Journal of Pakistan Association of Dermatologists. 2024;**34(4)**:1041-1047.

Review Article

Antibiotics used for erysipelas and cellulitis

Olivia Awwalin Sunarto, Hasnikmah Mappamasing

Dermatology and Venereology Department, Faculty of Medicine, Airlangga University, RSUD Dr. Soetomo Surabaya, Indonesia.

Abstract Erysipelas and cellulitis are common and often require hospitalization for observation of their progression. The main therapy is antibiotics. The objective of the study is to review antibiotics used for cellulitis and erysipelas. Bacteria which cause erysipelas and cellulitis are usually gram-positive bacteria, commonly beta hemolytic streptococcus bacteria such as Streptococcus pyogenes or hemolyticus and Staphylococcus aureus. The main therapy is antibiotics and symptomatic therapy. These are several classes of antibiotics used for erysipelas and cellulitis, such as beta lactamase derivate, macrolides and fluoroquinolones. However, current systemic reviews do not report any particular class of antibiotics as superior to others. Local guidelines based on localresistance patterns should be followed if available. Therapy for erysipelas and cellulitis are antibiotics and symptomatic therapy. Various classes of antibiotics can be used, but therapy should be adjusted based on the local resistance pattern of a particular center.

Key words
Erysipelas; Cellulitis; Antibiotics.

Introduction

Acute conditions like cellulitis and erysipelas are caused by bacterial infections of the skin and soft tissues.[1] Cellulitis is an infection that frequently affects the deep dermis and subcutaneous tissue. It manifests as redness (rubor), swelling (tumor), heat (calor), and pain (dolor), which are all common signs of inflammation. Meanwhile, the superficial lymphatic vessels and surrounding tissue are primarily impacted by the cellulitis variety known as erysipelas. Cellulitis is characterized by plaques with unclear boundaries, in contrast to erysipelas which is characterized by the presence of edematous plaques with clear boundaries and a bright red color.[2] Epidemiological studies on this disease are still few and have only been conducted in large hospitals, although it can actually be managed in primary health care facilities.[3] Erysipelas occurs in 10-100 cases per year, but cellulitis occurs in 24.6 incidences for every 1.000 patients per year.[4]

Cases of erysipelas and cellulitis are among the diseases that have indications for short inpatient observation and consume quite significant health funds. This is because improper diagnosis and administration of therapy results in unnecessary antibiotics being administered.[5] This review discusses appropriate antibiotic therapy to be given to patients with erysipelas and cellulitis.

Manuscript: Received on: October 16, 2023
Revision on: December 16,2023
Accepted on: April 29, 2024
Address for correspondence
Dr. AO Sunarto
Dermatology and Venereology Department,
Faculty of Medicine, Airlangga University, RSUD
Dr. Soetomo Surabaya, Indonesia.
Email: Oliviawwalin@gmail.com

Erisipelas and cellulitis

Superficial (dermal) involvement of erysipelas, a bacterial infection of the dermis and superficial subcutaneous tissue, results in a well defined lesion. Acute, subacute, or chronic connective tissue inflammation is referred to as cellulitis.

Cellulitis can spread superficially and deeper. The bacteria that cause cellulitis and erysipelas are the same.[6] The bacteria that cause cellulitis are usually predominantly gram-positive bacteria, most commonly beta hemolytic streptococcus bacteria such as Streptococcus pyogenes/hemolyticus and Staphylococcus aureus.[7] Cellulitis is classified into two, namely purulent and non-purulent. Purulent cellulitis is characterized by pustules, abscesses or purulent drainage.[8]

Physical barriers and active defense mechanism can prevent skin commensals invasion to the skin, hence preventing the infection. Blood vessels which are still intact can keep them good in integrity and function Immunity, blood vessels, or integrity of the skin can be regarded as risk factors for cellulitis. Patients with cellulitis who are hospitalized frequently exhibit this combination of risk factors. A history of cellulitis is the major risk factor for the condition.[11]

The elderly population suffers from comorbid conditions including diabetes or congestive heart failure, immune senescence, poor circulation, and skin atrophy. Malnutrition results in slower wound healing, less elastic and healthy skin, and decrease of immune system. Incidence, complications, and hospitalization rates are increased in diabetes patients.[9] These complications are bacteremia, osteomyelitis, and endocarditis. The majority of cellulitis in diabetes patients are caused by skin defects due to diabetic foot. In patients who have obesity morbidity, their skin are more easily damaged and heals more slowly.[11]

Minor trauma and skin injury can be port the entry of Haemolyticus Streptococcus, but many patients have unclear primary lesion. Insect bite and sting lesions are often be port the entry of infection. [12]

Recurrent erysipelas affects patients with obesity, insulin-dependent diabetes mellitus, history of malignant disease, tonsillectomy, peripheral arterial occlusive disease, chronic edema/ lymphedema, fungal infections of the leg, and chronic ulcers. Patients with recurrent erysipelas often have ipsilateral dermatitis.[13]

Inflammatory destruction of lymphatic, accompanied by lymphedema, is a primary pathogenesis of recurrent erysipelas. The lymphatic system has a role in host defense against skin and soft tissue infections. Lymphatic damage cause lymphedema, immunity disorders, impaired of phagocytosis function by polymorphonuclear leukocytes and easy to get infections.[14]

Antibiotics for erysipelas and cellulitis

Several groups of antibiotics are used to treat cellulitis and erysipelas. The chromosomal and plasmid beta-lactamases produced by Staphylococcus aureus and enterobacteriaceae are both effectively inhibited by beta-lactamases. Three derivatives are used in clinical settings: clavulanic acid, sulbactam, and tazobactam. Amoxicillin and ticarcillin (when combined with clavulanic acid), ampicillin (when combined with sulbactam), piperacillin and cefoperazone (when combined with tazobactam), and other gram-positive streptococci, including Staphylococcus (but not strains of methicillin-resistant Staphylococcus aureus), regain some of their antibacterial activity when combined with beta-lactamase. Ticacillin and piperacillin have a combination to against Pseudomonas aeruginosa.[15,16]

Tazobactam binds to chromosomally encoded enzymes produced by klebsiella and bacteroides species, clavulanic acid and sulbactam principally bind to plasmid-encoded beta-lactamases. The pharmacokinetics of clavulanic

acid and sulbactam in humans are comparable to those of amoxicillin and ampicillin.[15,16]

Cephalosporins are categorized into four generations based on their beta-lactamase stability and in vitro activity. They are antibiotics with a broad spectrum. While the third and fourth generations are more effective against gram-negative nosocomials including enterobacteriaceae and pseudomonas aeruginosa. The first and second generations are more effective against gram-positive cocci. In comparison to third generation agents, fourth generation drugs cover a wider range of gram-positive species.[15,16]

The most effective drugs against staphylococci are cephalothin, cephradine, cefazolin, ceforanide, and cefamandole. Bacteroides fragilis can be successfully treated with cefoxitin and cefotetan, however resistance has becoming more common. Ceftazidime is the most effective drug to against Pseudomonas aeruginosa, but it has less effectiveness to against Streptococcus and Staphylococcus. No agents from the first, second, third, or fourth generations are effective to against MRS. Patients with generalized skin and soft tissue infections can not be given combination of beta lactam/beta lactamase inhibitors and cephalosporins due to they are a broad spectrum antibiotics. These antibiotics combination can disrupt the normal flora. Cephalosporins are effective against resistant bacteria, particularly gram-negative species that naturally produce the extended-spectrum beta-lactamase (ESBL) enzyme. Cephalosporins can not protect MRSA.[15,16]

Group of macrolides include erythromycin, roxithromycin, azithromycin, and clarithromycin and lincosamides such as lincomycin and clindamycin have similar characteristics. Erythromycin comes in second place after clarithromycin in terms of in vitro activity against group A Streptococcus and methicillin-susceptible Staphylococci (MSSA) strains, while azithromycin is less effective than erythromycin. Streptococcus pyogenes erythromycin resistance is a problem that is getting worse the macrolide-resistant MRSA strains. 20–85% of MRSA strains, including 50% of erythromycin-resistant bacteria, have been reported to be clindamycin or lincomycin resistant. Stronger than lincomycin but comparable to erythromycin, clindamycin has anti-Streptococcus action.[15,16]

Fluoroquinolones group includes norfloxacin, ciprofloxacin, ofloxacin, moxifloxacin, levofloxacin, and prulifloxacin. This group is widely tolerated and engages in a variety of activities. The majority of these medications can be administered parentally and orally. They have comparable bioavailability pathways. Fluoroquinolones, with the exception of moxifloxacin, are ineffective against Streptococcus, anaerobes, and MSSA despite their broad spectrum of activity.[15,16]

The use of combination antibiotics was not supported by clinical trial data, according to a systematic analysis of the selection of antibiotics for erysipelas and cellulitis, which found no superiority of one antibiotic over another. There was insufficient evidence to support the use of intravenous antibiotics compared to oral antibiotics for treatments more than five days.[17]

United States (US) and United Kingdom (UK) national guideline recommend several antibiotics which we present in **Table 1**. Amoxicillin or flucloxacillin can be used for typical cellulitis caused by *Streptococcus pyogenes*. In typical pus-forming cellulitis caused by Staphylococcus aureus, flucloxacillin can be used. Doxycycline, minocycline, clindamycin, or vancomycin can be used in cases of cellulitis with MRSA bacteria. Macrolides such as erythromycin,

Tabel 1 Therapy recommendations based on organism.[18]

Clinical Presentation	*Organism*	*Antibiotics*
Typical cellulitis	*Streptococcus pyogenes*	Amoxicillin or flucloxacillin
Typical cellulitis-pus forming	*Staphylococcus aureus*	Flucloxacillin
Typical cellulitis-pus forming according to The Infectious Diseases Society of America National Guideline	*Community acquired meticillin Resistant staphylococus aureus* (CA-MRSA), *Hospital Acquired Meticillin Resistant Staphylococus aureus* (HA-MRSA)	Doxycycline or minocycline or clindamycin or vancomycin
Penicillin allergy	-	Erythromycin or clarithromycin or clindamycin
Cat or dog bite	*Pasteurella multocida*	Co-amoxiclav; if allergic to penicillin: doxycycline and metronidazole
Water exposure	*Aeromonas hydophila*	Ciprofloxacin
Sea water exposure	*Vibrio vulnificus*	Doxycycline
Necrotizing fasciitis	*Clostridium perfringens*	Benzylpenicillin, ciprofloxacin, and clindamycin
Butcher and fish	*Erysipelothrix*	Ciprofloxacin

clarithromycin, or clindamycin can be used in patients who have allergic with penicillin.[18]

Cellulitis can be divided into nonpurulent and purulent. Nonpurulent and purulent cellulitis are divided into three types based on their severity: mild, moderate, and severe. Fitzpatrick's Dermatology 9th edition states direct empirical antibiotic therapy against streptococcal and staphylococcal species is recommended in cellulitis therapy, but there is no evidence that states first choice of antibiotic. Therapy recommendations are based on purulence, systemic symptoms and clinical appearance, the patient's risk factors, and the level of drug-resistant pathogen communities **(Table 2)**.[19]

The duration of antibiotic administration according to *The Infectious Disease Society of America* (IDSA) guidelines is 5 days for patients without complications, with extension of therapy if symptoms of infection still occur. In general, it is usually 5 to 10 days for uncomplicated patients with extension of therapy in immunocompromised patients for 7 to 14 days. Diagnostic evaluation follow up at 24 to 72 hours, it is important to evaluate the therapy response.[19,20]

Recurrent cases of cellulitis are given prophylactic antibiotics such as low dose penicillin or erythromycin. This prophylaxis is given if there are recurrences 3 to 4 times per year.[19,21]

According to the European Handbook of Dermatological Treatments, the mainstays of treatment for erysipelas are bed rest, wet bandaging with saline, parenteral or oral penicillin, elevation of the lower limbs, and parenteral or oral penicillin. Penicillin procaine IM at a dose of 600,000 units 1-2 times per day, oral penicillin V at a dose of 250–500 mg every 6 hours, and erythromycin at a dose of 250–500 mg every 6 hours can all be used to treat mild cases of erysipelas in adult patients. In severe cases of erysipelas, the patient should be hospitalized while receiving parenteral aqueous penicillin G 600.000–2.000.000 units every six hours for 5–10 days. Clindamycin therapy can be used to treat erysipelas-related septic shock. Additionally, surgical debridement of the skin in cases of severe cellulitis or necrotizing fasciitis.[15]

Other varieties of macrolides, such as roxitomycin, clarithromycin, and azithromycin,

can be used as alternative treatments. The efficacy of these three medications is same as parenteral penicillin G. Erysipelas cases can use caphalosporins as a second line therapy. In special cases typical erysipelas can be difficult to differentiate with cellulitis.[25] Benzylpenicillin benzathine (tardocillin) 2.4 million units every three weeks for one or two years, erythromycin 250–500 mg twice a day, and routine minor wound treatment can be used for therapeutic prophylaxis.[15]

The Indonesian Association of Dermatology and Venereology (INSDV) made clinical Practice Guideline for erysipelas and cellulitis. According to these guidelines, the first line of antibiotics which can be used are cloxacillin/ dicloxacillin (adults 4x250-500 mg/day orally; children 25-50 mg/kgBW/day, it is divided to 4 doses a day), amoxicillin and clavulanic acid (adults 3x250- 500 mg/day; children 25 mg/kgBW/day, it is divided to 3 doses a day), or cephalexin (25-50 mg/kgBW/day, it is divided to 4 doses a day). Second-line antibiotics are azithromycin (1x500 mg/day on the first day followed by 1x250 mg on the second to fifth fingers), clindamycin (15 mg/kgBW/day divided into 3 doses), or erythromycin (adults 4x250-500 mg/day; children 20-50 mg/kgBW/day divided into 4 doses). In MRSA cases, INSDV 2021 recommends the use of trimethoprim-sulfomethoxazole (160/800 mg, 2 times a day), doxycycline, minocycline (2x100 mg, but not recommended for children aged 8 years), clindamycin (15 mg/kgBW/day divided into 3 doses). In severe cases accompanied by systemic infections or infections in areas at risk (for example the maxilla) parenteral antibiotics can be given. Antibiotics that can be used are nafcillin (1-2 grams IV every 4 hours, children 100-150 mg/kgBW/day divided into 4 doses), IV penicillin G (2-4 million units every 4-6 hours a day, children: 60- 100.000 units/kgBW every 6 hours), IV cefazolin (1 gram every 8

Tabel 2 Bacterial cellulitis therapy.[19]

Diseases	*Severity*	*First line antibiotics*	*Alternative antibiotics*
Nonpurulent cellulitis	Mild (no systemic disease); outpatient treatment with oral therapy	Cephalexin, Dicloxacillin, Penicillin V	Clindamycin, Macrolids (azithromycin, erythromycin)
	Moderate (≥2 criteria SIRS or failed therapy patient); acute conditions with IV therapy -Incision and drainage; culture and sensitivity	Cefazolin, Ceftriaxone, Penicillin G	Clindamycin, Vancomycin can be considered if associated MRSA colonization/infection
	Severe (≥2 criteria with rapid progression, hypotension or organ damage) or immunocompromised; hospitalization with IV therapy -Surgical evaluation for necrotizing soft tissue infection -Culture and sensitivity	-Broad spectrum with vancomycin and piperacillin-tazobactam -According to culture and sensitivity result	
Purulent cellulitis	Mild (no systemic disease); outpatient treatment with oral therapy. -Incision and drainage; can be considered for culture and sensitivity	Suspect MSSA: Cephalexin, Dicloxacillin Suspect MRSA: Clindamycin, Tetracycline (doxycycline, minocycline, tetracycline), Trimethoprim-sulfamethoxazole	Clindamycin
	Moderate (≥2 criteria or failed therapy patient); acute conditions with IV therapy) -Incision and drainage; culture and sensitivity	Suspect MSSA: Oxacillin, Nafcillin, Cefazolin Suspect MRSA: Vancomycin, Clindamycin	Clindamycin, Linezolid (MRSA)
	-Severe (≥2 criteria with rapid progression, hypotension or organ damage) or immunocompromised; hospitalization with IV therapy -Surgical evaluation for necrotizing soft tissue infection -Incision and drainage; Culture and sensitivity	Broad spectrum with vancomycin and piperacillin-tazobactam, According to culture and sensitivity result	Clindamycin, Daptomycin, Ceftaroline, Telavancin, Tigecycline

hours, children: 50 mg/kgBW/day, it is divided to 3 doses a day), or IV ceftriaxone (1-2 grams/day). If MRSA is present/suspected in severe infections, the antibiotic that can be used is vancomycin (1-2 grams/day in divided doses or 15-20 mg/kgBW every 8-12 hours intravenously, for 7-14 days) and in pediatric patients namely vancomycin (15 mg/kgBW IV every 6 hours). Other antibiotics include linezolid (600 mg IV or orally twice a day for 7-14 days, in children 10 mg/kgBW orally or intravenously every 8 hours) or IV clindamycin (600 mg every 8 hours or 10-13 mg/ kgBW every 6-8 hours).[22]

Local guidelines are based on regional bacterial resistance and updated more frequently to account for changes in pathogenicity and the latest evidence. Narrow-spectrum antimicrobials which focus on the causing organisms are typically selected for the treatment of cellulitis and erysipelas. A clinical microbiologist should be consulted if we suspect resistance of antimicrobial and there is any doubt about the choice of antibiotic. Therapy response should be evaluated based on clinical and biochemical markers.[23,24]

Prognosis

Erysipelas and cellulitis typically have good prognoses. Lymphatic and blood circulation are two ways which cellulitis and erysipelas can spread. In a retrospective case study, 42% of patients with cellulitis who were hospitalized also had systemic symptoms, like fever and an increased white blood cell count. Involvement of the lymphatic system can cause obstruction and damage the lymphatic system, which can be predisposing factors for recurring cellulitis. According to a prospective cohort study, 29% of erysipelas patients had a further episode within three years. There may also be localized necrosis and abscess development.[25]

Conclusion

Therapy for erysipelas and cellulitis is antibiotics and symptomatic therapy. Appropiate antibiotics according to the type of erysipelas and cellulitis can increase the recovery rate of patients with erysipelas and cellulitis. It can reduce the risk of severe complications. Patients with reccurent erysipelas and cellulitis 3 to 4 times a year, can give antibiotics 5 to 10 days for patient without complications.

Financial support and sponsorship None.

Conflict of interest Authors declared no conflict of interest.

Author's contribution

OAS, HM: Have made substantial contributions to the conception/ design of the work, dradting the work, reviewing it critically for important intellectual, have given final approval of the version to be published.

References

1. Sapuła M, Krankowska D, Wiercińska-Drapało A. In Search of Risk Factors for Recurrent Erysipelas and Cellulitis of the Lower Limb: A Cross-Sectional Study of Epidemiological Characteristics of Patients Hospitalized due to Skin and Soft-Tissue Infections. *Interdiscip Perspect Infect Dis*. 2020;**2020**:1307232.
2. Pearson D, Margolis D. Cellulitis and erysipelas. 9th ed. Kang S, editor. Vol. 1. New York: McGraw-Hill Education; 2019. 2746–2756 p.
3. Zuraida R. Penatalaksanaan Erisipelas pada Pasien Dewasa Usia 42 Tahun Melalui Pendekatan Dokter Keluarga. Medula. 2020;**10**:557–62.
4. Meilia Novarina R. The Profile of Erysipelas and Cellulitis Patients. *BIKKK - Berkala Ilmu Kesehatan Kulit dan Kelamin-(Periodicals of Skin and Venereology Health Sciences)*. 2015;**27(1)**:32-40
5. Ko LN, Garza-Mayers AC, St John J, Strazzula L, Vedak P, Shah R, *et al*. Effect of dermatology consultation on outcomes for patients with presumed cellulitis a randomized clinical trial. *JAMA Dermatol*. 2018;**154(5)**:529-36.

6. Griffiths CEM, Bleiker TO, Creamer D, Ingram JR, Simpson RC. Rook's Dermatology Handbook edited by Griffiths Bleiker Creamer Ingram Simpson.
7. Rositawati A. Studi Retrospektif: Profil Pasien Erisipelas dan Selulitis (A Retrospective Study: Erysipelas and Cellulitis Patients' Profile).
8. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJC, Gorbach SL, *et al*. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis*. 2014;59(2):e10-52.
9. Bläckberg A, Trell K, Rasmussen M. Erysipelas, a large retrospective study of aetiology and clinical presentation. *BMC Infect Dis*. 2015;**15(1)**:1-6.
10. Bystritsky RJ. Cellulitis. Vol. 35, Infectious Disease Clinics of North America. W.B. Saunders; 2021. p. 49-60.
11. Cranendonk DR, Lavrijsen APM, Prins JM, Wiersinga WJ. Cellulitis: Current insights into pathophysiology and clinical management. *Netherlands J Med*. 2017;**75(9)**:366–78.
12. Brindle RJ, O'Neill LA, Williams OM. Risk, Prevention, Diagnosis, and Management of Cellulitis and Erysipelas. *Curr Dermatol Rep*. 2020;**9(1)**:73-82.
13. Brishkoska-Boshkovski V, Dimitrovska I, Kondova-Topuzovska I. Clinical presentation and laboratory characteristics in acute and recurrent erysipelas. *Open Access Maced J Med Sci*. 2019;**7(5)**:771-4.
14. Chlebicki MP, Oh CC. Recurrent cellulitis: risk factors, etiology, pathogenesis and treatment. *Curr Infect Dis Rep*. 2014;**16(9)**:422.
15. Katsambas AD, Lotti TM, Dessinioti C, D'Erme AM. European handbook of dermatological treatments, third edition. European Handbook of Dermatological Treatments, Third Edition. 2015. 1–1579 p.
16. Etebu E, Ibemologi Arikekpar. Antibiotics: Classification and mechanisms of action with emphasis on molecular perspectives. *Int J Appl Microbiol Biotechnol Res*. 2016;**4**:90-101.
17. Brindle RJ, O'Neill LA, Williams OM. Risk, Prevention, Diagnosis, and Management of Cellulitis and Erysipelas. *Curr Dermatol Rep*. 2020;**9(1)**:73-82.
18. Phoenix G, Das S, Joshi M. Diagnosis and management of cellulitis. BMJ. 2012;**345**:e4955.
19. Sewon K, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, *et al*. Fitzpatrick's Dermatology. 9th editio. Sewon K, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, *et al*. editors. McGraw Hil Education; 2019.
20. Moran GJ, Abrahamian FM, Lovecchio F, Talan DA. Acute bacterial skin infections: developments since the 2005 Infectious Diseases Society of America (IDSA) guidelines. *J Emerg Med*. 2013;**44(6)**:e397-412.
21. Oh CC, Ko HC, Lee HY, Safdar N, Maki DG, Chlebicki MP. Antibiotic prophylaxis for preventing recurrent cellulitis: a systematic review and meta-analysis. *J Infect*. 2014;**69(1)**:26-34.
22. Perhimpunan Dokter Spesialis Kulit dan Kelamin Indonesia (PERDOSKI). Panduan Praktik Klinis. Perdoski. 2021;204–7.
23. Maxwell-Scott H, Kandil H. Diagnosis and management of cellulitis and erysipelas. *Br J Hosp Med*. 2015;**76(8)**:C114–7.
24. Brindle R, Williams OM, Barton E, Featherstone P. Assessment of Antibiotic Treatment of Cellulitis and Erysipelas: A Systematic Review and Meta-analysis. *JAMA Dermatol*. 2019;**155(9)**:1033-40.
25. Oh CC. Cellulitis and erysipelas: prevention. *BMJ Clin Evid*. 2015;2015:1-8.