On the pathophysiology and management of cellulitis

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Chapter 8

Summary, general discussion and future perspectives
Cellulitis is a skin infection which can affect people of all ages. It has been described in early written texts, but still remains poorly understood in this modern era. In this thesis we aimed to increase knowledge on clinical management of cellulitis, in order to optimize treatment for these patients and, in the process, hopefully reduce unnecessary antibiotic use. Our primary goal was to evaluate the optimal duration of antibiotic therapy for patients hospitalized with cellulitis, in the Duration of ANtibiotic therapy for CEllulitis (DANCE) trial. Adjacent to this trial, we sought to further elucidate the pathophysiology of cellulitis to improve our diagnostic and/or prognostic ability. For that, we performed ancillary studies on the skin microbiota as well as the coagulation system, and collected data to formulate other research questions which need to be addressed in the future.

SUMMARY

In chapter 2 we present a general introduction to the topic and provide a pathogenetic model for cellulitis. For cellulitis to occur, bacteria have to transfer the skin barrier and/or infiltrate the subcutaneous tissues. They then have to prevent being caught by the immune system before they get a chance to multiply excessively and become virulent. Normally, skin integrity helps keep bacteria out. Blood circulation keeps tissues in homeostatic conditions and populated with immune cells. The immune system serves to neutralize threats from infiltrated pathogens. Shortcomings in any of these three areas can lead to cellulitis. Traditionally, cellulitis was distinguished from erysipelas, which shared many features with cellulitis, but was thought to be different in origin. However, recent etiological studies, have led to the current concept that cellulitis is a clinical entity with different phenotypes, one of which is erysipelas. This is supported by the notion that physicians often find it difficult to properly make the accurate distinction between the two. Nevertheless, the diagnosis of cellulitis remains tricky as there are multiple diseases which mimic its signs and symptoms. Clinical studies show that up to one third of patients with the initial diagnosis of cellulitis actually have a different disease. Microbiological cultures are often negative, or unreliable, as bacteria cultured from suspected ports of entry could either be pathogens or commensals. At the time of writing, no validated scoring system for the severity of disease was available. This makes the decision to admit patients depend largely on circumstance and perceived illness. Antibiotic therapy is targeted against \textit{Staphylococcus aureus} and beta-hemolytic streptococci,
so beta-lactams are the antibiotics of choice, but the optimal therapy duration has not yet been identified. Of note, pre-antibiotic era studies reached cure rates of 70%, implying that for some patients the disease is self-limiting. When people have frequent recurrences, i.e. 2 or more episodes per year, prophylactic antibiotic therapy is shown to be effective. While adjuvant therapies, like compression therapy and non-steroidal anti-inflammatory drugs, may have some benefit on symptoms, this has been poorly investigated and the net effect on cure rates remains unknown.

Chapter 3 describes the setup of our DANCE trial. We performed a randomized placebo-controlled double-blind non-inferiority trial in which we included adult patients admitted for intravenous antibiotics for cellulitis, and compared 6 versus 12 days of treatment. Patients with allergies, concurrent infections, factors that justify Gram-negative coverage, or aspects of the disease that would normally require tailored therapy were excluded. The original power calculation showed that we would need 396 patients; after the publication of new trials on the antibiotic treatment of cellulitis this number was later adjusted to 316. Patients were recruited in initially 8 – and towards the end 11 – teaching and academic hospitals around Amsterdam and Utrecht. Participants were treated with flucloxacillin, which was given intravenously and at the discretion of the attending physician switched to oral administration. Participants with improving symptoms and resolution of fever were randomized, unless they needed escalation of antibiotics or prolonged intravenous treatment, ICU admission or surgery, or had positive blood cultures or allergic reactions. Treatment success was defined as cure by day 14 without relapse by day 28 in the modified intention-to-treat (mITT) population. Cure by day 14 was defined as the absence of pain and warmth, and a reduction of erythema and edema. Relapse was defined as the initiation of new antibiotics for cellulitis by non-trial physicians. Secondary outcomes included relapse by day 90, investigator- and patient assessed speed of recovery, quality of life, and per-protocol and subgroup analyses. Additionally, skin swabs and blood were sampled at multiple timepoints for additional studies.

The results of this trial are reported in chapter 4. In 2 years and 10 months’ time, 248 participants were included, of which 151 were randomized. Six days of antibiotic treatment for patients hospitalized for severe cellulitis appeared to be non-inferior to 12 days on the short term. However, a 6-day course resulted in more frequent relapses by day 90. Of note, only 48% of our intended sample size was obtained. The study was terminated early due to slow inclusion. While many
patients were ineligible for inclusion, a quarter of eligible patients was reluctant to participate, and some elderly participants were persuaded by family members to withdraw from the trial. Both of these are understandable, but unfortunate, effects of investigating reduction of therapy. In the modified intention-to-treat population, 71 participants received 12 days of therapy and 69 participants received 6 days. Treatment success rates reached ~50% in each group. It is possible that age, comorbidity and disease severity, which were high and plenty in our population, played parts in this relative low treatment success rate. However, it is more likely that the strict definition of treatment success which we used contributed to the observed low treatment success rate. Hence, before we broke the randomization code, we adjusted the operationalization of our parameters for a new treatment success definition, which means we devised new cure criteria using the variables that we had already collected (cellulitis severity score, its’ individual components, fever, new antibiotic use). With this new definition, treatment success rates were 74.6% and 71% for the 12- and 6-day groups, respectively. Although these differences appear small, in both analyses we could neither exclude or conclude non-inferiority of the 6-day therapy, due to the underpowered nature of the study. For participants who were successfully treated, irrespective of which analysis was used, the 90-day relapse rates and readmission rates were higher in the 6-day group. The underlying mechanism behind such late relapses is unclear. Even if short-term therapy success rates are indeed non-inferior, such long-term downsides provide a strong argument against shortening duration of therapy.

In chapter 5, we investigated the skin microbiota in patients with cellulitis and studied whether its analysis could help determine the causative pathogen, and explored whether skin microbiota composition was associated with clinical outcomes. We randomly chose samples from 58 DANCE trial participants, and compared them to 19 control subjects without recent or current cellulitis. The participants were representative of our DANCE cohort in terms of demographics and disease characteristics. Profiling of the microbiota showed that Firmicutes were the dominant phylum, with *Staphylococcus* and *Streptococcus* being the dominant genera. There was a large interpersonal variation between cellulitis patients in skin microbiota composition at the lesion site. We also observed a large variation in total bacterial abundance across all samples, with no clear signature correlating to the presence of cellulitis. Looking at the microbiota composition, we could not distinguish patients from healthy controls, arms from legs, or cellulitis lesions from
the patient’s contralateral site. There appeared to be no consistent association between traditional culture results and skin microbiota signatures in patients. Unfortunately, in cellulitis wound cultures are no golden standard for the determination of the causative pathogen. This means that it is up for multiple interpretations, and is not able to reliably confirm or dispute microbiota analysis results. Microbiota parameters were not associated with measures of severity of disease, such as erythema surface area, c-reactive protein level, or symptoms at admission, nor with clinical outcome measurements like length of stay or treatment success. All in all, with this exploratory study on the skin microbiota in patients hospitalized with cellulitis, we were unable to identify a typical cellulitis microbiota. The diagnostic and prognostic information that could be derived from skin microbiota profiling in this patient cohort was limited.

Coagulation and immunity are intertwined. Infections like pneumonia, urinary tract infections and sepsis all confer a risk for thrombotic events. Cellulitis however is not associated with an increased risk for venous thromboembolic events. In chapter 6, we investigated the coagulation system in 60 patients admitted with severe cellulitis compared to 30 healthy control subjects. Cellulitis patients were in a pro-coagulant state, as levels of thrombin-antithrombin complexes (TATc), prothrombin fragment F1+2, fibrinogen were strongly increased. Von Willebrand Factor (VWF) levels were higher in patients as well, indicating a strong activation of endothelial cells. Additionally, thrombin generation tests showed an increased endogenous thrombin potential, peak generation, and velocity index and a decreased lag time, all hinting at disturbances in antithrombin function. Additionally, a markedly increased thrombomodulin sensitivity ratio suggested partial deficiencies in protein S or protein C. This all suggests a net procoagulant state. However, we observed no thrombocytopenia, and the prothrombin time and activated partial thromboplastin time were not prolonged. Simultaneously, D-dimer and plasmin-alpha2-antiplasmin complexes (PAPc) were increased, indicating an increased rate of fibrinolysis. The ratio between TATc and PAPc was normal, or even slightly lower than normal, showing the fibrinolytic response (over)compensated the procoagulant changes. When fibrinolysis and coagulation are balanced, thrombi will not accumulate and thrombotic events should not occur. In summary, we could demonstrate that cellulitis is characterized by marked activation of both the coagulation and fibrinolysis. Elevated levels of fibrinogen, PAP, and VWF correlated to severity of disease and length of stay, but this evidence is circumstantial at best.
Their potential use as a clinical biomarker warrants further study.

As mentioned in the introduction, cellulitis is often considered a mild infection with low hospitalization rates, and even lower mortality rates. However, some patients do become severely ill and require intensive care unit (ICU) admission. In chapter 7, we described what characterizes these patients, and we compared them to necrotizing fasciitis patients, which can initially have a similar clinical presentation at admission to the emergency department. We found that patients with cellulitis were far less critically ill in terms of shock, organ failure, or necessity for mechanical ventilation when compared to patients with necrotizing fasciitis. However, their initial Acute Physiology and Chronic Health Evaluation (APACHE) IV scores were not different from those of patients with necrotizing fasciitis. That might be primarily due to cellulitis patients having more chronic comorbidities such as cardiovascular insufficiencies or immunodeficiencies. As ICU admission depends largely on the need for organ support, and cellulitis patients are less critically ill, length of stay in the ICU was shorter. Length of stay in the hospital seemed shorter as well (median 22 vs 36 days), but this was not statistically significant. Most notably, in-hospital and 90-day mortality were similar between groups, which is surprising due to the lesser severity of illness. Whereas necrotizing fasciitis patients are likely to die due to the severity of the infection, we postulate that cellulitis has a different mortality mechanism. We think cellulitis destabilizes comorbidities, which are abundant in cellulitis patients. If they are not (or cannot be) treated appropriately, this could lead to increased mortality in the sub-acute period.

**DISCUSSION AND FUTURE PERSPECTIVES**

**Pathogenesis and diagnostics**

Cellulitis remains one of the most common infectious diseases, and put simply it is the inflammation of skin and/or subcutaneous tissue after pathogens have invaded it and have been recognized as such by the immune system. Herman Koch’s postulates have been criticized and altered over the years, but one thing all experts can agree on is that all patients with an infection should have a microbiological substrate.4 Not being able to find a pathogen leaves room for the idea that there is no infection. This is why some authors have challenged the idea that cellulitis is caused mainly by S. aureus or beta-hemolytic streptococci; they are not often identified, and
these authors found primarily *Rhodanobacter* and *Dyella* species – species not known to carry virulence genes or infect humans – in their microbiota analysis of tissue aspirates, leading them to believe cellulitis may be an immune response to atypical non-pathogenic bacteria.\(^5\)

The classical presumption that one has to have a porte d’entrée also appears questionable. Often some toe-web intertrigo is designated as the origin of cellulitis of the lower leg, but there are plenty of lower leg cellulitis cases where toe-web intertrigo is present without inflammation of the foot. Considering the vast network of lymphatic vessels in the foot, which protected our hunter-gatherer ancestors from dying of simple foot lacerations, it seems unlikely that bacteria could just bypass the foot altogether without notice. Alternative explanations could be that there are microscopically small permeations in the skin at the site of the lesion that facilitate translocation, or that translocation happens in the absence of skin damage, or even that bacteria enter the body elsewhere and precipitate in the skin.

Some experts even suggest there should be a distinction between non-purulent cellulitis cases where there are no breaks in the skin, and wound infections or abscesses, as the latter requires directed therapy against culture-able pathogens, and the former might not even require antibiotics at all.\(^6\) This idea is further strengthened by studies which measured procalcitonin, a biomarker which is increasingly used for discriminating bacterial infections from viral infections and non-infectious inflammation.\(^7\) In one study up to 63% of patients had levels below 0.25 ug/l, which is generally the cut-off value above which antibiotics should be started.\(^8\) Another study reports only 45% of patients had procalcitonin levels ≥0.05 ug/l.\(^9\) So either these patients did not have a true bacterial skin infection, or their bacterial infection was not severe enough to require antibiotics.

This uncertainty, combined with the clinical presentation being mimicked by plenty of other dermatological or vascular diseases, gives rise to the major roadblock in cellulitis research today: we have no golden standard for diagnosis, nor even a silver standard, as the best thing we seem to have is the expert opinion of seasoned clinicians.\(^9\) Using dermatology consultations as golden standard, a recent study employed thermal imaging to measure lesion skin temperature, compared it to the corresponding unaffected area, and achieved decent results in terms of positive (82%) and negative (83%) predictive value, but this technique requires further validation in larger cohorts.\(^10\)

In textbox 3 of chapter 2 (page 41), we listed the primary research goals /
questions for cellulitis research. It is no coincidence that the top questions are related to establishing a diagnosis. These questions are of paramount importance, as impure study populations of cellulitis trials biases them to non-inferiority. Similarly, they could lead to negative results in observational studies if associations that do exist, are not found to be statistically significant due to those associations not occurring in wrongly-diagnosed patients. Even in our DANCE trial, where we have internists judge the accuracy of the diagnosis, and had a day 5-6 checkpoint that allowed for excluding mimickers that didn’t respond to antibiotics from being randomized, we might have been hindered by misdiagnosis.

We had hoped that our microbiota analysis would contribute to detection of cellulitis and/or its pathogens, and possibly might help predict outcome. Unfortunately, our first results on the analysis of the skin microbiome does not suggest it has anything of value to add to current clinical practice. There is an extensive crosstalk between the immune system, keratinocytes and the skin microbiota, allowing for peaceful symbiosis with commensals while eradicating pathogens that interfere with homeostasis. It is therefore difficult to imagine that the microbiota plays no role whatsoever in the etiology of cellulitis.\textsuperscript{11} However, the question is when, where, and how the changes that characterize cellulitis can be picked up. First, we need to know if the whole body microbiome is affected, or only the inflamed area. In a case-control study, patients with cellulitis had less access to clean clothes, which might affect the global microbiota constituency.\textsuperscript{12} Second, if only local changes affect the development of cellulitis, we would need to find out where “local” is. Is it the wound or laceration that cellulitis originates from, if it is present and visible by the time patients see a doctor? Is it the point of maximum erythema, heat or pain, or is it the leading edge? And should we sample the microbiota in the upper layer of dead corneocytes, or rather somewhere towards deeper layers?\textsuperscript{13} Third, we would need to know what to look for, as the variables within microbiota analysis are abundant, especially when including the novel –omics analyses. Analysing variables that have no involvement with the disease might lead us to conclude that the microbiota analysis cannot contribute to management. Perhaps once these issues have been figured out, microbiota analysis will give us a quick, cheap (by then, hopefully), and easy way of determining if we’re looking at cellulitis, and if so, which pathogen.
Outcomes

Of equal importance as proper diagnostic means is the development of universal outcome criteria. A recent systematic review looked at the outcome parameters from the 48 cellulitis trials published up to then. The amount of different time-points for measuring outcome, means of measuring outcome, and criteria for success within those means, is simply dazzling. Regrettably, the United States Food and Drug Authority (FDA) have not yet deviated from their – by now – obsolete measures of erythema surface area for the determination of early clinical response. These have neither foundation in validation studies nor common sense, as sometimes erythema responds by fading out rather than regressing, and symptoms can get worse early on before they get better.

We need a universal set of outcome parameters for cellulitis trials. Ideally, it would (1) incorporate the fact that patients can have varying degrees of each of the symptoms, that can get better at different speeds, (2) measure parameters as objectively and with as little room for human interpretation as possible, and (3) use both a time-point shortly after end of therapy to evaluate alleviation of symptoms, as well as a time-point sometime after end of therapy to evaluate true pathogen eradication. If these outcomes are developed and universally used, cellulitis trials will become more comparable.

Non-antibiotic management

Future research projects will also have to address the clinical management of cellulitis other than antibiotic therapy. In chapter 7, we hypothesize that destabilizing comorbidity can have as much a detrimental effect on mortality as devastating infections have. It therefore comes as no surprise that a recently validated scoring system, the Dundee severity classification, finds that elderly patients and patients with heart failure, a disease frequently exacerbated by infection, have increased mortality risk with odds ratios of 9.37 and 6.16 respectively. Addressing comorbidities is therefore important in management, but it is of equal importance in the prevention of cellulitis. Varicose veins, lymphedema, tinea pedis, obesity, rheumatological conditions and liver disease all predispose patients to primary episodes of cellulitis as well as recurrent infections. Other comorbidities like diabetes, renal disease, congestive heart failure, peripheral vascular disease and chronic pulmonary disease also predispose patients to either primary or recurrent cellulitis. By effectively managing these conditions, the total incidence of cellulitis will hopefully decrease.
Additional therapies like compression therapy and anti-inflammatory drugs might be beneficial, if they prove to be effective in future trials. Using the data collected in our DANCE trial, we soon hope to provide the first observational evidence for or against compression therapy, as this has been up for debate for a long time, in absence of evidence.

To summarize, important questions for future research are listed in chapter 2’s textbox 3 (page 41). A British task group also put forward a number of interesting ideas or research questions that deserve attention. Some of them have already been discussed here. These include the questions whether a higher initial dose leads to faster resolution; whether non-antibiotic interventions are effective in prevention of cellulitis; whether exercise or rather passive leg elevation aids the healing process; what the early prodromal symptoms of cellulitis are, and whether using “pills in the pocket” as on-demand therapy when patients experience these symptoms helps reduce severity and/or necessary treatment duration; which clinical features at what time mandate a switch of antibiotic therapy; and lastly what the ideal marker is for the end of the infection. But first and foremost though, we need a true golden standard for diagnosis.
REFERENCES


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