



## **Frequency of Urinary Tract Infections Among Febrile Children Presenting without Any Localizing Sign of Infection**

Dr. Usman <sup>\*1</sup>, Dr Sobia <sup>2</sup>, Dr Jahanzaib <sup>3</sup>, Dr Adeeba <sup>4</sup>

1. *Senior registrar at POF hospital, Wah.*
2. *Consultant Pediatrician at BHMC hospital and health and population department Punjab.*
3. *Senior Registrar at POF Hospital Wah.*
4. *Consultant pediatrician at health and population department Punjab.*

**\*Correspondence to:** Dr. Usman, Senior registrar at POF hospital, Wah.

### **Copyright**

© 2026: **Dr. Usman**. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received: 25 February 2026

Published: 09 March 2026

DOI: <https://doi.org/10.5281/zenodo.18921922>

**Abstract**

**Background:** Urinary tract infection (UTI) is a common pediatric condition, particularly affecting infants and older adolescents, with a higher prevalence among females and uncircumcised males. In children presenting with fever without an identifiable source, UTIs are often overlooked. Determining the local incidence of UTI in such cases is essential to guide empirical antibiotic therapy, reduce morbidity and mortality, and minimize unnecessary healthcare costs.

**Objective:** To determine the frequency of urinary tract infections in febrile children presenting without any localizing signs of infection.

**Study Design:**

Descriptive cross-sectional study.

**Setting and Duration:**

This study was conducted in the Department of Pediatrics, POF Hospital, Wah, from 10 July 2021 to 10 January 2022.

**Methods:** A total of 425 children of both genders, aged 2 to 12 years, presenting with an axillary temperature greater than 101°F, were enrolled. All participants underwent detailed history taking and thorough clinical examination at presentation. Urine samples were collected using sterile containers and analyzed in the Pathology Department of POF Hospital, Wah.

**Results:** The mean age of participants was  $5.14 \pm 2.31$  years, with a mean height of  $100.41 \pm 12.86$  cm and mean weight of  $14.60 \pm 3.70$  kg. The mean duration of fever was  $4.21 \pm 1.85$  days, and the mean admission temperature was  $102.11 \pm 0.64^\circ\text{F}$ . The mean leukocyte count per high-power field was  $1.88 \pm 1.92$ . Urinary tract infection was diagnosed in 6.8% of the study population.

**Conclusion:** A notable proportion of febrile children without localizing signs of infection were found to have urinary tract infections. Routine screening for UTI should therefore be considered in such presentations to enable early diagnosis and appropriate management.

**Keywords:** Febrile children; Fever without source; Urinary tract infection; Pediatric UTI

## Epidemiology and Background

Community-acquired urinary tract infections (UTIs) represent a significant global health burden, with an estimated worldwide prevalence of approximately 0.7%. In the United States, UTIs are the most common community-acquired bacterial infections, affecting nearly 11% of the population. The incidence increases with advancing age, with the notable exception of young women aged 14–24 years, in whom UTIs are also frequently observed. Approximately one-fifth of women over 65 years of age in the United States are affected. In Pakistan, available studies indicate a considerably higher prevalence, with UTIs identified in up to 36.1% of urine samples in certain populations. Nearly half of these cases occur in individuals older than 45 years, whereas children under 7 years of age constitute a much smaller proportion (approximately 7.2%). Due to this comparatively lower prevalence in the pediatric population, UTIs in children have historically received less clinical attention.

Among children, UTIs are most frequently encountered in infants and older adolescents, with a higher incidence in females and uncircumcised males. This gender difference is attributed to factors such as diaper use in infancy, the shorter female urethra, and the presence of foreskin in uncircumcised boys. In adolescent females, the onset of sexual activity is associated with a notable increase in UTI incidence. Additional risk factors include urinary stasis, which may result from anatomical or functional abnormalities such as vesicoureteral reflux and bladder–bowel dysfunction, creating an environment conducive to bacterial growth. Children frequently present with fever without an identifiable focus of infection, and a proportion of these cases may be attributable to underlying UTIs. Previous studies have reported variable prevalence rates of UTI in febrile children without localizing signs. Bhat et al. reported a prevalence of 13.2%, closely aligned with findings by Somaiah et al. (12.9%). In contrast, lower prevalence rates were documented by Nair et al. (7.5%) and Shaw et al. (3.3%). This variability highlights the uncertainty surrounding the true incidence of UTI in this clinical setting.

Given the absence of consistent data, clinicians often rely on empirical therapy when managing febrile children without localizing signs, which may lead to delayed diagnosis or inappropriate antibiotic use. Establishing reliable local incidence rates is therefore essential to guide empirical treatment strategies, reduce morbidity and mortality, and limit unnecessary healthcare expenditures.

## Diagnosis

According to the American Academy of Pediatrics (AAP) clinical practice guidelines, the diagnosis of UTI in children aged 2–24 months requires a combination of positive urinalysis (leukocyte esterase and/or nitrite positivity), microscopic evidence of pyuria or bacteriuria, and the isolation of  $\geq 50,000$  colony-forming units

(CFU)/mL of a single uropathogen from a catheterized or suprapubic aspiration specimen.

The Canadian Paediatric Society (CPS) recommends similar criteria, requiring a positive dipstick test along with a urine culture demonstrating  $\geq 100,000$  CFU/mL in a clean midstream specimen,  $\geq 50,000$  CFU/mL in catheterized specimens, or any growth from suprapubic aspiration.

The European Association of Urology (EAU) and the European Society for Paediatric Urology (ESPU) adopt a lower bacterial threshold, recognizing that growth of 1,000–10,000 CFU/mL from catheterized specimens or any growth from suprapubic aspiration is sufficient for diagnosis. In toilet-trained children, a clean-catch midstream urine specimen is preferred.

Clinical judgment remains critical, as UTIs may occasionally occur in the absence of pyuria, and urine cultures may be falsely negative in the presence of prior antimicrobial exposure or urinary tract obstruction. Additionally, infections caused by non-*Escherichia coli* organisms may present with lower bacterial counts.

### **Differential Diagnosis**

Asymptomatic bacteriuria refers to colonization of the urinary tract by non-virulent organisms without clinical symptoms or inflammatory response. It occurs in approximately 1% of children, predominantly affecting girls, and is more common in those with underlying genitourinary anomalies. In such cases, urine cultures are positive, but pyuria and clinical symptoms are absent.

Isolation of multiple organisms on urine culture typically indicates contamination rather than true infection, except in immunocompromised children or those with structural urinary tract abnormalities.

Improper urine collection, particularly failure to adequately separate the labia during voiding, may result in contamination with vaginal flora and false-positive results. Conditions such as vulvovaginitis, chemical urethritis, or exposure to irritants (e.g., bubble baths, harsh soaps) may cause dysuria without infection.

Functional disorders, including urge syndrome and dysfunctional voiding, may mimic UTI symptoms such as urinary frequency, urgency, and incontinence, even in the absence of infection. Persistence of symptoms after successful treatment of culture-proven UTI should prompt evaluation for these conditions.

Other differential diagnoses include viral infections, post-vaccination fever, urinary calculi, genital foreign bodies, orchitis, sexually transmitted infections, Kawasaki disease, appendicitis, group A streptococcal infection, and pelvic inflammatory disease in adolescent females.

### **Complications**

UTIs can significantly impact the child's well-being and family dynamics, leading to discomfort, anxiety, missed school days, and parental work absenteeism. Recurrent infections or permanent renal damage may

adversely affect quality of life. Bacteremia occurs in a notable proportion of pediatric UTIs, particularly in premature infants, children younger than one year, and those with elevated serum creatinine at presentation. Febrile seizures may occur in young children with high fever due to acute pyelonephritis.

Renal complications include electrolyte and acid–base disturbances, renal insufficiency, and long-term sequelae such as renal scarring, which may result from congenital renal dysplasia, vesicoureteral reflux, or urinary obstruction. Renal scarring develops in up to 5% of girls and 13% of boys following a first episode of pyelonephritis. Risk factors include early-life infection, delayed antibiotic therapy, recurrent febrile UTIs, bacterial virulence, and host susceptibility.

Approximately 10% of children with renal scarring later develop hypertension, and affected females are at increased risk of pregnancy-related complications. Rare but severe complications include renal abscess, pyonephrosis, emphysematous pyelonephritis, and xanthogranulomatous pyelonephritis.

### **Treatment**

Children should be encouraged to void regularly (every 1.5–2 hours), maintain proper voiding posture, ensure complete bladder emptying, practice meticulous perineal hygiene, and maintain adequate hydration. Contributing conditions such as constipation and dysfunctional voiding should be addressed.

Prompt initiation of empirical antibiotic therapy is recommended for symptomatic UTIs based on clinical findings and urinalysis while awaiting culture results. In contrast, asymptomatic bacteriuria does not require treatment. Empirical antibiotics should provide coverage against common uropathogens, particularly *E. coli*, and selection should consider local resistance patterns.

Commonly used agents include second- and third-generation cephalosporins, amoxicillin-clavulanate, nitrofurantoin, trimethoprim-sulfamethoxazole, and fluoroquinolones (reserved for resistant infections). Rising antimicrobial resistance, particularly due to extended-spectrum  $\beta$ -lactamase-producing organisms, underscores the importance of judicious antibiotic use.

Parenteral therapy is indicated for infants younger than two months, toxic or unstable patients, immunocompromised children, or those unable to tolerate oral medication. Treatment duration typically ranges from 5–7 days for lower UTIs and 7–10 days for febrile UTIs, depending on clinical severity and response.

### **Adjunctive Therapies**

Phenazopyridine may be used short-term in adolescents to alleviate severe dysuria. Emerging evidence suggests potential benefits of corticosteroids, vitamin E, and zinc supplementation in reducing inflammation

and symptoms, although larger randomized controlled trials are required before routine recommendation.

### **Prophylaxis and Prognosis**

Routine antibiotic prophylaxis is generally not recommended, except in selected cases such as recurrent febrile UTIs or high-grade vesicoureteral reflux, where risks and benefits must be carefully weighed. Non-pharmacologic preventive strategies include education on hygiene, bladder and bowel habits, and early recognition of recurrence.

The overall prognosis of UTI in children without structural abnormalities or renal scarring is favorable. However, delayed or inadequate treatment of febrile UTIs can result in permanent renal damage, emphasizing the importance of early diagnosis and appropriate management.

### **Materials and Methods**

#### **Study design and setting**

A descriptive cross-sectional study was conducted in the Department of Pediatrics, POF Hospital, Wah, from 10 July 2021 to 10 January 2022.

#### **Sample size and sampling technique**

The sample size was calculated using the WHO sample size calculator with a 95% confidence level, an anticipated population proportion (P) of 0.0339, and an absolute precision (d) of 1.5%, yielding a required sample of 425 participants. Patients were recruited using consecutive non-probability sampling.

#### **Eligibility criteria**

**Inclusion criteria:** Children aged 2–12 years presenting with an axillary temperature  $>101^{\circ}\text{F}$  and no identifiable source of infection based on history and clinical examination were eligible for enrollment.

**Exclusion criteria:** Children were excluded if consent was not provided; if they had a previous history of UTI; had received antibiotics for the current febrile episode; had a history of urological surgery other than circumcision; had known immunodeficiency or were taking immunosuppressive medications; had congenital urinary tract anomalies (e.g., ectopia vesicae or hypospadias) on examination; or had undergone urinary bladder catheterization within the preceding month.

### Data collection procedure

Ethical approval was obtained from the hospital ethics committee prior to initiation. Written informed consent was taken from parents/guardians (Annexure A). A total of 425 eligible children meeting the inclusion and exclusion criteria were enrolled to minimize confounding and selection bias. Each participant underwent a detailed medical history and complete clinical examination at presentation.

Urine samples were collected in sterile containers and transported to the Pathology Department for processing within one hour. The sample was centrifuged at 1500 rpm, and the sediment was examined microscopically using the  $\times 40$  objective to determine leukocyte count per high-power field (HPF). A leukocyte count of  $\geq 6$ /HPF was considered indicative of UTI based on the study's operational definition.

In addition, urine samples collected via urinary catheterization were cultured. Specimens were inoculated within one hour onto MacConkey agar, nutrient agar, cysteine plates, and lactose electrolyte-deficient media, then incubated at 37°C. Culture plates were assessed after 48 hours. A culture was considered positive when growth exceeded  $5 \times 10^4$  CFU/mL.

All study variables were documented on a standardized proforma (Annexure B), including age, sex, height/length, weight, duration of fever, admission temperature, urinalysis status (UTI present/absent), leukocyte count per HPF, culture result, and organism identified. Data collection was performed by the principal investigator to ensure uniformity and maintain data quality.

### Data analysis plan

Data were analyzed using SPSS version 26. Quantitative variables (age, height/length, weight, duration of fever, admission temperature, and leukocyte count/HPF) were summarized using mean and standard deviation, while qualitative variables (sex, urinalysis-based UTI status, culture positivity, and bacterial species) were summarized as frequency and percentage. Potential effect modifiers (age, sex, anthropometric measures, duration of fever, and admission temperature) were controlled using stratification, followed by application of the Chi-square test post-stratification to assess associations with UTI status. A p-value  $\leq 0.05$  was considered statistically significant.

### Results

Age range in this study was from ages of 2 to 12 years with mean age  $5.138 \pm 2.31$  years, mean height  $100.411 \pm 12.86$  cm, mean weight  $14.595 \pm 3.70$  Kg, mean duration of fever  $4.209 \pm 1.85$  days, mean temperature on admission  $102.112 \pm 0.64^\circ\text{F}$  and mean number of leucocytes per high power field was  $1.882 \pm 1.92$  as shown in Table-I. Male patients were 59.3% and females were 40.7% as shown in Table-II.

UTI infection was observed in 6.8% patients as shown in Table-III. Species of bacteria cultured were E.coli 62.1%, Klebsiella pneumonia 27.6% and others were 10.3% as shown in Table-IV.

Stratification of urinary tract infection with respect to age, gender, height, weight, duration of fever, and temperature on admission are shown in Tables-V, VI, VII, VIII, IX and X respectively.

Demographics		Mean±SD
1	Age (years)	5.138±2.31
2	Height (cm)	100.411±12.86
3	Weight (Kg)	14.595±3.70
4	Duration of fever (days)	4.209±1.85
5	Temperature on admission (°F)	102.112±0.64
6	Leucocytes (per high power field)	1.882±1.92

n=425

**Table- I:** Mean±SD of patients according to age, height, weight, duration of fever, temperature on admission and number of leucocytes per high power field

Gender	Frequency	%age
Male	252	59.3%
Female	173	40.7%
Total	425	100%

n=425

**Table- II:** Frequency and %age of patients according to gender

UTI infection	Frequency	%age
Yes	29	6.8%
No	396	93.2%
Total	425	100%

n=425

**Table- III:** Frequency and %age of patients according to UTI infection

Species of bacteria cultured	Frequency	%age
E. coli	18	62.1%
Klebsiella pneumonia	8	27.6%
Others	3	10.3%
Total	29	100%

n=29

**Table- IV:** Frequency and %age of patients according to species of bacteria

Age (years)	UTI infection		p-value
	Yes	No	
2-7	26(7.5%)	322(92.5%)	0.260
>7	3(3.9%)	74(96.1%)	
Total	29(6.8%)	396(93.2%)	

**Table-V:** Stratification of UTI infection with respect to age.

Gender	UTI infection		p-value
	Yes	No	
Male	15(6%)	237(94%)	0.390
Female	14(8.1%)	159(91.9%)	
Total	29(6.8%)	396(93.2%)	

**Table-VI:** Stratification of UTI infection with respect to gender

Height (cm)	UTI infection		p-value
	Yes	No	
≤100	18(9%)	181(91%)	0.088
>100	11(4.9%)	215(95.1%)	
Total	29(6.8%)	396(93.2%)	

**Table-VII:** Stratification of UTI infection with respect to height

Weight (Kg)	UTI infection		p-value
	Yes	No	
≤15	24(8.2%)	268(91.8%)	0.091
>15	5(3.8%)	128(96.2%)	
Total	29(6.8%)	396(93.2%)	

**Table-VIII:** Stratification of UTI infection with respect to weight.

Duration of fever (days)	UTI infection		p-value
	Yes	No	
1-5	3(0.9%)	319(99.1%)	0.000
>5	26(25.2%)	77(74.8%)	
Total	29(6.8%)	396(93.2%)	

**Table-IX:** Stratification of UTI infection with respect to duration of fever.

Temperature on admission (°F)	UTI infection		p-value
	Yes	No	
101-102	19(6.1%)	290(93.9%)	0.368
>102	10(8.6%)	106(91.4%)	
Total	29(6.8%)	396(93.2%)	

**Table-X:** Stratification of UTI infection with respect to temperature on admission

## Discussion

The primary objective of this study was to determine the frequency of urinary tract infections (UTIs) among febrile children aged 2 to 12 years presenting without an identifiable source of infection. Early recognition of UTIs in this clinical setting is essential, as delayed diagnosis may lead to avoidable complications, including renal damage. By establishing local incidence data, this study aims to support timely diagnosis and guide appropriate empirical management.

In the present cohort of 425 children, the majority belonged to the younger age group (2–7 years), with a mean age of  $5.14 \pm 2.31$  years. A male predominance was observed in the study population. The overall prevalence of UTI was 6.8%, which is comparable to rates reported in several regional and international studies assessing febrile children without localizing signs. These findings reinforce the concept that UTIs represent a clinically relevant cause of unexplained fever in children, even beyond infancy.

Previous literature has demonstrated wide variability in reported UTI prevalence among febrile children, particularly in younger age groups. Some studies have reported markedly higher rates, especially in children

younger than two years, where the probability of UTI in the absence of an alternative focus of infection may range broadly. Gender-related differences have also been consistently described, with females exhibiting a higher incidence of UTI compared to males, particularly after infancy. This disparity has been attributed to anatomical differences, including a shorter urethral length in females, as well as behavioral and hygiene-related factors.

In male children, circumcision status appears to play a significant role in UTI risk. Uncircumcised males have been shown to have a higher susceptibility to infection, likely due to bacterial colonization beneath the foreskin, which facilitates ascending infection. Studies comparing circumcised and uncircumcised boys have consistently demonstrated a protective effect of circumcision against UTIs, particularly during early childhood. Although circumcision rates were not directly analyzed in this study, the existing literature provides a plausible explanation for sex-based differences in infection rates.

Constipation has also been identified as an important risk factor for UTIs in children. Rectal distension secondary to constipation can impair bladder emptying and promote urinary stasis, thereby increasing susceptibility to infection. Effective management of constipation has been shown to restore normal bladder function and reduce recurrent UTIs. Socioeconomic factors may further contribute to UTI risk, as children from lower socioeconomic backgrounds are more likely to experience malnutrition, poor hygiene, and limited access to healthcare, all of which predispose to infection. In resource-limited settings, reported UTI prevalence rates vary widely, ranging from 6% to 37%, underscoring the influence of environmental and social determinants.

Microbiological analysis in the present study revealed *Escherichia coli* as the most frequently isolated pathogen, accounting for 62.1% of positive cultures, followed by *Klebsiella pneumoniae* (27.6%), with other organisms comprising a smaller proportion. This distribution is consistent with established epidemiological patterns, in which *E. coli* remains the dominant uropathogen in pediatric UTIs due to its virulence factors and ability to adhere to the uroepithelium. Comparable studies have similarly identified *E. coli* as the leading causative organism, with *Klebsiella* species ranking second in prevalence.

Overall, the findings of this study highlight that UTIs constitute a significant proportion of febrile illnesses without localizing signs in children. Given the nonspecific clinical presentation, clinicians should maintain a high index of suspicion for UTI in such cases, particularly in younger children and those with recognized risk factors. Routine consideration of urinalysis and urine culture in febrile children without an apparent focus of infection may facilitate early diagnosis, reduce complications, and improve clinical outcomes.

## Conclusion

A high percentage of urinary tract infection in febrile without any localizing sign for infection in our study favors having a heightened awareness among treating pediatricians to treat an easily manageable disease and to avoid future complications. Diagnosing UTI in children is an uphill task and missing a diagnosis in children puts these children at risk of developing chronic renal problems.

## References

1. Tandogdu Z, Wagenlehner FM. Global epidemiology of urinary tract infections. *Curr Opin Infect Dis*. 2016 Feb;29(1):73-9.
2. Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. *Ther Adv Urol*. 2019 May 2;11:1756287219832172.
3. Muhammad A, Khan SN, Ali N, Rehman MU, Ali I. Prevalence and antibiotic susceptibility pattern of uropathogens in outpatients at a tertiary care hospital. *New Microbes New Infect*. 2020 Jun 13;36:100716.
4. Kaufman J, Temple-Smith M, Sancic L. Urinary tract infections in children: an overview of diagnosis and management. *BMJ Paediatr Open*. 2019 Sep 24;3(1):e000487.
5. Leung AKC, Wong AHC, Leung AAM, Hon KL. Urinary Tract Infection in Children. *Recent Pat Inflamm Allergy Drug Discov*. 2019;13(1):2-18.
6. Bhat JA, Ashraf M, Wani KA, Rashid M, Manzoor J, Shaheen L. Non- localizing Fever as Urinary Tract Infection in Children. *J Ped Nephrology*. 2016;4(1):37-40.
7. Somaiah G, Mohinuddin Siddique A, Gupte S, Kiran S, Kumar BR, Ram PJ. Prevalence Of Urinary Tract Infection In Febrile Children Less Than Five Years Of Age. *Asian J Health Sci*. 2014. 2(1).
8. Nair BT, Rai AK. Prevalence of urinary tract infection in febrile children <2 years of age. *Sahel Med J*. 2018;21(1):47-51.

9. Shaw KN, Gorelick M, McGowan KL, Yakscoe NM, Schwartz JS. Prevalence of urinary tract infection in febrile young children in the emergency department. *Pediatrics*. 1998 Aug;102(2):e16
10. Lo E, et al. Strategies to prevent catheter-associated urinary tract infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35:464–479.
11. Chenoweth CE, Gould CV, Saint S. Diagnosis, management, and prevention of catheter-associated urinary tract infections. *Infect Dis Clin North Am*. 2014;28:105–119.
12. Kline KA, Schwartz DJ, Lewis WG, Hultgren SJ, Lewis AL. Immune activation and suppression by group B *Streptococcus* in a murine model of urinary tract infection. *Infect Immun*. 2011;79:3588–3595.
13. Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *Am J Med*. 2002;113 (Suppl 1A):14S–19S.
14. Fisher JF, Kavanagh K, Sobel JD, Kauffman CA, Newman C. A *Candida* urinary tract infection: pathogenesis. *Clin Infect Dis*. 2011;52 (Suppl 6):S437–S451.
15. Chen YH, Ko WC, Hsueh PR. Emerging resistance problems and future perspectives in pharmacotherapy for complicated urinary tract infections. *Expert Opin Pharmacother*. 2013;14:587–596. This paper highlights the emerging resistance among bacterial pathogens, the problems we face in combating these resistant bacteria and potential effective agents for the treatment of UTIs caused by multidrug-resistant pathogens.
16. Jacobsen SM, Stickler DJ, Mobley HL, Shirtliff ME. Complicated catheter-associated urinary tract infections due to *Escherichia coli* and *Proteus mirabilis*. *Clin Microbiol Rev*. 2008;21:26–59.
17. Kostakioti M, Hultgren SJ, Hadjifrangiskou M. Molecular blueprint of uropathogenic *Escherichia coli* virulence provides clues toward the development of anti-virulence therapeutics. *Virulence*. 2012;3:592–594.
18. Subashchandranose S, et al. Host-specific induction of *Escherichia coli* fitness genes during human urinary tract infection. *Proc Natl Acad Sci USA*. 2014;111:18327–18332.

19. Khandelwal P, Abraham SN, Apodaca G. Cell biology and physiology of the uroepithelium. *Am J Physiol Renal Physiol.* 2009;297:F1477– F1501.
20. Lee G. Uroplakins in the lower urinary tract. *Int Neurourol J.* 2011;15:4–12.
21. Eto DS, Jones TA, Sundsbak JL, Mulvey MA. Integrin-mediated host cell invasion by type 1-piliated uropathogenic *Escherichia coli*. *PLoS Pathog.* 2007;3:e100.
22. Niveditha S, Pramodhini S, Umadevi S, Kumar S, Stephen S. The isolation and the biofilm formation of uropathogens in the patients with catheter associated urinary tract infections (UTIs) *J Clin Diagn Res.* 2012;6:1478–1482.
23. Jacobsen SM, Shirtliff ME. *Proteus mirabilis* biofilms and catheter-associated urinary tract infections. *Virulence.* 2011;2:460–465. This paper briefly outlines the steps of *P. mirabilis* crystalline-biofilm formation during CAUTIs.
24. Kline KA, Dodson KW, Caparon MG, Hultgren SJ. A tale of two pili: assembly and function of pili in bacteria. *Trends Microbiol.* 2010;18:224– 232.
25. Wurpel DJ, Beatson SA, Totsika M, Petty NK, Schembri MA. Chaperone–usher fimbriae of *Escherichia coli*. *PLoS ONE.* 2013;8:e52835.
26. Waksman G, Hultgren SJ. Structural biology of the chaperone–usher pathway of pilus biogenesis. *Nature Rev Microbiol.* 2009;7:765–774. This review presents the most current, in-depth understanding of how pili are assembled through the chaperone–usher pathway.
27. Vallet I, Olson JW, Lory S, Lazdunski A, Filloux A. The chaperone/usher pathways of *Pseudomonas aeruginosa*: identification of fimbrial gene clusters (cup) and their involvement in biofilm formation. *Proc Natl Acad Sci USA.* 2001;98:6911–6916.
28. Chorell E, et al. Mapping pilicide anti-virulence effect in *Escherichia coli*, a comprehensive structure-activity study. *Bioorg Med Chem.* 2012;20:3128–3142.
29. Thanassi DG, Saulino ET, Hultgren SJ. The chaperone/usher pathway: a major terminal branch of the general secretory pathway. *Curr Opin Microbiol.* 1998;1:223–231.

30. Piatek R, et al. Pilicides inhibit the FGL chaperone/usher assisted biogenesis of the Dr fimbrial polyadhesin from uropathogenic *Escherichia coli*. *BMC Microbiol.* 2013;13:131. This paper provides a brief overview of two similar CUP pilus assembly pathways and shows that antivirulence compounds (pilicides) which were originally designed to specifically target one pathway have broad-spectrum activity against both CUP pilus pathways in *E. coli*.



Medtronic