On the pathophysiology and management of cellulitis

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Citation for published version (APA):

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Chapter 1

General introduction and outline of this thesis
Cellulitis and its burden

Cellulitis is a bacterial infection of the skin and/or subcutaneous tissue, characterized by redness, swelling, warmth and pain in varying degrees (Figure 1). It is one of the most prevalent bacterial infections: depending on level of care, reports estimate it is the third or fourth most common reason for initiating antibiotic treatment. In the Netherlands in 2018, the total cases of cellulitis and erysipelas (a subtype of cellulitis) added up to 11.1 cases per 1000 inhabitants, and roughly 7% of patients are reported to be admitted to the hospital. Hospitalized patients then make up for the bulk of the costs, as average costs of hospitalization are €5348. Luckily, only a small (but nonetheless significant) fraction of hospitalized patients will not survive: their 30-day all-cause mortality rate is estimated at 2%. This gives cellulitis the reputation of being a relatively mild infection compared to other major infections.

However, it is a frequently recurring disease, with 5-year relapse rates estimated to be over 40%. Data from the United States shows that patients with recurrent disease are admitted a little over 10% of the time, and health-care related costs are estimated at $587 per recurrent episode. This figure excludes admission costs, though, and is thus likely to grossly underestimate the total economic burden.

The pathophysiology of cellulitis

The origin of cellulitis remains shrouded in mystery. Historical teachings describe
a port of entry (port d’entrée) for bacteria somewhere on the skin, such as damaged interdigital webbing due to fungal infections, or small ulcers or lacerations. Potential pathogens which can normally be part of the normal skin flora, like *Staphylococcus aureus* or beta-hemolytic streptococci, find their way across the skin barrier. Cells of the immune system notice the intruders, and subsequent host response mechanisms initiate inflammation. The classical signs of inflammation – calor, rubor, tumor and dolor – ensue, sometimes accompanied by systemic symptoms like fever and nausea. These non-specific symptoms are seen in other diseases as well, making the diagnosis harder to establish, as evidenced by reports of up to 30% of cellulitis diagnoses being false. The most common sites of infection are the lower extremities, particularly the lower legs and feet.

Establishing a diagnosis remains difficult, partly because it is hard to reliably find the causative pathogen, thus proving the presence of infection. Using traditional culture techniques, a pathogen can only be detected in roughly half of all patients. Serology can be used retrospectively to determine if patients were likely infected with beta-hemolytic streptococci, and the clinical response to penicillin – a narrow-spectrum antibiotic – also narrows down the list of potential pathogens. Cultures results could also mislead physicians as it favors bacteria that can thrive on standard culture media. Recent studies show that simply harboring potential pathogens does not necessarily imply that they will become virulent and cause infections. Bacterial behavior is determined by multiple factors, such as the absence or presence of other species in the vicinity. With this background knowledge, it might be prudent to look at the entirety of the microbiota at the infected site. This is underscored by the notion that other skin diseases such as eczema and psoriasis are also known to have a pathogenic origin in a dysbiosis of the skin microbiota.

Regardless of causative pathogen, during an infection the body responds with multiple defensive mechanisms, ultimately all directed at pathogen clearance and host survival. Inflammation is the first step, but the coagulation system is a key player as well. Not only does the immune system activate the coagulation system, generally resulting in a procoagulant state that can result in coagulopathy, but coagulation conversely regulates the inflammatory response. These changes have been studied in multiple infection models, but cellulitis remains the odd one out. Interestingly though, where coagulopathy in other diseases can present itself both on the microvascular level, in the form of disseminated intravascular coagulation, and macrovascular level, in the form of deep vein thrombosis, such presentations
have not been described for cellulitis.\textsuperscript{15, 16} Rather, cellulitis has been shown not to have an increased risk for deep vein thrombosis, raising the question why this differs from other infections.\textsuperscript{17}

**Optimizing antibiotic therapy to reduce antibiotic resistance**

The cornerstone of cellulitis treatment is antibiotic therapy. Antibiotics are one of the most well-known forms of medicine in modern society. Although several antibiotic compounds have been utilized throughout ancient history, the year 1909 heralded the beginning of the modern antibiotic era with the discovery of the first antibiotic, arsphenamine, although the discovery of penicillin by Alexander Fleming two decades later was far more notable.\textsuperscript{18}

In 1928 Fleming was said to have exposed his culture plates with staphylococcal species to the air on his laboratory bench. After several days he noticed a mould had contaminated some of these plates, and had miraculously cleared the surrounding area of bacterial colonies. This substance with antimicrobial properties would later be called penicillin, as the mould was identified as a member of the *Penicillium* genus. This accidentally found antibiotic turned out to be effective against all Gram-positive pathogens, and it could be used in patients to cure pneumonia, syphilis, meningitis, diphtheria, skin infections and so on.\textsuperscript{19, 20}

The discovery of penicillin and other antibiotics has made infections which were previously lethal curable. Additionally, medical procedures that are potentially life-saving but come with an inherent high infection risk, such as surgery or chemotherapy, were now safe to perform thanks to the protective effects of antibiotics. Antibiotics therefore have had a significant impact on life expectancy, helping to increase the United States’ average of 47 years to 78 years in roughly a century’s time.\textsuperscript{21}

Antibiotics are certainly no panacea, but clearly play a central role in the healthcare system. In one study where they reviewed all hospitalizations from 323 U.S. hospitals within 2010, more than half of all hospitalized patients received at least one antibiotic during their stay.\textsuperscript{22} Between 2000 and 2010 the global consumption of antibiotics increased by 35\%, to an astronomical total of 70,440,786,553 defined daily doses, which equates to each person in the world receiving an average of circa 10 days of antibiotics per year.\textsuperscript{23}

Increasing consumption has a downside. The widespread use of antibiotics has led to a decrease in effectiveness, due to antibiotic resistance: the ability of
bacteria to circumvent the detrimental effects of antibiotics.\textsuperscript{24} Countries with low consumption like the Netherlands, where physicians tend to be strict in prescribing antibiotics and consumption is roughly 30-80\% of the amount of some other European countries, have resistance rates that are still manageable.\textsuperscript{25} The reason why bacteria are able to develop resistance as response to antibiotic use in such a short time period, is the fact that they multiply rapidly.

Similar to Charles Darwin’s finches on the Galapagos islands, which had evolved to thrive in a challenging environment, bacteria can adapt to become resistant to antibiotics.\textsuperscript{26} This is visualized perfectly in an experiment by Michael Baym and colleagues (Figure 2).\textsuperscript{27} In the experiment it took bacteria only eleven

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**Figure 2. Visualization of bacterial evolution to overcome antibiotics.**

The experimental setup used by Baym et al\textsuperscript{27} (A), where bacteria are nested on the outside of the agar plate with increasing concentrations of antibiotics towards the center, urging bacteria to evolve resistance mechanisms. Paths of evolution as established by determination of clones and video analysis (B). Sequential image captures taken 44h apart, showing the outgrowth of \textit{Escherichia coli} through multiple pathways over time (C).
days, which equates to several hundreds of bacterial generations, to evolve in such a way that they could endure an antibiotic concentration 1000 times higher than wild type bacteria could survive in.

There are several mechanisms through which bacteria can be resistant to antibiotics. Through mutations during cell division, or by adopting plasmids from other bacteria, they can acquire mechanisms to (1) modify or disable the antibiotics, (2) prevent the antibiotic from reaching its target, (3) preventing binding of the antibiotic to its target, or (4) indirectly affect susceptibility to antibiotics, for example by switching to different metabolism pathways. These mechanisms consume energy, making it a costly and risky asset for bacteria, unless they find themselves in situations where they actually use them.

Given enough time, bacteria can devolve such mechanisms as not spending energy on useless mechanisms allows them to thrive more, transferring back to an antibiotic-susceptible status. To give bacteria an incentive to lose their resistance mechanisms, or not gain them to begin with, we have to reduce their exposure to antibiotics. To achieve this on a global scale requires tremendous effort from multiple parties. Health care workers face the difficult challenge of improving their prescription practice, through increasing infection prevention, optimizing diagnostics to allow more specific treatments and reduce unnecessary prescriptions, and by cutting antibiotic usage in patients with infections to a minimum while not harming effectiveness.

Attempting to do the latter, researchers have shown in recent years that it is possible to treat several severe infections such as pneumonia and urinary tract infections, with shorter therapy durations. These infections carry an inherent high mortality risk and also have a high incidence, which makes research into novel treatment strategies appealing. Specifically, testing shorter durations of therapy can be risky considering the consequences of therapy failure, nevertheless it has been done and successfully so for other infections before. Evaluation of the optimal duration of antibiotic therapy for patients admitted with severe cellulitis has not been done before, although a 2004 study suggested mild cellulitis could be treated with shorter durations. Amidst a paucity of evidence on treatment, and thus a heterogeneity in treatment options, a multidisciplinary guideline has been developed and published in 2013. Taking into account the likely pathogens and their susceptibility to antibiotics, flucloxacillin is recommended as agent of choice. The optimal duration of therapy is yet unknown. Traditionally infections were treated for
somewhat arbitrary durations of therapy, usually in multiples of 5 or 7 days, equating to fingers on each hand or days in a week. Hence, the recommended duration for cellulitis is 10-14 days. Additionally, some physicians employ compression bandages or garments to reduce edema, although the possible positive or negative effects of this intervention have not yet been investigated. However, most interventions have not been investigated in proper clinical trials, which leaves clinicians divided on such issues.

**Scope of this thesis**

The overall aim of this thesis is to increase knowledge on clinical management of cellulitis, and to gain more insight in its pathophysiology. Primarily, this was achieved by means of the DANCE project: a randomized clinical trial investigating the duration of antibiotic therapy for cellulitis, in which we tried to find the optimal therapy duration. Subsidiary studies were performed within this trial, and cellulitis data in other existing databases were studied.

The key objective was to investigate if the antibiotic therapy duration could be shortened for patients hospitalized with cellulitis, and if we could identify subgroups within the heterogeneous population of cellulitis patients for which either diagnostics or therapy could be individualized.

**Part I** starts with a general introduction of the thesis’ subject. **Chapter 2** addresses the epidemiology of cellulitis and provides an insight of the pathophysiology as we currently know it, combining fragmentally reported risk factors into an all-encompassing model. It discusses the current diagnostic process with its challenges and its pitfalls, the current guideline on, and future prospects of, antibiotic therapy, and also other parts of clinical management, including considerations for admission, non-antibiotic management and preventing recurrences.

**Part II** entails the primary project of this thesis, the DANCE trial. In this clinical trial, we investigated whether patients hospitalized for intravenous antibiotic treatment of cellulitis were as effectively treated with a 6-day course of antibiotic therapy as with the guideline-recommended therapy duration of 12 days. We used flucloxacillin as study drug, which is the guideline-recommended agent. Until now, only one trial investigated the optimal duration of therapy duration in cellulitis. This was a small trial performed in the United States among primarily outpatients with mild cellulitis using a quinolone (levofloxacin) as intervention drug. **Chapter 3** is
Chapter 1

the published version of the study protocol of our large multicenter randomized clinical trial among patients admitted with severe cellulitis – the DANCE trial –, and details our methods and considerations. Chapter 4 presents the results of this trial.

In Part III, we further investigate the clinical phenotype that characterizes cellulitis patients in novel ways. The pathophysiological model which we describe in chapter 2 allows for clinical reasoning, and can provide clues in hindsight why patients developed cellulitis. However, we currently have no real way of predicting who will be afflicted. With the advent of affordable analysis of large amounts of bacterial DNA, it is now possible to discover which bacteria are present on a surface and in which quantities. As already mentioned, several skin diseases have been associated with disturbances in the skin microbiota as compared to individuals without skin disease.\textsuperscript{14} In chapter 5, we report on our study of the skin microbiota, in which we aimed to establish the relationship between the microbiota and the development and course of cellulitis, as well as find a means to detect the causative pathogen.

As noted above, the coagulation and immune systems both contribute to defense against intruding pathogens. For example, the coagulation system can contain pathogens in fibrin depositions, whereas the immune system kills pathogens directly or through antibody mediated mechanisms. In severe infections, both systems influence each other, and activation of coagulation, inhibition of anticoagulant mechanisms, and decrease in fibrinolysis, result in an overall net procoagulant state.\textsuperscript{36, 37} Chapter 6 describes the changes in the coagulation and fibrinolytic systems that occur in patients with cellulitis, and associates them with disease severity and outcome.

The majority of cellulitis patients are outpatients, and in general cellulitis is not considered to be a severe infection. However, a small fraction of patients become severely ill, enough so to be admitted to the intensive care unit (ICU). The problem with low incidence rates of events or diseases in general, is that it is troublesome to collect specific data on these patients. In recent years, a large prospective cohort study was performed in our tertiary ICU, as well as the ICU of the University Medical Center Utrecht.\textsuperscript{38} Of all participants, a plethora of clinical information was collected. This large-scale study allowed us to not only describe patients with cellulitis who were admitted to the ICU, but also to compare them to patients with necrotizing fasciitis. Necrotizing fasciitis is a lethal and debilitating skin infection, which initially is poorly distinguishable from cellulitis. The results of this study are
presented in chapter 7.

Lastly, all findings from the previous chapters are summarized and discussed in Part IV’s chapter 8, and a future perspective for the research field is provided.
REFERENCES


35. Lavrijsen APM, Damstra RJ, van Dissel JT,
et al. Richtlijn cellulitis en erysipelas van
dele onderste extremiteiten 2013. Available
from: http://www.nvdv.nl/wp-content/
uploads/2014/08/Richtlijn-erysipelas-en-
cellulitis-2013.pdf [last accessed 22-1-2019].

36. Sax PE. New England Journal Watch -
How to figure out the length of antibiotic
jwatch.org/hiv-id-observations/index.php/
how-to-figure-out-the-length-of-antibiotic-
therapy/2010/10/22/ [last accessed 22-1-2019].

37. Levi M, van der Poll T. Inflammation and
coagulation. Crit Care Med. 2010;38(2
Suppl):S26-34.

38. Wiersinga WJ, Leopold SJ, Cranendonk
DR, van der Poll T. Host innate immune
responses to sepsis. Virulence. 2014;5(1):36-
44.

39. van Vught LA, Klein Klouwenberg PM,
Spitoni C, et al. Incidence, Risk Factors,
and Attributable Mortality of Secondary
Infections in the Intensive Care Unit
After Admission for Sepsis. JAMA.