

## Case Report



# Treatment of Recurrent Severe Cellulitis with a Pill in Pocket Approach

James B. Doub

Division of Clinical Care and Research, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, USA



Received: Sep 1, 2021

Accepted: Nov 15, 2021

Published online: Jan 14, 2022

### Corresponding Author

James B. Doub, MD

Division of Clinical Care and Research, Institute of Human Virology, University of Maryland School of Medicine, 725 west Lombard Street, Baltimore, MD 21201, USA.

Tel: +1-410-706-3454

Fax: +1-410-328-9106

Email: Jdoub@ihv.umaryland.edu

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### ORCID iDs

James B. Doub

<https://orcid.org/0000-0002-4977-0968>

### Funding

None.

### Ethics statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

### Conflict of Interest

JBD receives consultant fees from Adaptive Phage Therapeutics.

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## ABSTRACT

Cellulitis is a common condition that plagues healthcare systems and is associated with significant healthcare costs and resource allocations. With ample antimicrobial therapy this infectious syndrome can be easily treated but recurrence is common. Many conditions predispose patients to be at risk for recurrent cellulitis with chronic lymphoedema being a significant risk factor secondary to pooling of lymphatic fluid and impaired local immune responses. Moreover, patients with chronic lymphoedema can be at risk for acute onset of severe cellulitis requiring urgent medical evaluation and treatment. Consequently, to prevent recurrent cellulitis episodes, the use of long-term oral antibiotics has been advocated, but when recurrences occur despite long-term antibiotic use limited options are available. In this case report, a unique treatment approach for preventing severe cellulitis is discussed with a pill in the pocket approach with the use of oral tedizolid. This has thwarted the need for recurrent hospitalizations and reduced health care costs for this individual patient. Herein this treatment approach is discussed as is the rationale for using tedizolid instead of other antibiotics.

**Keywords:** Cellulitis; Lymphoedema; Oxazolidinones; *Streptococcus*; Tedizolid

## INTRODUCTION

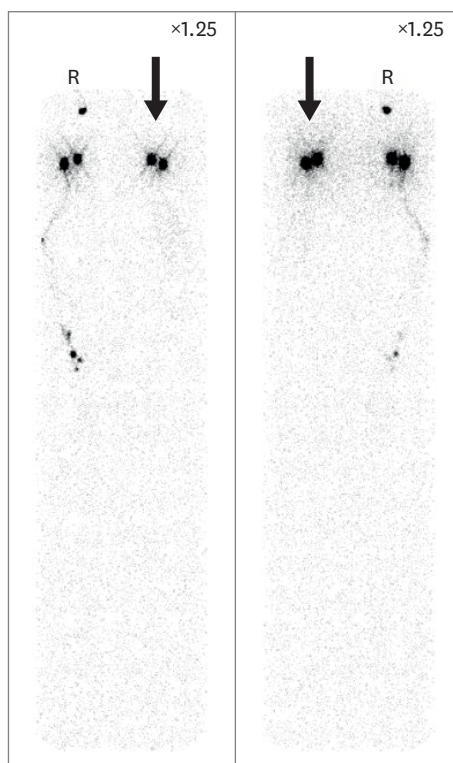
Cellulitis of the extremities is a common but painful condition that is associated with enormous healthcare costs and resource allocations [1]. This condition is a result of bacteria breaching the outermost layer of skin leading to a wide spectrum of soft tissue infections that range from erysipelas to necrotizing fasciitis [2]. *Streptococcus* and *Staphylococcus* are the most common bacterial pathogens responsible for these infections but in rare circumstances other bacteria such as *Pseudomonas*, *Pasteurella* and *Vibrio* can be causative pathogens [3]. Common risk factors include intravenous drug use, diabetes, obesity, immunosuppression, alcoholism and lymphoedema [4].

Recurrence of cellulitis is common and can occur in up to 50% of patients [2, 5]. Those that suffer from recurrences usually have chronic lymphoedema, obesity and/or a history of cancer [2, 5]. Chronic lymphoedema is especially prone to cause recurrence given the pooling of lymphatic fluid in the tissues and the associated poor local immune response [6]. Techniques such as manual massage, compression stockings, exercise and weight loss are conservative

management options that mitigate risk of recurrence but effectiveness of these techniques is patient dependent [7]. Consequently, the use of prophylactic long-term oral antibiotics such as penicillin has been advocated to prevent recurrent episodes [8]. When patients fail these interventions limited options are available. Herein a unique approach to treating recurrent cellulitis in a patient with chronic lymphoedema of her upper extremity is discussed. In this case, the use of a “pill in the pocket” approach with tedizolid has prevented recurrent severe cellulitis episodes thereby thwarting repeat hospitalization and reducing overall healthcare costs.

## CASE REPORT

58-year-old female presented to University of Maryland infectious disease clinic for alternative strategies to prevent recurrent severe cellulitis episodes that required frequent hospitalizations for intravenous antibiotics. Historically, the patient was diagnosed with adenocarcinoma of her left breast and underwent bilateral mastectomy as well as left axilla lymph node resections. After the surgery, she suffered from recurrent swelling of left upper extremity and was diagnosed with lymphoedema as seen on lymphoscintigraphy (**Fig. 1**). Conservative managements directed by a lymphoedema clinic with manual lymphatic drainage, compression garments, exercise and elevation, gave temporary relief but did not allow for long term improvements. Subsequently, she attempted alternative surgical interventions that included liposuction of left arm with limited success. With all these techniques she continued to have three severe upper extremity cellulitis episodes a year. These episodes were rapid onset and did not improve with any oral antibiotics: cephalexin, cefpodoxime, clindamycin doxycycline or sulfamethoxazole-trimethoprim. Thus, each episode would



**Figure 1.** Lymphoscintigraphy demonstrating lymphatic obstruction in the left upper extremity (black arrows) evidenced by absent lymphatic channels, absent axillary lymph nodes and presence of dermal backflow.

require hospitalization for intravenous antibiotics. Therefore, she sought consultation with an infectious disease physician who prescribed chronic daily oral penicillin therapy, but despite this long-term antibiotic therapy she continued to have recurrent severe cellulitis episodes necessitating hospitalization for intravenous antibiotics. Therefore, given her desire to reduce morbidity and financial ramifications she sought a second opinion.

On evaluation the patient was hemodynamically stable with a body mass index of 26 and mild left upper extremity edema but no erythema or chronic ulcers were observed on her left upper extremity. No dry skin or cracking was seen in the webs between her fingers and fingernails were clean and well kept. She commented that before each episode of cellulitis she would have sharp pain and tingling and then approximately six hours later her arm would become severely swollen and erythematous. This would then worsen and progress to fever and chills approximately 24 to 48 hours thereafter, prompting urgent medical evaluation in the emergency room even despite the use of different oral antibiotics.

After prolonged discussions, the patient elected to attempt to prevent the severity of her symptoms and hospitalization by having a prescription of tedizolid (Cubist Pharmaceuticals, Kenilworth, NJ, USA) to immediately take when symptoms started. Given the patient's use of chronic duloxetine, tedizolid was used instead of linezolid. For the past twenty months the patient has kept a six-day prescription of tedizolid in her pocket in case her symptoms recurred. Over this time course, she has had four episodes of recurrent cellulitis each successfully treated with immediate administration of tedizolid and consequently none of these episodes caused severe symptoms requiring hospitalization. With each episode the patient would have erythema and swelling of her arm, but the erythema would quickly resolve within 36 hours after initiation of tedizolid. After starting each six day course the patient would call the infectious disease clinic to ensure improvements were occurring on this medication and no adverse drug reactions. After complete improvement of symptoms another prescription was prescribed to be used with her next episode. Over the past twenty months, the patient has been content with the reduction in severe symptoms, thwarting the need for hospitalization as well as the reduced financial ramifications with this pill in pocket approach.

## DISCUSSION

The lymphatic system is responsible for maintaining hemostasis of interstitial fluids as well as filtering out bacteria that enter the interstitial space [9]. With chronic lymphoedema the disruption of lymphatic flow causes insufficient drainage of interstitial fluid resulting in high protein concentrations and therefore increased interstitial fluid colloid osmotic pressure leading to chronic swelling and fat distribution in the soft tissues [9]. Consequently, poor innate immune responses occur in these environments thereby predisposes these patients to be at risk for recurrent cellulitis episodes [7, 9]. Mitigation strategies include meticulous monitoring for distal digit cracks and ulcers, compression garments, elevation, manual drainage and chronic oral penicillin therapy [7-9]. However, these strategies are not universally effective and alternative surgical techniques such as liposuction have varying degrees of effectiveness [10, 11]. In this case, the patient had failed conservative therapies and even liposuction of her upper extremity. Obstinate, her recurrent cellulitis episodes were also recalcitrant to traditional oral antibiotics causing recurrent hospitalizations for intravenous antibiotics. It wasn't until she used tedizolid similar to that of a pill in the pocket used with beta-blockers for atrial fibrillation, that she was able to thwart the need for hospitalizations.

The pharmacokinetics of tedizolid make this an advantageous agent to be used in the manner discussed here. These properties of tedizolid include: 1) high bioavailability with oral administration, 2) long half-life of approximately 12 hours, 3) highly lipophilic with a large volume of distribution and 4) broad-spectrum of activity against Gram-positive bacteria [12, 13]. Therefore, using oral tedizolid at the initiation of her symptoms allowed for quick delivery of tedizolid to interstitial spaces and soft tissues thereby preventing escalation of symptoms. Clinical trials have demonstrated that tedizolid used for bacterial soft tissue infection had a better clinical response than vancomycin [14, 15]. Similar studies have also shown similar effectiveness of tedizolid when compared to ceftaroline, daptomycin and other intravenous agents [14, 15]. Therefore, tedizolid has similar effectiveness compared to intravenous antibiotics when used for Gram-positive bacterial soft tissue infections.

Moreover, bacterial toxin production may also be responsible for symptomology especially with streptococcal infections [16-18]. Consequently, not only killing and preventing bacterial growth in the soft tissues but also reducing the bacterial toxin production may be important in the treatment of severe soft tissue infections [16-18]. Beta-lactam antibiotics are poor inhibitors of toxin production but tedizolid is a potent inhibitor of bacterial protein synthesis [12, 13]. Therefore, tedizolid not only is similar to intravenous antibiotics in the treatment of soft tissue infections but it is also inhibits toxin production making it an ideal agent to be used as discussed here.

The main drawback of tedizolid use is the cost and consequently the need for prior authorization from insurance companies. In correlation this drug is not readily available to be dispensed at local pharmacies. These hindrances subsequently delay administration when this drug is prescribed ad hoc. In this case, it was imperative to have the patient have a prescription already filled by a pharmacist and be ready to be used when symptoms started. This mitigated the delays in getting the patient this medication and utilized tedizolid's advantageous pharmacokinetics to prevent severe symptoms. The other drawback with oxazolidinone use is the risk of serotonin syndrome when patients are taking medicines that prevent serotonin reuptake. While this severe side effect is low risk with the use of linezolid, the risk with tedizolid is theoretically lower [19]. This is secondary to tedizolid having a weaker, reversible interaction of monoamine oxidase compared to linezolid [19]. As discussed here, no adverse side effects from this therapy have occurred despite her duloxetine use.

While this approach is novel with recurrent soft tissue infections, a similar pill in pocket approach has been used with post coital urinary tract infections [20]. It should be noted that with each use, the patient was advised to call the infectious disease clinic to ensure improvement of symptoms and no side effects from tedizolid. If providers are to use this approach, close follow up is likely needed to ensure improvement and reinforce compliance with full antibiotic course. This is important as the rapid improvement of symptoms may sway some patients to erroneously consider their infections are cured thereby truncating durations and predisposing them to potential rapid recurrences.

In conclusion, chronic lymphoedema is a main risk factor for recurrent cellulitis and when patients fail conventional prevention strategies limited options are available. As seen here, this pill in pocket approach with tedizolid allowed for immediate high interstitial fluid and soft tissue concentrations of this antibiotic, have broad Gram-positive coverage and reduce toxin production thereby resulting in quick resolution of cellulitis symptoms. While this is a single case, prospective studies could evaluate the efficacy of this approach compared to

chronic oral antibiotic therapy to determine if this approach can reduce health care resources and costs for patients who have recurrent cellulitis.

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