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Gruppo Italiano per la Medicina Basata sulle Evidenze

Evidence-Based Medicine Italian Group

Workshop

L'EBM nell'ambulatorio del pediatra di base

Sesto S. Giovanni (MI), 24 settembre 2005

arseducandi
Società Scientifica per l'Educazione Continua

Workshop Clinici Interattivi (2)

INFEZIONI DELLE VIE URINARIE

Dalle evidenze scientifiche all'appropriatezza degli interventi sanitari

Nino Cartabellotta
Maria Laura Chiozza
Milena Lo Giudice

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Sandell A

Management of urinary tract infections in children: no evidence exists

BMJ 2003;327:1346

GIMBE® © 1996-2005

clinical evidence

Urinary tract infection in children

Search date January 2004

James Larcombe

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Linee guida IVU

- Prodigy. April 2002
- European Association of Urology, 2001
- American Academy of Pediatrics, April 1999

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Scenario Clinico (1)

- Cristina è una bambina di 11 mesi, terzogenita nata alla 37 settimana da parto eutocico con peso di Kg 2,550.

- Nulla di rilevante nella storia familare.

- La bambina, allattata esclusivamente al seno per 4 mesi, è stata progressivamente svezzata a partire dal 5° mese di vita.

- L'accrescimento staturo-ponderale è regolare (peso Kg 8,200, 10° centile), ma lo scarso interesse per l'alimentazione ha motivato, all'età di sei mesi, la richiesta di un esame di urine che ha avuto esito negativo.

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Scenario Clinico (2)

- Nel mese di agosto, mentre sono in partenza per le vacanze, la mamma di Cristina mi contatta telefonicamente per la comparsa febbre (sino a 39,5°C), senza altri sintomi/segni di rilevo, fatta eccezione per l'usuale scarso appetito.

- Prescrivo paracetamolo al bisogno e richiedo un esame microscopico delle urine: rassicuro la mamma, invitandola a contattarmi se dovessero insorgere altri problemi.

- Purtroppo, come spesso accade, i genitori hanno difficoltà a raccogliere le urine e Cristina non esegue l'esame prescritto.

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CLINICAL QUESTIONS

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A. In una piccola paziente con sospetta IVU, quale metodo consigli ai genitori per la raccolta delle urine?

1. Contenitore sterile
2. Sacchetto adesivo
3. Catererismo uretrale
4. Aspirazione sovrapubica delle urine in vescica

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Diagnosing urinary tract infection in the under fives

Centre for Reviews and Dissemination, 2004

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URINE SAMPLING

- All the different methods for collection of a urine sample are susceptible to contamination, which is associated with false-positive results
- Suprapubic aspiration (SPA) is the reference standard, but it is invasive and ultrasound guidance may be needed.
- Five studies assessed the diagnostic accuracy of a clean voided urine (CVU) sample, using an SPA urine sample as the reference standard.
- When both samples were cultured the agreement between the two sampling methods was good, suggesting that CVU may be an appropriate routine method of urine collection.

CRD, 2004

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URINE SAMPLING

- CVU samples are difficult to collect in young children who are not potty trained.
- A number of alternative collection methods have been developed
- The limited data available suggests that bag may be acceptable substitute for SPA.
- Further research is needed to confirm this.

CRD, 2004

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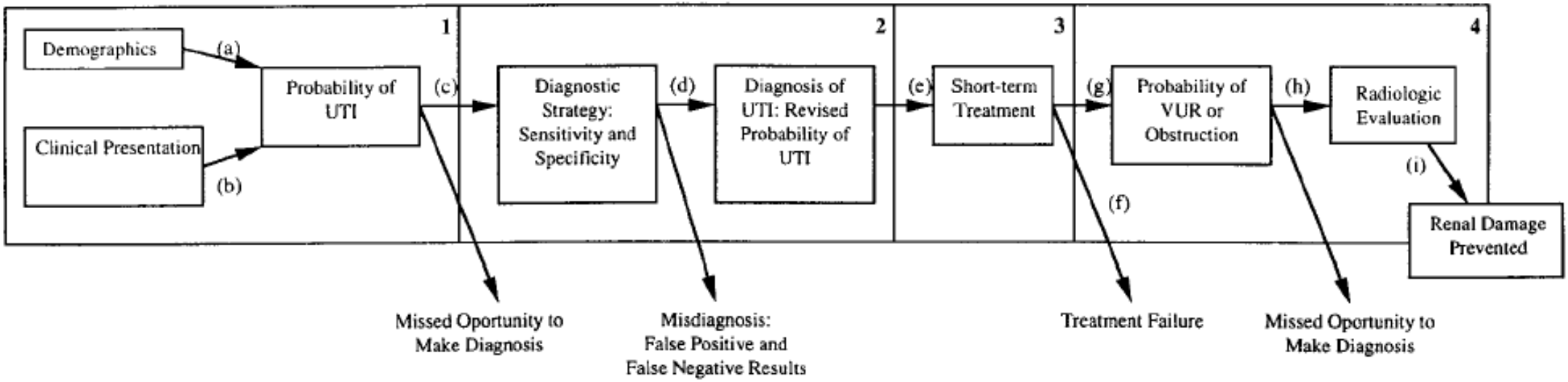

AAP, 1999

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Scenario Clinico (3)

- Il giorno dopo, visito la bambina che non presenta nulla di patologico: mi limito solo a sollecitare l'esame delle urine.

- In terza giornata dall'esordio dei sintomi persiste febbre elevata (>39 °C) parzialmente sensibile al paracetamolo: la temperatura, infatti, si riduce modestamente per poi risalire subito con brividi scuotenti.

- La mattina del quarto giorno dopo avere rilevato 40°C ascellari, i genitori in preda al panico - non trovandomi al cellulare - decidono di ricoverare la piccola Cristina.

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CLINICAL QUESTIONS

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B. Considerato il quadro clinico ed il ritardo nell'esecuzione dell'esame delle urine, ritieni che un dipstick urinario avrebbe modificato la decisione clinica?

1. No
2. Sì

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Diagnosing urinary tract infection in the under fives

Centre for Reviews and Dissemination, 2004

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DIPSTICK TESTS

- Dipsticks have the advantage of providing an immediate result, and of being cheap and easy to perform and interpret.
- A total of 39 studies reporting 107 data sets evaluated dipstick tests for the diagnosis of UTI.
- These studies assessed the usefulness of dipstick tests for nitrite, leukocyte esterase (LE), protein, glucose and blood, alone and in combination.
- Considerable heterogeneity exist between the studies (in terms of methods, samples, populations, analysis, etc), so the results should be interpreted with caution.

CRD, 2004

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DIPSTICK TESTS

- A strategy that combines the results of LE and nitrite testing appears to offer the best performance for ruling disease both in and out.
  - Likelihood Ratio + = 28.2
  - Likelihood Ratio - = 0.20

- There was insufficient information to make any judgement regarding the overall diagnostic accuracy of dipstick tests for protein, blood, or for combinations of three different tests.

CRD, 2004

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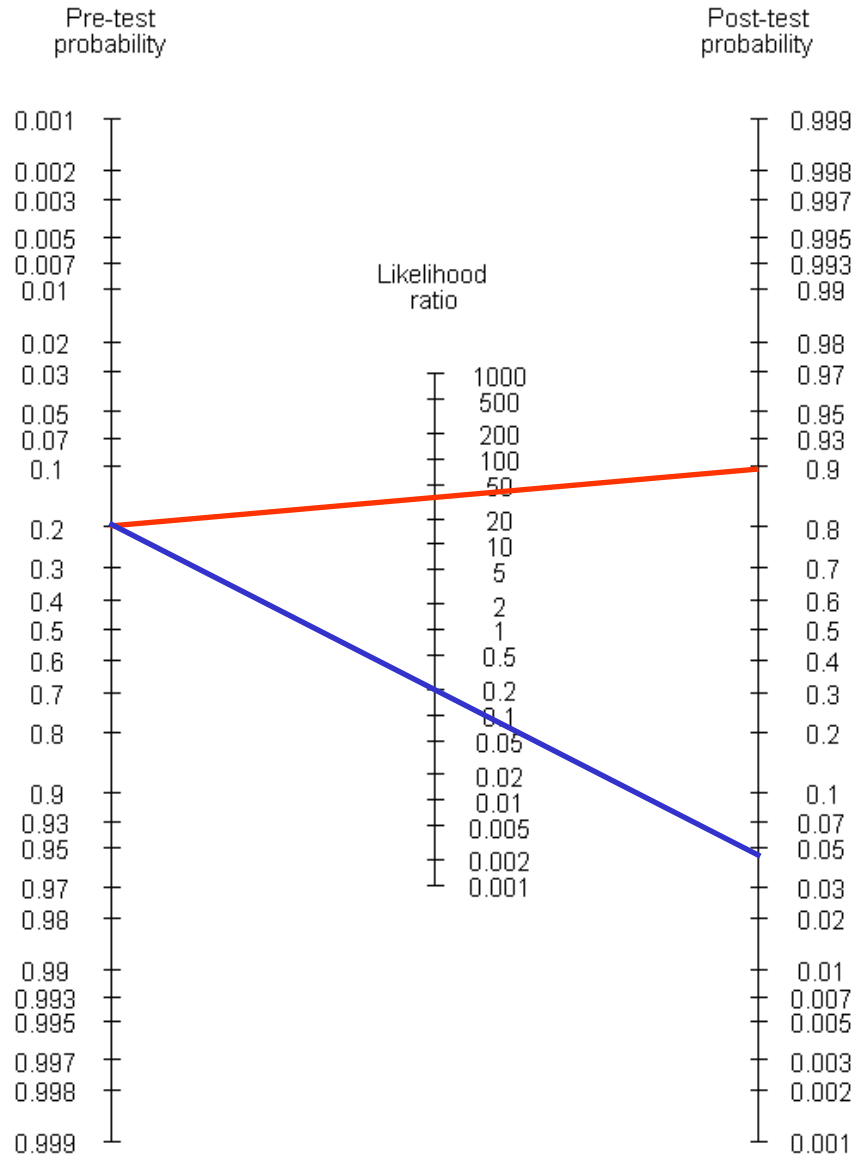
Probabilità pre-test 20%

- **Se LE e nitriti + (LR+ 28.2) probabilità post-test 90%**
- **Se LE e nitriti - (LR- 0.20), probabilità post-test 5%**



Nomogramma di Fagan

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Dipstick urinalysis for screening of childhood urinary tract infection

Centre for Clinical Effectiveness, 2003

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- There is good evidence that in children aged 2-10 years old, dipstick urinalysis combing leukocyte and nitrite testing is an effective and appropriate screening method for UTI

- There is less homogeneity in the literature regarding the use of dipstick urinalysis as a screening method for UTI in children under 2 years old.

CCE, 2003

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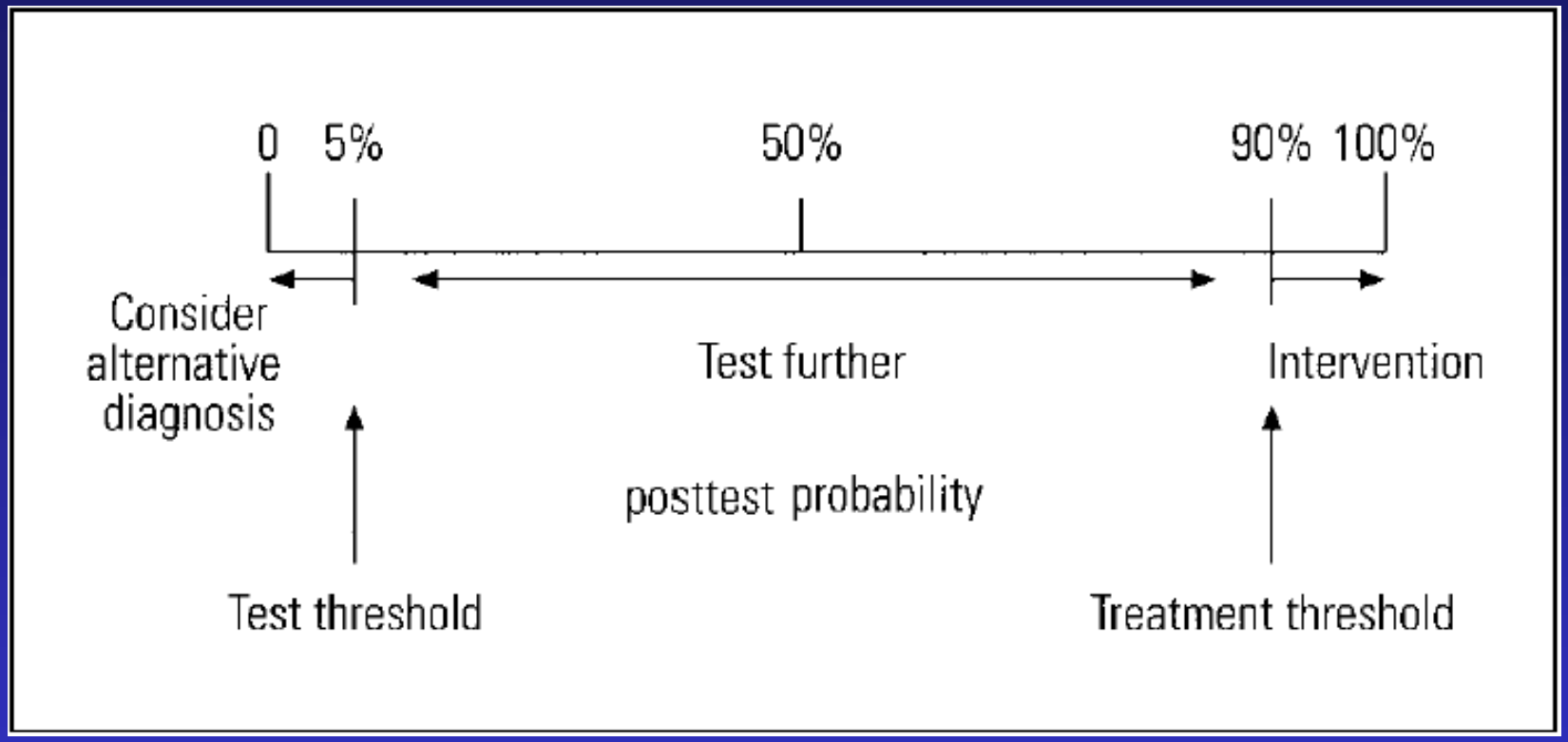
The threshold approach to medical decision making



- The choice of a therapeutic option requires a sufficient level of diagnostic probability.
- The appropriate probability threshold to treat is higher if the treatment is invasive, risky or expensive, and lower if a delayed intervention can result in a serious damage to the patient, and/or the treatment is safe

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Urinary tract infection in children

clinical evidence

Search date January 2004

James Larcombe

- **Prolonged delay in treatment (> 4 days)** We found no RCTs. Five retrospective studies found that medium to long term delays (4 days to 7 years) in treatment may be associated with an increased risk of renal scarring.

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Scenario Clinico (4)

• Cristina viene ricoverata nella divisione di pediatria dove vengono subito eseguite alcune indagini:

- VES 110 mm alla prima ora
- PCR 12,23 (val.norm.<0,9)
- Leucociti 12.400 mmc (61,4% di neutrofili)
- Sedimento urinario: 500 leucociti/ul, 82 emazie/ul, nitriti assenti, pH 6,5

• Nella verosimile ipotesi di infezione delle vie urinarie, viene subito iniziata terapia con ceftriaxone i.m. 400 mg x 2.

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CLINICAL QUESTIONS

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C. Ritieni che, in una bambina con IVU, la terapia mirata sia più efficace del trattamento antibiotico empirico?

1. Sì
2. No
3. Nessuna differenza

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Urinary tract infection in children

clinical evidence

Search date January 2004

James Larcombe

OPTION IMMEDIATE EMPIRICAL VERSUS DELAYED ANTIBIOTIC TREATMENT

We found no RCTs comparing early empirical treatment with delayed treatment based on the results of microscopy or culture in acute urinary tract infection in children. Retrospective analysis of one RCT found no significant difference in risk of renal scarring between cephalosporin treatment within 24 hours compared with 24 hours after the onset of fever in children under 2 years of age with urinary tract infections. Five retrospective studies found that medium to long term delays (4 days to 7 years) in treatment may be associated with an increased risk of renal scarring.

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UTI in children

Immediate empirical versus delayed antibiotic treatment

1. Utile
2. Probabilmente utile
3. Da valutare caso per caso
4. **Di utilità non determinata**
5. Di utilità discutibile
6. Inutile o dannoso

Clinical Evidence. June 2005

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Scenario Clinico (5)

- Dopo 24 ore, per la persistenza della febbre il ceftriaxone viene sostituito con ampicillina-sulbactam (400 mg x 2) e gentamicina (25 mg x 2) per otto giorni.

- Intanto, parto per le vacanze, ma continuo a tenermi in contatto telefonico sia con i genitori di Cristina, sia con l'Ospedale

- In quinta giornata giunge l'esame colturale ematico ed urinario: viene isolato un E. Coli:
  - sensibile alle cefalosporine di seconda e terza generazione, agli aminoglicosidi ed al cotrimoxazolo
  - resistente all'amoxicillina.

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Scenario Clinico (6)

- Sulla base di tali risultati, l'ampicillina-sulbactam viene sostituita con ceftriaxone i.m (400 mg x 2): dopo 48 ore Cristina sfebbra

- Le sue condizioni, comunque, si sono mantenute discrete durante la degenza: non ha mai vomitato, né ha perso peso.

- Viene eseguita anche una ecografia renale, che risulta negativa

- In decima giornata, Cristina viene dimessa con diagnosi di "pielonefrite e sepsi".

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CLINICAL QUESTIONS

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D. In una piccola paziente con verosimile pielonefrite, è sempre appropriato eseguire una ecografia renale?

1. Sì
2. No

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Diagnosing urinary tract infection in the under fives

Centre for Reviews and Dissemination, 2004

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Summary of tests used for the different clinical applications

Aim	Main tests used or evaluated	Current reference standard
Localisation of UTI	Clinical features Laboratory-based ● Ultrasound (US) Dimercaptosuccinic acid scintigraphy (DMSA)	Acute DMSA
Detection of reflux	● Ultrasound Cystosonography Radionuclide cystography Micturating cystourethrography (MCUG)	MCUG
Prediction of scarring	Clinical features ● Ultrasound MCUG Acute DMSA	Follow-up DMSA
Detection of scarring	● Ultrasound Intravenous Urography (IVU) MAG3 renogram DMSA	Follow-up DMSA

CRD, 2004

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1. Localisation of UTI

- Acute Tc-99m-DMSA is the reference standard test for the localisation of UTI.
- A total of 31 studies investigated the diagnostic accuracy of one or more tests to localise infection.
- Ultrasound was evaluated in 20 studies
- Performance was poor both in terms of ruling in and ruling out renal involvement.

CRD, 2004

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2. Detection of reflux

• The idea that detection of reflux, thought to lead to an increased risk of scarring, is an important part of further investigation, is currently the subject of debate. Moreover, a recent systematic review found that renal damage was frequently present in the absence of reflux.

• MCUG (currently the reference standard test for reflux) is invasive and costly, involving considerable exposure to ionising radiation.

• All the alternative tests for reflux (included standard ultrasound) were all found to be relatively poor.

CRD, 2004

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3. Prediction of renal scarring

• Four studies investigated the ability of a variety of tests to predict renal scarring.

• The diagnostic accuracies reported in these studies were poor and none of the tests (US, IVU, and presence of fever and elevated CRP levels) showed good accuracy.

• A recent systematic review also found that reflux is a weak predictor for renal damage in children hospitalised with UTI.

CRD, 2004

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4. Presence of renal scarring

- Renal scintigraphy, using Tc-99m-DMSA, is the accepted reference standard.
- Seven studies evaluating ultrasound found it to be reasonable for ruling in scarring but poor for ruling out scarring (low sensitivity).
- Colour and doppler ultrasound, proved no better than routine ultrasound in the detection of renal scars.
- It may be that ultrasound only detects more severe scarring

CRD, 2004

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CONCLUSIONS

- Routine imaging for children aged 2–10 years with an initial UTI is not recommended. For children under two there is no firm evidence base.
- All children aged 2–5 with an initial UTI should be monitored and investigated further if they experience a second UTI.
- Further research is required regarding the accuracy of ultrasound in diagnosing underlying abnormalities, and its impact on patient outcome.
- There is insufficient evidence to recommend any routine further investigation.

CRD, 2004

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Scenario Clinico (7)

- Alla dimissione:

  - Viene prescritta terapia domiciliare con:
    - Ceftriaxone 400 mg/die per altri 4 giorni
    - Cefaclor 40mg/kg/die per os per 1 mese

  - Viene consigliato di ripetere l'esame di urine ogni 15 giorni per tre mesi

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CLINICAL QUESTIONS

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E. Ritieni che nella piccola Cristina, 14 giorni (complessivi) di terapia antibiotica parenterale siano:

1. Appropriati
2. Inappropriati in eccesso
3. Inappropriati in difetto

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Urinary tract infection in children

clinical evidence

Search date January 2004

James Larcombe

OPTION LONGER VERSUS SHORT COURSES OF INITIAL INTRAVENOUS ANTIBIOTICS IN CHILDREN WITH PYELONEPHRITIS

One systematic review found no significant difference between long (7–14 days) and short (3–4 days) courses of initial intravenous antibiotics in persistence of bacteriuria after treatment, recurrent urinary tract infection at 6–12 months, or renal scarring at 3–6 months in children with acute pyelonephritis.

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Bloomfield P, Hodson EM, Craig JC

Antibiotics for acute pyelonephritis in children

The Cochrane Database of Systematic Reviews 2005

GIMBE® © 1996-2005

RESULTS

- Eighteen trials (2612 children) were eligible for inclusion.
- No significant differences were found in persistent renal damage at six months or in duration of fever between oral cefixime (14 days) and IV therapy (three days) followed by oral therapy (10 days).
- Similarly no significant differences in persistent renal damage (three trials, 315 children) were found between IV therapy (3-4 days) followed by oral therapy and IV therapy for 7-14 days.
- No significant differences in efficacy were found between daily and thrice daily administration of aminoglycosides

Williams GJ, et al. Cochrane Library 2005

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CONCLUSIONS

- These results suggest that children with acute pyelonephritis can be treated effectively with oral cefixime or with short courses (2-4 days) of IV therapy followed by oral therapy.

- If IV therapy is chosen, single daily dosing with aminoglycosides is safe and effective.

- Trials are required to determine the optimal total duration of therapy and if other oral antibiotics can be used in the initial treatment of acute pyelonephritis

Williams GJ, et al. Cochrane Library 2005

GIMBE® © 1996-2005

UTI in children

Longer versus short courses of initial intravenous antibiotics in children with pyelonephritis

1. Utile
2. Probabilmente utile
3. Da valutare caso per caso
4. Di utilità non determinata
5. **Di utilità discutibile**
6. Inutile o dannoso

Clinical Evidence. September 2005

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CLINICAL QUESTIONS

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F. Ritieni appropriata, in una bambina al primo episodio di IVU, una profilassi antibiotica per 30 giorni?

1. Sì
2. No

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Urinary tract infection in children

clinical evidence

Search date January 2004

James Larcombe

OPTION PROPHYLACTIC ANTIBIOTICS

One systematic review found limited evidence that prophylactic antibiotics (co-trimoxazole, nitrofurantoin, given for 10 weeks to 12 months) reduced urinary tract infection recurrence in children compared with placebo or no treatment. One RCT found that nitrofurantoin reduced recurrence of urinary tract infection over 6 months compared with trimethoprim. However, more children discontinued treatment with nitrofurantoin because of adverse effects. We found no RCTs evaluating the optimum duration of prophylactic antibiotics.

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UTI in children
Prophylactic antibiotics

1. Utile
2. **Probabilmente utile**
3. Da valutare caso per caso
4. Di utilità non determinata
5. Di utilità discutibile
6. Inutile o dannoso

Clinical Evidence. June 2005

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Williams GJ, Lee A, Craig JC

Long-term antibiotics for preventing recurrent urinary tract infection in children

The Cochrane Database of Systematic Reviews 2005

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RESULTS

- Three trials (151 patients) comparing antibiotics with placebo/no treatment.
- The duration of antibiotic prophylaxis varied among the studies (10 weeks to 12 months).
- The method of allocation concealment in the three trials was inadequate, unclear and adequate.
- The overall rate of recurrent UTI in the placebo/no treatment group was 63% (48/76).
- Compared to placebo/no treatment, antibiotics reduced the risk of recurrent UTI (RR 0.36).

Williams GJ, et al. Cochrane Library 2005

GIMBE® © 1996-2005

CONCLUSIONS

- Most published studies to date have been poorly designed with biases known to overestimate the true treatment effect.

- Large, properly randomised, double blinded trials are needed to determine the efficacy of long-term antibiotics for the prevention of UTI in susceptible children.

Williams GJ, et al. Cochrane Library 2005

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Le Saux N, Pham B, Moher D

Evaluating the benefits of antimicrobial efficacy of low dose prophylactic antibiotics to prevent urinary tract infections in children: a systemic review

CMAJ 2000;163:523–9

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- The available evidence for using antimicrobial prophylaxis to prevent UTI in children with normal urinary tracts or neurogenic bladder is of low quality.
- This suggests that the magnitude of any benefit should at best be questioned.
- Well-designed trials are needed to optimize the use of antimicrobials in children with recurrent urinary tract infection.

Le Saux N, et al. CMAJ 2000

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Williams G, Lee A, Craig J

Antibiotics for the prevention of urinary tract infection in children: A systematic review of randomized controlled trials

J Pediatr 2001;138:868-74

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- Methodologic and applicability problems with published trials mean that there is considerable uncertainty about whether long-term, low-dose antibiotic administration prevents UTI in children.
- Well-designed, randomized, placebo-controlled trials are still required to evaluate this commonly used intervention

Williams G, et al. J Pediatr 2001

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Recommendation 10

After a 7- to 14-day course of antimicrobial therapy and sterilization of the urine, infants and young children 2 months to 2 years of age with UTI should receive antimicrobials in therapeutic or prophylactic dosages until the imaging studies are completed (strength of evidence: good).

…sic!

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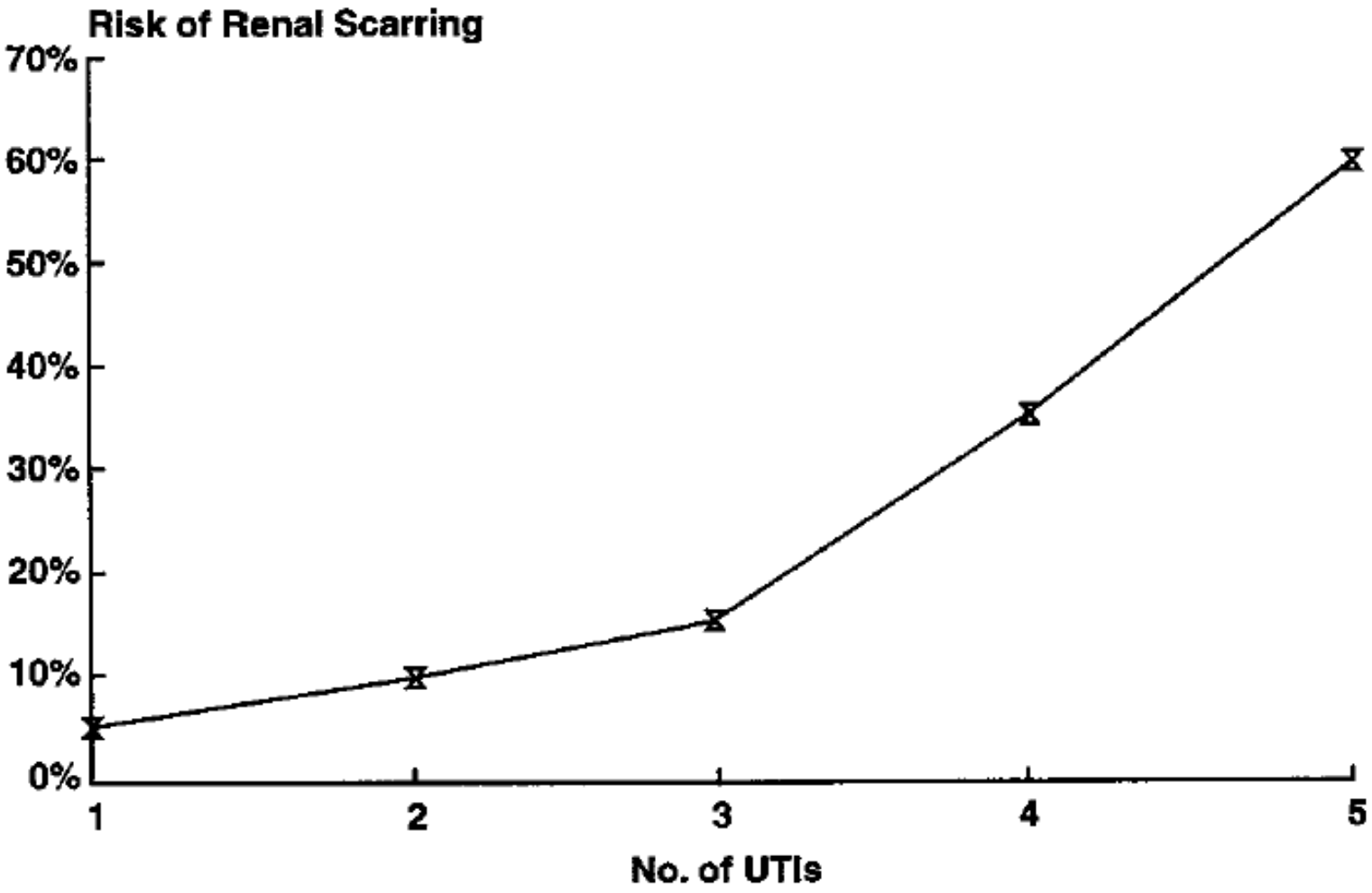

Fig 2. Relationship between renal scarring and number of urinary tract infections.[16]

Prodigy 2002

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Sackett DL

The arrogance of preventive medicine

CMAJ 2002;167:363-4

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Preventive medicine displays all **3 elements of arrogance**

1. It is **aggressively assertive**, pursuing symptomless individuals and telling them what they must do to remain healthy.

2. Is **presumptuous**, confident that the interventions it espouses will, on average, do more good than harm to those who accept and adhere to them.

3. Is **overbearing**, attacking those who question the value of its recommendations.

Sackett DL. CMAJ 2002

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What recommendations in absence of evidence?

- Treat each episode of acute uncomplicated UTI the same as a first episode
- If a second episode occurs within a year:
  - Check for predisposing conditions (anatomical abnormalities of the urinary tract, voiding dysfunction, constipation)
  - Start prophylactic antibiotic therapy
  - Refer for assessment and possible long-term prophylactic antibiotics
  - Advise parents/carers on the importance of adhering to treatment regimens

Prodigy 2002

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Altman DG, Bland JM

Absence of evidence is not evidence of absence

BMJ 1995;311:485

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Sandell A

Management of urinary tract infections in children: no evidence exists

BMJ 2003;327:1346

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- Serious renal disease is comparatively rare, whereas urinary tract infection in childhood is common.

- Even if effective, the number needed to screen to prevent one adverse outcome is likely to be huge.

- Arguments for an aggressive approach are largely theoretical: theory is crucial but has generally proved a dismal basis for screening programmes.

- General practitioners are often the first port of call for children who might have urinary tract infections.

Sandell A. BMJ, 2003

GIMBE® © 1996-2005

- Many would enthusiastically adopt the proposed approach if the balance of evidence, or even of common sense, weighed in its favour, but this does not yet seem to be clearly so.

- Investigation has costs: worry and inconvenience for families, exposure to radiation, funding, and time no longer available for more evidence based activities—but then again, it might work.

- I will be keeping my eyes open for the much needed prospective trial with adequate follow up and meaningful outcome measures.

Sandell A. BMJ, 2003

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