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Atypical pathogens in urinary tract infections: a systematic review

Abstract

Urinary tract infection [UTI] accounts for a significant portion of the worldwide infections, whose cause occurs predominantly through Gram-negative bacilli, followed by Gram-positive bacteria and fungi. However, a number of cases by atypical pathogens are increasing. Thus, a systematic review was carried out on UTIs caused by atypical/emerging agents, covering etiological, epidemiological, clinical and therapeutic aspects. The search conducted via PubMed database and 59 articles composed the final sample. The laboratory approaches reported have included uroculture with special media; molecular methods such as PCR, real-time PCR, and nucleic acid sequencing; and MALDI-TOF mass spectrometry. Pathogens found among bacteria, including Gram-negative bacilli, Gram-positive cocci, diphtheroids, Mycoplasmataceae members, actinomycetes, and Gram-variable coccobacilli; yeasts, molds and microsporidia; virus, including BK polyomavirus, HPV, CMV and HSV-2; and a protozoan, *Trichomonas vaginalis*. The risk factors appear to be associated with patients' intrinsic features, such as advanced age, female gender, chronic diseases, prostatic hyperplasia, immunocompromised, genitourinary tract alteration; or risky situations as long-term urinary catheter usage, urinary tract manipulation, cancer chemotherapy, alcoholism, prolonged use of antibiotics and risky sexual behavior. The difficulty in identifying these agents was also evident, due to their peculiar characteristics or the unavailability of more sophisticated methods in the laboratorial routines, which implicates in the clinical management. Therefore, it is important that the medical and the microbiology teams are aware of the possibility of these agents in order to assess the need for further testing. The importance of antimicrobial susceptibility tests is also emphasized because of these organisms' different profiles.

Keywords: atypical pathogens, emerging pathogen, uncommon pathogen, unusual pathogen, urinary tract infections

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Abbreviations: BKV, BK polyomavirus; *bopD,* biofilm-associated transcriptional regulator gene homolog; CAPES, *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior;* CMV, Cytomegalovirus; CNPq, *Conselho Nacional de Desenvolvimento Científico e Tecnológico;* CNS, central nervous system; GBS, Group B *Streptococcus;* HC, hemorrhagic cystitis; HPV, human papillomavirus; HSV-2, herpes simplex virus-2; JCV, JC virus; LAMIP, laboratory of microbiology and parasitology; MALDI-TOF, matrix-assisted laser desorption ionization-time of flight; MH, *Mycoplasma hominis;* PIBIC, *Programa Institucional de Bolsas de Iniciação Cinetífica;* PRISMA, preferred reporting items for systematic reviews and meta-analyses; PV, polyomaviruses; PVN, polyomavirus nephropathy; RFLP, restriction fragment length polymorphism; UTI, urinary tract infection; UU, *Ureaplasma urealyticum*

Introduction

Urinary tract infection (UTI) is the most common hospital acquired infection and has been regarded as the second most common community-acquired infections.[1] In addition to the overt epidemiological importance, there may be medical relevance related to the possible complications in some prone groups such as children, pregnant women and patients with diabetes.[2]

As for the etiology, UTI is considered the most common bacterial infection type,[2] with many well-characterized agents, including different serotypes of *Escherichia coli*.[3] In fact, Gram-negative aerobic or facultative anaerobic bacilli are described as the main UTI's agents[4] the role of gram-positive bacteria, such as *Staphylococcus saprophyticus* and *Staphylococcus epidermidis*, and some fungal species, including *Candida* spp., cannot be denied.[4]

However, case reports claim the role of unusual etiological agents in causing UTIs. In some of them, clinical presentations are similar to those caused by common pathogens; however, different sensitivity profile of antibiotics has been taken into account and that can lead to ineffective treatment.[5] On the other hand, there are also reports of patients with unusual clinical recovery, which in turn, can hinder diagnosis and adequate treatment.[1]

By the early 1980s, it was reported in case of an elderly woman with a history of recurrent UTI caused by *Streptococcus milleri* (also known as the *Streptococcus anginosus* group) sometimes associated with some obligate anaerobic bacteria, namely: *Peptococcus* spp. or *Prevotella* (*Bacteroides*) *melaninogenicus*.[6] Two decades later, *Peptostreptococcus asaccharolyticus* was isolated in a boy with renal abscess.[7] Since then, publications have revealed an increasing number of atypical agents in UTI cases.[7]

Based on the growing body of evidence and the relevance of the subject, we decided to gather the information available in the scientific literature. This article aims to perform a systematic review of literature addressing UTI caused by atypical/emerging pathogens, in order to overview the etiological and epidemiological features, as well as the clinical manifestations, and the therapeutic management.

Material and methods

The present study is a systematic literature review following Cochrane Handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8]

The search was conducted via electronic database PubMed, on June 11, 2020. The search terms browsed on the database were #1.

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Urinary tract infections [MeSH term]; #2 "atypical" [keyword]; #3 "emerging" [keyword]; #4 "uncommon" [keyword]; #5 "rare" [keyword]; comprising the period from January 1, 2008 to December 31, 2019 (Fig. 1). This search period was chosen in order to gather the most reliable amount of information on the subject published until last year, allowing performing a more accurate analysis. In addition, it was applied the filter "Title/Abstract". The strategy used to search the articles was #1 AND (#2 OR #3 OR #4 OR #5). The query in PubMed Advanced Search Builder was edited as follows: Urinary tract infections [Title/Abstract] AND (atypical [Title/Abstract] OR emerging [Title/Abstract] OR uncommon [Title/Abstract] OR rare [Title/Abstract]).

After the first stage of the selection (sifting) by titles and abstracts of the records, a full analysis of the articles was conducted to assess their relevance based on the inclusion criteria. Three independent researchers carried out a three-step literature search. The study coordinator resolved any discrepancies among the three reviewers that blind to each other, examined the studies for possible inclusion.

The article analysis followed predefined eligibility criteria for inclusion, namely: (1) manuscripts written in English; (2) articles addressing human patients diagnosed with urinary tract infection caused by an atypical microorganism; (3) prospective or retrospective observational (analytical or descriptive), experimental or quasi-experimental studies or case report.

Considering the scarce data about atypical urinary tract infections, and that the cases are published in the literature mainly as case reports, we decided to include this kind of publication in our search in order to better explore uncommon UTIs. The full text of the selected articles (sample) was obtained in their entirety through the Coordination of Improvement of Higher Education Personnel (CAPES) Portal of Journals, a virtual library linked to Brazil's board of Education and subjected to content subscription.

We adopted the following exclusion criteria: (1) repeated articles; (2) non-original studies, including editorials, reviews, and prefaces; (3) article retracted or abrogated by the publisher; (4) author's name not disclosed; and (5) out of context. Each paper in the sample was fully read. The data elements were, then extracted and put into a spreadsheet that included authors, year of publication, study sample description, and main findings.

Results

Based on the search strategy, 649 publications were retrieved. After analyzing the content according to the eligibility criteria, 59 studies were included in the final sample. Regarding the 590 excluded articles that have not addressed the involvement of atypical agents in UTIs.

About the types of studies that comprised the sample, there were 43 (75.88%) case reports, 4 (6.78%) case series, 5 (8.47%) retrospective studies, 4 (6.78%) cross-sectional studies, 2 letters to the editor (3.69%) and 1 (1.69%) prospective study. Moreover, 24 studies (40.68%) were performed in Asia, 16 (27.12%) in Europe, 11 (18.64%) in North America, 5 (8.47%) in Africa, 1 (1.69%) in South America, and two (3.29%) in Eurasia.

Considering the microorganisms found, most studies dealt with bacteria, more precisely 42 (71.19%). Among them, 25 (42.37%) studies reported Gram-negative bacteria, representing the largest group in this review; followed by Gram-positive bacteria which accounted to 15 (25.42%) of these studies, of which 9 addressed actinomycetes. In addition, there was a publication about Gram-variable bacteria (1.69%) and one about members of the *Mycoplasmataceae* family (1.69%). The others consisted of 14 (23.73%) studies involving fungi, 2 (3.39%) involving viruses, and a study (1.69%) addressing numerous agents (viruses, bacteria, fungi, and protozoa).

Figure 1 presents a flow diagram of the steps, strategy, and quantitative aspects in the analysis process. Similarly, table 1 shows an overview of selected articles, which comprise the final sample, including data on publications, clinical samples, methods employed, and the main findings. Figure 2 shows the infectious agents' frequencies grouped by their taxonomic families.

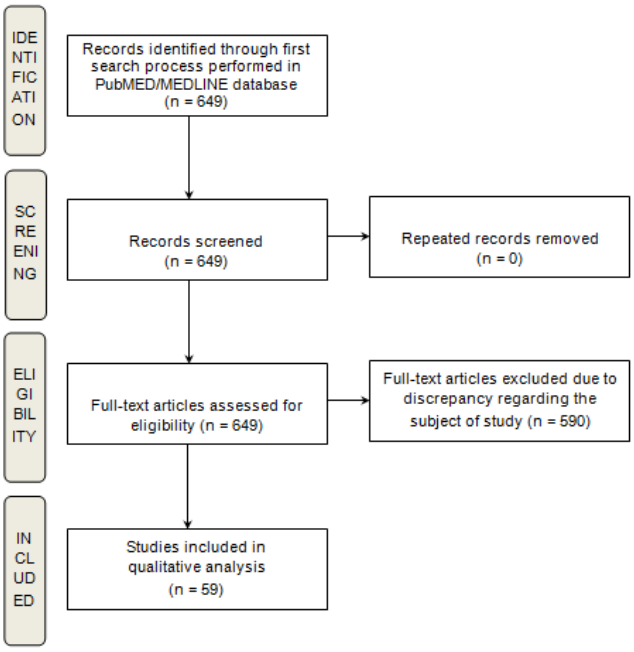

Figure 1 Flow diagram summarizes the process of the study included in this review.

Figure 2 The infectious agent's frequencies grouped by their taxonomic families.

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Discussion

Gram-negative bacteria infections

The group of Gram-negative bacteria seems to predominate not only in numerical terms but is also found in different habitats. Depending on the particularity of each species, they can be found in hospital settings, including urinary catheters,[26] sinks, and other wet surfaces. In environmental sources, such as soil, water, and sewage; in plants,[13,20] animals or insects;[5] in the domestic environment, as in food;[17] and colonizing some areas of the human body, such as gastrointestinal tract,[15] genitourinary tract[18] and respiratory system.[21] In general, they are able to cause community-acquired and/or nosocomial urinary tract infections (Table 1). Some studies still describe a high degree of resistance to antimicrobials, and their inappropriate use is discussed, as well as the release of their residues in the environment as a selection factor for resistant bacteria, to which humans can be exposed.[23]

Table 1 Main findings of the sample on atypical/emerging urinary tract infections

Agent	Title	Sample or comments	Main findings	Limitations	Reference and country
Achromobacter xylosoxidans	Clinical Characteristics of Postoperative Febrile Urinary Tract Infections After Ureteroscopic Lithotripsy	304 patients underwent ureteroscopic lithotripsy.	One case of UTI due to *A. xylosoxidans*. 43 cases of postoperative febrile urinary tract infections. The time of operations was evidenced as a independent risk factor.	Small sample. The effects of irrigation (pressure or volume) as risk factors were not evaluated.	South Korea[9]
Brevundimonas vesicularis	Hospital acquired urinary tract infection by multidrug-resistant *Brevundimonas vesicularis*	24-year-old male.	Infections by this agent are very rare. In this case, the patient was successfully treated with piperacillin-tazobactam and amikacin.	Growth difficulty in MacConkey Agar.	India[10]
Burkholderia pseudomallei	Genitourinary Melioidosis in a Bangladeshi Farmer With IgA Nephropathy Complicated by Steroid-Induced Diabetes Mellitus	38-year-old Bangladeshi farmer.	Urinary tract infections caused by *B. pseudomallei* should be suspected in high-risk populations, such as farmers and people with immunosuppressive conditions or diabetes.	Only one case reported.	Bangladesh[11]
Chryseobacterium gleum	Urinary tract infection due to *Chryseobacterium gleum*, an uncommon pathogen	58-year-old diabetic male.	The identification was made with Matrix-Assisted Laser Desorption Ionization Time-of-Flight and antibiotic sensitivity test was performed by VITEK-2 systems. The patient responded well with intravenous ciprofloxacin.	Limited clinical data.	India[12]
Chryseobacterium indologenes	Urinary tract infection by *Chryseobacterium indologenes*	19-year-old girl.	The patient underwent surgery for kidney stones and was successfully treated with piperacillin-tazobactam.	Information on antimicrobial susceptibility is very limited.	India[13]
Chryseobacterium indologenes	*Chryseobacterium indologenes* in a woman with acute leukemia in Senegal: a case report	42-year-old woman of Wolof ethnicity.	*C. indologenes* is an uncommon human pathogen reported in hospital outbreaks and mainly in immunosuppressed patients.	The management of these cases needs more data about identification, drug susceptibility testing and monitoring of immunocompromised patients with long hospitalizations.	Senegal[14]
Edwardsiella tarda	Urosepsis caused by *Edwardsiella tarda*	69-year-old Japanese female patient, suffering from end-stage endometrial cancer.	*E. tarda* as agent of fatal urosepsis. The patient's underlying condition of advanced uterine cancer may have contributed to the development of the infection.	The sources and portals of entry mostly remain unknown.	Japan[15]
Elizabethkingia meningoseptica	*Elizabethkingia meningoseptica*: Emerging Multidrug Resistance in a Nosocomial Pathogen	46-year-old male.	It has the ability to exist as biofilm structures allowing the organism to colonise intravascular devices, catheters and ventilators. The patient was treated with oral minocycline for 14 days after which he was symptomatically better with sterile urine.	Further studies are required on the resistance pattern of *E meningoseptica* in an attempt to establish empiric treatment protocols	India[16]

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Table Continued...

Agent	Title	Sample or comments	Main findings	Limitations	Reference and country
Enterobacter sakazakii	Urinary tract infection due to *Enterobacter sakazakii*	63-year-old woman with chronic renal failure and chief complaints of breathlessness.	UTI by *E. sakazakii* in a patient with end stage renal damage on maintenance hemodialysis, which died six days after hospitalization, despite the treatment.	The literature search did not reveal any document of UTI caused by *E. sakazakii*.	India[17]
Haemophilus quentini	Genotypic and phenotypic characterization and clinical significance of '*Haemophilus quentini*' isolated from the urinary tract of adult men	Six cases in males.	The isolation of *H. quentini* in urine tests in adult men can help in the diagnosis of unresolved urethritis and possible UTI.	Case reports in adult men are rare and the potential for the disease in this population is unknown.	USA[18]
Klebsiella variicola	Population Structure, Antibiotic Resistance, and Uropathogenicity of *Klebsiella Variicola*	113 clinical isolates.	Population structure, antibiotic resistance, and uropathogenicity of *K. variicola* are generally similar to *K. pneumoniae*. Variability of *K. variicola* genomes has important clinical implications with strain efficacies in a murine model of UTI.	Mouse infections and phenotypic analyses are performed with nonisogenic strains.	USA[19]
Kluyvera ascorbata	A case of urinary tract infection caused by *Kluyvera ascorbata* in an infant: case report and review of the literature	3-month-old child.	Reports of *Kluyvera* infection have increased, including in UTI.	In pediatrics, only seven cases of UTI by the agent have been reported.	Japan[20]
Kluyvera ascorbata	Urinary tract infection caused by *Kluyvera ascorbata* in a child: case report and review of the Kluyvera infections in children	3-month-old female baby.	In children, *Kluyvera* infection can cause infections of the urinary and digestive tracts, soft tissue, peritonitis, infections by central venous catheters and sepsis.	Little information about the use of antimicrobials.	Italy[21]
Kluyvera ascorbata	*Kluyvera ascorbata* as a Pathogen in Adults and Children: Clinical Features and Antibiotic Susceptibilities in a Single Center Study	6 *K. ascorbata* isolates.	*K. ascorbata* was identified in three samples of wounds, one of blood, one of sputum and one of urine.	There are few cases reported to provide an adequate description.	South Korea[22]
Myroides odoratimimus	*Myroides odoratimimus* Urinary Tract Infection in an Immunocompromised Patient: An Emerging Multidrug-Resistant Microorganism	69-year-old man.	It is necessary to pay attention to atypical pathogens, mainly in immunocompromised patients, and it is recommended that uroculture be considered at an earlier stage.	There are cases of infection by a less virulent microorganism, but with multidrug resistance.	Italy[23]
Ochrobactrum anthro	Late-onset *Ochrobactrum anthropi* sepsis in a preterm neonate with congenital urinary tract abnormalities	Male infant born at 30 3/7 weeks via cesarean delivery.	Late sepsis secondary to UTI by *O. anthropi* in a premature newborn with posterior urethral valves.	The determination of antibiotic therapy and its duration is not clear.	USA[24]
Raoultella planticola	A case of urinary tract infection caused by *Raoultella planticola* after a urodynamic study	57-year-old male.	It was theorized that the UTI was due to direct invasion due to urodynamic study equipment contaminated by *R. planticola*.	Infection due to contaminated urodynamic study equipment is rare.	Turkey[25]
Raoultella ornithinolytica	Emergence of *Raoultella ornithinolytica* on O'ahu: a case of community-acquired *R. ornithinolytica* urinary tract infection	73-year-old Japanese woman.	*R. ornithinolytica* is emerging as a causative agent of community-acquired UTIs.	There is usually an identification error with *Klebsiella pneumoniae* due to similar characteristics.	USA[5]
Raoultella ornithinolytica	Emerging role of *Raoultella ornithinolytica* in human infections: a series of cases and review of the literature	Cases at four university hospital centres.	*R. ornithinolytica* is an underreported and emerging hospital infection associated with invasive procedures.	Identification is difficult by conventional phenotypic methods.	France[26]

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Table Continued...

Agent	Title	Sample or comments	Main findings	Limitations	Reference and country
Salmonella serogroup C, *S. stanleyville, S. typhi, S. enterica*	Urinary tract infection due to salmonella in an otherwise healthy child	7-year-old boy.	Pyelonephritis case due to *Salmonella* spp. in a healthy boy without history of recent gastroenteritis.	*Salmonella* spp. UTI may be more frequent than is generally believed.	Iran[27]
Salmonella anatum	Pyelonephritis Caused by *Salmonella Anatum*: An Unusual Case	9-year-old girl.	First case of *S. anatum* pyelonephritis in a healthy child.	UTI by *Salmonella* spp. is rare in children and infection by nontyphoidal serotypes can be difficult to treat.	Turkey[28]
Salmonella entérica	Non-typhi *Salmonella enterica* urinary tract infections.	20 urine cytobacteriological examination.	There were seven cases of pyelonephritis, seven of acute cystitis, four of prostatitis (five, one and two associated with bacteremia, respectively) and two cases of asymptomatic bacteriuria. Ten patients had previous or simultaneous diarrhea.	Small sample and retrospective analysis.	France[29]
Salmonella gallinarum	Case Report of *Salmonella gallinarum* Urinary Tract Infection in a Renal Allograft Recipient	36-year-old woman, renal allograft recipient.	*S. gallinarum* is a rare cause of UTI and this was the first report in a renal allograft recipient.	UTI in kidney transplant recipient by nontyphoidal *Salmonella* is rare.	India[30]
Salmonella typhi	Pyonephrosis Caused by *Salmonella typhi*: A Case Report	47-year-old man.	A case of pyonephrosis due to *S. typhi* complication: a stone-related obstructive pyelonephritis.	Mechanisms of stone colonization by *S. typhi* little known.	France[31]
Salmonella Typhi	Chronic urinary carrier state due to *Salmonella Typhi* causing urinary tract infection in an immunocompetent healthy woman.	50-year-old woman.	Patients with a subclinical or treated history of typhoid fever can become chronic carriers.	The higher incidence of multiresistance strains and their increase during carrier status makes effective treatment of typhoid fever difficult.	India[32]
Aerococcus sanguinicola	Six cases of *Aerococcus sanguinicola* infection: clinical relevance and bacterial identification	6 cases.	6 cases of bacteraemia, 2 of which were associated with infective endocarditis. In 3 cases, the primary focus of infection was the urinary tract. The patients had a median age of 70 years and most of them had underlying neurological disorders. Reflecting the frailty of the patients, long-term prognosis was poor.	An optimal treatment option remains to be determined.	Denmark[33]
Aerococcus urinae	*Aerococcus urinae*, a rare cause of infective endocarditis	74-year-old male with a benign prostatic hyperplasia.	An elderly male with previous UTI was found with bacteraemia with *A. urinae*. Severe mitral regurgitation and a vegetation involving the mitral valve was demonstrated in an transesophageal echocardiogram.	*A. urinae* has difficult identification.	USA[34]
Aerococcus sanguinicola and *Aerococcus urinae*	Genomic characterization, phylogenetic analysis, and identification of virulence factors in *Aerococcus sanguinicola* and *Aerococcus urinae* strains isolated from infection episodes.	Eight strains of *A. sanguinicola* and 40 of *A. urinae* from patients with UTIs.	Gene homologs associated with antiphagocytosis and bacterial adherence were identified. Also genetic variability was observed within *A. urinae* genomes. Only strains of *Aerococcus sanguinicola* had genes implicated with biofilm formation and betahemolysin/cytolysin.	Inclusion of more clinical strains are needed to extend these analysis.	Denmark[35]

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Agent	Title	Sample or comments	Main findings	Limitations	Reference and country
Group B *Streptococcus*	Late onset group B beta-hemolytic *streptococcus* infection in a neonate manifesting as a urinary tract infection: a rare clinical presentation	A newborn at day 22 of life.	A neonate with UTI with prolonged neonatal jaundice due to late onset GBS infection. This manifestation of late-onset GBS disease in neonates is rare.	Only one case reported.	Malaysia[36]
Streptococcus pneumoniae	Pneumococcusuria: From bench to bedside	Six cases.	Coexisting predisposing factor with the isolation of *S. pneumoniae* in urine was present in all patients. Five out of the six patients having signs and symptoms of UTI were treated and cured.	Relevant data about this condition are scarce and the significance of isolation of *S. pneumoniae* in urine is not known.	India[37]
Viridans Streptococcus	Urethral defect due to periurethral abscess treated with a tunica vaginalis flap: A case report	36-year-old man	A good method for selected patients needing urethral reconstruction is the use of a tunica vaginalis flap. Pedicle-sparing tunica vaginalis is an advantageous material for resolving urethral defects. During treatment, the patient presented UTI due to methicillin-susceptible *Viridans streptococcus*	Studies with long-term follow-up are needed.	South Korea[38]
Corynebacterium riegelii and *Globicatella sanguinis*	Urosepsis caused by *Globicatella sanguinis* and *Corynebacterium riegelii* in an adult: case report and literature review	94-year-old Japanese man.	It is reported a rare case of urosepsis in a patient with nephrolithiasis caused by *G. sanguinis* and *C. riegelii*.	These pathogens are difficult to identify, and may have been misidentified in the past.	Japan[39]
Actinotignum (Actinobaculum) schaalii	Recurrent obstructive acute pyelonephritis: A rare form of *Actinotignum (Actinobaculum) schaalii* infection in a HIV-1 infected patient	47-year-old woman infected by HIV-1.	It is reported that the patient had five recurrent episodes of obstructive pyelonephritis due to multiple kidney stones. A pathogen was only isolated on the fifth UTI, with the diagnosis of *A. schaalii* infection. The patient was successfully treated with amoxicillin for six months.	Identification using standard laboratory methods is difficult. It is necessary to use enriched media and the presence of this pathogen can be neglected due to the growth of other bacteria.	France[40]
Actinotignum (Actinobaculum) schaalii	*Actinobaculum schaalii* an emerging pediatric pathogen?	8-month-old boy with hydrocephalus and a lumbosacral myelomeningocele.	Due to a high amount of leukocyte esterase in the urine, pyuria and bacteriuria, co-trimoxazole was started. After 48 h, small colonies of Gram-positive rods were observed, identified as *A. schaali* by sequencing the 16S *rRNA* gene. The treatment was changed to oral amoxicillin for 14 days, and it was successful.	The use of molecular techniques is often necessary due the challenging identification.	Switzerland[41]
Actinotignum (Actinobaculum) schaalii	First report of *Actinobaculum schaalii* urinary tract infection in North America	76-year-old female.	The patient's first urine cultures were negative. After the use of anaerobic cultures, it was possible to isolate, identify and appropriate antimicrobial treatment.	Correct diagnosis can be delayed due to current protocols for urine cultures.	Canada[42]
Actinotignum (Actinobaculum) schaalii	Infections related to *Actinotignum schaalii* (formerly *Actinobaculum schaalii)*: a 3-year	1602 bed hospital.	Among all analyzes, 27 infections were found, the majority (14) of UTI.	Sample recruitment bias.	France[43]

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Table Continued...

Agent	Title	Sample or comments	Main findings	Limitations	Reference and country
Actinomycetes	A case of frozen pelvis: primary actinomycosis of urinary bladder in a young boy	7-year-old boy.	The patient had abdominal pain, dysuria and a left hypochondrial mass, revealed by physical examination. A biopsy was performed and diagnosis of actinomycosis was made possible.	As actinomycosis hardly involves the urinary tract in children, it can be misdiagnosed.	Italy[44]
Corynebacterium aurimucosum	Urinary tract infection with *Corynebacterium aurimucosum* after urethroplasty stricture of the urethra: a case report	52-year-old man of Wolof ethnicity.	*C. aurimucosum* was identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry after repeated growth of the corynebacteria in three samples from the patient's urine.	Only one case reported.	Senegal[3]
Corynebacterium pseudodiphtheriticum	*Corynebacterium pseudodiphtheriticum* isolated from relevant clinical sites of infection: a human pathogen overlooked in emerging countries	113 strains.	These microorganisms were mostly related to infections in the urinary (29.2%) and respiratory tracts (27.45%) and intravenous sites (18.6%). Most strains (>50%) were resistant to oxacillin, erythromycin and clindamycin.	There are few reports on the profiles of antimicrobial susceptibility of the clinical isolates from varied sources.	Brazil[45]
Corynebacterium urealyticum	Encrusting cystitis due to *Corynebacterium urealyticum* in a patient with ANCA-associated vasculitis: case report and review of the literature	39-year-old woman.	Several encrusted calcifications in the bladder mucosa were revealed by computerized tomography and cystoscopy. Urine culture led to the diagnosis of *C. urealyticum* infection.	This condition can mimic (or complicate) a vasculitis flare involving the bladder.	France[46]
Mycoplasma hominis and *Ureaplasma urealyticum*	*Mycoplasma* and *Ureaplasma* colonisation in women with lower urinary tract symptoms	1,032 urine specimens.	319 were studies for atypical organisms (31 were repeated on the same patients). There were 97 positive cultures: 75 of ureaplasma only, 22 of combined *Mycoplasma* and *Ureaplasma* and 33 were also positive for typical organisms.	It was a retrospective observational study.	UK[1]
Gardnerella vaginalis	*Gardnerella vaginalis* bacteremia in a previously healthy man: case report and characterization of the isolate	*G. vaginalis* bacteremia in a previously healthy man with renal calculi and urosepsis.	First case of urolithiasis complicated by bacteremia by *G. vaginalis* in a man.	Initially, there was a misclassification of the causative agent.	Canada[47]
Alternaria alternata	Visceral phaeohyphomycosis caused by *Alternaria alternata* offering a diagnostic as well as a therapeutic challenge	21-year-old male.	Visceral phaeohyphomycosis caused by *A. alternata*, affecting the left kidney, associated with an immunocompromised state in a young patient with insulin-dependent type I diabetes.	The treatment is not standardized and therapeutic failure is documented in several reports.	Pakistan[48]
Aspergillus spp.	Urinary tract aspergillosis in a patient with chronic kidney disease	46-year-old man with chronic renal disease.	Infection with non-Candida fungus such as Aspergillus were suspected in patients with iterative flocculi in urine. The diagnosis depends on pathological examinations and culture. Posaconazole may be a suitable antifungal option for UTI due to fungus.	The diagnosis and treatment of this condition remains a clinical challenge.	China[49]

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Agent	Title	Sample or comments	Main findings	Limitations	Reference and country
Aspergillus fumigatus	Renal Allograft *Aspergillus* Infection Presenting With Obstructive Uropathy: A Case Report	29-year-old man with living non-related kidney transplantation.	A uroculture revealed growth of *A. fumigatus*. Ultrasound imaging showed hydronephrosis with echogenic material within the renal pelvis. Biopsy of the allograft kidney revealed severe necrotizing granulomatous inflammation consistent with Aspergillus species.	The route of infection in the patient was unclear.	Pakistan[50]
Aspergillus sp.	A rare cause of anuria in a case of pre-B acute lymphoblastic leukaemia.	18-year-old man.	When a hypoechoic mass is noted on ultrasonography of immunocompromised patients, high index of suspicion to fungal ball is needed. A bilateral fungal ball leading to anuria is a rare condition.	Clinical guidelines are still lacking.	India[51]
Candida kefyr	Candidiasis caused by *Candida kefyr* in a neonate: case report	Term neonate.	Candidiasis remains a major worry in neonates with risk factors. Knowledge about non albican Candida species and their sensitivities is of major importance.	It is not known the reason that makes *C. kefyr* more common in adult patients in oncohematology.	German[52]
Cryptococcus neoformans	Cryptococcoma of a transplanted kidney in a patient presenting with recurrent urinary tract infection: a case report.	30-year-old woman.	The lesion was visualized by FDG-PET/TC. The cryptococcosis in organ transplant patients should be included in the differential diagnosis by the clinicians.	The thesis that the cryptococcoma played a role in the relapsing bacterial is still an intriguing hypothesis.	South Africa[53]
Enterocytozoon bieneusi and *Encephalitozoon cuniculi*	Dual infection of urinary tract with *Enterocytozoon bieneusi* and *Encephalitozoon cuniculi* in HIV/AIDS patients.	Three HIV/AIDS patients, two men and one woman.	Microsporidiosis should be part of the routine investigation of HIV-positive patients, even asymptomatic. This is because this condition can cause severe complications or even death in these ones.	A large population study is still lacking.	Poland[54]
Geotrichum capitatum	*Geotrichum capitatum* septicemia: case report and review of the literature	Six cases.	UTI was documented in two patients due to multiple positive urocultures for *G. capitatum*. Overall the prognostic is poor with mortality over 50%.	No optimal curative therapy has been established.	Tunisia[55]
Saccharomyces cerevisiae	Invasive *Saccharomyces cerevisiae* infection: a friend turning foe?	51-year-old female.	Pyelonephritis due to a ordinarily benign human commensal organism was observed in a patient with chronic kidney disease and diabetes.	Diagnosing is difficult because it is a member of the human normal flora.	USA[56]
Trichosporon asahii	A rare case of urinary tract infection due *to Trichosporon asahii* in a diabetic patient	58-year-old diabetic patient.	This condition is rare, but its incidence is increasing.	The diagnosis is difficult.	Marroco[57]
Trichosporon asahii	*Trichosporon asahii* Infection in a Patient with Metastatic Prostate Cancer as an Example of an Emerging Fungal Pathogen	59-year-old white man.	The patient had nephrostomy tubes and ureteral stents implanted and *T. asahii* was cultured from the stent.	Due to database limitations, identification is not always 100% accurate.	USA[58]

Table Continued...

Agent	Title	Sample or comments	Main findings	Limitations	Reference and country
Trichosporon asahii	Emerging *Trichosporon asahii* in elderly patients: epidemiological and molecular analysis by the DiversiLab system	32 hospitalized patients.	The results present *T. asahii* as an emergent pathogen in elderly patients with urinary drainage devices.	Amphotericin B may remain inadequate against some strains.	Spain[59]
Trichosporon asahii	*Trichosporon asahii* as a cause of urinary tract infection: A rare human pathogen	55-year-old male.	Diabetic patient with a history of trauma, undergoing catheterization, who developed trichosporonosis.	Difficulty in etiological identification.	India[60]
Zygomycetes	Reno-invasive fungal infection presenting as acute renal failure: importance of renal biopsy for early diagnosis	34-year-old male.	The patients did not present predisposing factors for systemic fungal infection. A urine smear for fungal examination showed right angle branching hyphae and kidney biopsy showed fungal hyphae within the glomeruli, tubules and interstitium.	Culture identification of zygomycetes has been difficult.	India[61]
Human papillomavirus (HPV)	Condyloma Acuminata of the Urethra in a Male Renal Transplant Recipient: A Case Report	33-year-old man.	It is reported a case of condyloma acuminatum in a male deceased donor renal transplantation recipient. This conditions is rare and immunosuppressive conditions may allow the occurrence of condyloma acuminatum in an uncommon location.	The sampling for HPV testing in men is still lacking of established methodology.	Japan[62]
BK *polyomavirus* (BKV)	*Polyomavirus* infection of the urinary tract presenting as hemorrhagic cystitis in an immunocompetent five-year-old boy	Immunocompetent 5-year-old boy.	Sudden complaint of dysuria and hematuria due to BKV UTI detected by urine culture and confirmed with real-time PCR.	The primary source and means of transmission are poorly understood.	USA[63]
Citomegalovirus (CMV), *Gardnerella vaginalis, Ureaplasma* spp., *Mycoplasma hominis,* Herpes simplex virus-2 and *Trichomonas vaginalis*	Results of Real-time Multiplex Polymerase Chain Reaction Assay in Renal Transplant Recipients With Sterile Pyuria	60 consecutive patients (30 male and 30 female patients) who had undergone renal transplantation.	Sterile pyuria can suggest genitourinary pathogens that may not be showed by conventional uroculture method in renal transplantation patients. *G vaginalis* and obligate anaerobes should be considered as one of the infectious causes.	Further studies with larger series are needed on this topic.	USA[64]

The exact mechanisms that made atypical microorganisms emerge as cause of the disease are not yet well established for the majority of species, and sometimes even the sources and portal of entry remain little known.[15] Although these infections can occur in healthy individuals, some studies have demonstrated that risk factors are associated with the patients, essentially with individuals' intrinsic conditions, including their previous medical history and physical status, while others have implicated risky situations to which the patients are submitted (Figure 3).

The main risk factors for urinary tract infection include female gender, post-menopausal, in addition to the advanced age, prolonged use of methotrexate, and previous history of urinary tract infection.[5] Moreover, it has been mentioned some chronic diseases that contribute to the infection, such as diabetes mellitus and chronic renal failure,[25] also immunosuppressed status, and even urinary tract abnormalities.[27] There is also a rare case report of a late-onset *Ochrobactrum anthropi* sepsis in a preterm neonate with a posterior urethral valve.[24] In this case, no direct relationship was established between the newborn's clinical condition and gestational conditions, despite the need to place bladder shunts three times during pregnancy, in addition to highlighting the importance of performing invasive procedures and the immunocompromised condition for the development of infection.[24]

As mentioned, there are risk situations that enhances the proximity between patient and pathogen. In this scope, there is a greater emphasis on some acute clinical, circumstantial, or even behavioral conditions, which have also been related to urinary tract infections by specific Gram-negative bacteria. Namely, prematurity and *Enterobacter sakazakii,*[17] changed to *Cronobacter sakazakii*;[65] urethral trauma and *Raoultella ornithinolytica;*[26] *Edwardsiella tarda* and colonization of the gastrointestinal tract or gastroenteritis;[15] *Burkholderia pseudomallei* and agriculture or environmental exposure.[11]

Typhoidal and nontyphoidal representatives of *Salmonella* spp. were also isolated.[28,29,32] In addition to immunocompromised patients and those with chronic diseases, urinary tract abnormalities, such as lithiasis and fistulas, are related to urinary disease by nontyphoidal

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serotypes.[28] In parallel, it has also been discussed that the occurrence of a chronic carrier state enhances the access to the urinary system, relapse, and release in the environment.[29,32] Other examples include *Salmonella Gallinarum* in renal transplant recipient;[30] *Salmonella Stanleyville* after an episode of gastroenteritis;[30] and *Salmonella Typhi* associated with urolithiasis and identified in urine after a recent episode of typhoid fever, suggesting poor sanitary.[31]

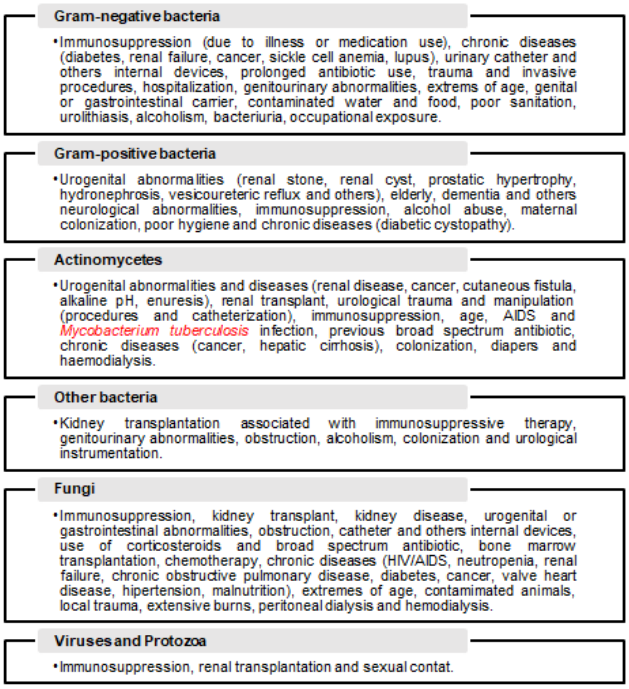

Figure 3 Risk factors by microorganism groups.

In addition, a few documented cases propose an association of the urinary tract infection with sexually acquired *Haemophilus quentini*.[18] Furthermore, it has been reported UTI by *Burkholderia pseudomallei* due to trauma during sexual intercourse,[11] in the same way as typhoidal *Salmonella* through sexual intercourse with anal penetration,[32] thereby suggesting the risky sexual behavior as another predisposing factor for atypical UTIs.

In the hospital context, hospitalizations and invasive procedures involving manipulation of the urinary tract, mainly catheterization,[13,24] since it uses potentially contaminated materials,[25] and the prolonged use of antibiotics for more than 14 days[14] are also likely to facilitate infection. In several cases, the microorganism's virulence factors, which may be involved in the infection establishment, require a very clear description. According to the studies, some factors are involved in: tissue adherence, as shown by *Ochrobactrum anthropi;*[24] biofilm production;[31] production of substances such as proteases, resistance to chlorination as demonstrated by *Chryseobacterium indologenes*;[13,14] and others, as shown in Table 2.

Depending on the characteristics of the agents and the hosts, as in the usual infections, atypical microorganisms can promote varied clinical presentations, and the same organism can cause variable morbidity and mortality. Additionally, Lee et al.[22] in a discussion about *Kluyvera ascorbata*, as a pathogen in adults and children, it is shown the possibility of patients with different ages and health status presenting infection with clinical significance and varied prognosis. Generally, the cases can range from an asymptomatic picture as seen in the *Haemophilus quentini* infection[18] or uncomplicated cystitis with *Brevundimonas vesiculari*[5] to infections that are more serious, such as *Raoultella planticola* in immunocompromised patients.[25]

Some Gram-negative bacteria are easy to identify by urine culture and biochemical tests with standard culture medium, like *Brevundimonas vesicularis.*[10] However, other species are not detected satisfactorily by traditional methods used in laboratory routines, either because these organisms can be mistakenly identified, confused with other organisms of similar patterns, such as the case of *Kluyvera ascorbata* with colonies similar to *Escherichia coli*;[20] considered contaminant;[11] or simply unidentified.[20]

Based on the studies assessed, urine culture is still an effective tool to identify some of the organisms, but alternative methods have been cited for reliable identification and confirmation of atypical/emerging species, including culture automated system; and matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry;[25,26] nucleic acid sequencing;[18] and restriction fragment length polymorphism (RFLP).[19]

Due to the low frequency of UTI associated with such bacteria, the discussion of the therapeutic approach becomes more difficult. The sensitivity and resistance patterns vary and might even depend on the strain origin (community or nosocomial).[10] Hence, the drugs empirical choice based on what is commonly used in UTI is not always convenient: in this scenario, it is important that empirical antibiotic therapy protocols consider sensitivity profiles according to temporal and geographical variations,[9] and take into consideration the emergence of the atypical organisms, some of them multi-resistant. Therefore, antibiotic susceptibility testing (antibiogram) is essential and is indicated as mandatory in specific cases, because it allows choosing the most appropriate therapy, based on the response of the organism to the drugs tested.[12] Table 2 shows the information on the sensitivity/resistance patterns of each microorganism, as well as diagnostic methods used and other characteristics inherent to the agents.

Gram-positive bacterial infections

Krishna et al.,[37] reported six cases of pneumococcusuria which validates the role of Gram-positive cocci. Five out of 6 patients having UTIs signs and symptoms were successfully treated. In this context, urinary tract abnormalities like hydronephrosis and kidney stones may predispose to UTI by *Streptococcus pneumoniae*. These cases reveal that *S. pneumoniae* strains usually seem to be uniformly sensitive to amoxicillin-clavulanic acid, cefuroxime, ceftriaxone, ciprofloxacin, nitrofurantoin, and co-trimoxazole. In addition, the authors assume that *S. pneumoniae* may not be a relevant cause of UTI, but it is important to be aware of the possibility of this unlisted emerging pathogen for antibiotic therapy.[37]

A neonate also was reported with late-onset neonatal Group B *Streptococcus* (GBS) infection, manifesting as a UTI and presenting with prolonged neonatal jaundice. GBS infection is characterized as either early-onset (presenting within the first seven days of life) or late-onset disease (presenting between 7 days and 3 months of life), but, although GBS remains a major cause of sepsis and death in neonates, its isolation from the urinary tract at this age is rare.[36] In addition, *viridians group Streptococcus* has been described as a periurethral abscess agent.[38]

A large number of UTI-causing bacteria are often associated with urosepsis, in which the pathogenic strains get access into the bloodstream.[35] Three members of the *Aerococcaceae* family were reported in cases of urosepsis, namely: *Aerococcus sanguinicola*,

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Aerococcus urinae, and *Globicatella sanguinis*.[33,35,39] The genus *Aerococcus* includes seven distinct species, five of which are known to be human pathogens: *A. christensenii, A. sanguinicola, A. urinae, A. urinaehominis*, and *A. viridians*.[66] The first time that *A. urinae* was isolated from a urine sample of a patient with UTI was in 1984.[35] Although *A. sanguinicola* has not been frequently found in clinical specimens,[33] it is currently the second bacteria of the genus most often isolated in urine cultures, after *A. urinae*.[66] These species identification has been difficult, with probable several misdiagnoses.[34,66] Nevertheless, DNA sequencing usage increased significantly as a method for bacteria demonstration and identification.[33] Moreover, mass spectrometry technology is an alternative for identifying the most relevant *Aerococcus* species.[66]

UTI has been known because of the interaction between uropathogens and the host.[4,5] Nevertheless, there is still very limited knowledge regarding the bacterial pathogenicity and virulence mechanisms that lead members of the *Aerococcaceae* family to cause and maintain infections.[35] Carkaci et al.,[35] performed a genomic characterization of several strains of *A. sanguinicola* and *A. urinae*, finding core-genes associated with antiphagocytosis, adherence, and endotoxin. Moreover, genomic characterization also described that only *A. sanguinicola* strains contained a biofilm-associated transcriptional regulator gene homolog (*bopD*) with low sequence identities.[35]

In another article, an extremely rare case of urosepsis caused by *G. sanguinis* and *Corynebacterium riegelii* coinfection in a 94-year-old Japanese man with nephrolithiasis has been reported.[39] The authors emphasize the relevance of this find, since these two bacteria rarely are encountered in clinical laboratories, and most technicians and microbiologists are not familiar with their phenotypic characteristics as well as how to identify them.[39] In order to illustrate the difficulty, *A. urinae* is frequently misidentified as *Staphylococcus* spp. (growing in clusters), *Streptococcus* spp. (α-hemolysis), or as *Enterococcus* spp. (with similar antibiotic resistance pattern).[34]

The evidence gathered has led to considering *Aerococcus* as a possible emerging pathogen, since that it is highly likely that its prevalence will be underestimated considering the difficulties in diagnosis.[66] Regarding the clinical characterization, it seems that *A. sanguinicola* has a pathogenic role in predisposed, elderly, immunocompromised patients or those with a history of urogenital abnormalities, neurological deficiencies, and alcohol abuse.[33,66] It is worth mentioning that recommendations for the antibiotic treatment for *A. sanguinicola* are lacking, but the genus *Aerococcus* seems to be sensitive to beta-lactams and vancomycin.[33,66]

Actinomycetes infections

Actinotignum schaalii (formerly known as *Actinobaculum schaalii*) is a small Gram-positive, non-motile, facultative anaerobic coccid rod with slow growth,[40] member of the family *Actinomycetaceae*[65] which is frequently overlooked or considered as a contaminant in urine specimens.[67] Although, it has often been underestimated as a cause of UTI,[43] since the initial description of the genus, this species has been the most frequently reported in human infections.[41] The current protocol for urine cultures can lead to a delay in the correct diagnosis, so the recommendation is that clinicians consider unusual pathogens such as *A. schaalii* as a cause of UTIs when common bacterial agents cannot be established.[42] Thus, the visualization of Gram-positive rods in microscopy with an absence of microbiological growth in culture methods should prompt the search for unusual pathogens including *A. schaalii*.[41]

Certain species, such as *A. suis*, *A. urinale* and *A. massiliense*, can also be responsible for UTIs.[40] It was many times reported in elderly people with underlying urological diseases.[41,67] Although the role of *A. schaalii* in UTI in elderly patients is emerging, its implication in young adults is rare, and the infection description is rare in immunocompromised hosts.[40]

Colonization with *A. schaalii* depends on the risk factors, including age, presence of diapers, and enuresis.[41] Prostatic hyperplasia, besides long-term urinary catheter usage, anatomical disorders, and genitourinary tract cancer are also potential risk factors for the infection.[40] Therefore, these conditions should be taken into account in patients with difficult-to-diagnose UTIs.[40] Communication between the clinician and the microbiology laboratory is crucial to establish if further testing can be conducted.[42]

Moreover, *A. schaalii* seems to be naturally resistant to ciprofloxacin and metronidazole, and the vast majority is resistant to co-trimoxazole.[67] Considering this situation, further studies must be carried out in order to evaluate additional risk factors and define optimal choice and the antimicrobial treatment duration.[41]

Other bacterial infections

In addition to the bacteria already mentioned, there are other groups with less representativeness in our sample that emerge as cause of UTIs, such as members of the *Mycoplasmataceae* family and Gram-variable bacteria.

In a British study assessing the *Mycoplasma hominis* (MH) prevalence and *Ureaplasma urealyticum* (UU) in women with bladder symptoms with or without sterile pyuria, out of 1,032 urine samples analyzed 319 were submitted to culture, of which 97 were positive for atypical organisms: 75 UU only, 1 MH only, and 21 combined UU and MH infection.[1]

Although the course of the disease depends on the microorganism virulence and antimicrobial resistance, as well as the host's response. The study suggests that investigating the presence of atypical infection may be useful in cases of significant pyuria or female patient with repetitive episodes of cystitis that shows significant improvement of symptoms with the use of antimicrobial, but return after interruption.[1]

These agents have complex nutritional requirements and may not grow in routine culture media and methods. However, supported by studies that show that treatment with doxycycline has been effective in more than two-thirds of the patients who have frequent complaints such as polyuria, urgency, dysuria, and recurrent UTI,[68] even in face of difficulties exposed. A suggestion is that the urine culture and the treatment of these agents have to be taken into account before assessing the need for more complex diagnostic methods.[1]

Sarier et al.,[64] evaluated the pathogenic agent's identification in cases of sterile pyuria of kidney transplant recipients using immunosuppressive drugs and found *G. vaginalis*, *Ureaplasma* spp. and *M. hominis*. According to the authors, sterile pyuria is a probable indicator of identification failure by conventional uroculture, indicate the real-time multiplex polymerase chain reaction as an interesting alternative, since it is effective, and still allows the multiple organisms identification.[64]

In another study, Lagacé-Wiens et al.,[47] describe a case of bacteremia with urinary focus caused by *Gardnerella vaginalis* (Gram-variable agent) in a man with urolithiasis, but without comorbidities. Interestingly, this agent is an uncommon cause of bacteremia, especially in men, and, in these cases, generally

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associated with an immunocompromised state.[47] Furthermore, there was difficulty in microorganism identification. First, there was the growth of *E. coli* in urine culture, but not in blood culture. Then, considered as a contaminant in blood cultures performed later, initially the organism classification was a Gram-negative coccobacillus; and, finally, *G. vaginalis* that was correctly identified using API Strep strip (bioMérieux) and 16S *rRNA* genes sequence analysis. In this case, the treatment was successful, consisting of stone extraction and the use of ciprofloxacin, with no major complications.[47]

Fungal infections

It is a widely held view that the *Trichosporon asahii* is an emerging pathogen.[58] Yeasts of the genus *Trichosporon* are cosmopolitan, widespread in the environment (soil, water, organic substrates, and plants).[57] This yeast-like organism is able to cause superficial infections, such as white piedra, and mucosal-associated infections, known as trichosporonosis brought about by *T. asahii.*[58] It is reported that Invasive UTI caused by this agent is rare,[61] but it may occur especially in patients with urinary obstruction,[58] and elderly patients with urinary drainage devices.[59] It is also reported the role of this species as an emerging opportunistic pathogen for invasive infections in immunocompromised patients[57] who have cancer or other diseases,[58] such as diabetes.[60]

Although rare, these basidiomycota yeasts are involved in deep infections, which are difficult to diagnose and have a guarded prognosis.[57] *Trichosporon* spp. has several virulence factors that allow the development of disease and dissemination throughout the host, such as biofilms, enzymes, and cell wall components.[58] The virulence could have a connection to host defense since the profound trichosporonosis occur in patients with impaired cellular immunity and macrophage functions, but it may also depend on the species itself.[57] The ability to form biofilms, for instance, could enhance adherence on implanted devices, which contributes to the progress of invasive trichosporonosis, and favors escape from antifungal drugs and the host immune response.[58]

Therefore, the pathogen's early detection and identification are necessary in order to provide specific and appropriate treatment.[61] The mycological study based on direct examination allows establishing the diagnosis and initiating rapid and effective treatment.[57] Although deep-seated trichosporonosis is an emerging mycosis with high mortality, information on its causes is still restricted, there are still uncertainties regarding the optimal drug to be chosen for treatment, and there are few studies about the *in vitro* activity.[59] Increasing data show that amphotericin B has limited *in vitro* and *in vivo* activity against *Trichosporon* spp., including *T. asahii*,[58] so, this drug should not be a recommendation for the treatment of trichosporonosis.[59] Furthermore, echinocandins have demonstrated little to no activity against *Trichosporon* spp. additionally, they are not recommended for immunotherapy.[58] It has also reported that it can be adequately treated with diazoles, with voriconazole being the most active.[59] In overall, *Trichosporon* remains a challenge for diagnosis, species identification, and treatment.[58]

Kidney fungal infections usually occur in immunocompromised hosts, caused by opportunistic pathogens such as *Alternaria alternate.*[48] Some emerging fungi have been announced as rarely responsible for invasive infections and septicemia in profoundly immunocompromised patients, for example, *Geotrichum capitatum*, which was found in multiple positive urine cultures from two patients with UTI.[55]

Aspergillus spp., a common airborne mold that accounts for up to 40% of fungal contamination, has also reported as a cause of UTIs.[49–51] Nevertheless, aspergillosis limited to the urinary tract is an uncommon invasive aspergillosis type, which most often affects the lungs.[49] Pathological renal disease caused by Aspergillus infection has as characteristic multiple micro-abscesses, which indicate a hematogenous spread to the kidney.[50] Moreover, it has been reported as a causative of the ureteric fungal ball leading to obstructive uropathy in leukemia and renal allograft patients.[50,51]

There are three major transmission routes, including ascending infections (usually from indwelling bladder catheters), trauma or surgical interventions, and hematogenous spread (common in immunocompromised patients).[49]

According to the authors, a high level of suspicion is required in immunocompromised patients, particularly when hypoechoic mass is noted on ultrasonography[51] and when the patients are presenting with flocculi in urine, thus direct microscopy or culture of floccules in urine could be helpful.[49]

Taking into account that this entity is rare, data on the most effective treatment modality continue being limited.[50] However, a combined approach seems to be more suitable for renal aspergillosis management.[49] The pressure prompt relief is important for preventing permanent damage to kidneys in patients with aspergilloma and a minimally invasive approach should be chosen mainly in immunocompromised individuals to avoid additional complications.[51] For immunocompromised patients, posaconazole may be an appropriate alternative antifungal for urinary tract fungal infections.[49]

Another possible pathogen is the *Saccharomyces cerevisiae,* which does not produce toxins that are harmful to humans or animals, thus concerning the infections reported, the evidence is in favor of the increased vulnerability of the host rather than the increased virulence of the pathogen in causing invasive disease.[56] *Enterocytozoon bieneusi* and *Encephalitozoon cuniculi* can also cause severe diseases in immunosuppressed patients, such as those after organ transplantation, chemotherapy recipients, and patients with HIV-infection.[54]

In reno-invasive fungal infections, the kidneys can be involved in a focal or diffuse manner.[61] The clinical feature of this kind of infection is often non-specific[55] with the usual occurrence of renal failure and fever.[50,61] Considering that the definitive diagnosis is to be performed by kidney biopsy, in cases with a high level of suspicion, histology must be sought even in situations where other infectious agents have been isolated.[61]

Viral and Protozoal infections

Probably there are few studies addressing viral UTIs in literature. Hence, only three articles were included in our final sample. One of them reports a case of an immunocompetent 5-year-old boy with a sudden onset of dysuria and hematuria due to a self-limited BK polyomavirus (BKV) UTI detected in routine urine cytology (viruria), and confirmed by real-time polymerase chain reaction (real-time PCR).[63]

Polyomaviruses (PV), among them BKV and JCV, are known to be able to promote opportunistic infection in the immunosuppression context promoted by the microenvironment of the graft. The BKV most commonly causes polyomavirus nephropathy (PVN) and is strongly associated with hemorrhagic cystitis (HC) in bone marrow transplant recipients. On the other hand, the JCV is typically associated with central nervous system (CNS) disease and is a much less common cause of PVN.[69] Indeed, little is still known about the primary source of human exposure and the means of viral transmission regarding these kinds of viruses.[63]

On top of that, several causative etiologies may directly contribute to the development of hemorrhagic cystitis in pediatric and adult populations. According to Decker et al.,[70] damage to the bladder transitional epithelium and blood vessels by toxins, drugs, radiation, and viruses/bacteria may lead to HC. Furthermore, the exact viral mechanisms contributing to the HC pathophysiology as well as the etiological potential for viruses such as JCV, adenovirus, and Cytomegalovirus (CMV) remain quite unclear. However, there are numerous shreds of evidence linking BKV to HC.[70]

The other case report regarding the virus as an atypical pathogen in a UTI refers to a 33-year-old man who suffered chronic renal impairment with congenital hypoplastic kidney, requiring hemodialysis since the age of eighteen, and submitted to cadaveric renal transplant when he was 28-year-old. The patient presented with condyloma acuminata, caused by Human Papillomavirus (HPV), in the penile urethra, which led to mictional pain and urethral discharge.[62]

Kidney-transplanted patients were also involved with urinary symptoms. Sarier et al. (2017), using quantitative real-time multiplex PCR, analyzed the urine of 60 patients with sterile pyuria and 40 patients without sterile pyuria (control group) to detect unusual microorganisms that were not found using traditional methods. One of these patients with sterile pyuria had *Trichomonas vaginalis*, the only reported protozoan in atypical UTI of our sample. A patient presented herpes simplex virus-2 (HSV-2), and 10 patients with sterile pyuria presented CMV, but with no significant difference in relation to the control group.[64]

The importance of knowing that certain viruses have urological significance is that clinicians have to consider these kinds of infections in UTI clinical presentation because they can mimic signs and symptoms caused by typical urological pathogens, or even by certain types of urological cancer, but the treatment is completely different depending on each case.[63]

Conclusion

Urinary tract infection represents an important health issue, not only due to its clinical implications but also due to the epidemiological aspects since it comprises an expressive part of the (nosocomial and community-acquired) infections worldwide. Additionally, several studies were reported, mainly in the last two decades, an increasing number of UTI cases caused by atypical/emerging agents, which were made possible through the application, or combination, of new techniques as well as by the recognition of the pathogenic role of other microorganisms. In this context, some species detections are not easy by traditional methods used in laboratory routines due to their peculiarities, which denote the complexity in the detection of these agents and indicate that the list of atypical pathogens may increase in the coming years. In the present study, we verified cases caused by atypical bacteria, fungi, viruses, and a protozoan. Among bacteria, in line with the general epidemiology, there was a predominance of Gram-negative agents, not only in a number of articles found but also in terms of genus and species diversity. Regarding Gram-positive bacteria, it was observed a set of cocci and diphtheroids promoting infections. Moreover, some members of the *Mycoplasmataceae* family, actinomycetes, and Gram-variable bacteria were involved in some cases. Some uncommon species of yeasts, molds, and two microsporidia were also reported. Moreover, we found some atypical viral agents in the urinary tract, including BKV, HSV-2, CMV, and HPV; and one protozoan, *T. vaginalis*.

Overall, most of the studies demonstrated that the risk factors have an association with: (i) intrinsic individuals condition such as advanced age, female gender, enuresis, preexistence of chronic diseases, prostatic hyperplasia, immunocompromised individuals, obstruction, genitourinary tract anatomical alteration, or cancer. (ii) exposure to risky situations, for instance, diapers usage, long-term urinary catheter usage, and other invasive procedures involving the urinary tract manipulation, chemotherapy for cancer, alcoholism, prolonged use of antibiotics, and even risky sexual behavior. Mostly, the microorganisms assessed in the present study show opportunistic pathogens characteristics.

The major clinical implication of the occurrence of these atypical infections relies on the difficulty to diagnose since they can mimic signs and UTI symptoms caused by common agents, or because the laboratory test results can be inconclusive, consequently, compromising the proper clinical management. In this regard, we believe that the communication between the clinician and microbiology laboratory team is essential in order to assess whether additional testing can be performed and, thereby, increase the chances of diagnosis. Anyway, it is important that both are aware of the possibility of infections by these agents. Most of the pathogens addressed here required more sophisticated methods for identification, which not always are available in the laboratory routines, including urine culture with special media; molecular methods such as PCR, real-time PCR, and nucleic acid sequencing; and MALDI-TOF mass spectrometry. In addition, the sensitivity/resistance patterns of these organisms vary widely, thus, resorting to antimicrobial susceptibility testing is crucial, as it allows choosing the most appropriate therapy.

In conclusion, we recognize the difficulty to retrieve the studies that deal with this theme, due to the lack of standardized terms, which may have limited our search. Simultaneously, we emphasized the need for further studies to deepen the subject and clarify the pending aspects. Ultimately, we hope this article may contribute to expanding the knowledge on UTIs etiological agents.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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