ISPN guideline 2022: UTI & VUR

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Overview

How new guidelines are different

- Methodology

- Diagnosis & therapy of UTI
- Imaging after UTI
- Recurrent UTI, bladder bowel dysfunction
- Vesicoureteric reflux, renal scarring
  - Surgery/endoscopic treatment
  - Antibiotics prophylaxis, duration
  - Non antimicrobial intervention
- VUR and ESKD

ISPN guideline on UTI & VUR

Revised Statement on Management of Urinary Tract Infections

INDIAN SOCIETY OF PEDIATRIC NEPHROLOGY Indian Pediatrics 2011

Excluded UTI in complex abnormalities (obstructive uropathy, neurogenic bladder)

PROCESS

Appoint Work Groups, Evidence Review Team (ERT)

– Discuss process, Refine topics/questions

Assign topics to systematic review or narrative review

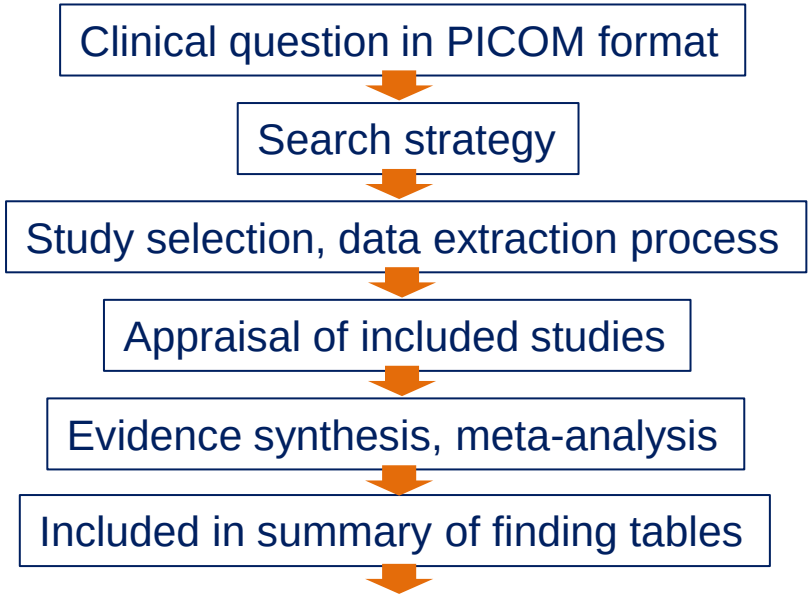
– Perform new or update existing

Create evidence profile

Rate **quality of evidence** for each outcome and overall

GRADE and formulate recommendation

Adapted IOM systematic review standards



Clinical practice points *vs.* recommendations

Clinical practice points

- No systematic review conducted
- Insufficient evidence
- Evidence inconclusive
- Guidance not actionable
- Guidance as table/figures/algorithm

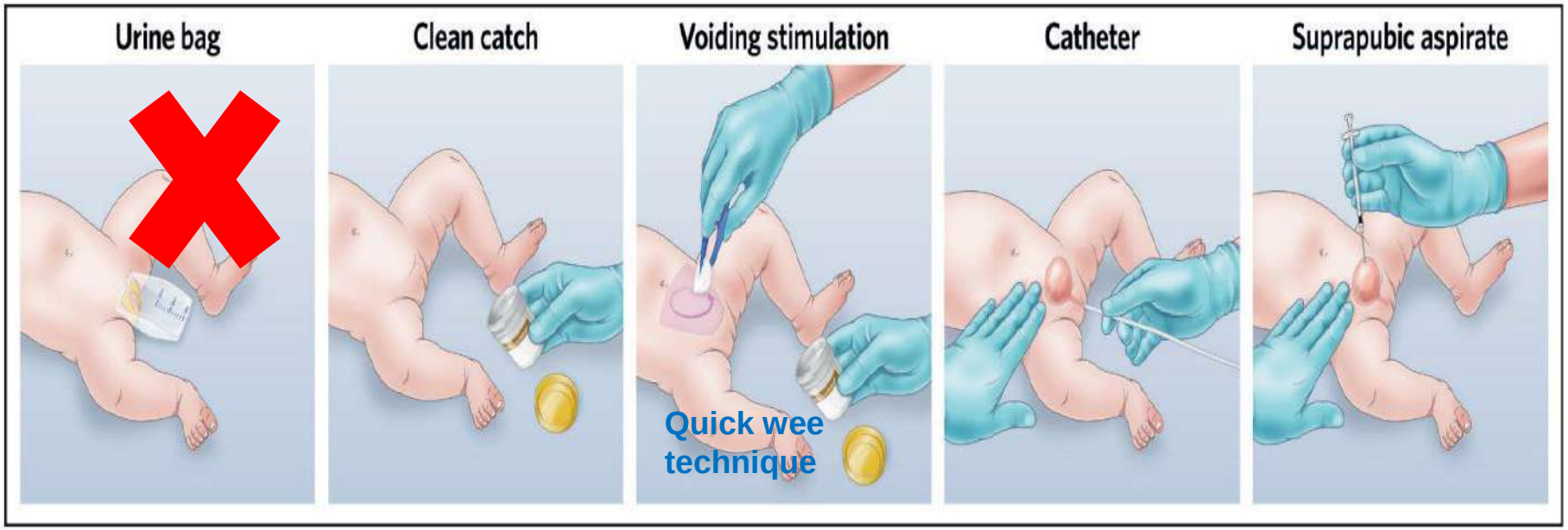
Recommendations

- Systematic review conducted
- Ample evidence available
- Evidence shows clear preference of one action over other
- Guidance is actionable
- Statements supported with
  - Quality of evidence
  - Balance of benefit and harm
  - Values & preferences
  - Feasibility, equity, acceptability
  - Resource

Adapted from KDIGO Guidelines on glomerular diseases 2020

Method of urine collection

PRECONTINENT CHILDREN :



Clinical practice point: suggest using clean-catch in toilet-trained

- Non-toiled trained stable children: clean-catch should be attempted initially, if unsuccessful catheterization or suprapubic aspiration (SPA) can be used
- Sick infants: catheterization or SPA preferred

Urine can be stored at 4°C for up to 24 h

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Screening test for UTI

TEST	SENSITIVITY %	SPECIFICITY %
Leukocyte esterase positive	83	78
Nitrite test positive	53	98
Leukocyte esterase/ Nitrite positive	**93**	72
Microscopy, WBC	73	81
Microscopy, Bacteria	81	83
LE, Nitrite, Microscopy positive	**99.8**	70

AAP Clinical Practice Guidelines, Pediatrics 2016

Microscopy for bacteria and Gram stain has excellent accuracy; microscopy for WBC can be replaced by leukocyte esterase; **Dipstick negative in 10%; cannot replace urine culture** *Williams, Lancet 2010*

Recommendation:

- Suggest using urine dipstick (leukocyte esterase + nitrite combination) as a screening test
- When feasible urine microscopy, (for bacteriuria and pyuria) in a freshly voided sample, can be used as an alternative for screening of UTI (2⊕⊕⊕◯)

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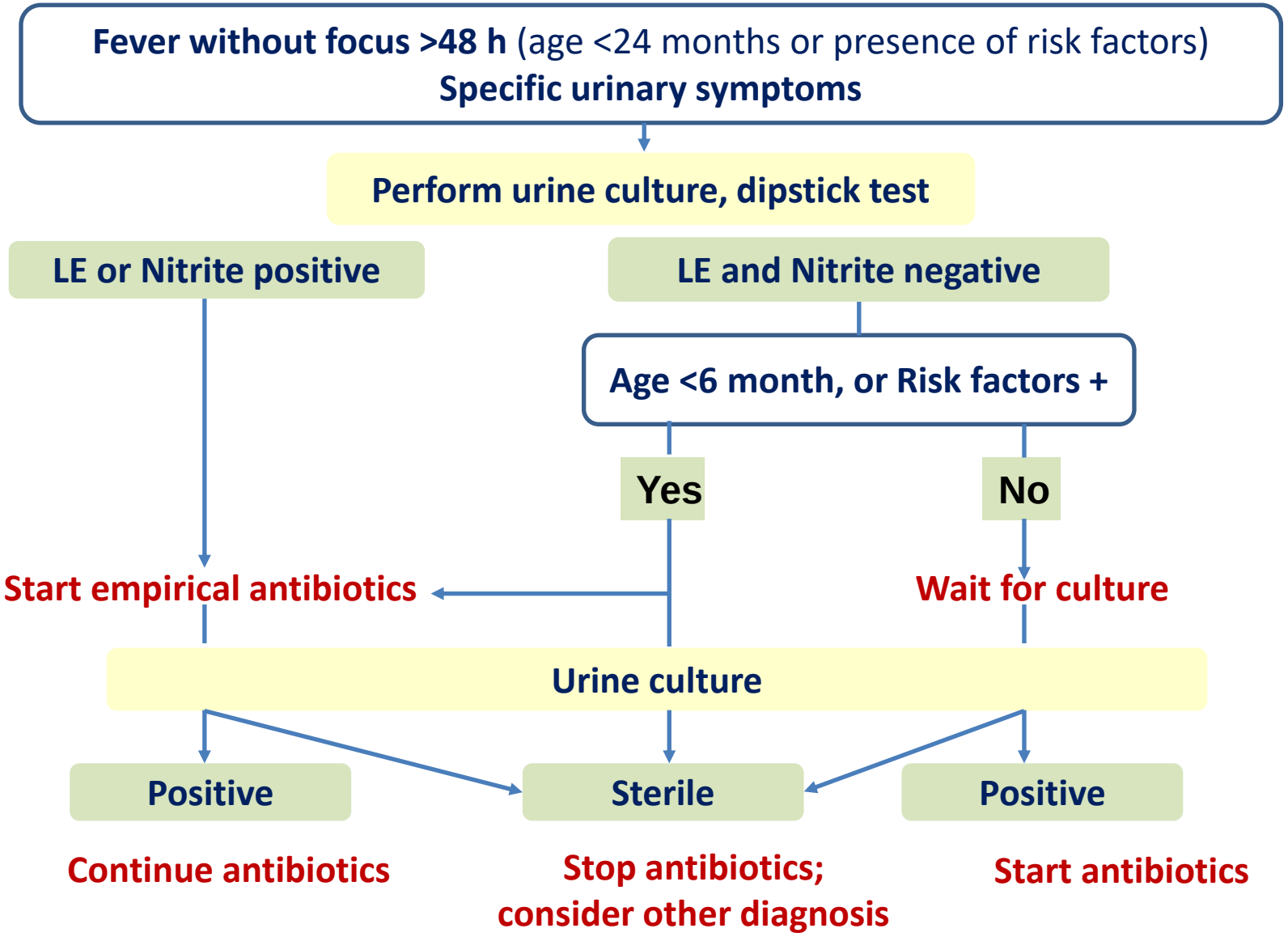
Fig.1 Approach to Diagnosis of UTI



Risk factors: Bladder-bowel dysfunction, primary vesicoureteric reflux, previous history of UTI

UTI: diagnosis

Clinical practice point:

- Suggest diagnosis of UTI be based on the significant growth of a single bacterial species in presence of symptoms
- Growth of single uropathogenic bacteria $\geq 10^3$, $\geq 10^4$, and $\geq 10^{4\text{-}5}$ (CFU/ml) by suprapubic aspiration, catheterization, and clean-catch, are highly suggestive of UTI

Asymptomatic bacteriuria

- ***Clinical practice point:*** Suggest **NOT** to perform routine culture or repeat urine culture after treatment if there is clinical response
- Not to treat asymptomatic bacteriuria

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UTI: treatment guidelines

- **Recommendation:** Use oral antibiotics for acute pyelonephritis except

  i) infants aged <1 month ii) children with bacteremia/sepsis iii) children unable to ingest (1⊕⊕⊕◯)

  Suggest IV for initial 3-4 days or till defervescence, followed by oral

- ***Clinical practice point:*** Suggest initial intravenous antibiotic to treat acute pyelonephritis in children aged 1-3 month

- **Recommendation:** suggest using 3rd generation cephalosporins or amoxicillin-clavulanic acid as empirical antibiotic in febrile UTI (2⊕◯◯◯)

- **Recommendation:** short course (3-5 days) of oral antibiotic for lower UTI (1⊕⊕⊕◯)

- ***Clinical practice point:*** 7-10 days of antibiotic treatment for acute pyelonephritis in children aged >6 month

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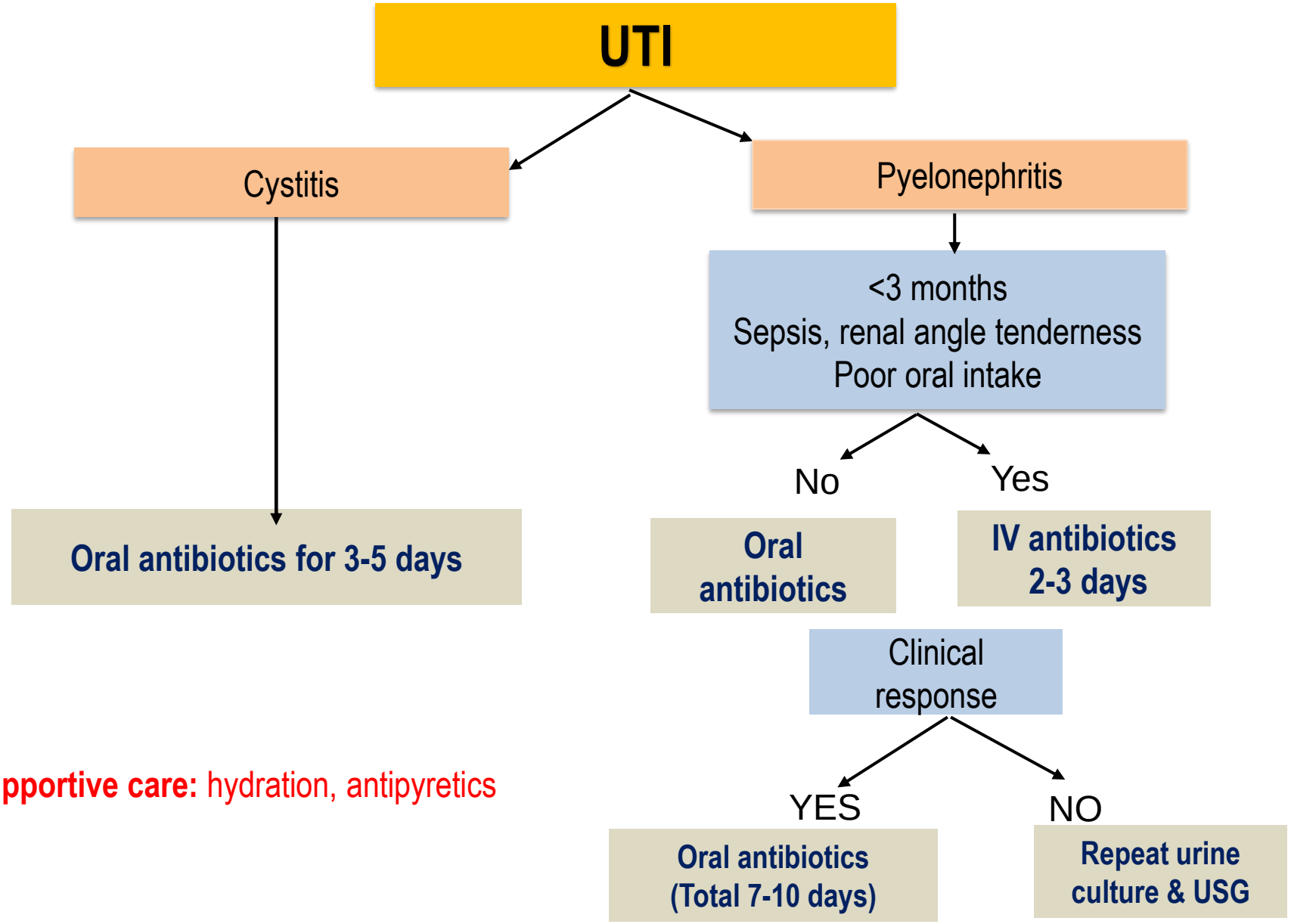
Fig.2 Treatment of Urinary Tract Infection



Supportive care: hydration, antipyretics

BBD & Recurrent UTI

Bladder bowel dysfunction (BBD): combined bladder and bowel dysfunction in the absence of neurological abnormality *(ICCS, 2017)*

Independent predictor of UTI; delays resolution of VUR; therapy results in downgrading of VUR

Bladder	Bowel
• Urgency Wetting of pants Holding maneuvers • Hesitancy • Frequency	Constipation – <3 stools/wk – Hard stools blocking toilet – Painful defecation

Clinical practice point

Suggest all children with UTI should be evaluated for BBD

Prophylaxis should be given in recurrent febrile UTI and BBD irrespective of presence or absence of VUR

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Imaging after UTI

Imaging in selected children after first UTI

Findings suggestive of VUR

- Renal hypoplasia (B/L or U/L)
- Abnormal echogenicity
- Hydronephrosis
- Ureteric dilatation
- Uroepithelial thickening
- Bladder abnormality

Perform after 4-6 weeks; during UTI if

- urosepsis, non response, renal dysfunction

Clinical practice point

Ultrasound scan of the urinary tract should be performed after an episode of UTI in children

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Dimercaptosuccinic acid (DMSA) scan

Early DMSA (within 2 wk)

Recommendation:
Do not perform acute-phase DMSA scan in children with febrile UTI (2⊕◯◯◯)

Late DMSA (4-6 mo after acute infection)

Clinical practice point

suggest performing a late-phase DMSA scan to assess kidney scarring in children with recurrent UTI or high-grade VUR

More relevant, since it detects damage!

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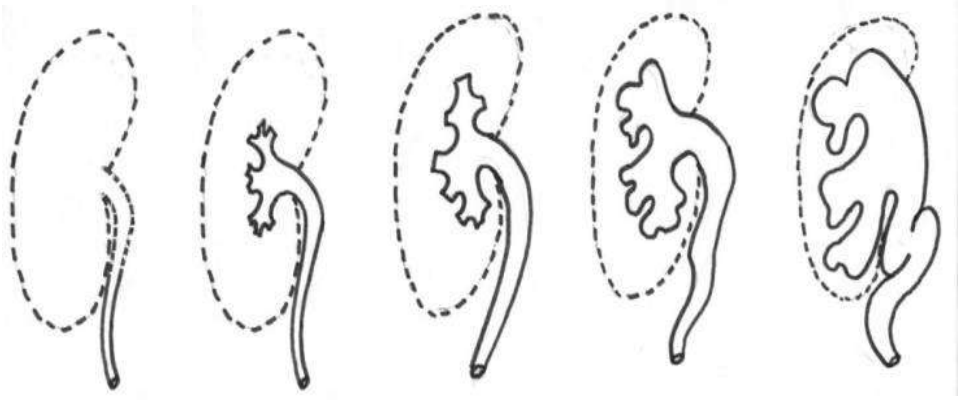
Micturating cystourethrography

- Gold standard for VUR; provides anatomy of urinary tract
- Invasive & radiation



Grade I Grade II Grade III Grade IV Grade V

Clinical practice point

Suggest performing MCU in children with one of the following: (a) children <2 yr with non-*E.coli UTI* (b) abnormal ultrasound scan (c) recurrent UTI

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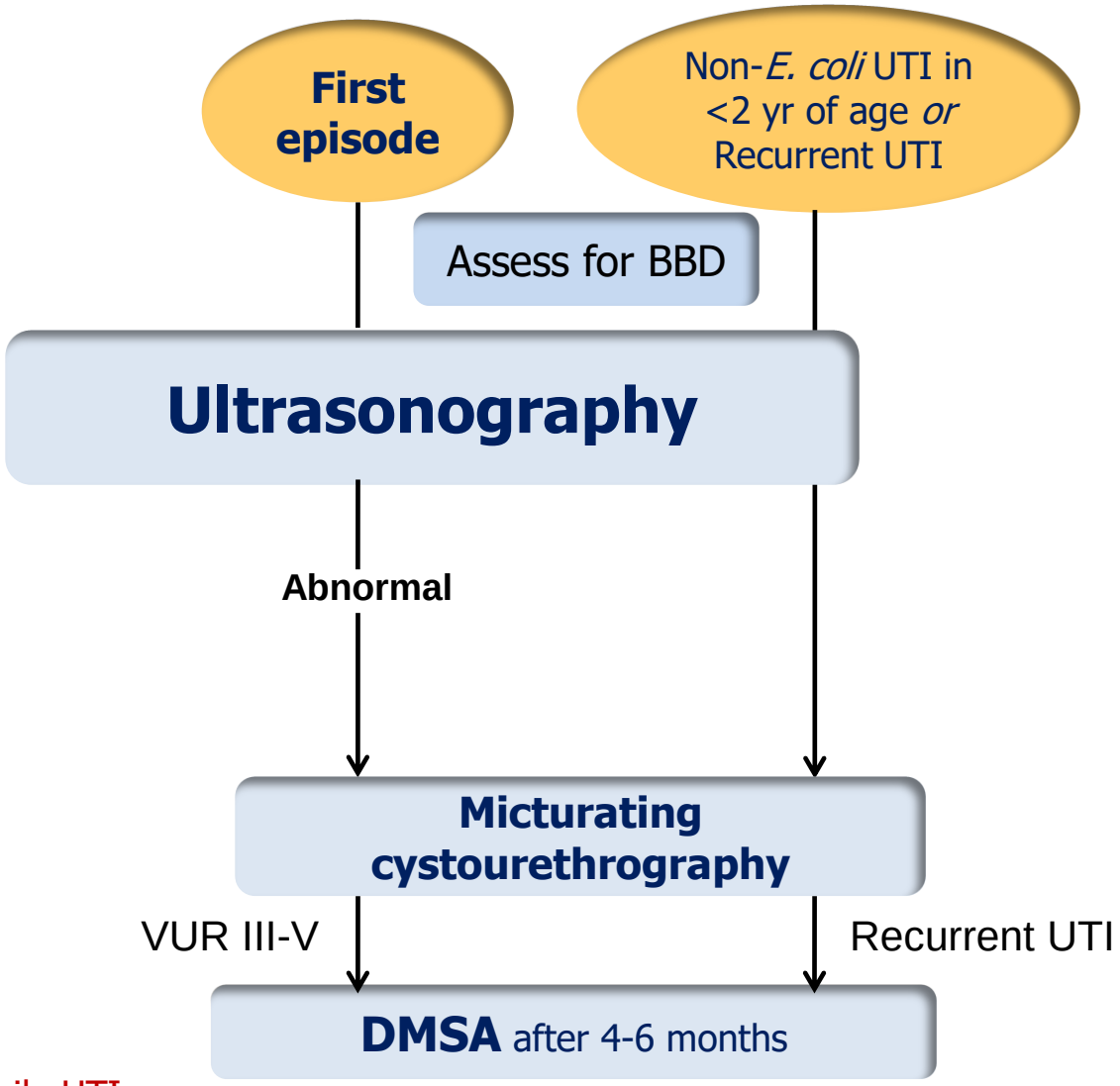
Fig.3 Approach to imaging after UTI



Recurrent UTI: 2 episodes of febrile UTI

BBD; bladder bowel dysfunction, DMSA; Dimercaptosuccinic acid VUR; vesicoureteric reflux

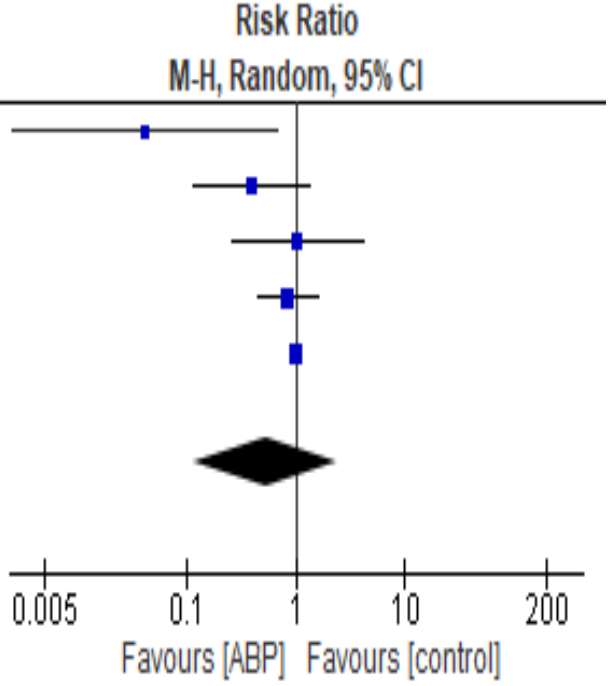
Is prophylaxis useful in normal urinary tracts?

Recurrence of UTI

	ABP		placebo/ no therapy			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Smellie 1978	0	25	10	22	13.2%	0.04 [0.00, 0.68]	1978
Garin 2006	3	45	10	60	20.5%	0.40 [0.12, 1.37]	2006
Montini 2008	5	129	3	81	19.7%	1.05 [0.26, 4.26]	2008
Craig (PRIVENT) 2009	15	119	17	115	22.8%	0.85 [0.45, 1.63]	2009
Liern 2011	26	26	24	24	23.8%	1.00 [0.93, 1.08]	2011
Total (95% CI)		344		302	100.0%	0.53 [0.12, 2.40]	
Total events	49		64				

Heterogeneity: $Tau^2 = 2.49$; $Chi^2 = 73.73$, $df = 4$ ($P < 0.00001$); $I^2 = 95\%$

Test for overall effect: $Z = 0.82$ ($P = 0.41$)



Recommend against using prophylaxis for prevention of UTI in children with normal urinary tract (1⊕⊕⊕◯)

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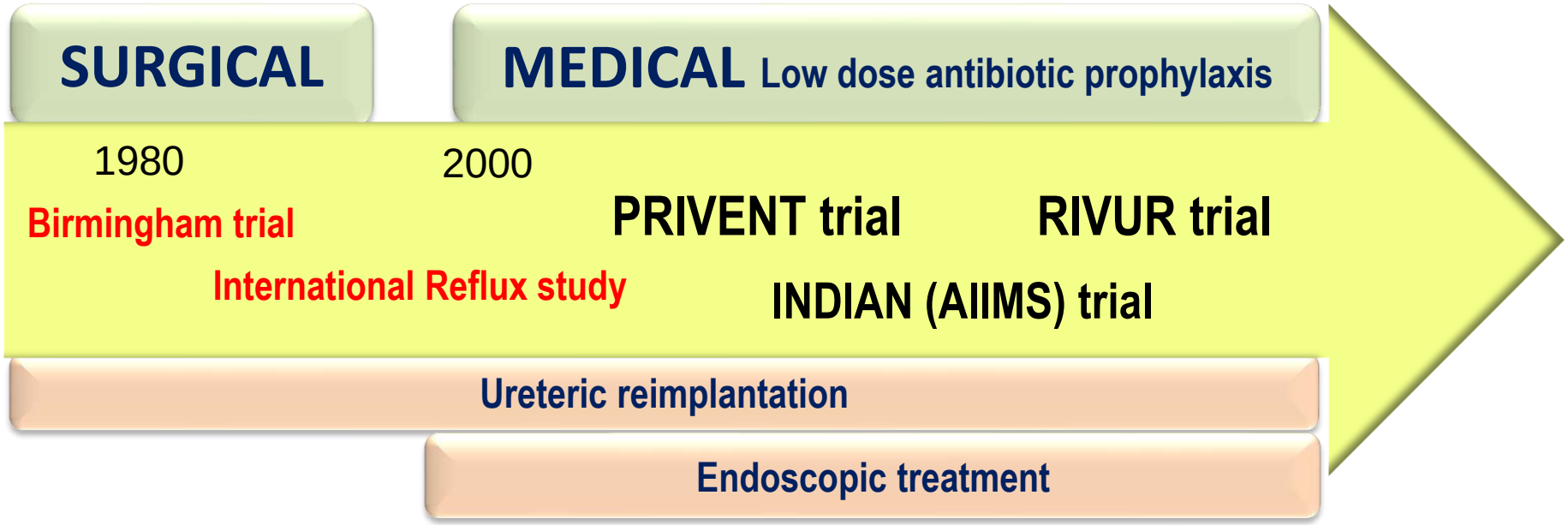
Primary VUR: how therapy changed



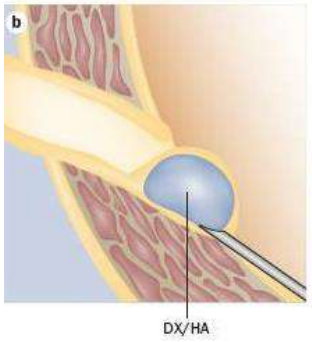
Antibiotic versus surgery/endoscopic injection

Meta-analysis: recurrence of symptomatic UTI similar after surgery & antibiotic prophylaxis; less febrile UTI

No difference in renal scarring at 5, 10 years

Surgery does not prevent progression to ESRD

% change of GFR similar at 5 and 10 yr; majority of reflux improve



Endoscopic treatment

- Success 60-95%; improves with second injection, depends on grade of reflux, expertise
- Recurrence 11-26% over 3-12 mo, ureteral obstruction 0.6%
- NO benefit over prophylaxis

Cochrane database of systematic reviews, 2019

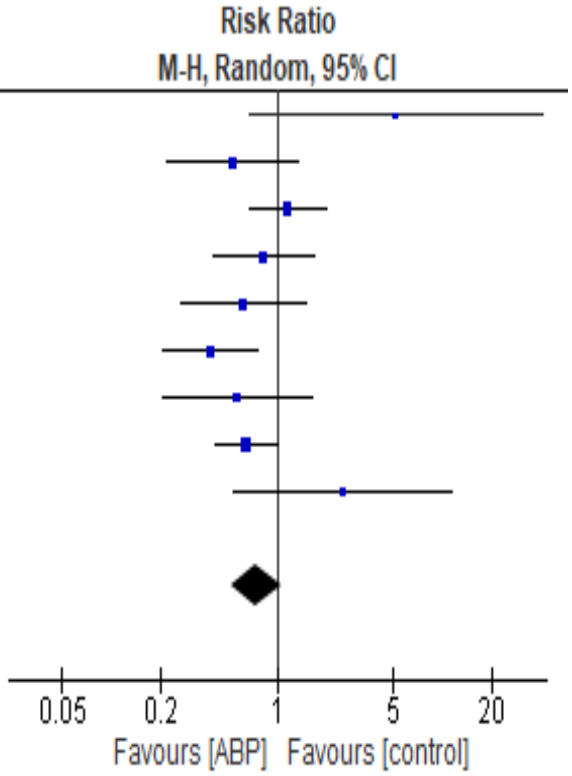
Prophylaxis in high grade VUR is marginally beneficial

Prophylaxis for high grade (III-IV) VUR

Study or Subgroup	ABP Events	ABP Total	placebo/ no therapy Events	placebo/ no therapy Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Garin 2006	5	18	1	19	2.6%	5.28 [0.68, 40.91]	2006
Montini 2008	6	26	6	14	9.5%	0.54 [0.21, 1.36]	2008
Pennesi 2008	17	39	15	40	17.4%	1.16 [0.68, 1.99]	2008
Roussey-Kesler 2008	8	24	12	30	13.1%	0.83 [0.41, 1.70]	2008
Craig (PRIVENT) 2009	7	65	11	64	10.2%	0.63 [0.26, 1.51]	2009
Brandström 2009	10	69	25	68	14.5%	0.39 [0.21, 0.76]	2009
Espino 2012	3	9	7	12	8.1%	0.57 [0.20, 1.62]	2012
Hoberman (RIVUR) 2014	26	143	38	137	20.2%	0.66 [0.42, 1.02]	2014
Hari 2015	6	37	2	31	4.4%	2.51 [0.55, 11.58]	2015
Total (95% CI)		**430**		**415**	**100.0%**	**0.75 [0.53, 1.06]**	
Total events	88		117				

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 13.52$, df = 8 (P = 0.10); $I^2 = 41\%$

Test for overall effect: Z = 1.62 (P = 0.10)



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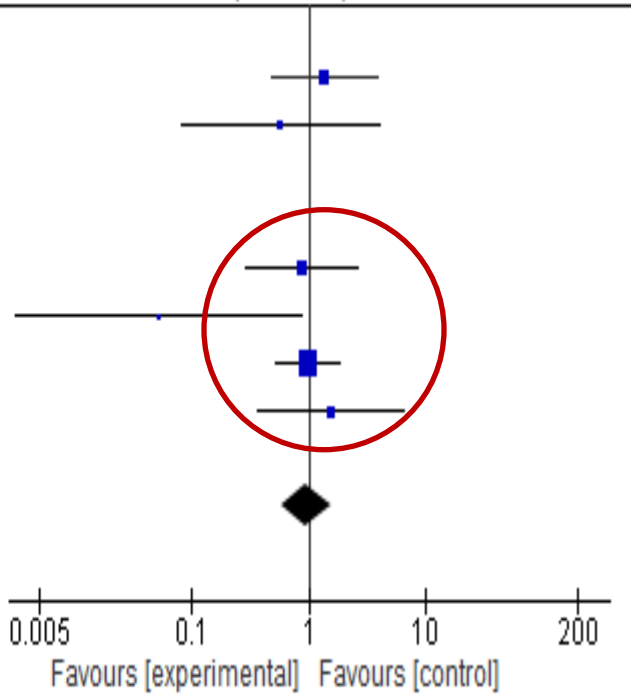
Renal scarring not prevented by prophylaxis in VUR

Study or Subgroup	ABP Events	ABP Total	placebo/ no therapy Events	placebo/ no therapy Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Smellie 1978	0	0	0	0		Not estimable	1978
Garin 2006	7	100	6	118	18.9%	1.38 [0.48, 3.96]	2006
Montini 2008	2	187	2	108	6.2%	0.58 [0.08, 4.04]	2008
Roussey-Kesler 2008	0	0	0	0		Not estimable	2008
Pennesi 2008	0	50	0	50		Not estimable	2008
Craig (PRIVENT) 2009	5	68	7	83	17.6%	0.87 [0.29, 2.62]	2009
Brandström 2009	0	68	9	68	3.0%	0.05 [0.00, 0.89]	2009
Hoberman (RIVUR) 2014	18	220	19	227	43.2%	0.98 [0.53, 1.81]	2014
Hari 2015	4	37	3	43	11.1%	1.55 [0.37, 6.48]	2015
Total (95% CI)		**730**		**697**	**100.0%**	**0.95 [0.58, 1.57]**	
Total events	36		46				

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 5.68$, $df = 5$ ($P = 0.34$); $I^2 = 12\%$

Test for overall effect: $Z = 0.19$ ($P = 0.85$)



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Why has renal scarring remain unchanged ?

Should host's inflammatory response be diminished

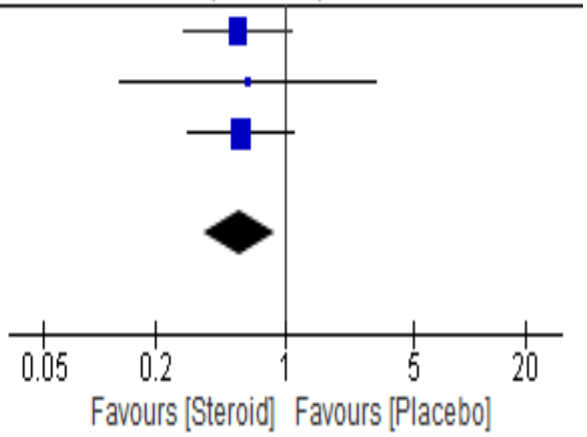
Corticosteroids

Meta-analysis: Renal scarring rate on late DMSA in steroid versus placebo

Study or Subgroup	Steroid plus antibiotic Events	Total	Placebo plus antibiotic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Huang 2011	6	18	39	65	44.4%	0.56 [0.28, 1.10]	2011
Ghaffari 2019	2	23	4	29	8.0%	0.63 [0.13, 3.14]	2019
Shaikh 2020	12	123	22	131	47.6%	0.58 [0.30, 1.12]	2020
Total (95% CI)		**164**		**225**	**100.0%**	**0.57 [0.36, 0.90]**	
Total events	20		65				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 2 (P = 0.99); $I^2 = 0\%$

Test for overall effect: Z = 2.40 (P = 0.02)



Insufficient evidence to recommend its use

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Prophylaxis & antimicrobial resistance

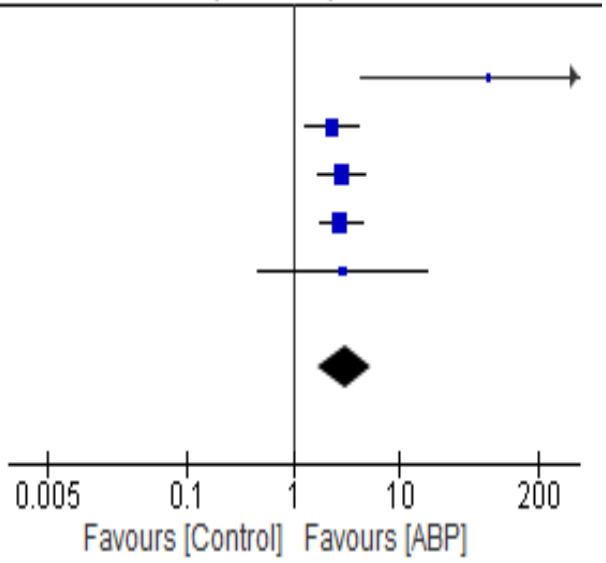
Odds of multidrug resistance 6.4 times more on prophylaxis;
1 MDR infection in every 21 VUR treated

Pediatrics 2018

	ABP		placebo/ no therapy			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Roussey-Kesler 2008	0	0	0	0		Not estimable	2008
Pennesi 2008	41	43	0	35	4.1%	67.91 [4.33, 1065.94]	2008
Brandström 2009	7	8	9	24	27.8%	2.33 [1.31, 4.16]	2009
Craig (PRIVENT) 2009	24	36	13	55	29.1%	2.82 [1.66, 4.78]	2009
Hoberman (RIVUR) 2014	26	38	17	69	30.7%	2.78 [1.74, 4.42]	2014
Hari 2015	7	12	1	5	8.3%	2.92 [0.47, 17.95]	2015
Total (95% CI)		**137**		**188**	**100.0%**	**3.04 [1.68, 5.51]**	
Total events	105		40				

Heterogeneity: Tau² = 0.24; Chi² = 11.33, df = 4 (P = 0.02); I² = 65%

Test for overall effect: Z = 3.68 (P = 0.0002)



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Prophylaxis in high grade VUR

Recommendations

Suggest prophylaxis for prevention of febrile UTI only in children with high-grade primary VUR. (2⊕⊕◯◯)

We suggest using co-trimoxazole or nitrofurantoin as the first-line antibiotic for prophylaxis in children older than 6 months. (2⊕⊕◯◯)

Clinical practice point

- Consider using prophylaxis in low-grade VUR in infants with febrile UTI
- Suggest discontinuation of prophylaxis in older than 2 years if: i) toilet trained, ii) absence of BBD, iii) no febrile UTI in last 1 yr

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Cranberry for prevention of UTI

Large polymeric compound (pro-anthocyanidin) inhibits bacterial adherence

Children with recurrent UTI (4 studies) (RR 0.39, 95% CI 0.25 to 0.61), one study in VUR

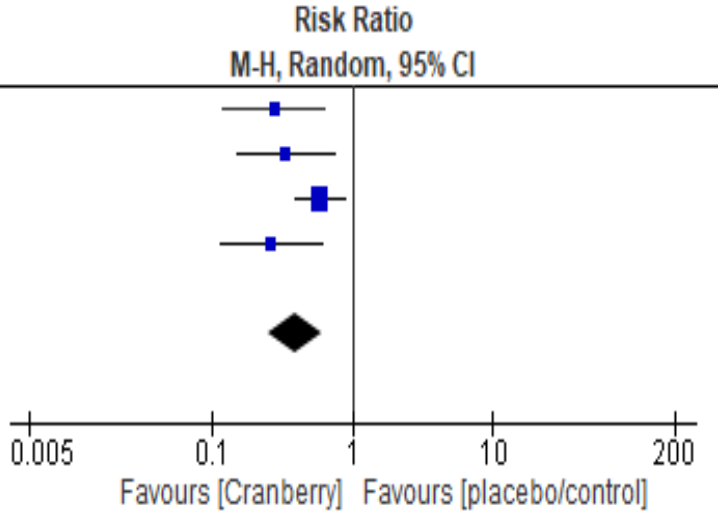
Not better than antibiotic prophylaxis

Quantity of active ingredient (36-72 mg/d), Availability

Study or Subgroup	Cranberry Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Ferrara 2009 (1)	5	27	18	27	19.4%	0.28 [0.12, 0.64]	2009
Afshar 2012	5	20	15	20	20.5%	0.33 [0.15, 0.74]	2012
Salo 2012	27	126	47	129	40.8%	0.59 [0.39, 0.88]	2012
Dotis 2018	5	30	22	35	19.2%	0.27 [0.11, 0.61]	2018
Total (95% CI)		**203**		**211**	**100.0%**	**0.39 [0.25, 0.61]**	
Total events	42		102				

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 5.02$, df = 3 (P = 0.17); $I^2 = 40\%$

Test for overall effect: Z = 4.18 (P < 0.0001)



Recommendation

Suggest using cranberry products for the prevention of UTI in children with recurrent UTI and normal urinary tract. (2⊕⊕◯◯)

ISPN guidelines, 2021

Circumcision and recurrent UTI

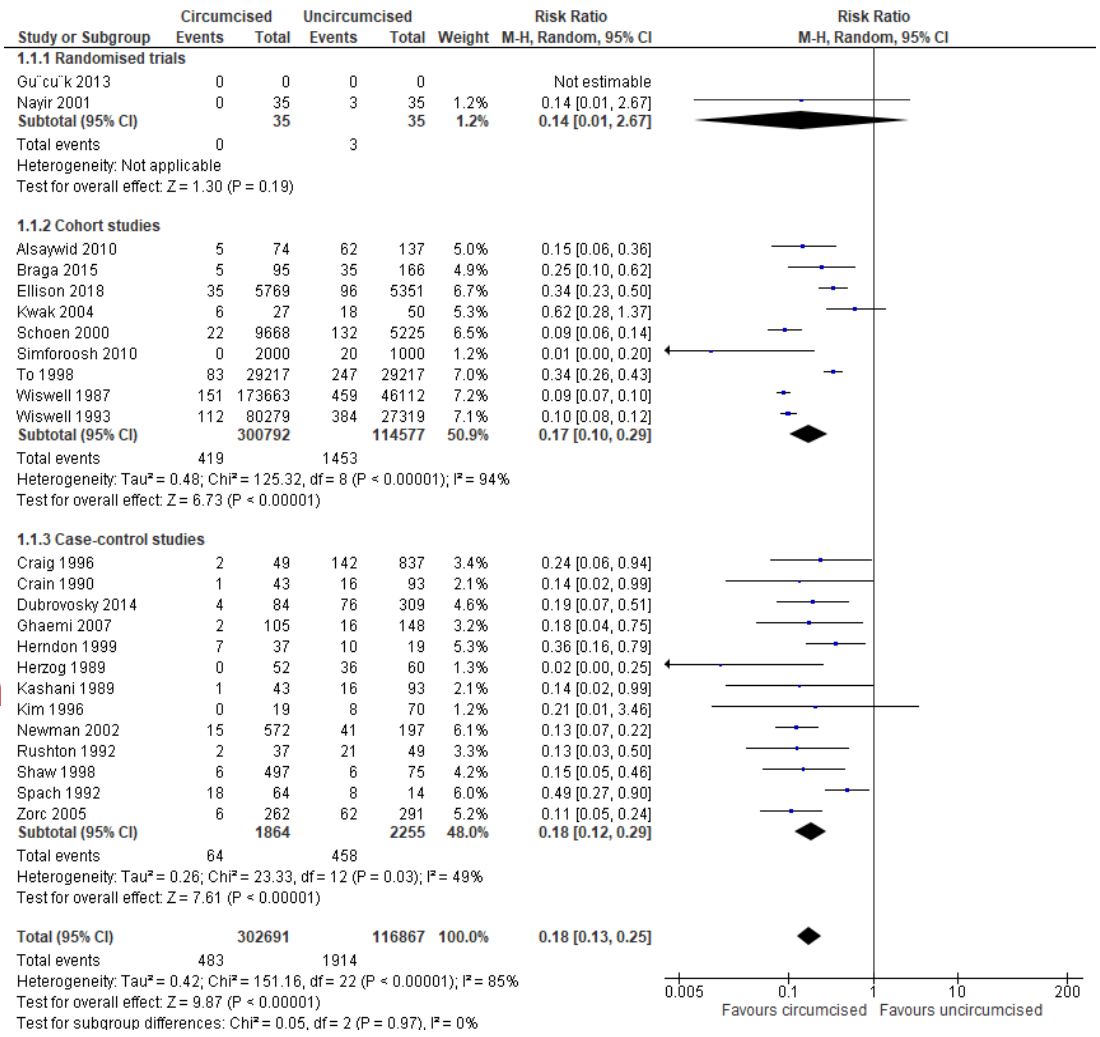
No. needed to treat to prevent 1 UTI

Normal: 111

High grade VUR: 4

Recommendation

Suggest circumcision should be offered for prevention of UTI only in children at risk of recurrence (2⊕⊕⊕◯)



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VUR: treatment guidelines

Recommendation

- Suggest prophylaxis should be the first line of management in high grade VUR (2⊕⊕⊕◯)
- Suggest surgical reimplantation be considered in high grade VUR with recurrent breakthrough febrile UTI on prophylaxis (2⊕⊕⊕◯)

Clinical practice point:

- Suggest open reimplantation be preferred over endoscopic treatment
- In high-grade VUR, surgical intervention may be an alternative for parenteral hesitancy to use antibiotics
- No consensus on the type of surgical (open/robotic/laproscopic)

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Follow up of VUR

Clinical Practice Points

VUR need periodic follow up till considered clinically insignificant; reflux nephropathy need long term follow-up

Suggest

- Screening siblings (aged less than 3 years) of the children with primary VUR with an ultrasound scan
- Renal USG to monitor renal growth in high-grade reflux & those with scarred kidney
- DMSA be repeated during follow up, only in recurrent febrile UTI
- In high-grade reflux, repeat MCU be performed only if surgical intervention is planned
- DRCG may be done for documenting for resolution of reflux at 4-8 yr of age, in high-grade reflux

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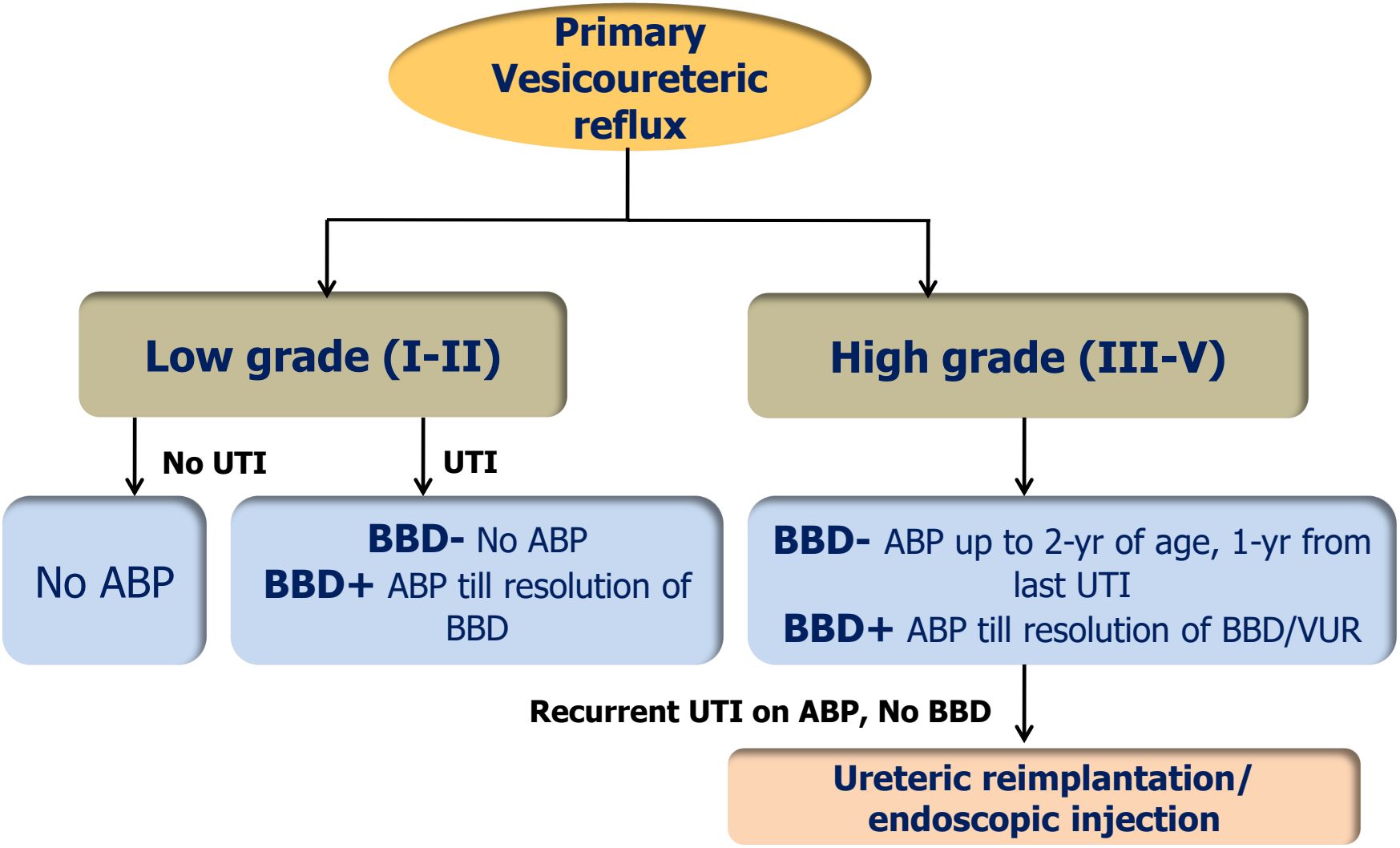
Fig.4 Treatment of primary VUR



Recurrent UTI:2 episodes of febrile UTI

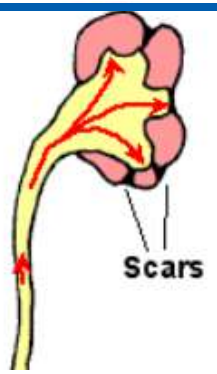
ABP; antibiotic prophylaxis, BBD; bladder-bowel dysfunction

VUR: risk of ESKD

Reflux nephropathy

- About 5% ESKD

Annual Report NAPRTCS 2014



Retrospective study of 735 children with VUR (1970 -2004)

- Mean follow-up 76 mo
- 3% developed hypertension
- Probability of CKD & ESRD at 10 yr was 15% & 5%
- **No CKD if normal DMSA at diagnosis**

Silva et al Ped Nephrol 2006

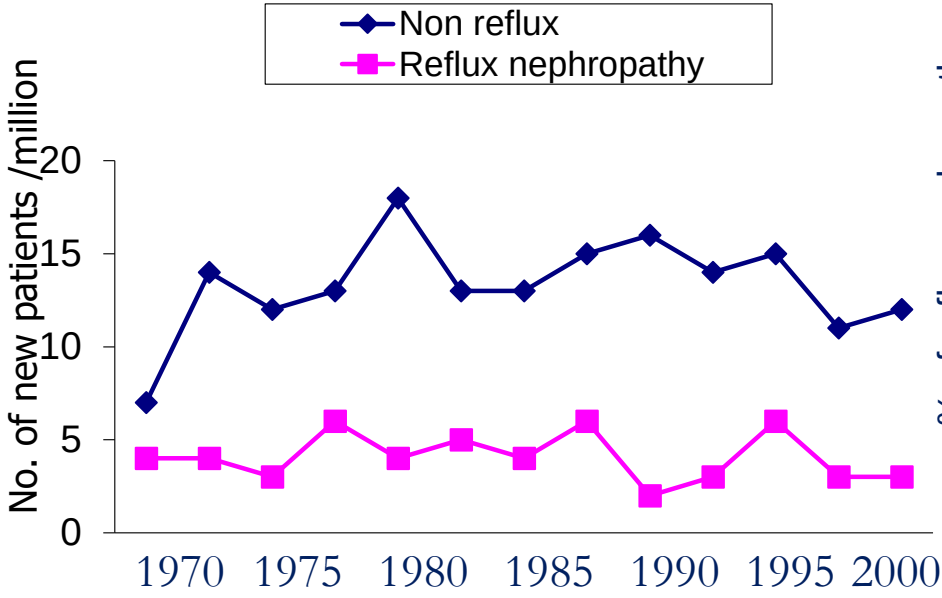
Prevalence of VUR: 1 to 17% or 100000 per million

Reflux ESRD: 0.7 per million population

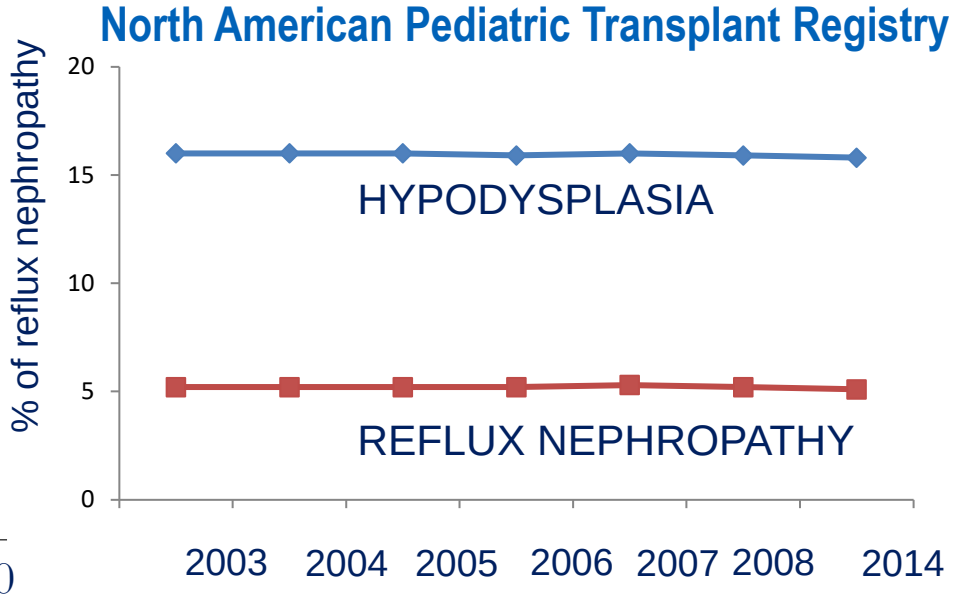
USRDS 2007

Renal scarring in VUR and ESKD

- ANZ dialysis transplant registry from 1971-1998
- age specific incidence of ESRD attributable to reflux



ANZ DATA Craig JC Pediatrics 2000



Annual Reports NAPRTCS

Treatment of VUR has not reduced in incidence of ESRD attributable to reflux

Key Points

New guidelines have followed rigorous methodology

- Post UTI imaging is selective, less aggressive
- Emphasis on BBD; associated with recurrence
- **Surgery as good as prophylaxis** for VUR; indications limited
- Prophylaxis
  - **Recurrent UTI, BBD, high grades of VUR;** risk of antimicrobial resistance

Non-antibiotic interventions should be explored

Acknowledgements

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Thank you!