Although approximately 4 million cases of non-healing ulcers are diagnosed annually in Europe, non-healing ulcers have been considered a negligible problem in society. Since there are only a few who understand the significance of the problem, there are very few in the health profession who are updated in terms of evaluation, diagnosis, and treatment of such wounds. In addition, many ulcers are never diagnosed, a fact that reflects both a lack of knowledge and also a low quality of care.

One problem among patients with non-healing ulcers is an excess usage of antibiotics. As early as 1998, Tammelin et al. reported that 60.1% of all ulcer patients were treated with at least one antibiotic within a six-month period. However, the indication for antibiotics was considered unfounded in most cases.

The bacterial environment in ulcers has been found to be more complicated than previously assumed. Based on new knowledge about the microbiology of non-healing ulcers, antibiotics may not be the most effective choice as a treatment strategy. Recently, there has been an increased focus on the formation of so-called “biofilms” on ulcers. Therefore, a paradigm shift in the treatment of non-healing ulcers is needed, especially among primary health services, to focus on better diagnoses and treatment of the underlying cause of the ulcer that reduces the incidence of unnecessary antibiotic therapy.

This article presents the results from an investigation on the use of antibiotics in ulcer patients who were referred to the wound healing unit at the Flekkefjord Hospital in Sørland from primary health services.

**MATERIALS AND METHODS**

The present investigation was performed as a prospective observational study from 1 January 2008 to 11 December 2008. The medical records for all patients with non-healing ulcers referred to Sørlandet Hospital Flekkefjord were obtained from doctors in the primary health services (e.g., on-duty doctors, personal physicians, and nursing home physicians). For cases that lacked the information needed for the investigation, questionnaires were mailed to the family doctor. Data from 105 of a total of 110 patients were evaluated in this investigation.

In addition to this investigation, a non-systematic literature search was conducted in PubMed.

**RESULTS**

The average age of the patients was 68.6 years (age range: 2-98). The average age of the ulcers was 7.1 months (1-36 months). Figure 1 shows a distribution of the ulcer diagnoses among these patients.

60 (75.1%) patients received treatment with antibiotics before they were referred to the Wound healing unit.

56 (53.3%) patients were treated with systemic antibiotics and 9 (8.6%) patients were treated with local antibiotics. Two or more antibiotic treatments had been prescribed in 14 (13.3%) patients.
Antibiotic treatments were administered in 78.3% of patients with traumatic or postoperative ulcers, 66.6% of patients with venous ulcers of the legs, 36.4% of patients with pressure ulcers, and 30% of patients with arterial ulcers (Figure 2).

A bacteriological examination was conducted in 33 (31.4%) of patients. *Staphylococcus aureus* was found in 43% of these patients. Normal skin flora was found in 13% of these patients (Figure 3).

Antibiotics were administered in 84.5% of the cases in which bacteriological samples had been taken. Dicloxacillin, which is a beta-lactamase-resistant penicillin, was prescribed in 41% of these cases (Figure 4).

The personnel at the wound healing unit agreed with the indication for antibiotic therapy in only one case (0.9%). However, the Wound healing unit identified a need for systemic antimicrobial therapy in 6 (5.4%) patients who had not received this treatment from primary health services. Five of these 6 patients (83.3%) had an undiscovered and untreated cases of either osteitis or osteomyelitis, which is a clear indication for antibiotic treatment.

**DISCUSSION**

**Microbiology of chronic ulcers**

Conditions such as chronic venous insufficiency, arterial insufficiency, and pressure over time, can lead to the reduced reparation capacity of skin injuries, which can lead to non-healing ulcers. A non-healing ulcer, however, should not be regarded as a disease, but rather as a symptom of an underlying state. Bacteria will colonize within the ulcer if the protective barrier of the skin is broken. Therefore, the appearance of a chronic ulcer depends on several factors (Table 1). These
Table 1. Factors that enhance the risk of development of ulcer infections

<table>
<thead>
<tr>
<th>Systemic factors</th>
<th>Local factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic diseases, such as diabetes mellitus</td>
<td>Size of the ulcer</td>
</tr>
<tr>
<td>Systemic diseases, such as rheumatic diseases</td>
<td>Age of the ulcer</td>
</tr>
<tr>
<td>Other forms of chronic disease, such as HIV infection</td>
<td>Location of the ulcer</td>
</tr>
<tr>
<td>Old age</td>
<td>Local circulation</td>
</tr>
<tr>
<td>Malnutrition/poor diet</td>
<td>Necrosis</td>
</tr>
<tr>
<td>Alcohol/narcotics abuse</td>
<td>Suppuration and maceration</td>
</tr>
<tr>
<td>Medicines, such as steroids, oestrogens, and vitamin K antagonists</td>
<td>Edema</td>
</tr>
<tr>
<td>Smoking</td>
<td>Exposed bones or capsules</td>
</tr>
</tbody>
</table>

Factors also contribute to the development of infections in the ulcer. As Louis Pasteur (1822-1895), the father of modern microbiology, said: “The germ is nothing. It is the terrain in which it is found that is everything.”

There are various hypotheses regarding the interactions between ulcers and bacteria. The contamination–infection continuum hypothesis is based on the fact that chronic ulcers are contaminated or colonized by planktonics, i.e., free bacteria. In such situations, the healing of an ulcer takes place undisturbed, despite the fact that bacteria are present. Critical colonization, however, occurs when microorganisms begin to negatively affect the healing process. In such cases, subtle signs of infection can be observed, such as friable granulation tissue, lack of epithelial growth, and increased suppuration. Infection is present when at least three of the following classical signs of infection have been observed clinically:

- Redness (due to vasodilation)
- Local heat (due to vasodilation)
- Pain (due to the stimulation of nociceptive nerve fibres by cytokines)
- Swelling (due to increased vascular permeability)

This contamination-infection continuum hypothesis adequately explains the inflammation observed in acute ulcers, e.g., in cases of postoperative infection.

Bacteria are always found in chronic ulcers. There are often multiple types of bacteria observed within a single ulcer. For example, the flora usually found in cases of venous ulcers of the legs include Staphylococcus aureus (90.5%), Enterococcus faecalis (71.7%), and Pseudomonas aeruginosa (52.2%). The bacterial flora found in a non-healing ulcer change as the ulcer ages. Staphylococci and streptococci bacteria are normally found in new ulcers, while gram-negative mixed flora are often found in older ulcers. In addition, different types of ulcers are influenced by different types of bacteria. For example, a clinical infection will develop in 60% of diabetic foot ulcers but only 20% of venous leg ulcers that are colonized by Staphylococcus aureus. Other systemic and local factors also influence the development of an ulcer infection.

Between 1.6 and 4.4 species of bacteria are found per ulcer by conventional culturing methods. However, molecular biological methods suggest that even more species of bacteria are present in the average ulcer. The number of ulcers with anaerobic bacterial growth is estimated to be between 25% and 82%. The most common anaerobic bacterial species are Peptostreptococcus and Prevotella. However, many ulcers heal despite the fact the presence of these microorganisms. The presence of anaerobic bacteria is therefore not necessarily a sign of an ulcer infection.

Recent research has indicated that the presence of bacterial biofilm contributes to the development of chronic ulcers. Biofilm, which is a well-known cause of periodontitis, has also been observed in cases of infection that involve medical implants and catheters. Studies performed by James et al. have shown that biofilm is present in 60% of chronic ulcers but only 6% of acute ulcers. This supports the view that biofilm probably plays an important role in the formation of chronic ulcerations.

In contrast to planktonic, i.e., free bacteria, the bacteria in biofilm are organized into a layer that consists of proteins, nucleic acids, and polysaccharides. The biofilm is affixed to the surface of the ulcer. The physical properties of the biofilm protect the bacteria against most forms of chemical, biological, and physical stress. These properties also protect the bacteria against antibiotics and the immune response (e.g., neutrophil granulocytes). In addition, the biofilm assures the maintenance of a chronic inflammation in the ulcer. The bacteria in the biofilm release proteases. These proteases contribute to the breakdown of growth factors and tissue proteins that are responsible for repair processes in the tissue. The breakdown and decomposition products from the neutrophil granulocytes killed by bacteria play a role in the inhibition of the “search and destroy” capabilities of the macrophages. This breakdown and decomposition also leads to the destruction of tissue.
as well as an increased production of pro-inflammatory cytokines. Together, these processes contribute to the chronic inflammatory state of the ulcer.4

Pseudomonas aeruginosa is a microorganism whose ability to form biofilm has been well studied. When Pseudomonas aeruginosa is organized into a biofilm, it releases virulence factors that are capable of eliminating polymorphonucleated neutrophil granulocytes. Instead of removing bacteria and tissue residues, the leukocytes are dissolved and proteolytic enzymes are released. Some of these enzymes are so-called metalloproteases, which break down the extracellular matrix, including collagen and growth factors. Together with an increase in free radicals, the breakdown of the extracellular matrix prevents the initiation of the normal repair processes. A high level of harmful enzymes in combination with the breakdown of tissue, however, stimulates the immune system and constantly attracts new polymorphonucleated granulocytes. The immune system is maximally stimulated, which starts a vicious cycle that can be counteracted with antibiotics. In such a situation, Pseudomonas aeruginosa is prepared to “kidnap” the immune response of the host to create a bacteria-friendly environment. The maximally stimulated immune system brings an increased supply of blood to the injured area, which provides the bacteria with sufficient nutrients. Anaerobic bacteria are attracted to this site due to the consumption of oxygen around the biofilm. An oxygen gradient has also been demonstrated inside the biofilm, which means that the anaerobic bacteria are able to penetrate into deeper tissue15,16. These observations therefore suggest a synergistic interaction between ulcers and bacteria that have a greater importance than the isolated presence of any other pathogen.

A biofilm in an ulcer often appears as a membrane. Other characteristics include hypergranulated tissue that bleeds easily on contact, the absence of epithelial growth from the edges, suppuration, cyanotic discoloration due to oxygen deficiency, and a distinct odor from the ulcer site (Figure 5).

The results from our investigation on the use of antibiotics in patients with non-healing ulcers demonstrate that antimicrobial medications were administered in 84.5% of the cases in which microbiological samples had been examined. These results also suggest that the detection of bacteria provides an indication for antibiotic treatment. Figure 2 report the proportion of antibiotic-treated ulcers relative to the absolute number of ulcers. For example, 66.6% of all patients with venous ulcers of the leg (i.e., ulcus cruris venosum; UCV) had received antibiotics. However, venous ulcers of the leg have an inflammatory cause such that antibiotic treatment will not be effective. There may be either a lack of knowledge among primary care doctors about the aetiology of venous ulcers or a misinterpretation of the symptoms of inflammation as symptoms of infection that causes the doctor to analyse a microbiological sample. The current study was not designed to tease out the reasons why a doctor may order such a bacterial test.

An investigation performed by Kirketerp-Møller et al. showed discrepancies between ordinary cultures and genetic analyses (i.e., peptide nuclear acid fluorized in situ hybridization – PAN-FISH) from ulcers.17 Conventional laboratory methods to detect bacteria favor Staphylococcus aureus, which may explain why Staphylococcus aureus are observed in the majority of non-healing ulcers.

Figure 5. Ulcers on the forehead following skin transplantation after the removal of a basal cell carcinoma. Several clinical findings (e.g., hypergranulation, absent epithelial growth, suppuration) suggested that this ulcer was covered by a biofilm.
The occurrence of highly virulent organisms, such as *Pseudomonas aeruginosa*, is underestimated by conventional culturing methods. Dowd et al. used genetic methods to demonstrate that obligate anaerobes are present in 62% of chronic ulcers. This study concluded that bacterial cultures from ulcers rarely reflect the true bacterial population of the ulcer.

There are several indications that conventional microbiological methods reveal only organisms that grow relatively rapidly and are simple to detect in the culture medium. Importantly, biofilm cannot be detected by these methods. Therefore, better microbiological methods are needed to understand the bacterial environment of the ulcer. In clinical practice, samples from ulcers should be taken only in cases in which there is an indication for infection that could benefit from antibiotic therapy. Indications for systemic antibiotic treatment are shown in Table 2. As outlined in Table 2, there is a low threshold for administering antibiotics in patients with diabetic foot ulcers and in patients who are on immunosuppressive medications. However, an ulcer will never be sterilized by antibiotics. The assessment of the results provided by the microbiologist should focus on the correct choice of antibiotic that reduces the risk for resistant strains to develop.

Systematic reviews have not shown that antibiotics are an effective treatment for chronic ulcers. Clinical experience demonstrates that ulcers treated with antibiotics may improve over brief periods, but deteriorate after the antibiotic has been withdrawn. The results of the current study suggest that 13.3% of patients received repeated “cures” with antibiotics. However, the assumption based on current evidence is that, although the bacterial flora within an ulcer may be reduced over a brief period during antibiotic treatment, the polymicrobial flora return when the medication is stopped.

The excess use of antibiotics in ulcer patients was studied as early as 1998 by Tammelin et al. in Sweden. Their investigation showed that 60.1% of patients had received an antibiotic treatment over an observation period of 6 months. Their investigation also found resistant *Staphylococcus aureus* in 12.5% of these cases. The risk of developing methicillin resistance increases with the administration of systemic antimicrobial therapy.

Local antibiotic treatment of ulcers is not recommended because of the rapid development of resistance and the risk of allergic reactions. Nevertheless, the results of the current study indicate that local antibiotic treatment is widely prescribed. Several studies have suggested that products containing silver, honey, or iodine are recommended if local antibiotic treatment is necessary. Secretions from fly larvae have also been shown to kill bacteria. These larvae have also been used to eradicate methicillin-resistant *Staphylococcus aureus* (MRSA) from ulcers. Ulcer rinsing agents or bandages that contain betaine and polyhexamidine have also been shown to be effective treatments to reduce bacteria in ulcers.

A total of 80-90% of antibiotic use takes place outside of the hospital. An English study of antibiotic use among ulcer patients reported that more than 2 out of 3 patients with non-healing ulcers received prescriptions for antibiotics from their family doctor over the course of 1 year. For comparison, only 1 out of 3 patients with other diagnoses (not related to non-healing wounds) were prescribed antibiotics. This study also showed that antibiotics were administered over a longer period of time in ulcer patients compared with patients without ulcers. The practice of antibiotic prescription therefore seems to reflect uncertainty among physicians about how to treat ulcers.

Updated Norwegian guidelines on the use of antibiotics can be found in both hospitals and primary health services. An article by Berild and Haug confirms that chronic ulcers of the legs are most frequently colonized by non-dangerous bacterial flora and that good local ulcer treatment without antibiotics is sufficient. The guidelines suggest that caution should be taken with respect to the use of antibiotics in ulcers, except in diabetic ulcers of the foot or cases of demonstrated streptococci, and indicate that topical antibiotics are contraindicated. Other guidelines on the use of antibiotics in primary health services describe conditions such as erysipelas, diabetic foot ulcers, and impetigo as examples of skin and soft tissue infections. These guidelines also caution against the use of antibiotics. However, these publications do not mention guidelines for common types of chronic ulcers, such as venous leg ulcers, pressure ulcers, and postopera-

### Table 2. Indications for use of antibiotic therapy in ulcer infections

- At least 3 of the following clinical signs of infection:
  - Local heat
  - Redness that spreads more than 2 cm around the ulcer
  - Pain
  - Swelling
- Contact with bone (osteomyelitis/ostitis)
- Progression of the ulcer with the formation of satellite ulcers
- Clinical signs of infection by streptococci group A (erysipelas)
- Diabetic foot ulcers
- Patients with immunosuppression
tive infections. This lack of information about chronic ulcers may contribute to the uncertainty among physicians regarding the use of antibiotic therapy in these cases. The National Guidelines for antibiotics issued by the Norwegian Health Directory for primary health services, which is assumed to be the primary reference point for doctors who are faced with a clinical uncertainty, should therefore provide further guidance about when the prescription of antibiotics is contraindicated.

CONCLUSION

The results of the current study suggest a significant excess use of antibiotics in patients with non-healing ulcers. Mounting evidence suggests that the use of antibiotics should be reduced significantly among this population because antibiotics do not treat the underlying cause of the ulcer. A reduction of antibiotic use among this patient population will significantly reduce antibiotic resistance and health care costs associated with the side effects of antibiotics.

Although the guidelines for antibiotic use should be updated and improved for use by doctors in the primary health services, research suggests that the guidelines are not read or utilized. This fact argues in favour of the creation of several specialized wound healing units in Norway. A rapid referral of ulcer patients to specialists will undoubtedly raise the standards in the diagnosis and treatment of non-healing ulcers and reduce the use of antibiotics.

The primary message

All non-healing ulcers will be influenced to various degrees by bacteria. There is therefore no reason to take routine bacteria samples from chronic ulcers. It is most important to find out the underlying cause of the ulcer and focus on its treatment.

Table 1 provides an overview of the indications for antibiotic treatment of non-healing ulcers. In such situations, bacteria samples should be taken from the ulcer. In most cases, empirical treatment will be necessary and narrow-spectrum antibiotics should be utilized to the greatest possible degree. The knowledge of the bacterial flora in different types of non-healing ulcers is therefore highly decisive. The treatment may have to be adjusted when resistance is determined.

References
