 16 non-comparative studies reported good effectiveness/safety outcomes for oral TMP/SMT in genital ulcers (mainly chancroid), respiratory tract infections and urinary tract infections (UTIs). Moreover, i.v. TMP/SMT was effective against *Pneumocystis jiroveci* infection in HIV-infected patients, severe pneumonia and UTIs. In one study, hypersensitivity reactions occurred in 18/52 (34.6%) of HIV-infected patients; 2/52 (3.8%) developed psychosis. Gastrointestinal adverse events were mild and rare. The excipients in i.v. TMP/SMT formulations might be less toxic compared with i.v. TMP/SMX formulations, particularly for children. In conclusion,

despite the scarcity of contemporary evidence, available data suggest that TMP/SMT could be an alternative treatment option to TMP/SMX, even in serious infections, when administered intravenously.

1. Introduction

The combination of trimethoprim (TMP) with sulfonamides is synergistic as it inhibits sequential steps in bacterial tetrahydrofolic acid synthesis.

Trimethoprim/sulfamethoxazole (TMP/SMX) has been extensively used for the prevention and treatment of various types of infections. Specifically, TMP/SMX has been used for the treatment of urinary tract infections (UTIs) [1] and respiratory tract infections (RTIs), particularly for acute bacterial exacerbations of chronic bronchitis [2,3]. TMP/SMX is also considered as the treatment of choice for *Pneumocystis jiroveci* infections in immunocompromised human immunodeficiency virus (HIV) patients as well as for *Burkholderia* spp. [4,5] and *Stenotrophomonas maltophilia* infections [6,7]. In addition, published evidence suggests that TMP/SMX may provide a useful treatment option for infections due to community-acquired meticillin-resistant *Staphylococcus aureus* (MRSA), particularly those of community-onset [8–10].

Emergence of resistance to TMP/SMX has raised considerations regarding its use [11–15]. Furthermore, a relatively high rate of adverse events (in particular allergic reactions) have been associated with TMP/SMX use in HIV-infected patients [16]. Specifically, the reported rates of TMP/SMX-related adverse events range from 25% to 50% in patients with HIV infection [17–19]. However, even higher rates were reported from some studies [20,21]. The abovementioned factors have created interest in other TMP/sulfonamide antibiotic combinations that could be equally as or more effective and safe and consequently provide a useful alternative therapeutic option for serious infections, including infections in HIV-infected patients and community-acquired MRSA infections.

In this review, we chose to focus on the combination of TMP with sulfametrole (SMT). Its clinical use may be rather limited, with the exception of the treatment of chancroid where it has been extensively used as multiple or single-dose oral treatment [22,23]. TMP/SMT is available in both an oral and an intravenous (i.v.) formulation. We aimed to retrieve and evaluate the available evidence regarding the clinical use of and pharmacokinetic/pharmacodynamic (PK/PD) aspects of TMP/SMT as well as comparative data with TMP/SMX.

2. Methods

2.1. Data sources

PubMed and Scopus databases were searched up to February 2011 to identify studies eligible for inclusion in the review; Google Scholar was also searched. The bibliographies of eligible and potentially eligible articles were also meticulously hand-searched. The search term applied to the PubMed database was '(sulfametrol OR sulphametrol OR sulphametrole OR co-soltrim)', whereas the keywords 'sulfametrole' and 'sulfametrol' were used for the search performed in the Scopus database. The keyword applied to Google Scholar was 'sulfametrol'. Time limits were not applied to any of the searches performed.

2.2. Study selection criteria

Any article providing any type of data (including in vitro, in vivo, PK/PD, clinical effectiveness and/or safety data) regarding i.v. and oral formulations of TMP/SMT was considered as eligible for inclusion in the review. Articles published in languages

other than English, Spanish, French, German, Italian, Dutch or Greek were not included.

2.3. Data extraction and evaluation

Data extracted from the included clinical studies consisted of type of study design, characteristics of study population, type of evaluated infections, treatment characteristics, outcome (clinical/microbiological) and adverse events. Data extracted from studies focusing on PK/PD aspects of TMP/SMT consisted mainly of type of study design, characteristics of study population, characteristics of TMP/SMT administration, sampling method, substances determined and plasma/blood/tissue inhibitory concentrations.

We evaluated and present separately data retrieved from eligible studies focusing on the clinical utility and PK/PD aspects of the i.v. formulation of TMP/SMT and those retrieved from studies focusing on the oral formulation of TMP/SMT. Furthermore, we collected, evaluated and present separately data retrieved from comparative studies providing comparative data for TMP/SMT and TMP/SMX.

3. Results

3.1. Extracted data

A total of 46 articles were identified as eligible for inclusion in the review, of which 7 provided data regarding the i.v. formulation of TMP/SMT [24–30] and 24 provided data regarding the oral formulation [22,31–53]. Fifteen articles provided data regarding the comparison of TMP/SMT with TMP/SMX [40,54–67]. Relevant

comparative data from a specialist publication were also identified and retrieved [68]. The detailed process of identification of the included studies is depicted in Fig. 1.

3.2. Intravenous formulation of TMP/SMT

3.2.1. Clinical data

Clinical data regarding i.v. TMP/SMT were provided from four studies published between 1980 and 1997 [24,27,29,30]. The two most recent studies involved a total of 61 HIV-infected patients with *P.* (*carinii*) *jiroveci* pneumonia (PCP). The 58 HIV-infected patients involved in the cohort study received high doses of TMP/SMT. Treatment failure occurred in 4/52 (7.6%) HIV-infected patients with microbiologically confirmed PCP, and hypersensitivity reactions requiring treatment change were reported in 18/52 (34.6%); hypersensitivity directly attributed to the drug was reported in 16/52 (31%). Two (3.4%) of the 58 HIV-infected patients included in the cohort study developed psychosis not directly attributable to the drug [29]. Another small case-series study included three HIV-infected patients who had received TMP/SMT for the treatment of *P. jiroveci* pneumonia and developed psychotic reactions during TMP/SMT that necessitated an antibiotic change. In these three cases, TMP/SMT was replaced with TMP/SMX and psychosis did not recur [27].

Another study involved 13 paediatric patients (mean age 5 years, age range 5 months to 9.5 years) with UTIs, severe pneumonia and a staphylococcal skin infection. Treatment duration ranged from 3 days to 7 days. Prompt clinical improvement was observed in 12/13 cases (92.3%) and microbiological eradication was achieved in 10/13 (76.9%). Mild gastrointestinal adverse events were noted in

one patient [30]. The remaining study involved 31 adults with severe infections (mainly UTIs and RTIs). Treatment duration ranged from 5 days to 27 days. Clinical success was observed in 22/31 (70.9%); data regarding microbiological outcome were not reported. Local tolerance at the infusion sites was excellent. Only 1 (3.2%) of the 31 patients developed urticaria [24].

3.2.2. Pharmacokinetic/pharmacodynamic data

PK/PD data regarding i.v. TMP/SMT were provided from four studies published between 1977 and 1983 [24–26,28]. Three of these four studies involved exclusively patients with renal co-morbidity (nephrectomy for various reasons [25], impaired renal status [26] and end-stage renal failure and haemodialysis treatment [28]). One of these three studies, which had a case–control study design, reported that the elimination half-life ($t_{1/2}$) of TMP and free and total SMT components in patients with impaired renal function were significantly higher compared with healthy volunteers [26]. In one of the other two studies, a reduction in the $t_{1/2}$ of free plasma SMT was observed during haemodialysis, whilst the $t_{1/2}$ of free plasma TMP before and during haemodialysis was similar [28]. In the remaining study, TMP was found to have better plasma levels compared with SMT, whereas SMT had better penetration in inflammatory kidney tissue [25]. In the remaining study that involved six healthy volunteers [24], the steady-state TMP and total and free SMT was reached at the third day. Detailed data are presented in Table 1.

3.3. Oral formulation of TMP/SMT

3.3.1. Clinical data

Twenty studies published between 1975 and 1988 provided data regarding oral TMP/SMT, of which four were randomised controlled trials (RCTs) [37,38,46,49]; one of them had a double-blind design [49]. Two of the RCTs involved men with genital ulcers. In the first of the latter studies, men with microbiologically confirmed chancroid were treated with either a single dose of TMP/SMT or a 3-day enoxacin regimen [46], whereas the other RCT involved men (the majority had microbiologically confirmed chancroid) who were randomised to receive a single dose of TMP/SMT, a 5-day regimen of TMP/SMT or a 5-day regimen of TMP [49]. In both RCTs the clinical and microbiological outcome was comparable between treatment groups. Detailed data are presented in Table 2. The remaining two RCTs involved paediatric patients with acute otitis media (AOM) treated with either TMP/SMT or amoxicillin for 5 days [38], and adult patients with acute UTIs treated with a single dose of TMP/SMT or amoxicillin, respectively [37]. In the latter two studies, no difference was found between the compared treatment regimens regarding clinical and microbiological outcome. However, in the subset of patients with *Escherichia coli* UTIs, TMP/SMT was found to be more effective compared with amoxicillin [37]. The safety profile of the compared drugs was also comparable in both RCTs.

Regarding the remaining 16 clinical studies referring to oral TMP/SMT, 5 involved patients with UTIs exclusively [31,43,44,48,52], 4 involved patients with RTIs exclusively [35,36,50,51], 3 involved patients with both RTIs and UTIs [32,41,47] and 3 involved patients with genital infections [22,34,42], whereas the remaining study

involved patients with various infections including RTIs, UTIs, osteomyelitis and appendicitis [32]. Moreover, 4 of these 16 studies involved exclusively paediatric patients [32,33,44,47]. Detailed data regarding TMP/SMT treatment and characteristics of the patients involved in these 16 studies are presented in Table 2. The reported clinical and/or microbiological outcomes were generally in favour of oral TMP/SMT treatment in all 16 studies (detailed data are presented in Table 2). Regarding the safety profile of oral TMP/SMT treatment, adverse events were encountered rarely and they were mainly mild gastrointestinal (nausea, vomiting, diarrhoea) and in some cases allergic reactions (rash, urticaria). Detailed data are presented in Table 2.

3.3.2. Pharmacokinetic/pharmacodynamic and in vivo data

Five studies (one case–control [39] and four case series [40,42,51,53]) provided PK/PD data for oral TMP/SMT. These studies involved cystic fibrosis (CF) patients compared with age-matched patients without CF [39], patients with acute/chronic bacterial prostatitis [42], RTIs [51], patients who underwent prostatectomy [53] and healthy volunteers [40], respectively. Detailed data are presented in Table 2. One study presented as an abstract in conference proceedings provided relevant in vivo data. Specifically, all mice with *P. jiroveci* infection were cured, whereas those that were not treated deteriorated [45].

3.4. Comparison of TMP/SMT with TMP/SMX

3.4.1. In vitro/in vivo comparative data

Five studies provided comparative in vitro microbiological data regarding TMP/SMT versus TMP/SMX [54,56,57,63,67]. Detailed data regarding the evaluated bacterial isolates are presented in Table 3. In three of the five studies, TMP/SMT and TMP/SMX had comparable antibacterial activity against the tested isolates [57,63,67]. In another study, the antimicrobial activity of TMP/SMT against coliforms, *S. aureus*–*Streptococcus pyogenes* isolates as well as *Salmonella* spp.–*Shigella* spp. isolates appeared numerically greater (higher percentage susceptible) for TMP/SMT compared with TMP/SMX; statistical significance was not assessed [54]. In the remaining study, the antibacterial activity of both combinations was comparable for the tested Gram-positive isolates, whereas TMP/SMT was found to be more active against the tested *E. coli* and *Proteus* spp. isolates [56]. Two studies provided comparative in vivo data [56,63]. Albino mice were used in both studies (Table 2). In one of these two studies, TMP/SMT was found to be more effective against *Proteus mirabilis* infection compared with TMP/SMX [56].

3.4.2. Pharmacokinetic/pharmacodynamic data

Three studies [40,55,58] as well as a specialist publication [68] provided comparative PK/PD data for SMT and SMX. Increased solubility of SMT and the N_4-acetyl SMT derivative was observed compared with SMX and the N_4-acetyl SMX derivative [40,58]. Finally, the $t_{1/2}$ of both SMT and SMX was found to be slightly longer under acidic compared with alkaline conditions [68].

3.4.3. Clinical effectiveness and/or safety data

Three studies (two RCTs [57,62], one of which had a double-blind design [62], and one double-blind comparative study [59]) provided relevant data. The two RCTs involved patients with acute RTIs or exacerbations of chronic RTIs [62], and men with genital ulcers (with either confirmed chancroid or not) [57]. TMP/SMT and TMP/SMX had comparable effectiveness (clinical/microbiological) and safety profiles in both studies. However, a trend in favour of TMP/SMT treatment regarding defervescence and sputum characteristics was observed in the study including patients with RTIs [62]. In the remaining double-blind comparative study, both regimens were found to be equally effective and safe in patients with microbiologically confirmed or clinically diagnosed chancroid [57].

3.4.4. Additional comparisons

Recent studies suggest an association between TMP/SMX and severe hypoglycaemia in glipizide and glyburide users [64] as well as an association between TMP/SMX with severe and protracted hypoglycaemia in patients with infections including *P. jiroveci* pneumonia, UTIs and RTIs [65]. An older double-blind cross-over trial suggested that TMP/SMT was not associated with hypoglycaemia in either insulin or sulfonylurea users [60]. In addition, according to the findings of another older study, observed TMP/SMT urine crystals were fewer than those of TMP/SMX [66]. Finally, in a small case series involving nine HIV-infected patients with PCP that developed an allergic rash to TMP/SMX, six of seven who were re-challenged with SMT had a recurrence of skin reaction [61].

4. Evaluation of the available evidence

The main finding of this study is that TMP/SMT appears to have at least a similar effectiveness and safety profile compared with TMP/SMX. In particular, despite the relative scarcity of available published evidence, the i.v. formulation of TMP/SMT appears to be effective against serious infections, including *P. jiroveci* infection in HIV-infected patients and severe pneumonia, as well as in other less severe urinary, respiratory and skin infections. Regarding the safety profile of i.v. TMP/SMT, the reported rates of hypersensitivity reactions to this drug in HIV-infected patients were comparable with TMP/SMX, for which the respective reported rates are 25–50%. Rare cases (3.4%) of psychotic adverse events were reported in the evaluated HIV-infected patients treated with i.v. TMP/SMT for *P. jiroveci* pneumonia. Of note, HIV infection, or even *P. jiroveci* infection, may possibly account for such adverse events [69–71]. Other adverse events reported consisted mainly of mild gastrointestinal adverse events, whilst local tolerance at the site of the injection was very good.

Regarding PK/PD aspects, the evidence reviewed here suggests that an adjustment of the dosage of i.v. TMP/SMT is needed in patients with impaired renal function owing to accumulation of the N_4-acetyl SMT derivative. SMT was also found to have better penetration to inflamed renal tissue compared with TMP.

The findings derived from a considerable number of studies (four of them RCTs) focusing on oral TMP/SMT were also favourable for this drug. Specifically, oral TMP/SMT appears to be an effective and safe treatment option for patients with various infections including UTIs, RTIs and genital infections in adult and paediatric

patients. This promising evidence regarding the oral formulation of TMP/SMT is also supportive to the i.v. formulation.

Comparative data regarding PK/PD aspects of TMP/SMT and TMP/SMX also provide useful information regarding the combination of TMP with SMT. First, SMT metabolism is limited to acetylation, whereas SMX undergoes acetylation, oxidation and glucuronidation [72]. No oxidised derivatives (hydroxylamine) of SMT are expected to be found in vivo. TMP/SMX use can cause haemolysis in patients with glucose-6-phosphatase dehydrogenase deficiency through oxidation, leading to disruption of the erythrocyte membrane [73]. In this regard, lack of production of oxidised derivatives of SMT may possibly be an advantage over TMP/SMX. Moreover, both SMT and N_4-acetylated SMT derivative have increased solubility compared with SMX and its derivative [40,58]. This may result in less crystalluria in patients treated with TMP/SMT compared with TMP/SMX [66]. In addition, given the high resistance rates to TMP/SMX reported from recent studies [12], it is worth mentioning that, according to the comparative in vitro data reviewed here, TMP/SMT has comparable antimicrobial activity to TMP/SMX for the evaluated Gram-positive isolates. For the evaluated *E. coli* and *Proteus* spp. isolates, a higher percentage were susceptible to TMP/SMT compared with TMP/SMX. However, statistical significance was not assessed in the respective studies. Finally, evidence from clinical studies (two of them RCTs) reported a similar effectiveness (clinical/microbiological/safety) profile to TMP/SMX [57,62].

Use of TMP/SMX for prophylaxis or treatment in HIV-infected patients has been associated with high rates of adverse events (particularly hypersensitivity reactions)

[16]. It has been postulated that the oxidised metabolite of SMX (SMX-hydroxylamine) is responsible for such reactions. Indeed, a cytotoxic effect of SMX-hydroxylamine on $CD8^+$ cells through enhancement of apoptosis has been reported in vitro [74]. Moreover, systemic glutathione deficiency in HIV-infected patients was suggested to contribute to hypersensitivity reactions to TMP/SMX since it fails to counteract the hydroxylamine activity. In this regard, a sulfonamide compound that does not undergo oxidation in vivo, such as SMT, could be a better option for HIV-infected patients. The reported rate of hypersensitivity reactions following i.v. TMP/SMT in HIV-infected patients was ca. 30%, whilst higher rates have been reported in some studies including HIV-infected patients who received TMP/SMX [29].

Many practices (including re-challenge and desensitisation) have been used for the management of TMP/SMX-associated hypersensitivity reactions in HIV-infected patients. Re-challenge with SMT also appears to be a potential option due to the lack of hydroxylamine production. In a small case series, nine HIV-infected patients developed a typical skin reaction to TMP/SMX. Seven of them were re-challenged with SMT and six of the latter patients re-developed a skin reaction [61]. This particular finding appears to contradict the hydroxylamine hypothesis. In this regard, a larger study is needed in order to identify any potential advantage of SMT.

Infections in paediatric patients could be one of the potential targets for clinical use of TMP/SMT, although it has not been formally evaluated for clinical use in very young children. Still, in one non-comparative study including children who received i.v. TMP/SMT for infections such as severe pneumonia, UTIs and impetigo

contagious, good clinical and microbiological outcomes were observed. Mild adverse events including nausea, vomiting and local phlebitis were reported [30]. Five additional studies (one RCT and four non-comparative studies) have evaluated the use of oral TMP/SMT in children [32,33,38,44,47]. In the RCT, oral TMP/SMT was found to have comparable clinical and microbiological outcomes with amoxicillin in 35 children aged 5–11 years with AOM, whereas two cases of mild gastrointestinal adverse events that could not be directly associated with TMP/SMT were reported [38]. In the remaining four studies, oral TMP/SMT appears to be associated with good clinical/microbiological outcomes as well as with a good safety profile in paediatric patients with various infections including RTIs, UTIs, appendicitis and osteomyelitis [32,33,44,47].

Specific excipients included in product formulations of different drugs might well play a role in toxicity, particularly for paediatric populations [75–78]. It has been suggested that excipients of i.v formulations of TMP/SMX, such as propylene glycol, sodium pyrosulfite and benzyl alcohol, could be associated with toxicity in children treated with TMP/SMX for *P. jiroveci* pneumonia and other infections [79]. This might be avoided for specific formulations of TMP/SMT that include non-toxic excipients such as sodium hydroxide, malic acid and glycerol [80]. In addition, the pH of specific i.v. TMP/SMT formulations is slightly acidic (pH 6.5–6.8), whilst the pH of TMP/SMX formulations is highly basic, a fact that may increase the risk of thrombophlebitis.

Published evidence suggests an association between TMP/SMX and severe hypoglycaemia in patients with renal co-morbidity as well as in HIV-infected patients [64,65]. In one of the evaluated studies, TMP/SMT was not found to be associated

with hypoglycaemia in diabetics treated either with insulin or sulfonylurea derivatives [61].

Specific limitations should be taken into consideration when interpreting the findings of this review. Our findings derive from the evaluation of relatively old studies. Consequently, one may consider that the reported effectiveness/safety data as well as the antimicrobial activities of TMP/SMT do not apply to infections caused by contemporary pathogens. We did not identify any data regarding the use of i.v. TMP/SMT for MRSA infections. Current evidence suggests that TMP/SMX may be a cost-effective drug for community-acquired MRSA infections [81]. In this regard, larger prospective studies focusing on infections caused by contemporary pathogens, including community-acquired MRSA, may provide further evidence regarding the clinical utility of this specific combination. Moreover, no data regarding the use of TMP/SMT for infections due to *S. maltophilia* and *Burkholderia cepacia*, for which TMP/SMX is considered as appropriate therapy, were identified.

In conclusion, despite the scarcity of current evidence, evaluation of data provided from studies focusing on PK/PD, in vitro and clinical aspects suggests that TMP/SMT could be further be evaluated as a treatment option for infections of different types and severity. In particular, the i.v. formulation of TMP/SMT can be a useful alternative to TMP/SMX for serious infections.

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Competing interests

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Ethical approval

Not required.

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Fig. 1. Flow diagram of the detailed selection process of the studies to be included in the review.

Table 1

Data derived from studies evaluating intravenous administration of trimethoprim/sulfametrole (TMP/SMT)

Clinical studies reporting effectiveness and safety data							
Reference	Study design	Study population	Type(s) of infection	Treatment characteristics (dosage; duration; concomitant antibiotic treatment)	Outcome		Adverse events
					Clinical	Microbiological	
Geit et al., 1997 [27]	Case series of HIV-infected patients who developed psychotic reactions	1 patient	PCP	2 infusions (250 mL) of 20 mg/kg TMP/80 mg/kg SMT three times daily; N/R; N/R	N/R	N/R	At Day 14: vertigo, aggressiveness (acute organic psychosyndrome). TMP/SMT was replaced with pentamidine. TMP/SMT was re-administered and vertigo occurred once again. TMP/SMT was replaced with TMP/SMX [a]
		1 patient, 39 years old	PCP	2 infusions (250 mL) of 20 mg/kg TMP/80 mg/kg SMT	N/R	N/R	Paranoia, disorientation,

				daily; N/R; N/R			auditory hallucinations (acute organic psychosyndrome). TMP/SMT was replaced with TMP/SMX [a]
		1 female patient, 38 years old	PCP	1 infusion of 20 mg/kg TMP/80 mg/kg SMT daily; N/R; N/R	N/R	N/R	Vertigo, headache, auditory hallucinations. TMP/SMT was finally replaced with TMP/SMX.[a] The patient also received haloperidol
van der Ven et al., 1996 [29]	Retrospective cohort study	58 HIV patients treated with TMP/SMT for PCP (microbiologically documented, 52/58; 90%)	PCP	High doses of TMP/SMT (1st centre, fixed total daily dose 5760 mg; 2nd centre, total daily dose range 3840–9600 mg); N/R; N/R	Patients with microbiologically documented PCP: treatment failure, 4/52 (7.6%) Death, 12/58 (20.6%) [treatment	N/R	Hypersensitivity reaction (occurring within 8–12 days of treatment) necessitating a change in treatment, 18/52 (34.6%) [rash

		failure, 4/12 (33.3%); other diseases (including cerebral *Cryptococcus neoformans*, lymphoma or *Pseudomonas* sepsis), 6/12 (50%); undetermined cause, 2/12 (16.6%)]	17/52 (32.6%); fever 1/52 (1.9%)]. Hypersensitivity directly attributed to TMP/SMT: 16/52 (31%) [b] Other toxicities: ALT 2–4× baseline values, 3/52 (5.7%); serum creatinine increase to 180 μmol/L, 1/52 (1.9%); thrombocytopenia (40–1 000 000/L), 1/52 (1.9%). All toxicities resolved spontaneously. Psychosis (uncertain

							relation to TMP/SMT treatment, 2/52 (3.8%)
Stoegmann, 1981 [30]	Case series	13 paediatric patients (7 female), mean age 5 years, age range 5 months to 9.5 years	Acute UTI, 9/13 (69.2%); severe pneumonia, 3/13 (23%); extensive staphylococcal impetigo contagious, 1/13 (7.6%)	800 mg SMT/160 mg TMP 250 mL 7% (short infusion within 30 min) b.i.d. Dose range, 2 × 3 mL to 2–10 mL, corresponding to 6–10 mg TMP/kg of body weight; 3–7 days [c]; N/R	Prompt clinical improvement (within a few days of i.v. treatment), 12/13 (92.3%); no improvement, 1/13 (7.6%) [d]	Eradication, 10/13 (76.9%); emergence of a different pathogen resistant to TMP/SMT, 2/13 (15.3%); isolation of a different pathogen in vitro susceptible to TMP/SMT, 1/13 (7.6%)	1 child had nausea, vomiting and local phlebitis that necessitated cessation of TMP/SMT treatment; 1 child had phlebitis not attributable with certainty to TMP/SMT treatment
Breyer et al., 1980 [24]	Cohort study	31 adult patients with severe infections, age range 34–83 years	RTI, 8/31 (25.8%); UTI, 15/31 (48.3%); RTI+UTI,	TMP/SMT b.i.d., 27/31 (87%); TMP/SMT t.i.d., 4/31 (12.9%); 5–27 days; none	Clinical success (cure), 22/31 (70.9%); failure (absence of clinical cure or	N/R	Urticarial exanthema, 1/31 (3.2%) (Day 10 of treatment); increase in

			2/31 (6.4%); typhus abdominalis, 2/31 (6.4%); febrile episode with malign underlying disease, 4/31 (12.9%)			need for replacement with another antibiotic), 9/31 (29%)	AST/ALT, 5/31 (16.1%) [e]
Studies reporting pharmacokinetic/pharmacokinetic (PK/PD) data							
Reference	Study design	Study population	TMP/SMT administration characteristics	Sampling method/substances determined	$t_{1/2}$ of free plasma SMT (h)	$t_{1/2}$ of plasma TMP (h)	Additional PK/PD data; comments
Friesen et al., 1983 [25]	Case series	7 patients (4 females) undergoing nephrectomy hospitalised in a urology department, mean age 43.5 years, range 36–53 years	2 infusions of 160 mg TMP/800 mg SMT of 30-min duration every 12 h and 1 infusion 2 h before nephrectomy	Peripheral vein and removed kidney tissue/(a) free SMT, (b) non-metabolised TMP	N/R	N/R	Mean ± S.D. C_{plasma} SMT: prior to infusion, 67.4 ± 23.1 mg/mL; during kidney removal, 72 ± 37.9 mg/mL. Mean ± S.D. C_{plasma} TMP: prior to infusion, 2.1 ±

	0.5 mg/mL; during kidney removal, 2.3 ± 1 mg/mL.
	Mean ± S.D. C_{plasma} SMT/TMP, 29.6 ± 2 mg/mL.[f]
	Mean ± S.D. C_{kidney} SMT/TMP, 2.0 ± 1.1 mg/g.[f]
	Mean ± S.D. $C_{kidney/plasma}$ SMT, 0.33 ± 0.11 mg/mL.[f]
	Mean ± S.D. $C_{kidney/plasma}$ TMP, 5.2 ± 2.9 mg/g.[f]
	Mean *C* in inflamed kidney: SMT, 27.8 mg/g; TMP, 9.3 mg/g.
	Mean *C* in normal kidney: SMT, 18.2 mg/g; TMP,

							13.4 mg/g. 1 patient with kidney tumour: SMT, 4.4 mg/g; TMP, 12.2 mg/g. Adverse events, none
Schmidt et al., 1980 [28]	Case series	6 patients (3 females) with end-stage renal failure receiving regular haemodialysis treatment, mean age 50.2 years, range 23–73 years	30 min after the start of dialysis, 800 mg SMT/160 mg TMP	Immediately prior to the injection and 2, 3, 4, 6 and 8 h afterwards/plasma levels of (a) TMP, (b) free SMT, (c) N_4-acetylated metabolite and (d) glucuronised SMT	During dialysis-free interval: mean ± S.D., 8.9 ± 3.9. During dialysis: mean ± S.D., 4.3 ± 1.1	During dialysis-free interval: mean ± S.D., 13.0 ± 4.1. During dialysis: mean ± S.D., 12.3 ± 5.5	Plasma concentrations of N_4-acetylated metabolite tend to increase in the 8-h measurement period both during the dialysis and dialysis-free intervals. Plasma levels of glucuronised SMT so low that could not be measured. TMP/SMT may be

							given in normal dosage to patients with severe renal insufficiency who receive haemodialysis only for short-term treatment
Breyer et al., 1980 [24]	Cohort study	6 healthy volunteers	10 days in an interval of 12 h	Immediately after the infusion and at 08:00h on each of the 2 days following the last infusion/(a) free SMT, (b) total SMT and (c) non-metabolised TMP	Free SMT: mean ± S.D., 8.95 ± 2.99 Total SMT: mean ± S.D., 11.31 ± 2.74	Non-metabolised TMP: mean ± S.D., 9,62 ± 2.26	Plasma steady-state: (a) TMP, 1.4–1.6 μg/mL; (b) free SMT, 40–50 μg/mL; (c) total SMT, 60–70 μg/mL.[g] Plasma concentration 48 h after the last infusion: (a) TMP, 0.27 μg/mL; (b) total SMT, 13.22 μg/mL; (c) free

							sulfonamide, 5.84 μg/mL
Hitzenberger et al., 1977 [26]	Case–control study	6 patients (5 females), age range 44–92 years [h] (5 with chronic pyelonephritis, 1 with chronic glomerulonephritis) with various degrees of impaired renal function 6 male healthy volunteers with normal renal function, age range 20–30 years	2 ampoules of 80 mg TMP/400 mg SMT	Blood samples drawn hourly over a period of 8 h/plasma levels of TMP, free/glucuronised/acetylated sulfonamide	Patients vs. healthy controls Free SMT, mean ± S.D. (range) 7.23 ± 0.78 (6.44–8.64) vs. 5.70 ± 0.75 (4.95–6.93); $P < 0.01$ Total SMT, mean ± S.D. (range) 51.78 ± 33.82 (16.04–91.19) vs. 7.22 ± 2.56 (4.08–11.55); $P < 0.01$	Patients vs. healthy controls: mean ± S.D. (range) 14.67 ± 4.88 (9.65–23.12) vs. 9.02 ± 2.04 (6.93–11.55); $P < 0.05$	Mean $t_{1/2}$ of TMP is slightly but significantly higher in patients with reduced renal function compared with healthy volunteers. Mean $t_{1/2}$ of both free and total SMT was significantly higher compared with healthy volunteers

HIV, human immunodeficiency virus; PCP, *Pneumocystis (carinii) jiroveci* pneumonia; N/R, not reported; SMX, sulfamethoxazole; ALT, alanine aminotransferase; UTI, urinary tract infection; b.i.d., twice daily; i.v., intravenous; RTI, respiratory tract infection; t.i.d., three times daily; AST, aspartate aminotransferase; $t_{1/2}$, elimination half-life; S.D., standard deviation; *C*, concentration.

[a] All three patients received secondary prophylaxis with TMP/SMX; no further psychotic reactions were observed.

[b] In seven patients who developed hypersensitivity reactions treatment was switched to trimethoprim/dapsone, and in one patient to trimethoprim/sulfamethizole. No hypersensitivity reaction occurred after treatment change in these eight patients. In the remaining nine patients who developed a hypersensitivity reaction treatment was changed to pentamidine.

[c] In 10 of the 13 paediatric patients, treatment was switched to oral after completion of the i.v. trimethoprim/SMT treatment for 7–10 days or until clinical cure.

[d] One child had primary suppurating pneumonia that did not resolve after i.v. TMP/SMT treatment; chloramphenicol was added.

[e] Three of these five patients had malignancies with hepatic metastases and abnormal pre-treatment levels.

[f] Plasma concentrations are those measured during removal of the kidney.

[g] The plasma steady state of free SMT, total SMT and TMP was attained at the third day.

[h] Plasma creatinine range, 2.4–5.7 mg/100 mL; creatinine clearance range, 8.8–51.0 mL/min.

Table 2

Data derived from clinical studies evaluating oral administration of trimethoprim/sulfametrole (TMP/SMT)

Clinical studies providing effectiveness and/or safety data						
Reference	Study design	Study population	Treatment characteristics (dosage; duration)	Outcome		Adverse events
				Clinical	Microbiological	
Naamara et al., 1988 [46]	RCT	169 men with microbiologically confirmed chancroid presenting in a special treatment clinic	Group I, single-dose TMP/SMT 640/3200 mg (83 patients) Group II, 3 doses of enoxacin 400 mg at intervals of 12 h (86 patients)	TMP/SMT vs. enoxacin: Cure, 31/70 (44.2%) vs. 41/73 (56.1%); *P* = 0.21 [a] Improvement, 26/70 (37.1%) vs. 24/73 (32.8%); *P* = 0.71 [a] Failure, 13/70 (18.5%) vs. 7/73 (9.5%); *P* = 0.19 [a]	Group I vs. Group II: Eradication, 67/74 (90.5%) vs. 72/77 (93.5%); *P* = 0.7 [a] Persistence, 7/74 (9.4%) vs. 5/77 (6.4%) [b]; *P* = 0.7 [a]	N/R

				Relapse, 0/70 (0%) vs. 1/73 (1.3%); *P* > 0.99		
Dylewski et al., 1986 [22]	Non-comparative study	37 women with microbiologically confirmed chancroid, mean age 23 years	Total dose, 4 double-strength tablets of 650 mg TMP/3200 mg SMT	Ulcers: cure, 27/27 (100%) Inguinal buboes: response to treatment, 5/6 (83.3%)	Eradication, 32/32 (100%)	No rash or other adverse reactions occurred
Godfrey et al., 1985 [38]	RCT	35 children with AOM, age range 5–11 years	Group A, 18 patients received amoxicillin syrup 125 mg t.i.d., 5 days Group B, 17 patients received 80 mg TMP/400 mg SMT syrup b.i.d., 5 days	Cure: amoxicillin group, 17/18 (94.4%) vs. TMP/SMT group, 16/17 (94.1%); *P* > 0.99 [a]	Eradication: Group A, 17/18 (94.4%) vs. Group B, 16/17 (94.1%); *P* > 0.99 [a]	Group A, 1 episode of diarrhoea and 1 episode of vomiting, doubtfully related to treatment. Group B, none
Limson, 1984 [31]	Non-comparative study	40 ambulatory patients (31 female) with culture-proven acute lower UTI [c]	Single oral dose of four tablets of 160 mg TMP/800 mg SMT, or a total	All 40 patients became symptom-free 24–48 h post	Eradication: total, 33/40 (82.5%); women, 87.3%; men: 66.6%	Generalised skin erythema, 1/40 (2.5%); mild nausea that disappeared

			massive dose of 640 mg TMP/3200 mg SMT	therapy		spontaneously after 3 h, 1/40 (2.5%)
Monnet, 1984 [47]	Non-comparative study	32 infants with different types of infections: lower RTIs, 12 patients, mean age 2.1 years; upper RTIs, 12 patients, mean age 3.11 years; UTIs, 8 patients, mean age 8.5 years	0.8 g TMP/4 g SMT in 100 mL Patients 6 months–5 years, 1 tsp/5 kg b.i.d. Patients >5 years, 4 tsp/day	Lower RTI group: good, 9/12 (75%); moderate, 2/12 (16.6%); failure, 1/12 (8.3%) Upper RTI group: good, 10/12 (83.3%); not evaluable, 2/12 (16.6%) UTI group: good, 7/8; failure, 1/8		Lower RTI group: vomiting, 1/12 (8.3%) Upper RTI group: possible exanthema subitum, 1/12 (8.3%); allergic reaction, 1/12 (8.3%) UTI group: vomiting, 1/8
Scheiber et al., 1984 [42]	Non-comparative study	41 patients with bacterial prostatitis or pyospermia (16 patients with CBP, 14 with ABP, 11 patients with pyospermia)	Days 1–5, 640 mg TMP/3200 mg SMT daily Days 5–10, 480 mg TMP/2400 mg SMT daily Days 10–15, 320 mg TMP/1600 mg SMT daily	ABP: cure, 13/14 (92.8%); improvement, 1/14 (7.1%) CBP: cure, 4/15 (26.6%); improvement, 6/15 (40%); unchanged, 5/15 (33.3%)	CBP: eradication at the end of treatment, 27% Pyospermia: eradication at the end of treatment, 18%	N/R
Grolleau et al., 1983 [41]	Non-comparativ	39 patients (27 females), mean age 70.6 years, age range 40–88	2 tablets of 160 mg TMP/800 mg	Complete resolution of	UTIs: eradication, 12/13 (92.3%); persistence,	3 cases of adverse events related to

	e study	years; 13 patients with UTIs, 8 patients with acute bronchitis, 10 patients with bronchitis and superinfections, 6 patients with bronchopneumonopathies, 1 patient with sinusitis, 1 patient with pulmonary oedema	SMT daily, 36 patients; 3 tablets of 160 mg TMP/800 mg SMT daily, 3 patients	symptoms, 31/39 (79.5%); resolution of some signs, 4/39 (10.3%); persistence or worsening of symptoms, 1/39 (2.6%); uninterpretable (treatment was stopped prematurely), 3/39 (7.7%)	1/13 (7.6%) Bronchopneumonopathies: eradication, 2/2	treatment: nausea, 2 patients; diffuse macular erythema that disappeared after treatment, 1 patient 3 other cases of adverse events were uninterpretable: 2 cases of erythema and 1 case of nausea and vomiting
Plummer et al., 1983 [49]	Double-blind, placebo-controlled RCT	95 men with genital ulcers (78 with cultures positive for *Haemophilus ducreyi* and 17 with negative cultures), age range 18–60 years	Group I, 8 tablets as a single dose of TMP/SMT 640/3200 mg followed by 2 tablets of placebo for 5 days (27 patients) Group II, 8 tablets of placebo	Clinical failure: Group I, 0/27 (0%) vs. Group II, 0/23 (0%) vs. Group III, 2/28 (7.1%) Bacteriological cure but clinical failure: Group I, 1/27 (3.7%) vs. Group II, 1/23 (4.3%) vs. Group III, 0/28 (0%)	Re-infections: 1 patient in each treatment group	Group I: 1 patient had headache Group II: 1 patient had abdominal pain of short duration and 1 patient had evidence of possible haemolysis

			followed by TMP/SMT 160/800 mg b.i.d. for 5 days (23 patients) Group III, 8 tablets of placebo followed by TMP 200 mg b.i.d. for 5 day (28 patients)			
Fischer and Escher, 1982 [37]	Multicentre, open-label RCT	107 patients (91 females) with acute UTIs, age range 18–83 years	Group I: 2 tablets of 160 mg TMP/800 mg SMT (54 patients) Group II: 3 tablets of 750 mg amoxicillin (53 patients)	Clinical effectiveness was good in both groups	*Escherichia coli*: eradication (Group I) vs. (Group II): 89.2% vs. 70.4%	Group I vs. Group II: 6/54 (11.1%) vs. 11/53 (20.7%); $P = 0.2$ [a] (Group I, fatigue, nausea, tachycardia, trembling; Group II, exanthema, nausea, diarrhoea, vertigo, urticaria, trembling)
Martinez-Gallardo, 1982 [36]	Non-comparative study	40 adults (18 females) with acute pharyngotonsillitis, age range 22–76 years	2 tablets of TMP 80 mg/SMT 400 mg every 12 h for 5 days	Improvement, 52%; 85% (at the end of treatment)	Eradication, 32/36 (88.8%)	Mainly gastrointestinal adverse events, 4/40 (10%); treatment discontinuation due to adverse events, 1/40 (2.5%)

Piguet and Mitroi, 1982 [48]	Non-comparative study	61 patients (47 females) with chronic UTIs with or without urinary catheters, mean age 75.5 years, age range 47–95 years	Patients with resistant pathogens: 2 tablets/day for first 3 days and 2 tablets/day for the following 11 days of 160 mg TMP/800 mg SMT Patients with sensitive pathogens: 2 tablets/day for 14 days	N/R	Patients with in vitro susceptible pathogens and without urinary catheters: eradication, 30/38 (78.9%) Patients with in vitro resistant pathogens and with a urinary catheter: eradication, 10/23 (43.4%)	3 cases of gastrointestinal adverse events (requiring treatment discontinuation in 2 of these 3 cases) 2 cases had allergic skin reaction
Burmucic et al., 1981 [34]	Non-comparative study	40 female patients with subacute adnexitis, mean age 25.2 years, age range 17–42 years: subacute adnexitis, 32/40 (80%); subacute adnexitis due to retained IUD, 4/40 (10%); subacute adnexitis after curettage, 2/40 (5%); subacute adnexitis after miscarriage, 2/40 (5%)	2 tablets of TMP/SMT b.i.d.; N/R; none	Cure, 27/40 (67.5%); evident improvement, 10/40 (25%); moderate improvement, 3/40 (7.5%)	N/R	Nausea and allergic rash, 1/40 (2.5%); diarrhoea, 1/40 (2.5%)
Kisten and	Non-	29 patients with transverse lesions	Group I: 2 tablets	N/R	Group I: eradication, 12/19	N/R

Kahle, 1981 [43]	comparative study	of the spinal cord with paraplegia and UTIs	of TMP/SMT b.i.d. for 10 days Group II: 2 tablets of TMP/SMT b.i.d. for 20 days		(63.1%); bacterial count reduction, 3/19 (15.7%); failure, 4/19 (21%) Group II: eradication, 8/10; failure, 2/10	
Malinas, 1981 [52]	Non-comparative study	21 women of reproductive age with UTIs hospitalised for benign gynaecological conditions, mean age 26.3 years, age range 7–14 years	2 tablets of 160 mg TMP/800 mg SMT daily for 5 days (in 2 cases treatment duration was 6 days)	Temperature was normal or was reduced to low-grade fever prior to treatment in all 21 patients. Pain was present initially in 13 patients; mean ± S.D. time to resolution, 2.5 ± 0.2 days. Polyuria was present	Eradication, 18/20 (90%)	Gastralgia and vomiting, 1/20 (5%)

				initially in 11 patients; mean ± S.D. time to resolution, 3 ± 0.3 days		
Wieser et al., 1981 [51]	Non-comparative study	29 patients (8 female) with bronchitis or pulmonary infiltrate that required antibiotic therapy prior to thoracic operation	4 tablets of 80 mg TMP/400 mg SMT b.i.d.; mean ± S.D. duration, 7 ± 2 days	N/R	N/R	No adverse event requiring drug discontinuation was observed
Borkenstein et al., 1979 [32]	Case series	20 children (13 females) with infections, age range 7 months to 11 years: pneumonia, 5/20 (25%); AOM, 2/20 (10%); UTIs, 13/20 (65%) (including 4 patients with chronic and 9 with acute UTIs)	Syrup for children (6 mg/kg TMP)/(30 mg/kg SMT) for 10 days	Clinical manifestations improved in all children within the first few days of treatment	Eradication: Day 7, 17/18 (94.4%); Day 14, 18/18 (100%)	No allergies/gastrointestinal adverse events. 1 case of leukopenia
Krepler et al., 1976 [44]	Case series	21 children (17 female) with UTIs (12 acute, 9 chronic), TMP/SMT for 15 days over a period of 8 months, age range 2–12.4 years Group I: acute pyelonephritis, 12/21 (57.1%) [d]	2 paediatric tablets of SMT 100 mg/TMP 20 mg each b.i.d.; 15 days; 1 child also received gentamicin and	Group I: N/R Group II: N/R Group III: N/R Group IV: N/R	Follow-up (3 weeks to 3 months after treatment discontinuation): Group I: eradication, 76.2%; persistence, 9.5% Group II: eradication, 6/6 (100%)	Gastrointestinal adverse events (transitory vomiting, inappetence, vomiting, frequent stools), 19% Allergic skin reactions (urticarial toxic

		Group II: chronic pyelonephritis with >2 relapses and/or pyelonephritis signs in the urogram, 6/21 (28.5%) [e] Group III: chronic pyelonephritis with low-pressure continuous reflux (operated), 2/21 (9.5%) [f] Group IV: chronic pyelonephritis without relief of obstruction, 1/21 (4.7%)	carbenicillin		Group III: eradication, 1/2 (after operation); persistence, 1/2 Group IV: eradication of *Proteus mirabilis*, persistence of *Pseudomonas aeruginosa*, isolation of a resistant enterococci spp.	exanthema), 4.8% Slight transitory decrease in platelets was observed three times
		30 children (27 female) with UTI, age range 5–7 years Group I: acute UTI, 23/30 (76.6%) Group II: chronic UTI, 7/30 (23.3%)	2 paediatric tablets of 100 mg SMT/TMP 20 mg each b.i.d.; mean duration 11.3 days; N/R	Group I: N/R Group II: N/R	Group I: eradication, 23/23 (100%) Group II: eradication, 5/7 (71.4%)	Toxic allergic exanthema, 1/30 (3.3%) Transitory leukopenia, 1/30 (3.3%)
Brandesky and Takacs, 1975 [33]	Case series	20 paediatric patients (10 female) from a paediatric surgical ward, age range 2–12 years: appendicitis, 6/20 (30%); UTI, 3/20 (15%); osteomyelitis, 2/20 (10%); hypospadia/operation/permanent catheter, 2/20 (10%); acute tonsillitis, 1/20 (5%); bronchitis,	Children 2–5 years: 1–2 tablets of 100 mg SMT/20 mg TMP b.i.d. Children 6–12 years: 2–4 tablets of 100 mg SMT/20 mg TMP	Inflammatory symptoms and a decline of fever was observed for all patients	N/R	Urticaria, 1/20 (5%), could be attributed to concomitant penicillin treatment. No other toxicities

		1/20 (5%); vulva abscess, 1/20 (5%); abdominal wall abscess following appendectomy, 1/20 (5%); gluteal abscess/furunculosis, 1/20 (5%)	b.i.d.; ≥7 days; gentamicin, 2/20 (10%); penicillin, 1/20 (5%); nitrofurantoin, 1/20 (5%)			
Danilewicz et al., 1975 [35]	Non-comparative study	41 patients (22 female) with chronic bronchitic syndrome, bronchitis or bronchopneumonia, mean age 69.7 years, range 31–80 years: bronchitic syndrome, 39/41 (95.1%); bronchitis secondary to emphysema, 19/41 (46.3%); bronchopneumonia, 2/41 (4.8%)	2 tablets of TMP/SMT b.i.d.; 10 days; N/R	Clinical success, 38/41 (92.6%); clinical failure, 3/41 (7.3%)	N/R	Gastrointestinal adverse events (pressure in the stomach) necessitated drug discontinuation in 2/41 cases (4.8%)
Steinbock and Sischka, 1975 [50]	Non-comparative study	47 patients (27 children) with infections of the ear–nose–throat region, age range 2–72 years: acute sinusitis, 12/47 (25.5%); AOM, 20/47 (42.5%); pharyngitis, 15/47 (31.9%)	Children 2–5 years: 4 tablets of SMT 100 mg/TMP 20 mg b.i.d. Children 5–12 years: 1 tablet of 400 mg SMT/TMP 80 mg b.i.d. Adults: 2 tablets of 400 mg	Decline of fever, 46/47 (97.8%); cure, 91.5%; improvement, 6.4%	N/R	A significant increase was observed after treatment in the number of leukocytes and monocytes ($P < 0.05$) as well as in the number of lymphocytes and blood sedimentation rate ($P < 0.01$)

			SMT/TMP 80 mg b.i.d.; 10 days			
Studies providing pharmacokinetic/pharmacodynamic (PK/PD) data						
Reference	Study design	Study population	TMP/SMT administration characteristics	Sampling method/substances determined	Blood/plasma inhibitor concentrations; tissue inhibitor concentrations	Other PK/PD data/comments
Guggenbichler et al., 1987 [39]	Case–control study	36 patients with CF, mean age 6 years, range 11 months to 19 years Age-matched controls without CF under treatment for acute RTIs	(6 mg/kg TMP)/(20 mg/kg SMT)	0.1 mL of capillary blood prior to drug administration and at 30, 60, 120 and 240 min after; urine collected in 2-h intervals following administration for 6–12 h; sputum collected at hourly intervals usually on the 2nd day of treatment	N/R	TMP shows a slower absorption and an unaltered renal elimination. SMT has faster elimination in patients with CF versus those without
Scheiber et	Cohort study	41 patients with	Days 1–5:	Concentrations of	Plasma (mean	Urine (mean ± S.D. in μg/mL) in patients with CBP:

al., 1984 [42]	ABP/CBP and pyospermia	640 mg TMP/3200 mg SMT daily Days 5–10: 480 mg TMP/2400 mg SMT daily Days 10–15: 320 mg TMP/1600 mg SMT daily	TMP and SMT in plasma, urine and seminal fluid at 3, 6, 12 and 24 weeks	± S.D. in μg/mL) in patients with CBP: TMP: 3 weeks, 2.8 ± 2.0; 6 weeks, 1.9 ± 0.7; 12 weeks, 2.2 ± 0.7; 24 weeks, 2.2/SMT: 3 weeks, 110 ± 81; 6 weeks, 74 ± 29; 12 weeks, 70 ± 20; 24 weeks, 53.1 Plasma (mean ± S.D. in μg/mL) in patients with pyospermia: TMP: 3 weeks,	TMP: 3 weeks, 176 ± 74; 6 weeks, 170 ± 66; 12 weeks, 86 ± 52; 24 weeks, 160/SMT: 3 weeks, 162 ± 20; 6 weeks, 130 ± 60; 12 weeks, 122 ± 81; 24 weeks, 189 Seminal fluid (mean ± S.D. in μg/mL) in patients with CBP: TMP: 3 weeks, 3.2 ± 2.3; 6 weeks, 3.2 ± 1.5; 12 weeks, 3.3 ± 0.2; 24 weeks, 3.3/SMT: 3 weeks, 14.1 ± 7.6; 6 weeks, 12.4 ± 6.3; 12 weeks, 12.6 ± 7.0; 24 weeks, 12.4 Urine (mean ± S.D. in μg/mL) in patients with pyospermia: TMP: 3 weeks, 118 ± 62; 6 weeks, 102 ± 88; 12 weeks, 75 ± 56; 24 weeks, 101 ± 8.5/SMT: 3 weeks, 59 ± 3.5; 6 weeks, 117 ± 72; 12 weeks, 128 ± 61; 24 weeks, 99 ± 51 Seminal fluid (mean ± S.D. in μg/mL) in patients with pyospermia: TMP: 3 weeks, 2.1 ± 1.2; 6 weeks, 2.2 ± 1.0; 12 weeks, 2.1 ± 0.7; 24 weeks, 2.2 ± 0.4/SMT: 3 weeks, 12.4 ± 6.5; 6 weeks, 11.8 ± 7; 12 weeks, 9.2 ± 6.4; 24 weeks, 9.3

					1.8 ± 1.0; 6 weeks, 1.6 ± 0.8; 12 weeks, 1.6 ± 0.9; 24 weeks, 1.3 ± 0.5/SMT: 3 weeks, 62 ± 24; 6 weeks, 59 ± 21; 12 weeks, 40 ± 20; 24 weeks, 40 ± 16	
Hekster et al., 1981 [40]	Phase I study	8 healthy Caucasian volunteers	1 capsule of 800 mg SMT/160 mg TMP	Blood samples of 0.2 mL collected at scheduled time intervals by fingertip puncture, spontaneously voided urine collected for 60 h/SMT and N_4-acetylderivatives	N/A	SMT has similar $t_{1/2}$ to SMX; SMT is acetylated in a unimodal way; SMT renal clearance depends on urine flow and urine pH; renal clearance of N_4-acetyl derivatives does not depend on the above; no tubular excretion of SMT; active tubular excretion for N_4-acetyl derivatives; TMP is excreted unchanged; probenecid co-medication decreases the rate of absorption of SMT and the tubular excretion of N_4-acetyl derivatives
Wieser et al., 1981 [51]	Cohort study	29 patients (8 female) with	4 tablets of 80 mg TMP/400	10 mL of blood from a peripheral	Blood: mean ± S.D.	Distribution ratio SMT: mean ± S.D. (tissue/blood), 0.67 ± 0.198

		bronchitis or pulmonary infiltrate	mg SMT b.i.d.; mean ± S.D. duration, 7 ± 2 days	vein and 10 g of resected lung as far as possible from the diseased tissue/active SMT, unmetabolised TMP	μg SMT/mL, 30.3 ± 15.83; mean ± S.D. μg TMP/mL, 2.0 ± 0.70 Lung: Mean ± S.D. μg SMT/g, 19.2 ± 10.35 mean ± S.D. μg TMP/g, 9.2 ± 3.83	Distribution ratio TMP: mean ± S.D. (tissue/blood), 4.88 ± 1.88 Higher concentration of TMP in the lung tissue
Bergmann et al., 1979 [53]	Case series	10 patients, mean age 71.6 years, range 64–77 years, with normal kidney and liver function admitted to a urology department for prostatectomy due to benign prostatic hypertrophy	2 tablets of 400 mg TMP/80 mg SMT b.i.d. for 4 days (last dose was given 4 h before surgery)	Venous blood samples were taken during enucleation of the prostatic adenoma and four tissue samples of different areas of the adenoma/active sulfonamide,	Plasma: mean ± S.D. mg SMT/L, 92.0 ± 16.06; mean ± S.D. mg TMP/L, 3.2 ± 0.6 Prostate: mean ± S.D. mg SMT/kg, 24.0 ± 8.61; mean ± S.D.	Distribution ratios: mean ± S.D. [(SMT $C_{prostate}$/SMT C_{plasma})], 0.26 ± 0.089 Mean [(TMP *C* prostate/TMP *C* plasma)] ± S.D., 2.21 ± 0.456

				unmetabolised TMP	mg TMP/kg, 7.1 ± 2.17		
Studies providing in vivo data							
Reference	Study design	Study subjects	TMP/SMT administration characteristics	Types of infections	Clinical outcome	Microbiological outcome	Adverse events
Bartlett et al., 1995 [45]	Experimental study	BALB/c female mice weighting ca. 18–20 g were immunosuppressed (0.2 mg of antibody directed to L3T4$^+$ cells twice a week), inoculated with ca. 10^6 *Pneumocystis jiroveci* transtracheally and treated with TMP/SMT	250 mL bottles of infusion containing 0.8 g SMT/0.16 g TMP and 15.5 g Sorbite. The drug was given in drinking water so that mice received doses of the combination of 50/350	*P. jiroveci* infection	Mice treated with TMP/SMT were cured from the infection. Mice that were not treated with TMP/SMT developed severe infections. Some cysts remained in the lungs; the numbers were reduced	No organisms were detected by Giemsa stain in either TMP/SMT- or TMP/SMX-treated mice	N/R

	mg/kg/day for 3 weeks	compared with untreated mice or mice treated with TMP/SMX

RCT, randomised controlled trial; N/R: not reported; AOM, acute otitis media; t.i.d., three times daily; b.i.d., twice daily; UTI, urinary tract infection; RTI, respiratory tract infection; tsp, teaspoon; CBP, chronic bacterial prostatitis; IUD, intrauterine device; S.D., standard deviation; CF, cystic fibrosis; N/A: non-applicable; $t_{1/2}$, elimination half-life; SMX, sulfamethoxazole; *C*, concentration.

[a] *P*-values were calculated using OpenEpi software (http://www.OpenEpi.com; accessed 28 March 2011). Yates' correction was used in all comparisons. In cases where at least one value was <5, Fischer's exact test was used.

[b] All isolates identified were susceptible to enoxacin at a concentration of 0.25 mg/L and TMP/SMX at a concentration of 0.25/5.0 mg/L.

[c] The pathogens isolated from urine cultures pre-therapy were *E. coli* in 24 patients, *Enterobacter aerogenes* in 8 patients, *Enterococcu*s spp. in 6 patients and *Staphylococcus aureus* in 2 patients.

[d] *Escherichia coli* was the causative organism in nine cases, whereas the remaining three patients had staphylococci spp. + streptococci spp., *Klebsiella* spp. + enterococci spp., and *P. mirabilis* + enterococci spp., respectively. Before treatment all *E. coli* strains were susceptible to TMP/SMT, whereas *Klebsiella*, *Proteus* and enterococci showed varying susceptibilities in the disk test.

[e] *Escherichia coli* was detected in the urine of five of these six patients, whereas non-haemolytic streptococci were detected in the urine of the remaining patient. All isolates were sensitive to TMP/SMT.

[f] One of these two patients had *P. aeruginosa* that was resistant to TMP/SMT and the other one had *Enterobacter* spp., *Streptococcus* spp. and *Staphylococcus* spp. They were all susceptible to TMP/SMT.

Table 3

Comparison of characteristics between trimethoprim/sulfametrole (TMP/SMT) and trimethoprim/sulfamethoxazole (TMP/SMX)

Reference	Study methodology	TMP/SMT	TMP/SMX	Comments
In vitro data				
van der Ven et al., 1996 [67]	To determine the in vitro susceptibility of *Toxoplasma gondii* to DHFR inhibitors and sulfonamides alone and in combination	In vitro effect on *T. gondii*: IC_{50} = 600–700 mg/L	In vitro effect on *T. gondii*: IC_{50} = 400–500 mg/L	SMX and SMT were about equally effective in vitro against *T. gondii*. The in vitro effect (IC_{50}) of SMX of 500 mg/L was reduced considerably when a DHFR inhibitor was added to the incubation medium. Specifically, addition of 0.005 mg/L pyrimethamine reduced the IC_{50} of SMX to 50 mg/L
Abdel-Messih et al., 1984 [54]	Tested isolates: 100 coliforms, 70 *Staphylococcus aureus*–*Streptococcus pyogenes*, 25 *Salmonella* spp.–*Shigella* spp.	Coliforms: S, 60%; I, 20% *S. aureus*–*S. pyogenes* isolates: S, 47.14%; I, 36% *Salmonella* spp.–*Shigella* spp.: S, 80%; I, 5%	Coliforms: S, 52%; I, 31% *S. aureus*–*S. pyogenes* isolates: S, 37.14%; I, 44% *Salmonella* spp.–*Shigella* spp.: S, 48%; I, 20%	Increased activity of TMP/SMT against tested isolates compared with TMP/SMX. Since the amount of TMP was the same in both

	Disk tests measuring 6 mm in diameter containing 1.25 μg TMP/23.75 μg SMT and 1.25 μg TMP/23.75 μg SMX, respectively			combinations, the observed increased activity may be attributed to SMT
Fast M et al., 1983 [57]	81 men with a genital ulcer and confirmed chancroid and 7 patients with negative cultures of the ulcer and concomitant infections: TMP/SMX (12 patients), 160 mg/800 mg, 7 days; TMP/SMT (12 patients), 640 mg/3200 mg, 1 dose	Correlation of in vitro susceptibility of *Haemophilus ducreyi* isolates and response to treatment of men with chancroid: No. of isolates susceptible, 8/12 (66.6%) No. of patients improved, 7/12 (58.3%) No. of isolates resistant, 0/12 (0%)	Correlation of in vitro susceptibility of *H. ducreyi* isolates and response to treatment of men with chancroid: No. of isolates susceptible, 4/12 (33.3%) No. of patients improved, 4/12 (33.3%) No. of isolates resistant, 0/12 (0%)	N/R
Scazzocchio and Repetto, 1983 [56]	Antimicrobial activity of TMP/SMT (ratio 5/1) and TMP/SMX (ratio 5/1) was evaluated against 22 *S. aureus*, 10 *Bacillus* spp., 38 *Escherichia coli*, 16 *Proteus* spp. and 13 additional different strains of Gram-negative bacteria	Cumulatively for the tested Gram-positive strains: antimicrobial activity of TMP/SMT was comparable with that of TMP/SMX. Antibacterial activity of TMP/SMT against the tested 38 *E. coli* strains was greater than that of TMP/SMX. Regarding the 16 *Proteus* spp. tested strains, TMP/SMT was much more active compared with TMP/SMX. Regarding the tested Gram-negative pathogens, the activity of TMP/SMT was comparable with that of TMP/SMX except for the two tested *Providencia alcalifaciens* strains for which TMP/SMT had a better activity		TMP/SMT has wide in vitro antibacterial activity

		compared with TMP/SMX		
Nabert-Bock and Grims, 1977 [63]	111 strains of bacteria of different species [a] from the laboratory and clinic were examined quantitatively and the MICs of SMT, TMP and their combination (ratio 1/20) were determined SMX served as a comparative substance (TMP/SMX ratio 1/20)	Synergy between TMP/SMT (quantitative dilution test): *E. coli*, 32/32 (100%); *Klebsiella–Enterobacter* spp., 10/12 (83.3%); *Proteus* spp., 13/14 (92.8%); Group A *S. pyogenes*, 3/4 [b]; *Salmonella typhi*, *Salmonella paratyphi* B and *Shigella sonnei*, 5/5 [c] Increase in effect of the combination against organisms of different sensitivity: strains susceptible to TMP and SMT, 35/35 (100%); strains resistant to TMP, 2/2; strains resistant to SMT, 28/47 (59.5%); strains resistant to TMP and SMT, 23/27 (85.1%) Synergy (disk test), 96/111 (86.4%) Experimental development of resistance (2 *E. coli*, 3 *S, aureus* and 4 *Proteus* spp. strains were tested 10 times repeated contact	Synergy between TMP/SMX (quantitative dilution test): *E. coli*, 32/32 (100%), *Klebsiella–Enterobacter*, 10/12 (83.3%); *Proteus* spp., 13/14 (92.8%); Group A *S. pyogenes*, 3/4 [b]; *S. typhi*, *S. paratyphi* B and *S. sonnei*, 5/5 [c] N/R	SMT enhanced the activity of TMP and vice versa. The increase in efficacy depended on the initial susceptibility pattern of the bacteria to TMP and/or sulfonamides. TMP/SMT (1/20) combination had the same antibacterial activity as TMP/SMX. Development of resistance could not be obtained when using the combination TMP/SMT

		with sub-bacteriostatic concentrations), no resistance		
In vivo data				
Scazzocchio and Repetto, 1983 [56]	Albino mice (20 g average weight) Infection was induced by *Proteus mirabilis* CH/1 and *S. paratyphi* ASA 12 PD_{50} (mg/kg) was determined for the combinations TMP/SMT and TMP/SMX as well as their single components [d]	*P. mirabilis* infection: PD_{50} determined SMT, 23 mg/kg PD_{50} determined TMP, 200 mg/kg PD_{50} determined TMP/SMT, 31 mg/kg PD_{50} expected TMP/SMT, 86.6 mg/kg PD_{50} (expected/determined), 2.79 *S. paratyphi* A infection: PD_{50} determined SMT, 32 mg/kg PD_{50} determined TMP, 42 mg/kg PD_{50} determined TMP/SMT, 25.2 mg/kg PD_{50} expected TMP/SMT, 39.9 mg/kg PD_{50} (expected/determined), 1.58	*P. mirabilis* infection: PD_{50} determined SMX, 23 mg/kg PD_{50} determined TMP, 200 mg/kg PD_{50} determined TMP/SMX, 61 mg/kg PD_{50} expected TMP/SMX, 86.6 mg/kg PD_{50} (expected/determined), 1.42 *S. paratyphi* A infection: PD_{50} determined SMX, 64 mg/kg PD_{50} determined TMP, 42 mg/kg PD_{50} determined TMP/SMX, 20.9 mg/kg PD_{50} expected TMP/SMX, 44.6 mg/kg PD_{50} (expected/determined), 2.13	Both combinations exert a protective antibacterial activity in experimentally infected animals. This effect is far greater than the simple additive action of the respective components. For infection with *P. mirabilis*, the observed protective effect of TMP/SMT was greater compared with that of TMP/SMX
Nabert-Bock and Grims, 1977 [63]	Albino mice of both sexes Pathogens used: *E. coli* haem, C15, Group A *S. pyogenes* haem. 2 and *P. mirabilis* 393 Drugs were administered	FICI (intensification of effect ≤1)[e]: *E. coli*, 0.21; *S. pyogenes*, 0.45; *P. mirabilis*, 0.27	FICI (intensification of effect ≤1)[e]: *E. coli*, 0.29; *S. pyogenes*, 0.58; *P. mirabilis*, 0.59	Enhancement of the antibacterial activity of the combination TMP/sulfonamide was confirmed, irrespective of the sulfonamide used

	orally			
Pharmacokinetic/pharmacodynamic data				
Vree and Hekster 1987 [68]	Book chapter: *Clinical pharmacokinetics of sulfonamides and their metabolites, an encyclopedia*	Influence of urinary pH on $t_{1/2}$ and on renal excretion of SMT: With urine pH 5.37 ± 0.23, for 5 subjects: $t_{1/2}$ (mean), 11 h; % excreted, 3.88 ± 1.50% With urine pH 7.72 ± 0.42, for 4 subjects: $t_{1/2}$ (mean), 9 h; % excreted, 24.4 ± 13.5%	Influence of urinary pH on $t_{1/2}$ and on renal excretion of SMX: With urine pH 5.90 ± 0.38, for 7 subjects: $t_{1/2}$ (mean ± S.D.), 12 ± 2.8 h, % excreted, 16.7 ± 10.4% With urine pH 7.28 ± 0.21, for 11 subjects: $t_{1/2}$ (mean ± S.D.), 9 ± 1.5 h; % excreted, 32.6 ± 6.2%	In both SMT and SMX, $t_{1/2}$ is slightly longer under acidic compared with alkaline conditions. In both SMT and SMX the excretion is increased under alkaline compared with acidic conditions
Hekster et al., 1982 [58]	Evaluation of clinical pharmacokinetics of sulfonamides and their N_4-acetyl derivatives	Solubility (mg/L, at 25 °C): pH 5.5, 460; pH 7.0, 1700	Solubility (mg/L, at 25 °C): pH 5.5, 300; pH 7.0, 1900	Increased solubility of SMT, may be associated with lower risk of crystalluria
Hekster et al., 1981 [40]	Pharmacokinetics of SMT and its N_4-acetyl derivatives, a study of 8 healthy Caucasian volunteers	Solubility (mg/L, at 25 °C): pH 5.5: N_4-acetyl SMT: 1100 pH 7.0: N_4-acetyl SMT: 6000	Solubility (mg/L, at 25 °C): pH 5.5: N_4-acetyl SMX: 115 pH 7.0: N_4-acetyl SMX: 1000	Increased solubility of N_4-acetyl SMT, may be associated with lower risk of crystalluria
Bernstein, 1982 [55]	Evaluation of combinations of TMP with sulfonamides other than SMX	Mean values: $t_{1/2}$, 6–9 h pKa, 4.8 Protein binding, 78% Metabolism to N_4-acetyl derivative, 80%	Mean values: $t_{1/2}$, 11 h pKa, 6.0 Protein binding, 68% Metabolism to N_4-acetyl derivative, 85%	TMP/SMT may be a useful alternative to TMP/SMX

Clinical effectiveness and/or safety data				
Fast et al., 1983 [57]	RCT involving 81 men with a genital ulcer and confirmed chancroid and 7 patients with negative cultures of the ulcer and concomitant infections Group A: sulfadimidine 1 g 4 times daily, 7 days Group B: tetracycline 500 mg 4 times daily, 7 days Group C: doxycycline 300 mg, 1 dose Group D: TMP/SMX 160/800 mg, 7 days Group E: TMP/SMT 640/3200 mg, 1 dose	*H. ducreyi*-positive men with chancroid 1 week after therapy: cure, 3/10 (30%); improvement, 6/10 (60%); failure, 1/10 (10%) *H. ducreyi*-negative men 1 week after therapy: cure, 4/6; improvement, 2/6; failure, 0/6 Time to complete epithelisation of ulcer in men with proven and possible chancroid: proven (7 patients), 12 days; possible (7 patients), 9 days	*H. ducreyi*-positive men with chancroid 1 week after therapy: cure, 4/8; improvement, 4/8; failure, N/R *H. ducreyi*-negative men 1 week after therapy: cure, 1/2; improvement, 1/2; failure, 0/2 Time to complete epithelisation of ulcer in men with proven and possible chancroid: proven (9 patients), 13 days; possible (2 patients), 14 days	TMP/SMX and TMP/SMT combinations were more effective compared with sulfadimidine, tetracycline and doxycycline
Luisetti et al., 1983 [62]	Double-blind RCT involving 40 male patients with acute/exacerbated chronic RTIs, mean age 56.7 years Group A: 20 patients received 2 tablets of TMP/SMT (80 mg/400 mg)	Microbiological outcome at end of treatment and 3 days thereafter: eradication, 38/40 (95%); persistence, 1/40 (2.5%); emergence of resistant pathogen, 1/40 (2.5%) Mean fever reduction after	Microbiological outcome at end of treatment and 3 days thereafter: eradication, 38/40 (95%); persistence, 2/40 (5%); emergence of resistant pathogen, 0/40 (0) Mean fever reduction after treatment:	Clinical–bacteriological activity of TMP/SMT appeared to be equivalent to that of TMP/SMX. TMP/SMT exerted a more rapid activity than TMP/SMX in fever.

	q12h for 10 days Group B: 20 patients received 2 tablets of TMP/SMX (80 mg/400 mg) q12h for 10 days [f] All isolates were susceptible to both TMP/SMT and TMP/SMX	treatment: (a) morning, –1.14 °C; (b) evening, –1.04 °C Fever values >37 °C: (a) morning: in favour of TMP/SMT ($P < 0.05$); (b) evening, P = N/S Heart rate: decreased with both treatment arms, P = N/S Variations in urinary parameters: similar in both groups Mean decrease of ESR: (a) after 1 h, 31.95; (b) after 2 h, 21.40 Daily sputum volume decrease, 28.50 Nature of sputum (mucoid or absent, mucopurulent or purulent) improved upon TMP/SMT treatment: $\chi^2 = 5.60$, $0.1 > P > 0.05$ Viscosity was better with TMP/SMT treatment: $\chi^2 = 9.60$, $P < 0.01$ Adverse events, 1/40 (2.5%), (1 patient had mild diarrhoea after administration of TMP/SMT and theophylline treatment) Effectiveness evaluation: excellent, 90%; good, 5%; fair, 5% Tolerance evaluation: excellent, 100%	(a) morning, –0.99 °C, P = N/S; (b) evening, –1.04 °C, P = N/S Mean decrease of ESR: (a) after 1 h, 22.60; (b) after 2 h, 12.25 Daily sputum volume decrease, 29.25, P = N/S Adverse events, 0/40 (0%) Effectiveness evaluation: excellent, 90%; fair, 10% Tolerance evaluation: excellent, 100%	TMP/SMT induced a better variation of sputum appearance and viscosity
Reynaert et al., 1979	Double-blind comparative study involving 89 patients	Microbiological results: re-infection, 2/28 (7%); eradication	Microbiological results: re-infection, 1/30 (3.3%); eradication of initial	TMP/SMT has an acceptable effectiveness

[59]	(86 females) with UTIs, mean age 54 years, range 22–78 years Group A: 30 patients received 2 tablets of 80 mg TMP/400 mg SMX Group B: 31 patients received 2 tablets of SMT Group C: 28 patients received 2 tablets of 80 mg TMP/400 mg SMT Duration 8–10 days	of initial pathogen, 24/28 (86%); recurrence, 4/28 (14%) Clinical results: cure, 22/28 (79%) Haematological and laboratory values were normal. No drug discontinuation due to adverse event occurred	pathogen, 26/30 (87%); recurrence: 4/30 (13%) Clinical results: cure, 25/30 (83%)	and safety profile
Additional comparisons between TMP/SMT and TMP/SMX				
Managing drug reactions to sulfonamides in HIV-infected patients; Koopmans and Burger, 1998 [61]		9 patients with severe HIV infection received TMP/SMX [6 for the treatment of *Pneumocystis jiroveci* pneumonia (high doses) and 3 for prophylaxis (960mg daily)]. In these 9 patients a drug reaction occurred: typical rash within 1–2 weeks after treatment initiation that disappeared after discontinuation. No patient had a serious reaction such as Stevens–Johnson syndrome or eosinophilic pneumonia. All 9 patients were re-challenged within 2 weeks, starting with 1 week of TMP (160 mg daily). None of the 9 patients developed a drug reaction to TMP alone. Re-challenge with SMT, 7/9; re-challenge with sulfamethizole, 2/9. Recurrence of skin reaction, 7/9 (6/7 were re-challenged with SMT and 1/7		These data do not support re-challenge with sulfonamides as a safe option. However, they refer to a limited number of patients. These data also do not support the hydroxylamine hypothesis. However, the hydroxylamine hypothesis cannot be completely rejected as cross-allergy

	was re-challenged with sulfamethizole). In 2/7 patients the skin reaction was more serious than the initial reaction to TMP/SMX. 1 of the 9 patients was subsequently re-challenged with dapsone, but the rash re-appeared within 2 weeks. 3 patients with a non-successful re-challenge with SMT were desensitised with low dosages of TMP/SMX		may play a role in this group with a history of drug reaction
Risk for induction of hypoglycaemia following administration of TMP/SMT and TMP/SMX (Kaspar, 1980 [60] vs. Schelleman et al., 2010 [64] vs. Strevel et al., 2006 [65])	Kaspar, 1980 [60]: Double-blind cross-over trial (10 diabetics treated with insulin and TMP/SMT) vs. (10 diabetics treated with sulfonylurea derivatives and TMP/SMT) No tendency towards hypoglycaemia observed in either group Within 5 days, creatinine and BUN levels had increased to pathological levels in patients with previous renal damage	Schelleman et al., 2010 [64]: 2 case–control studies and 2 case–cross-over studies using US Medicaid data: Glipizide users, risk of hypoglycaemia found for TMP/SMX, OR = 3.14, 95% CI 1.83–5.37; glyburide users, risk of hypoglycaemia found for TMP/SMX, OR = 2.68, 95% CI 1.59–4.52 Strevel et al., 2006 [65]: case of refractory hypoglycaemia complicated by seizure associated with TMP/SMX for treatment of *P. jiroveci* pneumonia in a patient with AIDS and a review of 13 previously reported cases of TMP/SMX-induced hypoglycaemia; renal insufficiency was the most prevalent predisposing risk factor (93%); serum insulin levels were	Lack of interaction between TMP/SMT and insulin or sulfonylurea derivatives was suggested in an old comparative study. Recent case reports and case–control/cross-over studies suggest that there is a risk for hypoglycaemia after TMP/SMX treatment in diabetic and non-diabetic patients with co-morbidity, including HIV infection and impaired renal function

		raised or inappropriately normal in 88% of cases in which they were measured, suggesting a sulfonylurea-like effect of TMP/SMX	
Development of crystalluria, von Pogglitsch et al., 1980 [66] [g]	pH <6: USG < 1600 g/mL, none; 1040 g/mL < USG < 1059 g/mL, none; USG > 1060 g/mL, 1 sulfonamide crystal pH 6–7: USG < 1600 g/mL, none; 1040 g/mL < USG < 1059 g/mL, none; USG > 1060 g/mL, none	pH <6: USG < 1600 g/mL, none; 1040 g/mL < USG < 1059 g/mL, none; USG > 1060 g/mL, 2 sulfonamide crystals pH 6–7: USG < 1600 g/mL, none; 1040 g/mL < USG < 1059 g/mL, none; USG > 1060 g/mL, none	Microscopically detectable crystals were not found below urinary densities of 1060 g/L, irrespective of the sulfonamide component used in combination with TMP

DHFR, dihydrofolate reductase; IC_{50}, 50% inhibitory concentration; S, susceptibility; I, intermediate susceptibility; N/R, not reported; MIC, minimum inhibitory concentration; PD_{50}, dose capable of protecting 50% of the treated mice; FICI, fractional inhibitory concentration index; $t_{1/2}$, elimination half-life; S.D., standard deviation; RCT, randomised controlled trial; RTI, respiratory tract infection; q12h, every 12 h; N/S, non-significant; ESR, erythrocyte sedimentation rate; UTI, urinary tract infection; HIV, human immunodeficiency virus; BUN, blood urea nitrogen; OR, odds ratio; CI, confidence interval; USG, urine special gravity.

[a] Tested strains were *E. coli* (32), *Klebsiella–Enterobacter* spp. (12), *Proteus* spp. (14), *Pseudomonas aeruginosa* (17), *S. aureus* (17), *Streptococcus faecalis* (10), Group A *Streptococcus pyogenes* (4), *S. typhi* and *S. paratyphi* B (4) and *S. sonnei* (1).

[b] In cases where the denominator was <10, percentages are not presented in the table.

[c] With regard to the *P. aeruginosa* and *S. faecalis* strains tested, 7/17 (41.1%) and 10/10 (100%) were found to be susceptible to both TMP/SMT and TMP/SMX. With regard to the *S. aureus* strains tested, the sulfonamides hardly exerted any influence.

[d] To evaluate the potential synergism of SMT and TMP (ratio 5/1), the experimental ('determined') PD_{50} of the combination TMP/SMT was compared with the PD_{50} calculated as a pure additive activity of the two combined chemotherapeutics ('expected' PD_{50}). This was also repeated for the combination of TMP/SMX. The ratio (expected PD_{50}/determined PD_{50}) was used to evaluate the combined effect of the two drugs. The effect was considered synergistic when the ratio was >1.

[e] FICI = (CD_{50} TMP + CD_{50} combination)/(CD_{50} TMP + CD_{50} single component), where CD_{50} is the 50% convulsive dose.

[f] If necessary, patients received concomitant cardiotonic, diuretic, bronchodilator and mucolytic therapy.

[g] The aim of the study was the aetiological exploration of primary acute and primary chronic interstitial nephritis in 183 female and 55 male patients. The crystallising tendency of TMP/SMX and TMP/SMT was also evaluated by continuous in-vitro-concentrating of urine. Data for TMP/SMX refer to the number of sulfonamide crystals in the urinary sediment after administration of TMP/SMX 800 mg/day for 3 days.