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A REVIEW ON RECENTLY APPROVED DRUGS TO TREAT URINARY TRACT INFECTION

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Abstract

Urinary tract infection is one of the commonest infections to affect humans. Uncomplicated infections occur most commonly in healthy women .when uropathogenic bacteria, usually Escherichia coli, ascend from the perineum into the bladder and overcome host innate immunity. Complicated infections occur in patients with an anatomical or functional abnormality of the urinary tract. The diagnosis is made on the basis of symptoms and diagnostic precision is improved by urinalysis. Urine culture is important with severe, recurrent or complicated infection and when the diagnosis is unclear, for example, in children and the elderly. Most women with symptoms that resolve quickly do not require further investigation but in children, men and patients with recurrent or severe infection, imaging of the renal tract, functional testing and cystoscopy should be considered to exclude an underlying abnormality. Pivmecillinam is the pro-drug of mecillinam, a β-lactam antibiotic with a novel site of action and with specific and high activity against Gram-negative organisms such as Escherichia coli and other Enterobacteriaceae. Since its introduction, it has been widely used for the treatment of acute lower urinary tract infections (UTI), primarily in the Nordic countries. In contrast to the increasing resistance of urinary pathogens to other β-lactams particularly ampicillin/amoxicillin and to other UTI antibiotics such as trimethoprim and trimethoprim/sulphamethoxazole (TMP/SMX), the level of resistance has remained on a low level. Less than 2% of E. coli community isolates are resistant to mecillinam. This paper reviews the clinical data on Pivmecillinam with a special focus on the safety aspects. Exblifep is a novel β-lactam/β-lactamase inhibitor combination and a potential empirical therapy for resistant gram-negative infections. Exblifep noninferior to piperacillin/tazobactam for the primary outcome of treatment efficacy in patients with complicated urinary tract infections (UTIs) or acute pyelonephritis.

Keywords: Cystitis, Composite response, Resistance, Pivmecillinam, Exblifep.

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Introduction

A Urinary Tract Infection (UTI) is an infection that occurs in any part of the urinary system, including the kidney, ureters, bladder and urethra. It is more common in females when compared with males. UTI can cause life-threatening sepsis, but most infections are less severe. Nevertheless, UTI causes significant distress to the individual and is associated with high healthcare and social costs. UTI is most commonly bacterial, but fungal, viral and parasitic infections can occur. Infection of the bladder causing cystitis is the most common UTI but infection can occur in other parts of the urinary tract, causing pyelonephritis, urethritis and prostatitis. Bacterial colonization of the urinary tract is not always symptomatic and asymptomatic bacteriuria is a common

finding in women and the elderly. Most women with symptoms that resolve quickly do not require further investigation but in children, men and patients with recurrent or severe infection, imaging of the renal tract, functional testing and cystoscopy should be considered to exclude an underlying abnormality. Empirical antibiotic treatment started on the basis of symptoms and directed by urinalysis is suitable for uncomplicated cystitis but should be altered based on culture results for more severe infections. Three days' antibiotic treatment is usually sufficient for uncomplicated cystitis in women. As with all bacterial infections the rate of antibiotic resistance among uropathogenic bacteria is increasing. As many uropathogenic bacteria are resident in the gut, they will be exposed to oral antibiotics used for any indication. The rates of antibiotic resistance of the common uropathogens in eight UK centres . E. coli will frequently be resistant to oral penicillins and cephalosporins, but retains sensitivity to nitrofurantoin and quinolones. Patients with resistant. Most women with symptoms that resolve quickly do not require further investigation but in children, men and patients with recurrent or severe infection, imaging of the renal tract, functional testing and cystoscopy should be considered to exclude an underlying abnormality. Empirical antibiotic treatment started on the basis of symptoms and directed by urinalysis is suitable for uncomplicated cystitis but should be altered based on culture results for more severe infections. Three days' antibiotic treatment is usually sufficient for uncomplicated cystitis in women. UTI can cause life-threatening sepsis, but most infections are less severe. Nevertheless, UTI causes significant distress to the individual and is associated with high healthcare and social costs [1].

Infectious organisms are emerging day by day through various adaptations and changes which lead to burden on global, social economics, environment and ecological factor . Infectious agents may transfer from animals to humans or disseminate from isolated groups into new populations . Knowledge towards emerging infectious organisms and mechanism of transmission is essential to prevent form spreading of diseases [2]..

The objectives include

- To provide a highly targeted antibiotic treatment specifically for UTI's caused by Escherichia coli and other gram-negative pathogens.
- To reduce the emergence of antimicrobial resistance.
- Particularly in regions where resistance to common UTI antibiotics, like Trimethoprim or fluoroquinolines, is prevalent.
- To improve patient outcomes by offering a safe and effective alternative.
- It is alternative to broad-spectrum antibiotics with fewer side effects.

Types of UTI'S

A. Based upon organ involved, UTI classified as:

Lower UTI's: Infection in the lower urinary system

- Cystitis: Infection in the bladder. It is a common infection.
- Urethritis: Infection in the urethra.
- Vaginitis: Infection in the vagina.

Upper UTI's

Infection in the upper urinary system

- Pyelonephritis: Infection in the kidneys.

B. Based upon severity of the infection, it is classified as:

Uncomplicated UTI's: These occur in healthy people with a normal urinary tract and no known defects. For example, cystitis & pyelonephritis in women with a normal urinary tract are considered as uncomplicated UTI's.

Complicated UTI's

These occur in people with underlying conditions or abnormalities that increases the risk of infection for example: UTI's in men, pregnant women, elderly people are considered as complicated UTI's and also associated with blockages or obstruction in the urinary tract, such as an enlarged prostate in men [2].

The most common bacteria causing UTI's are

- Escherichia coli
- Klebsiella pneumoniae
- Staphylococcus saprophyticus
- Enterococcus faecalis [3].

Causes and risk factors

The cause of UTI is a bacterial invasion of Urinary Tract organs. There are certain factors that increase the risk of this invasion. These are:

a. Female gender

In females, the urethra is short and near the vagina that allows easy invasion of normal anal into it, which then move upward to involve other organs. Thus, the introduction of any new bacteria and its invasion into urethra leads to UTI [4].

b. Postmenopausal effects

The postmenopausal effects because of the lack of estrogen increase the risk of UTI. When estrogen is no longer there, the tissues of the vagina and vulva start to degrade and become thin; this causes normal flora to gradually vanish. Thus, allowing other pathogenic bacteria to residue, ultimately increasing the risk of UTI [5].

c. Decreased immunity

If the immune system is compromised because of some other diseases, the body will not be able to effectively clear the harmful agent, resulting in disease. Hence, a weak immune system is prone to UTI's.

d. Obstruction

The standing of urine for long periods initiates bacterial multiplication and thus, increases the risk of UTI [6].

7. Symptoms

1. Painful urination [dysuria]
2. Frequent urination
3. Urgent need to urinate
4. Cloudy or strong-smelling urine
5. Blood in the urine
6. Fever and chills [7].

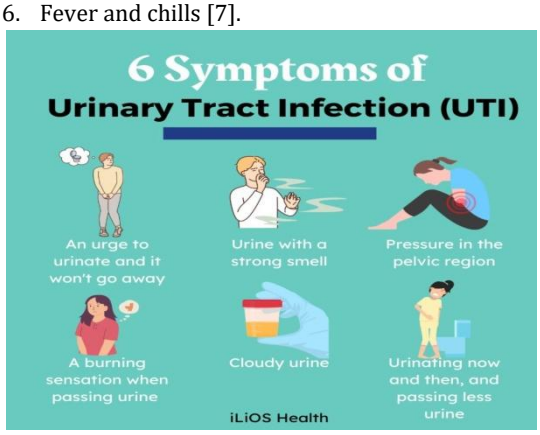

Figure 1: Symptoms of Urinary Tract Infection (UTI)

Diagnosis

- Diagnostic imaging
- Urinalysis
- Cystoscopy
- Renal function test (RFTs)

Treatment

1. Antibiotics: Targeted against the specific bacteria cause.
2. Pain management: for discomfort and pain.
3. Fluid intake: Adequate hydration to help flesh out bacteria.
4. Urinary Alkalinizers
5. Probiotics
6. Preventive measures

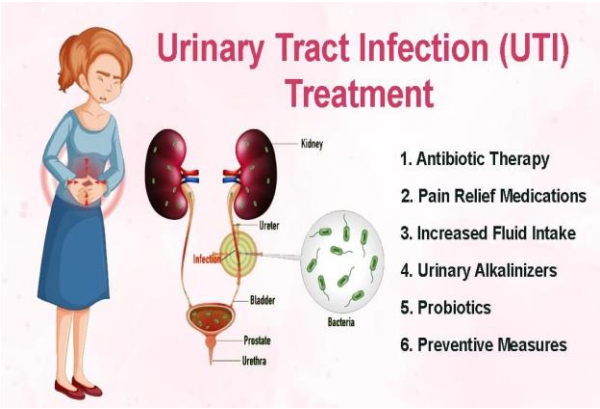

Figure 2: Treatment for Urinary Tract Infection (UTI)

Recently Approved Durgs to Tract UTI

PIVMECILLINAM (Pivya)

FDA Approval: April 24,2024

Drug Profile

1) Narrow-spectrum antibiotic.
2) Type of beta-lactam antibiotic
3) Prodrug (converted to the active form, Mecillinam in the body).

Other name: Amdinocillin pivoxil hydrochloride

Molecular weight: 476.03

Chemical formula: C21H34ClN3O5S

IUPAC Name:

[(2S,5R,6R)-6-{[(azepan-1-yl) methylidene] amino}-3,3-dimethly-7-oxo-4-thia-1-azabicyclo (3-2-0) heptane-2-carbonyloxy) methyl 2,2-dimethyl propionate hydrochloride [10].

Table 1: Trade names of pivmecillinam

Trade name	Dosage form	Dose	Manufacturer
Selexid	Tablet	185,200 &400mg	Leo pharma
Pivya	Tablet	200mg	Alkem laboratories
Pivmec	Tablet	400mg	Cipla
Mecillinam	Tablet	400mg	Glenmark

Absorption

well absorbed easily after oral administration

Distribution

widely distributed throughout the body tissues.
protein binding is 5 to 10% (as mecillinam)

Metabolism

pivmecillinam is hydrolysed to mecillinam

Excretion

Excreted through kidney & biliary mostly as mecillinam, elimination half-life is 1to 3hrs10

Uses

Pivmecillinam is primarily used to treat urinary tract infections (UTI's) and it's often used in the treatment of uncomplicated UTI's such as cystitis [12].

Side-effects

1. Gastrointestinal issues: nausea, vomiting, diarrhoea or abdominal pain
2. Allergic reactions: rash, itching or swelling
3. Altered taste: some people report a change in taste

Rare but serious side effects

Include severe allergic reactions(anaphylaxis), severe gastrointestinal conditions like pseudomembranous colitis, and liver enzyme changes [12].

Contraindications

1. Hypersensitivity

2. Pencilling allergy
3. Renal impairment
4. GIT disorders12

Clinical studies

The Efficacy of Exblifep was established in a double-blind, no inferiority study in adults with UTI, including pyelonephritis. Patients received Exblifep or Piperacillin/Tazobactam for 7days,or up to 14days for patients with concurrent bacteraemia. The microbiological modified intent-to-treat population included a total of 345 and 333 patients in the Exblifep and Piperacillin/Tazobactam treatment groups, respectively.

- In this trail Exblifep is given to 345 patients and piperacillin/Tazobactam are given to 333 patients.273 patients are cured with Exblifep and their composite response rate is 79.1% and 196 patients are cured with Piperacillin/Tazobactam and their composite response rate is 58.9%.
- Clinical cure rate is observed in Exblifep is 92.5% and in Piperacillin/Tazobactam is 88.9%.
- Bacteriological rate is observed in Exblifep is 82.9% and in Piperacillin/Tazobactam is 64.9%.16.

Conclusion

Men and women of any age can have urinary tract infections, but the incidence of urinary tract infections is higher in women than in men because of the female anatomy. Most patients attending outpatient clinics complaining of dysuria have a UTI, although it is possible that patients presenting with symptoms of a UTI are instead suffering from overactive bladder or interstitial cystitis. Diagnosis is not always straightforward. For many decades, midstream urinoculture has been considered the gold standard for UTI diagnosis. However, in about one-third of cases, a positive culture is not obtained, and it has become increasingly clear that bacteria may be present in the healthy bladder. The impact of UTIs on individuals is significant, as infections negatively affect individuals' mental health and sense of well-being. In addition, patients with recurrent UTI due to treatment failure caused by antimicrobial-resistant strains have a reduced quality of life. This trial compared a three-day regime of pivmecillinam with a three-day regime of sulfamethizole in patients with uncomplicated UTI. Both antibiotic regimes were followed by a rapid reduction of symptoms. However, patients treated with pivmecillinam experienced a faster relief of symptoms compared with patients treated with sulfamethizole. Among patients with complicated UTI or acute pyelonephritis caused by gram-negative pathogens, cefepime/enmetazobactam, compared with piperacillin/tazobactam, met criteria for no inferiority as well as superiority with respect to the primary outcome of clinical cure and microbiological eradication. Further research is needed to determine the potential role for cefepime/enmetazobactam in the treatment of complicated UTI and pyelonephritis.

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Conflict of interest

Author arte declared that no conflict on Interest

Ethical Statement and Inform Consent

Not Applicable.

Author Contribution

All authors are contributed equally.

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