Zeitschrift: Acta Tropica
Herausgeber: Schweizerisches Tropeninstitut (Basel)
Band: 37 (1980)
Heft: 3

Artikel: New trends in the chemotherapy of typhoid fever
Autor: Herzog, C.
DOI: https://doi.org/10.5169/seals-312662

Nutzungsbedingungen
Die ETH-Bibliothek ist die Anbieterin der digitalisierten Zeitschriften. Sie besitzt keine Urheberrechte an den Zeitschriften und ist nicht verantwortlich für deren Inhalte. Die Rechte liegen in der Regel bei den Herausgebern beziehungsweise den externen Rechteinhabern. Siehe Rechtliche Hinweise.

Conditions d'utilisation
L'ETH Library est le fournisseur des revues numérisées. Elle ne détient aucun droit d'auteur sur les revues et n'est pas responsable de leur contenu. En règle générale, les droits sont détenus par les éditeurs ou les détenteurs de droits externes. Voir Informations légales.

Terms of use
The ETH Library is the provider of the digitised journals. It does not own any copyrights to the journals and is not responsible for their content. The rights usually lie with the publishers or the external rights holders. See Legal notice.

Download PDF: 06.02.2025

ETH-Bibliothek Zürich, E-Periodica, https://www.e-periodica.ch

Acta Tropica 37, 275–280 (1980)

Medizinische Universitäts-Poliklinik (Prof. Dr. U. C. Dubach),
Departement für Innere Medizin, Kantonsspital Basel

New trends in the chemotherapy of typhoid fever

CH. HERZOG

The place of chloramphenicol as drug of choice in acute typhoid fever has repeatedly been questioned in recent years. The still reliable clinical effectiveness [37] is more and more outweighed by disadvantages. Chloramphenicol increases the relapse rate in acute typhoid fever and has neither influence on the convalescent excretor rate nor on the chronic carrier state; moreover in up to 5–10% of treated cases it can produce a toxic crisis [31]. The risk of chloramphenicol induced aplastic anemia in 1 case in 20,000 treatment courses, which seems to be higher in the East than in the West [8], is not a strong argument against the use of this drug in typhoid fever, considering the natural course of the disease with a lethality rate of up to 10–15% [37].

A major drawback, however, has been the occurrence of an R-factor mediated chloramphenicol resistance among *S. typhi* strains since 1972 [3, 6, 31, 69]. These R-factors confer usually a high level multiple resistance to chloramphenicol, sulfonamides, tetracyclines, streptomycin and partly also to ampicillin. In these resistant cases the course of the disease is not influenced at all by chloramphenicol [9, 31].

R-factor carrying S. typhi

Sporadic isolation of *S. typhi* strains conferring R-factor mediated chloramphenicol resistance has been reported from Greece, Israel, Kuwait and Spain [3, 31], Rumania [50], France and Algeria [31], Chile and Indonesia [69] and from Korea [12, 13). From the information available it seems that these multiple drug-resistant strains of *S. typhi* have been or still are endemic in Mexico (1972–75–?) [6, 31, 68, 69], India (1972–78) [31, 46, 56, 69, 70], Thailand (1973–75–?) [26, 31, 35], Cambodia (1974–?) [31], Formosa (1973–74–?) [31], Vietnam (1971/72–75–?) [9, 31, 52, 69] and may also be endemic in Peru (1974–76–?) [70] (Fig. 1).

Correspondence: Dr. Ch. Herzog, Medizinische Universitäts-Poliklinik, Kantonsspital, Petersgraben 4, CH-4031 Basel, Switzerland

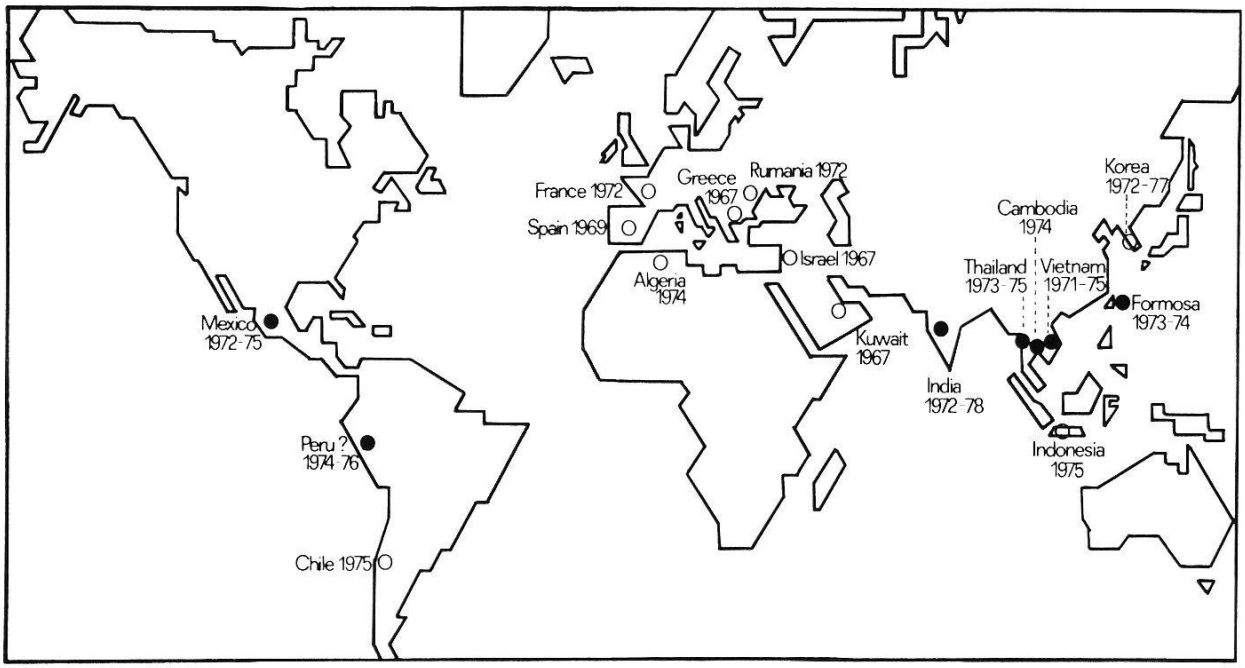

Fig. 1. Incidence of single or sporadic cases (○) and endemic occurrence (●) of typhoid fever due to *S. typhi* with R-factor mediated resistance to chloramphenicol (and other antibiotics) throughout the world (from the literature up to 1979).

The transmission of chloramphenicol-resistant typhoid fever in Mexico, which was a point-source-outbreak caused by mainly one phage type, declined rapidly after 1973 [6, 68]. This is contrary to the situation in South-East-Asia, where the transmission remained stable over years (up to 80% resistant isolates [31]), and where at least 7 phage types were involved [3, 67, 69].

R-factor mediated ampicillin resistance among *S. typhi* strains has, apart from isolated cases in Algeria, France [31] and Kuwait [4], so far been reported from India [46], Korea [12, 13], Mexico [3, 31], Thailand [31] and Vietnam [31, 52].

Multiple resistant *S. typhi* strains have been imported to Europe and North-America [4, 6, 66].

Typhoid fever, a therapeutic model?

The time until defervescence is generally accepted as the main criterion for a response to drug therapy in typhoid fever; additional parameters are: the relapse rate, the incidence of other complications and the convalescent excretor rate [31]. Therefore typhoid fever seems to be a practicable therapeutic model. The search for new drugs has, however, turned more difficult, not only by the lack of complete correlation between the in vitro susceptibility of *S. typhi* strains and the in vivo activity of most antimicrobial agents [31], and the lack of a suitable animal model [33], but there is often no correlation between bacteriological and clinical cure: The various symptoms of typhoid fever usually persist for several days after sterilization of the blood by chemotherapy [25, 63]; not seldom does bacteremia persist under adequate treatment despite a proven

susceptibility of the isolated salmonella strain [24, 47, 54]; successful treatment seems to be possible despite in vitro resistance of the pathogen isolated from the blood [51] (Resistant stool isolates may have acquired resistance – including R-factors – after the start of drug therapy [36]); symptomless bacteremia or a positive bone marrow culture have been described up to one year after successful treatment [28], as well as in chronic carriers and in subclinical infections [34].

Evaluation of alternative drugs for acute typhoid fever

To obtain conclusive results all clinical trials should be comparative to chloramphenicol (or perhaps to another standard drug in the future?), as e.g. the average number of days to achieve defervescence under chloramphenicol may vary from one trial to another from about 3 to 8 days. Preconditions for the assessment of the therapeutic response are: diagnosis by positive blood or bone marrow culture [27]; a stage of the disease not beyond the 2nd week of illness; no exclusion of severe cases; the drug to be tested should achieve serum levels several times in excess of the average MIC of *S. typhi;* determination of the MIC before and after treatment of all pathogens isolated; measurement of serum peak and through antibiotic concentration [64]; if possible determination of serum antibacterial activity at peak and through antibiotic levels [22, 64]; and continuation of the treatment for a sufficiently long period after achieving defervescence (at least 10 days).

The main criteria for evaluation are: failure rate after at least 7–10 days treatment; determination of defervescence; relapse rate after at least one month follow-up; and convalescent excretor rate during a regular follow-up of at least 4–6 weeks.

Comparative clinical trials

The majority of antimicrobial agents with an activity against *S. typhi* have in the past failed clinically, as e.g. sulfonamides, tetracyclines, and aminoglycosides. Only the aminopenicillines, co-trimoxazole and thiamphenicol have so far been used successfully as alternative drugs [31]. In acute typhoid fever ampicillin is clearly inferior to chloramphenicol regarding defervescence and failure rate [29, 31, 57]). It has now been replaced by amoxicillin [1, 2, 31, 54] and co-trimoxazole [14, 20, 31, 36, 48, 51, 57, 58], which are both even superior to chloramphenicol regarding relapse rate and convalescent excretor rate and are equal regarding defervescence and failure rate. Both drugs are now also available for parenteral application. Thiamphenicol offers no real advantage over chloramphenicol [31]. The same applies to epicillin [30, 60], which hardly differs from ampicillin in its qualities. The treatment schedules for these drugs can be seen in Table 1.

A recent comparative trial with furazolidon gave the devastating result of a 100% failure [51]. This is completely at variance with two earlier comparative trials, their failure rates being 0% and 1.5% only [31].

Table 1. Treatment schedules of drugs of choice in acute typhoid fever

		Route of administration	Daily dose in adults	Duration of treatment
1st	Chloramphenicol	p.o./i.m./i.v.	30–40 mg/kg	Full dose until
	Amoxicillin	p.o./i.m./i.v.	50–75 mg/kg	defervescence
	Co-trimoxazole	p.o./i.m./i.v.	TMP 7–8 mg/kg	has been
			SMZ 35–40 mg/kg	achieved for
2nd	Ampicillin	p.o./i.m./i.v.	100–150 mg/kg	2 days, then
	Epicillin	p.o./i.m./i.v.	50–75 mg/kg	half the dose
	Pivmecillinam/ Mecillinam	p.o.	25–50 mg/kg	for at least
		i.m./i.v.	25–50 mg/kg	another 10 days
	Thiamphenicol	p.o./i.m./i.v.	30–40 mg/kg	

Drug combinations [16, 21] show no real advantage compared to single drug therapy, neither with regard to defervescence [42, 49, 65], nor relapse rate [49, 65] or convalescent excretion [42, 49]. A possible exception is the chronic typhoid or Salmonella carrier. A combination of synergistically acting drugs may be superior to single drug therapy [22, 55, 59].

S. typhi excretors/carriers

There are only few comparative studies set up to evaluate the convalescent excretor rate. In typhoid fever the rate of excretion was found in one study to be four times higher after chloramphenicol (35–62%) than after co-trimoxazole (8.5–14.8%), at the time of discharge from hospital as well as one month later [20]. In another trial on paratyphoid B fever the rate was 42% for chloramphenicol and 6% for co-trimoxazole [36]. The epidemiological importance of a quick stool clearance is clearly shown by recent findings from Lesotho [19]; there the provision of clean water did not interrupt the transmission of endemic typhoid fever at all, which seems therefore to spread mainly from person to person in societies with poor personal and domestic hygiene.

Ampicillin [31, 38, 39], amoxicillin [31, 43, 44] and co-trimoxazole [11, 31, 38, 39, 53] seem to be equally effective in the treatment of chronic typhoid fever. Rifampicin may be a valuable addition in combination with co-trimoxazole [22].

Treatment of drug resistant typhoid fever

In the Mexico epidemic of drug resistant typhoid fever an R-factor associated enhancement of the virulence of *S. typhi* strains was postulated [23], but could consequently never be proven. The presence of R-factors seems to influence neither the biological characteristics [17] (probably with the exception of the phage type [62]) nor the pathogenicity of *S. typhi* as examined in virulence tests in the mouse model [10, 17].

Ampicillin, amoxicillin and co-trimoxazole are all effective in the treatment of chloramphenicol resistant typhoid fever [9, 31, 52, 61]. However, R-factor mediated resistance to ampicillin has been reported [4, 12, 13, 31, 46, 52], and there exists usually a cross-resistance between ampicillin and amoxicillin. Co-trimoxazole is even effective in the presence of sulfonamide resistance [9, 31]. The synergistic effect between sulfamethoxazole and trimethoprim could repeatedly be proven in strains of *S. typhi* with R-factor mediated sulfonamide resistance [9, 31].

Preliminary trials with newer antimicrobial agents

Newer antimicrobial agents, as e.g. fosfomycin [21], cyclacillin [27] and oxolonic acid [52] gave in small open trials only poor to moderate results, or the results were, due to the small number of patients involved, not conclusive, as e.g. with cefamandole [32] and cephradine [45]. Cefazoline was very effective in 9 patients in a carefully planned open trial [64].

Mecillinam and the corresponding orally active pivmecillinam, which are probably not cross-resistant to the other aminopenicillines [5], gave in several open trials [7, 15, 25, 40] and in two small comparative trials versus chloramphenicol and co-trimoxazole [36, 42] promising results. This could, however, not be confirmed in a recent investigation [41].

Trimethoprim, successfully used in other infectious diseases [18], deserves certainly evaluation in acute typhoid fever.

Drug costs

Chloramphenicol is cheap and readily obtainable throughout the world. Ampicillin and amoxicillin are in various parts of the world[1] both substantially more expensive (at least 5–10 times), whereas co-trimoxazole is even in the daily dose of 3×2 tablets equal in price or at most twice the price of chloramphenicol.

Conclusions

Chloramphenicol is still a very reliable drug in the treatment of acute typhoid fever. The imminent threat of the emergence of more widespread antibiotic resistance among *S. typhi* calls for a continuous search for alternative drugs. In the evaluation of new drugs "no patient should be considered a treatment failure with any drug unless the failure occurs in the presence of adequate and maintained serum antibacterial activity", as pointed out by Uwaydah [63].

Considering efficacy, possible resistance, expected side effects, available dosage forms, and expense, co-trimoxazole seems to be the best alternative to

[1] Based on data from Egypt, Indonesia, Mexico, Nigeria, Peru and Switzerland and from charitable bulk buying pharmaceutical supplies services as ECHO (England) and Action Medeor (Germany).

chloramphenicol as drug of choice in acute typhoid fever. On account of its low price and the fact that it is everywhere readily obtainable, chloramphenicol will probably remain the drug of choice in Third World Countries for the time being, despite its disadvantages with regard to possible resistance, relapse rate and convalescent and chronic excretion of *S. typhi.*

The list of references can be obtained from the author.