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Necrotizing Otitis Externa—Analysis of 83 Cases: Clinical Findings and Course of Disease

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Objectives: Evaluate the relationship between clinical findings and course of disease among patients with necrotizing otitis externa (NOE).
Study Design: Retrospective case series review.
Setting: Tertiary referral center.
Patients: Adult patients with no previous history of chronic ear disease, hospitalized due to NOE between the years 1990 to 2015.
Main Outcome Measures: 1) Duration of hospitalization and 2) necessity for surgery.
Results: Eighty-one patients were included in the study, corresponding to 83 effected ears. Thirty-two patients (38.5%) were hospitalized longer than 20 days and 20 patients (24.0%) underwent surgery. Otalgia was the most common complaint (n = 71, 85.5%). Pseudomonas Aeruginosa (PA) was the most common isolated bacteria (n = 40, 48.1%). Shifting incidence of culture results was noted, as rates of PA NOE decreased and rates of sterile culture and fungal NOE increased. Duration of complaints and presence of aural discharge at admission were associated with prolonged hospitalization ($p = 0.010$, $p = 0.011$, respectively). Advanced age, duration of hospitalization, and rates of readmission were associated with surgery ($p = 0.037$, $p < 0.001$, $p < 0.001$ respectively).
Conclusions: Duration of complaints and presence of aural discharge may indicate advanced NOE and require longer in-hospital treatment. Elderly patients are at increased risk for conservative treatment failure and are more likely to require surgery. With shifting incidence of pathogens, a wider empirical treatment covering nontraditional pathogens should be considered. **Key Words:** Diabetes—External otitis—Malignant—Necrotizing—Osteomyelitis.

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Necrotizing otitis externa (NOE) is a severe life-threatening disease affecting soft tissue and bone. Originally described by Chandler (1) in 1968, NOE affects mostly elderly diabetic patients. Other risk factors for NOE include HIV (2–4), hematological diseases (3,4), neoplasms (3,4), and other immune compromised conditions.

The diagnosis of NOE is based on a high index of suspicion and presence of classical clinical findings such as otalgia, canal edema, granulation tissue, and aural discharge. Imaging modalities such as high-resolution temporal bone computer tomography (HRTBCT), magnetic resonance imaging (MRI), and nuclear imaging (technetium-99, gallium-67) may also be helpful in the diagnosis of NOE and assessment of disease extent. The use of these modalities, however, is mostly based on the physician's preferences and availability and not upon a firm consensus (5).

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Several studies evaluated specific findings and their role in the prognosis of NOE. Patients' age was reported to be associated with increased in-hospital complications (6). Facial nerve involvement was examined as a prognostic factor with conflicting results (7–9). Findings on HRTBCT indicating involvement of the nasopharynx, middle ear and mastoid, temporomandibular joint, and temporal bone were associated with advanced NOE (10,11). Despite increasing data, the relation between clinical findings at admission and disease course and outcome is not well known. In part, this may be due to an inherent difficulty in the differentiation between severe otitis externa and NOE. It may also be due to the rarity of NOE and difficulty in obtaining large case series.

The aims of this study were to present our experience in a large case series of NOE patients and examine the relationship between clinical findings at admission and disease course and outcome.

METHODS

Ethical Considerations

The research was performed in compliance and approval of the requirements of the medical center's institutional review board; the Human Subjects Research Committee.

A retrospective case series analysis was conducted, including all patients hospitalized in our institution due to NOE between the years 1990 and 2015. Inclusion criteria included: 1) patients 18 years and above, 2) diagnosed NOE based on the Cohen and Friedman (12) classification, 3) no previous history of chronic middle ear disease, 4) no previous history of ear surgery due to chronic ear disease.

The following data was collected for analysis: 1) patients' age and sex, 2) affected ear, 3) medical history and comorbid conditions, 4) patients' complaints at admission, 5) clinical presentation, 6) culture results, 7) imaging modality performed, 8) treatment and need for surgery, and 9) duration of hospitalization (repeated admissions were combined to yield total hospitalization duration).

Two main measures were used for assessing course of disease and outcome: 1) duration of hospitalization—patients hospitalized less than 20 days *(Group A)* compared with patients hospitalized longer than 20 days *(Group B),* 2) Surgery—patients who did not require surgery *(Group 1)* compared with patients who required surgery under general anesthesia *(Group 2)*.

Data was collected and evaluated using the Statistical Program for Social Sciences (SPSS 18.0 for Windows; SPSS Inc., Chicago, IL).

Treatment Protocol

Upon admission all patients received empiric intravenous anti-Pseudomonas antibiotics (quinolone or cephalosporin) and topical drops (quinolone and/or aminoglycoside in combination with steroids). Further antibiotic treatment was tailored, based on the pathogen's sensitivity and following consultation with an infectious disease specialist. In cases where no pathogen was isolated, empiric anti-Pseudomonas antibiotic was continued. Antifungal treatment was initiated only in positive cultures and included systemic triazole and local drops based on the pathogen's sensitivity profile. All patients underwent daily local debridement. Granulation tissue was removed and sent for pathological evaluation in all patients. Indications for surgery were 1) no response to treatment, as assessed by a senior otologist; and 2) new onset facial palsy or facial palsy not responding to treatment. Patients were discharged home when the following criteria were met: Otalgia has resided, external ear canal edema have diminished, granulation tissue has resolved and the tympanic membrane could be visualized completely. After discharge all patients continued periodic evaluation in the outpatient clinic.

RESULTS

Eighty-one patients were included in the study, corresponding to 83 effected ears. Two patients presented with NOE and following complete resolution, presented again with contralateral NOE. Average age at presentation was 68.2 years. Forty-eight patients (59.2%) were males. Seventy-five patients (92.5%) were known diabetics. Average duration of hospitalization was 19.6 days. Thirty-two patients (38.5%) were hospitalized more than 20 days and 20 patients (24.0%) underwent surgery. Table 1 illustrates patients' characteristics.

TABLE 1. *Case series characteristics*

Patients (no.)	81
Affected ears (no.)	83
Age (avg yr)	68.2 (40–90)
Sex	
Male	48/81 (59.2%)
Female	33/81 (40.8%)
Affected ear	
Right	46/83 (55.4%)
Left	37/83 (44.6%)
Risk factors	
Diabetes	75/81 (92.5%)
Nondiabetic	6/81 (7.5%)
Myelofibrosis	*1*
Alcoholism	*1*
No known risk factors	*2*
No data	*2*
Complaints at admission	
Otalgia	71 (85.5%)
Aural discharge	38 (45.7%)
Hearing loss	3 (3.6%)
Fever	2 (2.4%)
Dizziness	1 (1.2%)
Confusion	1 (1.2%)
Findings at admission	
Edema of external canal	60 (72.2%)
Granulation tissue	59 (71.0%)
Aural discharge	36 (43.3%)
CN VII Palsy	5 (6.0%)
Abscess of external canal	3 (3.6%)
Soft tissue involvement	3 (3.6%)
Imaging	
Computer tomography	57
Technetium-99 (positive/total)	48/48
Gallium-67 (positive/total)	18/31
Duration of hospitalization (d)	19.6
Hospitalization $\geq$20 d	32/83 (38.5%)
Surgery	20/83 (24.0%)

Symptoms and Signs

Otalgia was the most common complaint (n = 71, 85.5%), followed by aural discharge (n = 38, 45.7%). On admission edema (n = 60, 72.2%), granulation tissue (n = 59, 71.0%) and aural discharge (n = 36, 43.3%) were the most common findings. Five patients (6.0%) presented with facial palsy (Table 1).

Microbiology

Swab cultures were taken from all patients. For analysis purposes pathogens were grouped into: 1) *Pseudomonas Aeruginosa (PA)*, 2) fungus, 3) other bacteria, 4) sterile culture. The incidence of specific pathogens is presented in Table 2. *PA* was the most common isolated bacterium (n = 40, 48.1%), followed by sterile culture (n = 18, 21.6%), fungus (n = 10, 12.0%), and other bacteria (n = 3, 3.6%). When comparing the pathogen's incidence in 5-year intervals, a shift is noted, as the incidence of PA decreased and the incidence of sterile and fungal NOE increase (Fig. 1).

Imaging

Fifty-seven patients (68.6%) underwent HRTBCT at admission. The most common findings included lack of

TABLE 2. *Prevalence of isolated pathogens*

Pathogen	Prevalence
Sterile	18 (21.6%)
Pseudomonas aeruginosa	40 (48.1%)
S aureus	1 (1.2%)
Klepsiella species	1 (1.2%)
Escherichia coli	1 (1.2%)
Mucor species	1 (1.2%)
Aspergillus species	2 (2.4%)
Candida species	7 (8.4%)
No data	11 (13.2%)

aeration of mastoid air cells (n = 37, 64.9%), edema of external ear canal (n = 35, 61.4%), lack of aeration of middle ear (n = 20, 35.0%), and bone erosion (n = 17, 29.8%). Forty-eight patients (57.8%) underwent technitium-99 scan, all with positive results. Thirty-one patients (37.3%) underwent gallium-67 scan, 18 of which were positive. Gallium scans however, were performed during hospitalization and not at admission (1–3 wk after admission).

Surgery

Twenty affected ears underwent surgery. Average timing of surgery was 16.4 days from admission (range 1–26 d). Surgical procedures included drainage of external ear abscess (n = 2), debridement of external ear canal and canalplasty (n = 5), canal wall up mastoidectomy (n = 4), canal wall down mastoidectomy (n = 7), and canal wall up mastoidectomy with facial nerve decompression (n = 2).

Hyperbaric Oxygen

One patient remained unresponsive to treatment and received supplementary treatment with hyperbaric oxygen treatment.

Pathology

Data was retrieved from 61 affected ears. Inflammatory reaction and necrotic tissue was seen in all cases.

Length of Hospital Stay

Fifty-one affected ears required hospitalization $\leq$19 days (group A), compared with 32 ears that required longer hospitalization (group B) (Table 3). There were 14 females (27.4%) in Group A, compared with 19 females (59.3%) in group B ($p = 0.004$). Average duration of complaints before hospitalization was 23 days in group A compared with 46.3 days in group B ($p = 0.010$). Otalgia and aural discharge were the most common complaints in both groups. Aural discharge, however, was found more common in group B (62.5% compared with 35.2%, $p = 0.011$). Facial nerve involvement was not associated with duration of hospitalization. Isolated pathogen was not associated with duration of hospitalization; however, when excluding sterile cultures, positive *non-PA* cultures (other bacteria and fungus) were associated with longer hospitalization compared with PA-NOE ($p = 0.039$).

Necessity for Surgery

Group 1 (no surgery) included 63 affected ears, compared with 20 in group 2 (surgery) (Table 4). Average age in group 1 was 66.5 years and 73.7 in group 2 ($p = 0.037$). Gllium-67 scans were positive in 11 of 23 patients in group 1 and 7 of 8 patients in group 2 ($p = 0.05$). Average duration of hospitalization was 16.3 days in group 1 and 30.3 days in group 2 ($p = 0.001$). Rate of readmission was 1.03 in group 1 compared with 1.45 in group 2 ($p = 0.001$). Duration of complaints before hospitalization, physical findings at admission and isolated pathogen were not associated with the necessity for surgery.

Mortality

Two patients died from disease during hospitalization. Up to the beginning of data collection 42 patients died from

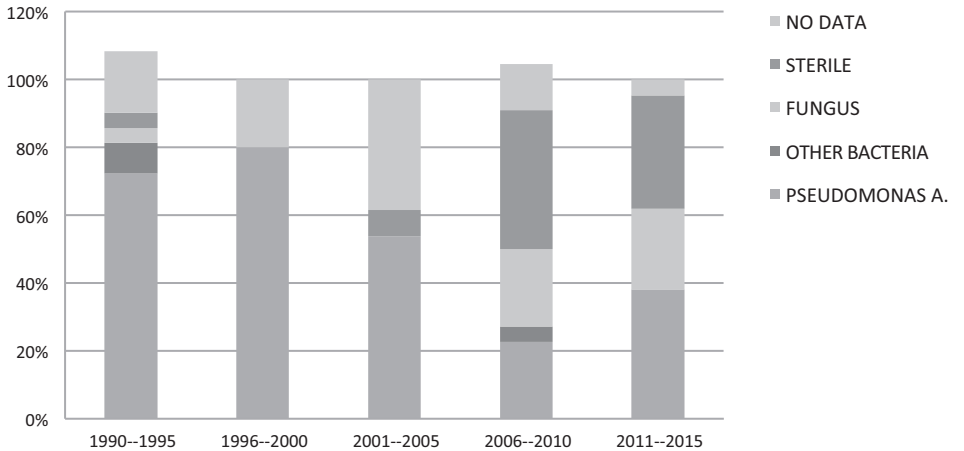

FIG. 1. Incidence of pathogens in 5 years interval.

TABLE 3. *Patient stratification based on duration of hospitalization*

	Group A Duration ≤19 d (n = 51)	Group B Duration ≥20 (n = 32)	*p* Value
Age (yr)	67.9	71.0	>0.5
Effected ear (Rt)	27 (52.9%)	19 (59.3%)	>0.5
Sex (female)	14 (27.4%)	19 (59.3%)	0.004
Duration of Complaints (d)	23	46.3	0.010
Complaints at admission			
Otalgia	46 (90.1%)	25 (71.4%)	>0.5
Aural discharge	18 (35.2%)	20 (62.5%)	0.011
Facial nerve palsy	4 (7.8%)	1 (3.1%)	>0.5
Physical findings			
Edema	38 (74.5%)	22 (68.7%)	>0.5
Discharge	18 (35.2%)	20 (62.5%)	0.011
Granulation Tissue	36 (70.5%)	23 (71.8%)	>0.5
Culture			
Sterile	12 (23.5%)	6 (18.7%)	>0.5
Pseudomonas	25 (49.0%)	15 (46.8%)	>0.5
Fungal	3 (5.8%)	7 (21.8%)	>0.5
Other	2 (3.9%)	2 (6.2%)	>0.5
*Non Pseudomonas culture positive	5 (9.8%)	9 (28.1%)	0.039
Positive Gallium-67 scan (positive/total)	9/18	9/13	>0.5

*Non Pseudomonas culture positive - Fungal NOE and NOE due to other bacteria.

other conditions not associated with the disease. Average time until death was 56.8 months (range 3–233 mo).

DISCUSSION

This study presents one of the largest single-center case series of NOE patients. Beyond reporting our experience with NOE, we also analyzed clinical variables at presentation in an attempt to characterize disease course and outcome. By doing so, treatment approach might be optimized and severe cases requiring aggressive treatment could be addressed at an earlier stage. Additionally, this knowledge is essential in counselling the patient and family on the possible clinical course and prognosis. Different publications evaluated disease prognosis by selecting several endpoints such as recovery from disease (13) or mortality (7). In our study two patients died during hospitalization and the rest had complete recovery. For these reasons we used other endpoints—length of hospitalization and surgery.

NOE presents a continuum of severe otitis externa and as such, there is no consensus regarding diagnosis. Cohen

TABLE 4. *Patient stratification based on need for surgery*

	Group 1 Nonsurgical (n = 63)	Group 2 Surgical (n = 20)	*p* Value
Age (yr)	66.5	73.7	0.037
Affected ear (Rt)	33	13	>0.5
Sex (female)	24	9	>0.5
Duration of Complaints (d)	25.2	46.8	>0.5
Complaints at admission			
Otalgia	54 (85.7%)	17 (85.0%)	>0.5
Aural discharge	26 (41.2%)	12 (60.0%)	>0.5
Facial nerve palsy	3 (4.7%)	2 (10.0%)	>0.5
Physical findings			
Edema	47 (74.6%)	13 (65.0%)	>0.5
Discharge	27 (42.8%)	9 (45.0%)	>0.5
Granulation Tissue	47 (74.6%)	12 (60.0%)	>0.5
Culture			
Sterile	14 (22.2%)	4 (20.0%)	>0.5
Pseudomonas	29 (46.0%)	11 (55.0%)	>0.5
Fungal	6 (9.5%)	4 (20.0%)	>0.5
Positive Gallium-67 scan (positive/total)	11/23	7/8	0.05
Duration of hospitalization (avg)	16.3	30.3	<0.001
Rate of rehospitalization (avg)	1.03	1.45	<0.001

and Friedman (12) proposed a diagnostic criteria based on obligatory findings (pain, edema, exudate, granulations tissue, micro abscess, and positive bone scan or treatment failure) and occasional findings (diabetes, cranial nerve involvement, debilitating conditions, and old age). Other parameters used for the diagnosis of NOE include raised serum inflammatory markers (3), radiographic findings (3), and evidence of tissue necrosis (14). Mahdyoun et al. (5) in their systemic review reported 27 different diagnostic criteria's among 48 publications. In the presented case series the diagnosis of NOE was based on the classification of Cohen and Friedman (12). Although the majority of patients presented with all obligatory symptoms, some patients did not. In these cases patients were hospitalized under the suspicion of NOE. Diagnosis was given once all obligatory findings were present.

HRTBCT is commonly used today as the initial imaging modality but has not been defined as a parameter for the diagnosis of NOE. HRTBCT is useful in the assessment of disease extent (15) and excluding other conditions (cholesteatoma, temporal bone malignancies). Additionally, in nonresponsive NOE patients considered for surgery, HRTBCT is valuable for planning surgical approach and extent. MRI may also be used in the evaluation of NOE due to its superiority in the detection of facial soft tissue and intracranial involvement. MRI was not used regularly in our center as we think that HRTBCT and daily observation and aural toilette is sufficient for evaluation of disease course.

In 1981 Ostfeld et al. (16) reported on the use of Technetium-99 scan for the diagnosis of NOE. A year later, Parisier et al. (17) reported on the combined use of Technetium-99 and Gallium-67 in the diagnosis and evaluation of treatment response in NOE patients. The main disadvantages of nuclear imaging remain however and include high cost and limited anatomic localization. Additionally there have been reports of false negative results (18) among NOE patients. We did not use technetium-99 and Gallium- 67 scans at admission. The use of Technetium-99 scan alone or in combination with Gallium-67 was decided on an individual basis by the treating physician during hospitalization and was found to be associated with the need for surgery ($p = 0.05$). As these scans were taken several weeks after admission it is reasonable to assume that this group presents an advanced infection which was resistant to conservative treatment.

Similar to reported data, the vast majority of our patients were known diabetics (92.5%). Four patients were nondiabetic—one patient had myelofibrosis, two patients had no known risk factors, and one patient suffered from severe alcohol abuse. In all nondiabetic patients blood tests were taken at admission which did not reveal occult diabetes or immune deficiency. This group of patients had classical signs of NOE at admission, and responded to treatment similar to diabetic NOE patients.

Patients' age was evaluated as a prognostic factor in several publications. Lee et al. (13) reported no association between patient's age and prognosis. Sylvester et al. (6), however, reported increased rates of in-hospital complications and mortality among elderly NOE patients (above 65 yr). We did not find increased in-hospital complications or mortality among elderly patients. In regard to sex, the presented case series found increased duration of hospitalization among female NOE patients. Although sex differences have been reported previously in other medical fields there is no data addressing sex differences in NOE. Since our study did not analyze NOE in females and males as separate study groups, looking at differences in all disease characteristics, we cannot conclude whether this finding is because of sex-associated disease differences or secondary to socioeconomic and sociodemographic differences.

In contrast to previous studies (9) our results showed that duration of complaints before hospitalization was twice as long among patients hospitalized for $\geq$20 days. Although not statistically significant, a similar trend was also observed when comparing the use of surgery (25.2 d in the nonsurgery group compared with 46.8 d in the surgery group). This might be explained by the fact that most of the patients were treated initially by general physicians and not otolaryngologists. Lack of close observation among high-risk patients by an otolaryngologist may lead to delayed diagnosis and as a consequence advanced disease at presentation and longer in-hospital duration. Presence of aural discharge was also found to be associated with duration of hospitalization. As we excluded from our study patients with chronic middle ear disease, it is possible that the purulent discharge originated from soft tissue microabscess formation or from extension of the disease into the middle ear. This might be further substantiated by the fact that all patients with otorrhea who underwent surgery showed either involvement of the middle ear or microabscess and necrosis of the external ear canal. It seems, therefore, that aural discharge might represent a clinical sign of advanced NOE, explaining the need for longer in-hospital treatment.

Facial nerve involvement and its role as a prognostic factor has been addressed by several publication2. In 2007, Soudry et al. (8) presented a case series of 48 NOE patients, 8 of them with facial nerve palsy and concluded that patients with facial nerve involvement do not have a worse prognosis. Nine years later, the same group published their result again on a case series of 88 patients and reported that patients with facial nerve paralysis have a 3-fold increase risk of mortality in the first year (7). Loh and Loh (9) reported a cases series of 19 NOE patients, among them 4 with facial nerve weakness. Although a trend was reported toward worse prognosis, no statistical correlation was observed. Lee et al. (13) reported on a group of 28 NOE patients, 13 of whom with facial nerve palsy and concluded that cranial nerve involvement is related to progression of the disease. Our study included 5 patients (6.0%) with facial nerve palsy and this finding was not associated with prolonged hospitalization or the need for surgery. Four patients had partial or complete resolution of facial weakness. All the five patients had complete resolution of the disease.

Similar to published data, PA was the most common isolated pathogen (48.1%), followed by sterile culture (21.6%), and fungal infection (12.0%). Mahdyoun et al. (5) reported decreasing incidence of PA NOE and increased incidence of sterile culture and attributed it to improper use of anti-PA antibiotics. Our results demonstrate a similar shift (graph 1). It is possible that the improper use of local solutions, which also contain steroids, increase PA resistance and decrease local immune response predisposing patients to fungal infection. This effect of local ear drops may also impact the reliability of local swab cultures in identifying the offending pathogen as it could represent secondary infection.

The above-mentioned shifts in incidence come into effect when we compare culture results to the selected endpoints. Initially, we found no correlation between culture results and hospitalization length or the need for surgery. However, when we compared PA NOE with other culture positive non-PA NOE (fungal NOE and NOE due to other bacteria) a statistical significance was observed as culture positive non-PA NOE patients were hospitalized substantially longer. It is very possible that longer duration of hospitalization in culture positive non-PA NOE patients was due to delayed treatment of appropriate antimicrobial therapy. This finding highlights the need to consider use of empiric treatment that also covers nontraditional pathogens.

Gruber et al. (19) reported three cases of culture-negative NOE patients which underwent deep tissue biopsy under sterile conditions. In all three cases PCR results were positive for fungal infection, indicating that sterile culture NOE might partially be due to fungal NOE. In our study 18 patients (21.6%) had a sterile ear culture and all were treated empirically with a single anti-PA antibiotic. Our experience was different, as all our patients with sterile cultures had complete resolution of the disease. This observation indicates that culture-negative NOE is mostly due to partially treated bacterial NOE rather than undiagnosed fungal NOE.

Twenty patients (24.0%) did not respond to conservative systemic treatment and required surgery. The decision to operate in nonresponsive patients is naturally subjective; however, it was the department's policy to consider surgery if no improvement was observed after 2 weeks. Patients who underwent surgery were 7.2 years older on average. Since all NOE patients included in the study underwent a similar treatment protocol, it is possible that lack of clinical response might be, in part, due to small vessel disease and microangiopathies, secondary to age-related changes and ongoing diabetes. Repeated admissions were also associated with increased risk of surgery. Several factors may account for this association such as reduced treatment adherence at home or resistance formation of the offending pathogen. It is also possible that early discharge and lack of daily aural toilet lead to disease relapse.

Steven et al. (20) reported a classification system for NOE based on clinical and radiographic variables and divided patients into severe and nonsevere groups. In their research the severe group had higher rates of adverse disease specific outcome, disease-specific mortality, and longer treatment duration. The authors concluded there is probably a subgroup of NOE patients who are not susceptible for conservative treatment and require surgery. This is in line with our findings of variables related to longer hospitalization (aural discharge and non-pseudomonas positive culture) and to the tendency for surgery (advanced age and readmission). It seems that increased age in combination with increased infective load and necrotic tissue prevent systemic antibiotics from reaching therapeutic levels in the effected tissue. Surgery substantially reduces local infective load, removes necrotic tissue, and allows formation of new tissue growth, which increase local vascularity allowing systemic antibiotics to reach the required area.

We consider two main limitations to our study:

1) Defining NOE. Similar to other studies, the diagnosis of NOE was based on high index of suspicion, clinical presentation, and the aid of nuclear imaging in selective cases. Although we excluded patients with a short hospital stay in an attempt to exclude cases of severe otitis externa, it is still possible that some patients did not have NOE but rather severe otitis externa.
2) We used *length of hospitalization* and *surgery* as indicators for advanced disease. Not surprisingly, these parameters were related ($p < 0.001$), as patients after surgery are expected to require a longer recovery time. We acknowledge the fact that these parameters are rather artificial and depend on the treating physician's approach; however, as almost all patients recovered from disease these were the most useful parameters we could use.

CONCLUSIONS

Main treatment approach to NOE includes daily aural toilette, systemic and topical antibiotic treatment, and surgery in unresponsive cases. Duration of complaints before admission and the presence of aural discharge may indicate advanced NOE and may require longer hospital treatment. Elderly patients are at increased risk for conservative treatment failure and are more likely to require surgery. With shifting incidence of pathogens, a wider empirical treatment covering nontraditional pathogens should be considered.

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