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Antibiotic Prophylaxis Following Urinary Tract Infection in Children: *A Systematic Review of Randomized Controlled Trials*

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RELEVANCE

As many as 2-3% boys and 8-11% girls are reported to have urinary tract infection(UTI) during childhood(1,2). Despite rapid diagnosis and treatment, there is a reported 5% risk of long term damage(3) owing to recurrence and consequent renal scarring with its (later) complications. Therefore, it is customary to prescribe long term antibiotic prophylaxis following UTI, irrespective of the presence or absence of 'risk factors'(4) such as anatomic malformations, vesico-ureteral reflux (VUR), female gender etc. Most guidelines recommend prophylaxis in the management of UTI(5,6). However, data supporting such recommendations is limited and based on outdated research; therefore it is relevant to examine current best evidence on the subject.

This systematic review addresses the question: "In children with urinary tract infection (*population*), does antibiotic prophylaxis (*intervention*), prevent recurrence, renal scarring, long-term complications, etc (*outcome*), as compared to no prophylaxis (*comparison*)?

CURRENT BEST EVIDENCE

Literature search was undertaken for systematic reviews and randomized controlled trials (RCT) comparing antibiotic prophylaxis versus no prophylaxis in children following episode(s) of UTI, irrespective of underlying renal condition(s). Trials comparing different antibiotics (against each other) were not considered. Outcomes of interest were recurrence of UTI, new or worse renal scarring, long term complications, cost, and antibiotic resistance.

Medline search (25 May 2010) using the Mesh terms for 'UTI' and 'antibiotic prophylaxis', with Limits "*Meta-Analysis, Randomized Controlled Trial, Review, All Child: 0-18 years*", yielded 66 citations. Simultaneous Cochrane Library search using "*urinary tract infection AND antibiotic"* in "*Record Title*", yielded 10 Cochrane reviews/ protocols, 4 other reviews, 46 clinical trials, 1 HTA and 4 economic evaluations. Two Cochrane reviews appeared relevant(7,8). One examined antibiotic prophylaxis(7), but does not include all currently available trials; it also combined older trials (with inappropriate UTI definitions) and recent trials. The other review(8) examined interventions for children with VUR only. Non-Cochrane reviews(9,10) were not up-to-date, necessitating a fresh systematic review.

Fifteen citations were shortlisted from the preliminary search and examination of References for additional trials. Among these, 10 were excluded for the following reasons: (*i*) not RCT (*n*=4)(11-14), (*ii*) definition of UTI not consistent with current definition (*n*=3)(15-17), (*iii*) cross-over study without randomization component(18), (*iv*) trial in children with VUR but not after UTI(19) and (*v*) description of ongoing RCT, but data not available(20). Thus, data from five RCTs (21-25) comprise current best evidence.

Table* I** summarizes the characteristics of included trials. All used co-trimoxazole in standard doses; three also included co-amoxyclav(23) or nitrofurantoin(24,25). Only one(21) was placebo-controlled. Two trials(22,25) included only children with VUR; one(24) enrolled participants after an episode of acute pyelonephritis. Two trials(21,25) included children up to 18 years of age. Various outcomes were examined including recurrence of UTI and scarring. One trial(24) examined renal scarring, but did not present results. Risk of bias (Table* II**) was low for three trials(21,23,24). The trials reported sample size calculations; one could not recruit the planned number(21) and another calculated sample-size for 70% power(23).

Meta-analysis showed that risk of UTI recurrence (***Fig.*1)** was reduced with antibiotic prophylaxis when all children (with VUR, without VUR and unknown status) were considered together (RR=0.73; CI=0.56-0.95; 3 trials; 1132 participants; I^2=0%). However, there was no benefit of prophylaxis when children with VUR (RR=0.82; CI=0.62-1.08; 5 trials; 809 participants; I^2=0%) and without VUR (RR=0.72; CI=0.43-1.20; 3 trials; 549 participants; I^2=0%) were examined separately. Antibiotic prophylaxis did not prevent new/worsening renal scarring in children with VUR (RR=2.64; CI=0.53-13.03; 1 trial; 113 participants), without VUR (RR=0.67; CI=0.13-3.48; 1 trial; 105 participants) and both groups combined (RR=1.00; CI=0.49-2.03; 3 trials; 667 participants; I^2=0%) (***Fig.*2**). The risk of adverse events/side effects increased significantly with antibiotics (RR=3.08; CI=0.02-549.95; 2 trials; 914 participants; I^2=92%). Likewise, children on prophylaxis appeared to have higher risk of UTI recurrence with a resistant organism (RR=8.60; CI=0.86-85.81; 3 trials; 190 participants; I^2=82%).

CRITICAL APPRAISAL

Recommendations for antibiotic prophylaxis following UTI were based on the expectation of increased risk of recurrence, and consequent long-term renal damage (through scarring) including hypertension etc. Supporting data was limited in quantity (4 RCT with 117 participants) and (methodological) quality. Additionally, the trial definitions of UTI are not currently accepted. Some recent trials with better (though not ideal) methodology have reported different results, necessitating better designed RCT and systematic review of evidence. Examination of current best evidence also raises the following issues:

The *definition of UTI* is a critical issue in RCT of antibiotic prophylaxis; all the older trials(15-18) defined UTI in a manner not accepted currently, including some participants without 'true' UTI. In contrast, all the recent trials(21-25) have used stringent definitions, reducing the risk of false-positives. Therefore, combining the older with the recent trials may be inappropriate.

Is concomitant fever a necessary component of UTI (to further reduce the risk of false-positives)? Although this will increase specificity, in real life, UTI is often treated even if fever is absent. It can also be argued that with modern practices of urine specimen collection and microbiologic criteria for UTI, fever strengthens the diagnosis, but may not be necessary. Therefore this review has not looked at symptomatic/febrile UTI separately.

Should children with and without VUR be considered separately? The argument in favour is that the risk of UTI recurrence is higher with VUR, hence these children should be viewed differently. The arguments against are that the risk does not appear to be very different with and without VUR, the relationship between VUR and renal scarring is not clear(24), diagnosis is often made after UTI, and VUR often resolves over time(26,27). In clinical practice, prophylaxis is often initiated empirically irrespective of presence/absence of VUR. Therefore this review has examined antibiotic prophylaxis separately among children with and without VUR, and also both groups combined.

Prolonged antibiotic therapy is not without risk; this includes individual as well as community risk in terms of adverse events/side effects and encouraging antimicrobial resistance(21,23,25). The latter risk has increased over the decades; therefore justification for antimicrobial prophylaxis today, should be stricter than three decades back (when the original trials were conducted). Based on this, the

TABLE I CHARACTERISTICS OF INCLUDED TRIALS

No	Setting	Study design	Participants	N (Px/ No Px)	Follow-up	Outcomes	Ref
1	Australia	MC, DB, PCT	*N*=576 < 18y with ≥1 episode symptomatic UTI*	288/288 CTX (10mg/kg/d) *vs* placebo	Every 3mo × 12 mo	Recurrence of symptomatic UTI, UTI with fever, hospitalization for UTI, hospitalization for other causes, antibiotic for concomitant illness, scarring, UTI with resistant bacteria, adverse events	21
2	France	MC, RCT	*N*=225 1mo-3y with VUR (I-III) diagnosed after UTI**with CTX sensitive organism	103/122 CTX (10mg/kg/d) *vs* nothing x 18 mo	Every 3 mo × 18 mo	Recurrence of UTI, symptoms, scarring, VUR status	22
3	Italy	MC, RCT	*N*=338 2mo-7y with 1st UTI# ± VUR (I-III)	211/127 CTX or CA (15mg/kg/d) *vs* nothing	Every 1-2 mo × 12 mo	Recurrence of UTI, new renal scarring, adverse events, recurrence with resistant organism.	23
4	Italy	MC, RCT	*N*=100<30 mo with VUR (II-IV) diagnosed after 1st episode of APN†	50/50 CTX (5-10mg/kg/d) or NF (2mg/kg) *vs* nothing x 2y	4 y	Recurrence of APN, new/worse scarring	24
5	USA, Canada, Spain, Peru	MC, RCT	*N*=236 3mo-18 y with APN‡ and VUR (I-III)	100/118 CTX (5-10mg/kg/d) or NF (1.5mg/kg/d) *vs* nothing	Every 3mo × 1 y	Recurrence of UTI, renal scarring	25

*APN=acute pyelonephritis, BS=bag specimen, CA=co-amoxyclav, CS=catheter specimen, CFU=colony forming units, CTX=cotrimoxazole equivalent, DB=double blinded, FU=follow-up, MC=multicentric, MSS=mid-stream sample, NF=nitrofurantoin, PCT=placebo controlled trial, Px=prophylaxis, SPT=supra-pubic tap, UTI=urinary tract infection, VUR=vesico-ureteral reflux; *Defined as symptoms consistent with UTI and positive culture (any growth of single pathogenic organism on SPT or ≥10^4CFU/ml from CS or ≥10^5CFU/ml from morning MSS); ** Defined as single organism ≥10^5CFU/ml from MSS or BS (if non toilet-trained); # Defined as fever >38 deg C + pyuria + single organism ≥10^5 CFU/ml (2 concordant consecutive results); †Defined as fever of unknown origin + bacteriuria and leucocytes in urine + ≥10^6 CFU/ml in two different samples collected by MSS or CS; ‡ Defined as fever, pyuria with ≥ 10WBC/hpf, ≥10^5 CFU/ml in CS or MSS + scan evidence of APN.*

TABLE II RISK OF BIAS AND OTHER DESIGN CHARACTERISTICS OF INCLUDED TRIALS (COCHRANE RISK OF BIAS TOOL)

Trial	Randomization	Allocation concealment	Blinding	ITT analysis	Risk of bias	Sample size	Ref
1	Adequate	Adequate	Adequate	Yes	Low	Yes	21
2	Unclear	Unclear	Inadequate	No	High	Yes	22
3	Adequate	Adequate	Inadequate	Yes	Low	Yes (power set at 70%)	23
4	Adequate	Adequate	Partial	Yes	Low	Yes	24
5	Unclear	Unclear	Inadequate	No	High	Yes	25

ITT = intention-to-treat.

balance of current evidence leans away from antibiotic prophylaxis.

Current evidence is unable to identify subgroup(s) of children who may benefit from antibiotic prophylaxis. This is an important issue because most trials exclude children with complex congenital malformations and/or higher grades of VUR (especially V). It is possible that the balance between benefit and harm of antimicrobial prophylaxis in children at greater risk of complications is different from those included in clinical trials, necessitating individualized decisions in the absence of evidence. Therefore, future research should focus on these specific high(er) risk groups rather than routine UTI (with or without lower grades of VUR).

Good evidence of the impact of compliance (or otherwise) to long term prophylaxis is not available. Lack of compliance could apparently reduce the beneficial effect of prophylaxis. Whereas, better compliance during clinical trials could suggest greater benefit than in real life (efficacy versus effectiveness).

EXTENDIBILITY

None of the trials comprising current best evidence were conducted in our country; however, there is no reason to suspect that Indian children behave differently in terms of UTI or risk of recurrence and/or complications. Hence, the evidence can be extended to our setting. On the other hand, the risk of inappropriate antibiotic usage and consequent antimicrobial resistance could be a bigger problem in our setting, necessitating greater caution.

Funding: None.

Competing interests: None stated.

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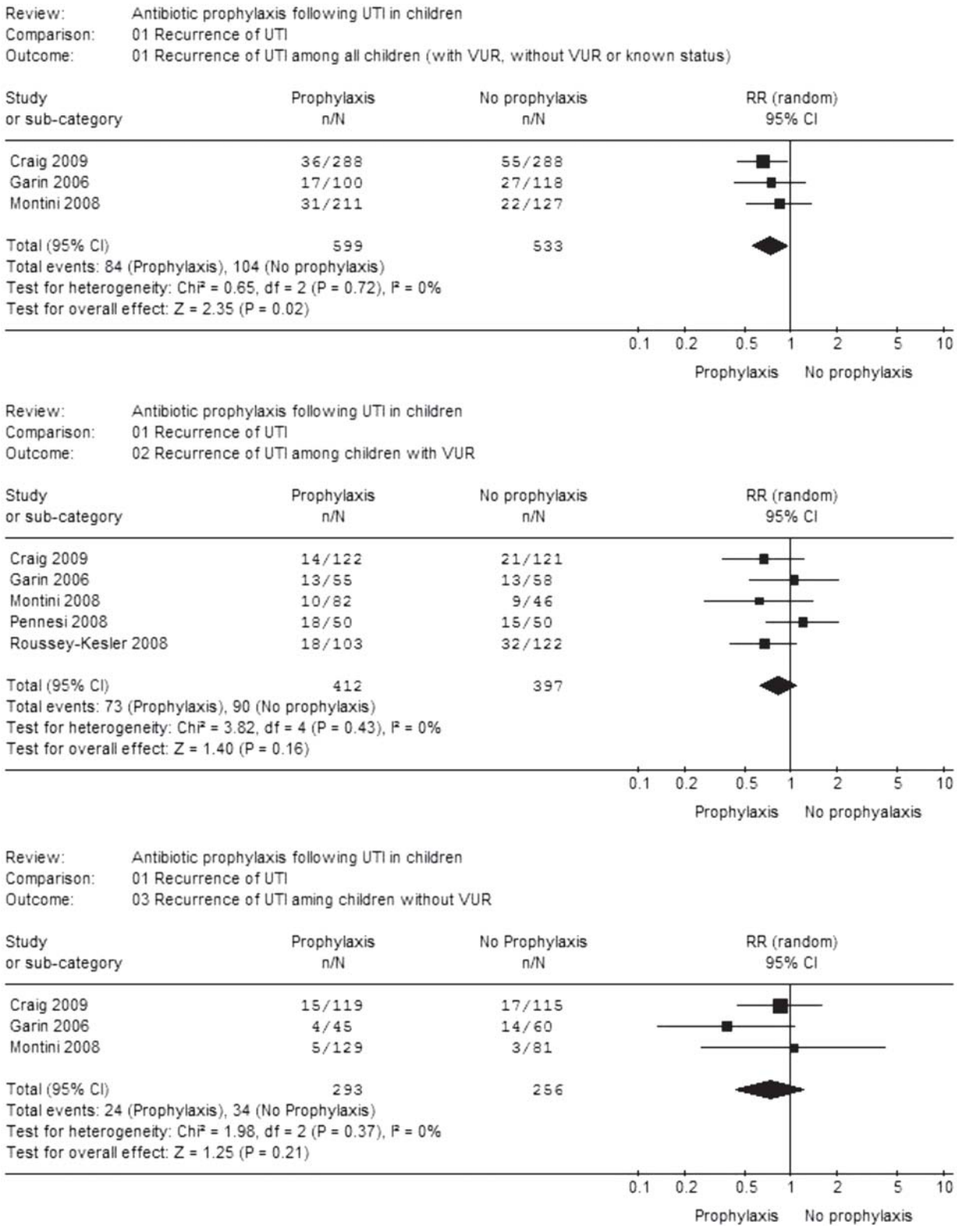

FIG.1 *Meta-analysis of data on recurrence of UTI*

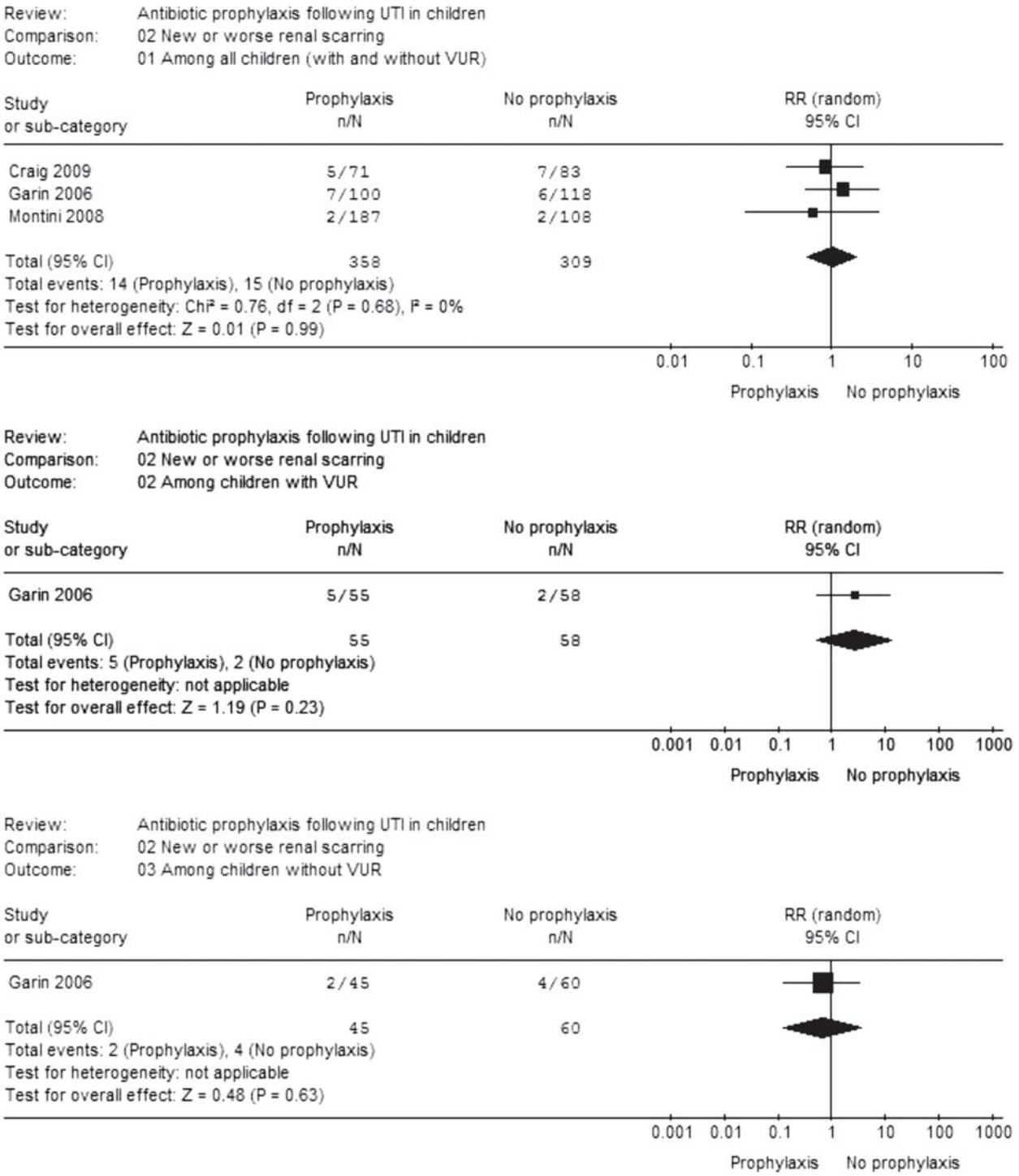

FIG.2 *Meta-analysis of data on new/worse renal scarring.*

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EURECA CONCLUSION IN THE INDIAN CONTEXT

- Antibiotic prophylaxis following UTI does not appear to prevent recurrence of infection and/or renal scarring in children with or without VUR, considered separately.
- Antibiotic prophylaxis could result in increased risk of recurrence with resistant organisms.

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