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ORIGINAL ARTICLE

Necrotizing fasciitis: is the bacterial spectrum changing?

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Abstract
Purpose Necrotizing fasciitis (NF) is a rare, but potentially fatal pathology. The aim of the present study was to identify the population characteristics of the NF patients, the responsible bacteria, and the differences between survivors and nonsurvivors.
Methods In this retrospective case–control study, all patients with NF from January 1, 2005, to December 31, 2010, treated in an academic level 1 trauma center, were identified, and their medical records were reviewed.
Results The mortality rate of the 24 identified patients was 20.8 %. The majority of the infections (54.2 %) (13/24) were monomicrobial. Hemolytic *Streptococcus* of group A (25 %) and methicillin-resistant *Staphylococcus aureus* (20.8 %) were the commonest germs. The mean number of comorbidities was 3.62 (standard deviation (SD) 3.58). Diabetes mellitus, cardiovascular disease, and immunosuppression were the commonest. Mean number of operations was 8.1 (SD 4.7). Five patients (20.8 %) developed a disseminated intravascular coagulation (DIC); all of them died. Nonsurvivors, who presented with deteriorated coagulation factors, developed a DIC ($p<0.001$) and received more often antibiotic monotherapy (ampicillin/sulbactam) as initial empirical therapy ($p<0.001$).
Conclusions The present study suggests a shift of the bacterial spectrum towards monomicrobial infections with multiresistant bacteria. The early recognition of high-risk patients and the aggressive surgical treatment with at least double-schema antibiotic therapy are of outmost importance.

Keywords Necrotizing fasciitis · Spectrum · Mortality

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Introduction

Necrotizing fasciitis (NF) is a rare, but potentially fatal pathology, as disease-related mortality rates are known to range between 15 and 46 % [1], depending on progression/stage of disease and involvement of extremities or trunk segments. NF was already described in the fifth century B.C. by Hippocrates [2]. Since that time, different names have appeared in the literature, such as hospital gangrene, necrotizing erysipelas, or flesh-eating infection. The term NF first appeared in 1952 by Jones [3] to describe this aggressive necrotic infection of the subcutaneous tissue and fascia. NF sets a great diagnostic and therapeutic challenge for both the attending physician and reconstructive surgeon. It is often initially misinterpreted as erysipelas, extravasate, or gangrenosum, as well as other pathological entities, such as the streptococcal toxic shock syndrome and the toxic epidermal necrolysis. The nonspecific symptoms, the extremely fulminant progression, the need for treatment on an emergency basis, as well as the extended and repeated necessary operations create a combination of factors that are often life-threatening. Over the last decades, improved clinical outcome has been observed [4]. Improvements in the treatment protocols, more efficient antibiotics, and close interdisciplinary teamwork have resulted in increased survival rates [5]. On the other hand, the increasing number of immunosuppressed patients and the higher incidence of multiresistant pathogens represent a challenge for the treatment of this

extremely aggressive infection [6, 7]. Under this scope, the recognition and identification of prognostically relevant parameters known to determine the morbidity and mortality, as well as the characterization of the most frequently involved bacteria, are of outmost importance. The aim of the present retrospective study was the evaluation of the therapeutic outcome in terms of mortality as well as the identification of the population characteristics and of the responsible microbiological spectrum.

Methods

For the present study, a computational ICD-9 research was conducted in order to include all patients that were treated in our center with the diagnosis of NF over a 6-year period (2005–2010). A population of 24 patients was identified (15 males and 8 females) with a mean age of 53.2 years (range 20–77). One patient sustained a recurrence after 2 years free of disease. The diagnosis was initially clinical, followed by intraoperative probes for the proof of microbiological culture. The diagnosis was confirmed by histological verification through examination of intraoperatively sampled tissue (necrosis of fascia and muscle; bacterial detection with the use of light microscopy). After establishment of the clinical diagnosis, aggressive surgical management was performed with extensive fasciotomy and repeated, serial radical debridement in all cases, initially with a 12–24-h rhythm (Fig. 1). From the clinical perspective, the typical temporal profile of local and systemic inflammation with rapidly progressing deterioration of local soft tissue conditions, the presence of necrotized tissue lacking capacity to bleed and of the typical for necrotizing fasciitis "dishwasher fluid," as well as the absence of normal soft tissue consistency, was indicative of NF. Following open wound treatment, radical serial redebridements, systemic anti-inflammatory intensive care unit (ICU) treatment, and after clinical and laboratory evidence of infection control, final soft tissue reconstruction was performed (Fig. 2). Patient data were evaluated retrospectively. The evaluated data included the following patient characteristics and surgery-associated parameters:

1. Patient characteristics:
   - (a) Comorbidities
   - (b) Presence of immunosuppression
   - (c) Preexisting need for hemodialysis
   - (d) Major infections in the past
   - (e) Localization of the infection
   - (f) Primary cause of infection
   - (g) Smoking
   - (h) Illicit drug use
   - (i) Alcohol abuse
   - (j) The number of transfused units of packed red blood cells (PRBCs) or fresh frozen plasma (FFP)
   - (k) The responsible bacterial spectrum (Table 1)
   - (l) Administered antibiotic therapy and laboratory data (Table 2)
2. Surgery-associated parameters:
   - (a) Length of intensive care unit
   - (b) Overall hospital stay
   - (c) Initial treatment at another hospital
   - (d) Number of operations
   - (e) Time from admission to operative room
   - (f) Amputation rates
   - (g) Necessity and type of skin reconstruction
   - (h) Mortality rates

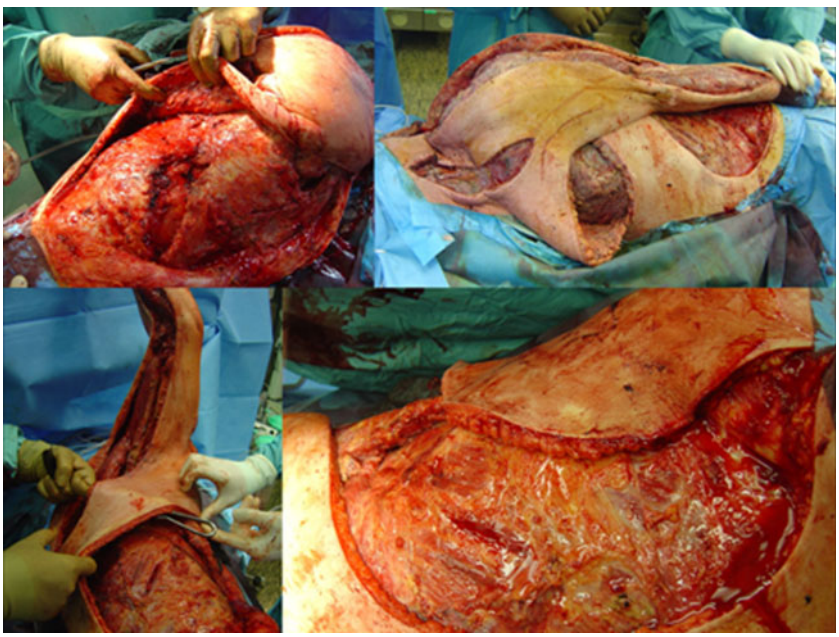

Fig. 1 Extensive aggressive debridement in a patient with recurrent NF of the trunk/thorax and upper extremity

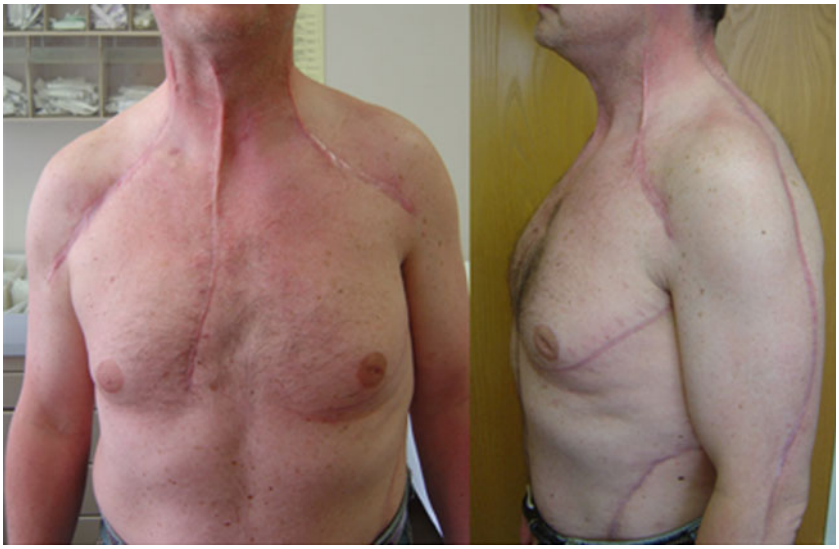

Fig. 2 Postoperative outcome 5 months after successful treatment and surgical soft tissue reconstruction

(i) Treatment-related complications
(j) Presence of disseminated intravascular coagulation (DIC)

Continuous variables were expressed as mean and standard deviation (SD). Nominal data were presented as percentages. Student's *t* test or Wilcoxon–Mann–Whitney test was used for comparison of continuous independent variables between two groups. Categorical data were compared with the use of χ^2 test or Fisher's exact test as appropriate. Statistical significance was set at $p<0.05$.

Results

The mean number of comorbidities in the population was 3.62 (SD 3.58). For population characteristics and parameters of clinical outcome, see Table 1. Notably, in eight patients (33.3 %) some type of immunosuppresion was present, either because of preexisting HIV infection ($n=3$) or following previous organ/bone marrow transplantation ($n=5$). All the patients presented initially with nonspecific inflammatory symptoms such as swelling and pain.

A multibacterial infection was diagnosed in 11 patients (45.8 %). A mixed infection of Gram-negative and Gram-positive bacteria or anaerobes was found in nine of these patients. A monobacterial infection was seen in 13 (54.2 %) of the patients. Hemolytic *Streptococcus* of group A was identified as the responsible germ in six (25 %); and of group G, in one (4.2 %); methicillin-resistant *Staphylococcus aureus* (MRSA), in five (20.8 %); and *Candida albicans* in one patient (4.7 %).

In nine patients (37.5 %), the infection occurred after minimal trauma; in four (16.7 %), postoperatively; in two (8.3 %), after abscess development; and in four (16.7 %), in response to an initial minor infection. No definitive cause could be recognized (idiopathic NF) in five patients (20.8 %). In five and nine patients, the infection site was localized in the upper and lower extremities (20.8/37.5 %), respectively. In five patients (20.8 %), an extensive involvement of the thorax/chest wall was present. Trunk, pelvis, and proximal low extremity insult was seen in five patients (20.8 %).

Amputation of lower/upper limb was necessary in two/two patients (one patient required upper and lower extremity amputation), while in one patient, a hemipelvectomy was conducted. In 13 patients (54.1 %), a mesh graft for plastic

Table 1 Population characteristics and parameters of clinical outcome

Variable	Number
Age (years)	53.2 (20–77)
Male gender (%)	62.5 (15/24)
Number of comorbidities	3.62 (SD 3.58)
Immunosuppression (%)	33.3 (8/24)
Hemodialysis (%)	20.8 (5/24)
Diabetes mellitus (%)	33.3 (8/24)
CVD (%)	33.3 (8/24)
Smoking (%)	54.2 (13/24)
Drug abuse (%)	12.5 (3/24)
Alcohol abuse (%)	33.3 (8/24)
ICU stay (days)	22.0 (SD 19.8)
Hospital stay (days)	50.7 (SD 25.6)
Transfer from another hospital (%)	42.8 (10/24)
Number of operations	8.1 (SD 4.7)
Time to OP <24 h (%)	62.5 (15/24)
Amputation (%)	16.7 (4/24)
Mortality (%)	20.8 (5/24)
DIC (%)	20.8 (5/24)
PRBCs units	11.1 (SD 15.47)
FFPs units	20 (SD 33.7)

reconstruction of the skin was necessary, while secondary wound closure was possible in 9 cases (37.5 %). Free flap plastic reconstruction was performed in two cases (8.3 %). In five patients (20.8 %), a disseminated intravascular coagulation was present; all of them died of NF-disease, not controllable by medication or surgery. The overall mortality rate was 20.8 % (5/24 patients).

The analysis of blood chemistry profile at admission revealed a deterioration of several parameters. The present population was hyponatremic, while potassium concentration was in normal range. An impairment of the renal function was evident, while hyperglycemia was also present. In addition, inflammation markers were also increased, while hemoglobin levels were also low (Table 2).

Patients were assigned to two groups, depending on disease-specific survival (Table 3). The statistical analysis of the data between those two groups revealed a statistically significant difference between the existence of DIC and the number of administered FFPs ($p<0.001$). A statistically significant difference was almost reached when the number of thrombocytes upon admission was compared between the two groups ($p=0.052$). Furthermore, a trend towards decreased coagulation values in the nonsurvival group existed. Involvement of the trunk was significantly more frequently observed in the nonsurvival group ($p<0.01$), whereas a combination of antibiotic therapy upon admission was significantly more frequently found in the survival group ($p<0.001$). In 60 % of the patients who died of NF-disease, the initial antibiotic therapy consisted of ampicillin/sulbactam.

Table 3 Survival vs. nonsurvival group

Variable	Survival Group ($n=19$)	Nonsurvival Group ($n=5$)	p value
Age (years)	51.8 (SD 18.2)	58.6 (SD 10.4)	0.43
Number of OPs	8.3 (SD 3.9)	7.4 (SD 7.6)	0.19
Hospital stay (days)	54.5 (SD 24.2)	36.0 (SD 27.8)	0.15
ICU stay (days)	19.1 (SD 17.0)	33.0 (SD 27.7)	0.17
Thrombocytes (/nL)	211.7 (SD 75.2)	134.4 (SD 62.7)	0.052
PTT (%)	72.1 (SD 14.4)	58.0 (SD 18.8)	0.09
INR	1.30 (SD 0.23)	1.55 (SD 0.38)	0.21
aPTT (s)	38.2 (SD 7.4)	40.6 (SD 6.3)	0.52
Leucocytes (/pL)	13.0 (SD 7.7)	8.5 (SD 6.6)	0.12
CRP (mg/dL)	23.9 (SD 21.3)	21.7 (SD 15.6)	0.85
Creatinine (mg/dL)	1.56 (SD 1.13)	2.39 (SD 1.57)	0.26
PRBCs (units)	7.4 (SD 8.8)	30.6 (SD 29.8)	0.09
FFPs (units)	6.6 (SD 10.8)	91.3 (SD 17.5)	0.003
DIC (%)	5.2 (1/19)	100 (5/5)	<0.001
Involvement of the pelvis or thorax (%)	21 (4/19)	100 (5/5)	0.003
Initial combination antibiotic therapy (%)	84.2 (16/19)	40 (2/5)	<0.001

Discussion

Necrotizing fasciitis is a fulminant life-threatening bacterial infection of the musculoskeletal soft tissues known to evolve with rapid progression, typically requiring emergency surgical treatment [8, 9]. Despite the fact that its incidence still remains low, its prevalence continues to rise [10, 11]. However, NF does not represent a static situation. On the contrary, the responsible underlying type of bacteria seems to be subject of change over time, thus affecting the indicated antibiotic regime. As far as the characteristics and the type of involved bacteria are concerned, the present study shows a shift towards monomicrobial multiresistant infections. These results confirm the data from previous studies [4, 11–13]. While in the past, polymicrobial infections (type I NF) were more frequently observed [14–16], and this finding could not be confirmed in our study. In the majority of the patients (54.2 %), a type II NF was present, with hemolytic *Streptococcus* of group A and *S. aureus* being the major responsible bacteria. Notably, in every *S. aureus* infection, a resistance towards methicillin was present (MRSA). This finding is in accordance with other recent studies that have shown an increase in the presentation of NF due to MRSA [7]. Interestingly, in one HIV-positive patient, the presence of an infection by *C. albicans* was demonstrated. These results make it tempting to conclude that prevalence of this type of infections will rise in future years; likewise, in parallel, the population of immunosuppressed patients continues to increase. In the type I cases, there was a mixture of aerobes Gram-positive and Gram-negative bacteria as well as of anaerobes. The patients who died were more often treated initially and before adjustment of the treatment according to antibiogram with only one antibiotical agent in contrast to surviving patients. This difference was statistically

Table 2 Blood analysis values of all the cases at admission

Variable	
Na^+ (mmol/L)	134.1 (SD 5.4)
K^+ (mmol/L)	4.1 (SD 1.2)
Creatinine (mg/dL)	1.76 (SD 1.25)
C-reactive protein (mg/dL)	23.4 (SD 19.9)
Glucose (mg/dL)	198.5 (SD 140.9)
Leucocytes (/pL)	12.0 (SD 7.5)
Erythrocytes (/pL)	3.8 (SD 0.7)
Hemoglobin (g/dL)	11.4 (SD 2.4)
Hematocrit (%)	0.33 (SD 0.66)
Thrombocytes (/nL)	193.3 (SD 78.6)
PTT (%)	68.6 (SD 16.34)
INR	1.35 (SD 0.27)
aPTT (s)	38.8 (SD 7.05)

significant ($p<0.001$). In nonsurviving patients, the first agent was ampicillin combined with sulbactam, a beta-lactam antibiotic with a beta-lactamase inhibitor. Despite the fact that this is a broad-spectrum agent, it cannot be considered sufficient for the treatment of such critical infections. The initial addition of clindamycin, which is a protein synthesis inhibitor, appears to profoundly affect antibiotic efficiency as in streptococcal or clostridial infections; it blocks the production of endotoxin and M protein [13]. In multimorbid patients with predisposing factors for NF that present with a musculoskeletal infection, we recommend a double antibiotic schema with a broad-spectrum beta-lactam antibiotic and clindamycin. Under suspicion of MRSA infection, vancomycin, linezolid, or daptomycin may be beneficial. However, considering the high prevalence of renal insufficiency in those patients, we would favor the initial use of linezolid. In critical patients, an initial triple schema with penicillin, aminoglycoside and clindamycin, or metronidazole is indicated until the antibiogram is available [17]. Considering the rising prevalence of MRSA infections worldwide, which was confirmed in the present study with MRSA being detected in 20.8 % of the cases, linezolid could replace penicillin in the initial triple schema for critical patients. Imipenem or meropenem, as initial monotherapy, could serve as alternatives.

As the importance of a quick and aggressive treatment of NF is lifesaving and cannot be overestimated [8], the physician should be acquainted with its characteristics. Unfortunately, the first stages of NF disease are frequently masked by nonspecific symptoms, preventing effective initial-specific therapy [18]. Therefore, unraveling the underlying pathways, clear identification of predisposing comorbidities and determination of patient-specific risk profile is essential in predicting the course of this otherwise devastating disease. Therefore, the early identification and diagnosis of these patients is mandatory and can hardly rely solely on the clinical examination [10, 19]. Consequently, prognostic indicators, such as laboratory profile markers and specific patient characteristics from the medical history, can assist in the early diagnosis and consecutive decision making as well as the stratification of high- and low-risk patients [12].

Precious time is also often lost, as the patients are initially treated in internistic ICUs because of the general problems resulting from the infection (renal failure, DIC, fever, etc.). The severity of the infection is unfortunately not immediately recognized by the attending physicians. Especially in centers without great experience in the treatment of NF, valuable time is often lost till the beginning of the surgical treatment. Nevertheless, it is unavoidable that many of these patients will be initially treated in internistic ICUs because of the above-mentioned problems. In order to avoid such delays, we would suggest that, in cases of multimorbid patients or immunosuppressed patients with a fulminant infection of the soft tissues, an experienced surgeon should be involved in the early stages of the treatment. This is the strategy followed in our institution and has resulted in a relatively early admission to surgery in the majority of the cases.

The characteristics of the present population in terms of predisposing factors are in accordance with previous studies [14, 20, 21] with a mean number of 3.62 (SD 3.58) comorbidities. Diabetes mellitus, immunosuppression due to underlying HIV infection or previous transplantation, CVD, and renal disease were most often encountered in this cohort. Previous studies have outlined the increasingly associated risk for NF in the presence of the above-mentioned pathologies [13]. Therefore, in such multimorbid patients, NF should be ruled out, even in absence of an obvious causative incidence. This notion becomes, in particular, evident in view of the fact that, in the majority of the patients, the cause of the infection can either be related to a minor trauma or cannot be determined at all [1]. This was also seen in the present study; as in 37.5 %, the infection occurred after minimal trauma, while in 20.8 % of the patients, there was no recollection of a causative relation to a previously sustained minor or major trauma.

The blood analysis parameters (Table 2) are in accordance with the studies of Wall et al. [22], Wong et al. [12], and Barie [23] who have found independent variables associated with NF. Interestingly, in the present study the coagulation parameters were additionally deranged. Although INR was not significantly altered, PTT and aPTT had abnormal low and high values, respectively, already upon hospital admission. Although the population was not thrombopenic in the nonsurvival group, the patients presented with a trend towards lower values, in contrast to the survival group. Although no statistically significant difference could be found, the p value of 0.052 with a power of only 0.40 is marginal, possibly representing a strong trend which with a greater sample could indeed reach statistical significance. Furthermore, 80 % of the patients in the nonsurvival group (4/5) that eventually suffered of DIC and died were already coagulopathic upon presentation. In addition, there was also a statistically significant difference between the two groups in terms of DIC incidence and the number of transfused FFPs units. These results imply that patients with coagulopathy, even if the values are at the lower threshold between normal and pathological values, are exposed to a higher risk for developing serious complications including death of disease. Thus, increased attention and critical care must be paid to those patients who should then be eventually scheduled for more generous substitution of coagulation factors [24]. In the survival group with better coagulation parameters upon admission, only one patient (5.2 %) suffered of DIC.

The localization and expansion of the infection site played also an obviously decisive role in the mortality. In all the cases in the nonsurvival group, there was an involvement of the trunk, while pelvis or thorax was affected in only 21 % (4/19) in the survival group ($p<0.01$). Whether this

increase in the mortality can be attributed to systematic alterations induced by the expansion of the NF proximally or to the surgical technique in the truncal region with incisions and counter-incisions, which leave a dermal bridge instead of radical debridement, remains to be clarified. Our data lend sufficient support to the hypothesis that NF, extending proximally to pelvis or trunk, significantly decreases the prognosis [25]. Therefore, early and aggressive treatment aimed at restriction of the infection away from the trunk, even with the means of amputation, could prove useful in achieving better survival rates. This can be outlined by the fact that the majority of the amputated patients (3/4) survived, while in the nonsurvival group, only one patient was amputated at the level of the lower extremity; however, the trunk had already been affected by the infection. Therefore, we favor a "life before limb" approach in the case of such critical infections.

The number of operations in the present study was higher compared to other studies in the literature [15]. This can be attributed to the aggressive surgical treatment concept at our center with extensive debridements and reoperations every 12 to 24 h. Additionally, the serial use of a vacuum-assisted closure (VAC) system and the frequent need for a plastic reconstruction increase the number of needed operations. The chances of a successful plastic mesh reconstruction can be increased through the use of either a VAC system for the stimulation of granulation or of an external fixator in order to assure adequate immobilization, thus supporting uneventful healing. Between the survival and nonsurvival groups, there was no statistically significant difference in the number of operations. Despite the great importance of the surgical treatment in the initial phase of the infection [26], it seems that additional factors influence mortality. An extensive removal of the necrotized tissue is a prerequisite for the successful treatment of NF [6, 27]; however, this alone cannot prove sufficient for the prevention of death. The importance of the antibiotic therapy and intensive care therapy significantly appear to affect the outcome.

While in the past decades up to 70 % of the patients with NF have died [28], today, with improved surgical and intensive care treatment, mortality rates have declined to less than 30 % [7, 11, 13, 29]. The 20.8 % mortality rate in the present population underscores the decreasing mortality described in recent studies.

Conclusion

Based on our study, in descending order of statistical significance, the following prognostic risk factors for decreased outcome include the initial antibiotic monotherapy, coagulopathy, involvement of the trunk/chest wall and of proximal extremity segments, as well as the increasing number of comorbidities or immunosuppression. Consequently, our data suggest a shift of the responsible bacterial spectrum towards monobacterial infections with multiresistant bacteria. This should be taken into account prior to the initiation of the antibiotic treatment. The data of this study also underscore the tremendous importance of early identification of high-risk patients and the performance of aggressive surgical treatment with substitution of coagulation factors. Future studies and continuative analysis of NF patients will show if the demonstrated prognostic indicators will assist in identification and stratification of high-risk NF patients and be integrated in improved current therapeutic algorithms. Understanding and recognition of the identified prognostic factors and altered bacterial spectrum may then possibly hold the key for early intervention and improve overall survival by preventing escalation of disease.

Conflicts of interest None.

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