Noma (cancrum oris)

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Noma is an opportunistic infection promoted by extreme poverty. It evolves rapidly from a gingival inflammation to grotesque orofacial gangrene. It occurs worldwide, but is most common in sub-Saharan Africa. The peak incidence of acute noma is at ages 1–4 years, coinciding with the period of linear growth retardation in deprived children. Noma is a scourge in communities with poor environmental sanitation. It results from complex interactions between malnutrition, infections, and compromised immunity. Diseases that commonly precede noma include measles, malaria, severe diarrhoea, and necrotising ulcerative gingivitis. The acute stage responds readily to antibiotic treatment. The sequelae after healing include variable functional and aesthetic impairments, which require reconstructive surgery. Noma can be prevented through promotion of national awareness of the disease, poverty reduction, improved nutrition, promotion of exclusive breastfeeding in the first 3–6 months of life, optimum prenatal care, and timely immunisations against the common childhood diseases.

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The WHO *International Statistical Classification of Diseases*, code A69.0 lists necrotising ulcerative stomatitis, which includes noma, cancrum oris, and fusospirochaetal gangrene. Noma is derived from the Greek *νομή*, which means to graze or to devour.[1,2] Orofacial noma is an infectious disease that starts as gingival ulceration and spreads rapidly through the orofacial tissues, establishing itself with a well-demarcated perimeter surrounding a blackened necrotic centre (figure 1).[1,3,4] The gangrene can involve not only the mandible and maxilla but also the nose and infraorbital margins (figure 2). Unlike other infectious processes of the face, which mostly expand along cellular spaces of the head and neck, the noma lesion spreads through anatomical barriers such as muscles.[5] Names for the disease include *cam-tan-ma* (oral inflammation like a galloping horse) in Vietnam[2] and *ciwon iska* (the wind disease), which metaphorically underscores its rapid development, among the Hausa tribe in Nigeria. In 1848, Tourdes[6] described orofacial noma as a "gangrenous affection of the mouth, especially attacking children in whom the constitution is altered by bad hygiene and serious illness, especially from the eruptive fevers, beginning as an ulcer of the mucous membrane with oedema of the face, extending from within out, rapidly destroying the soft parts and the bone, and almost always quickly fatal". This description is still accurate, except for the reduction in mortality rate with prompt treatment.[1,7–9]

Figure 1: **A 3-year-old malnourished girl with acute orofacial noma before removal of the tissue slough**
The lesion has a well-demarcated perimeter surrounding a blackened necrotic center. Courtesy Noma Children Hospital, Sokoto, Nigeria.

Acute **[A: OK?]** noma is seen predominantly in children aged 1–4 years, although late stages can occur in adolescents and adults.[1,2,10,11] The WHO designates noma a health priority.[12] There have been several recent reviews on noma,[2,13–16] and some[2,14] provide detailed information on the history of the disease dating back to classical and medieval civilisations in Europe. Surgical repair procedures for the sequelae of noma have also been reviewed lately.[2,14,17] This Seminar therefore focuses primarily on acute noma.

Search strategy and selection criteria

We did a comprehensive search of scientific publications including databases OLD MEDLINE via OVID (1951–65), MEDLINE via PubMed (1950–2005), and ISI web of science. The search terms used were "noma", "cancrum oris", "oral gangrene", "orofacial necrosis", "necrotiz[s]ing ulcerative gingivitis", and "noma, malnutrition AND oral health", "noma AND measles", "noma AND viral infections", and "noma AND HIV/AIDS". Many published reports on noma were also identified through searches of COE's extensive records collected over the past four decades. The historical references were limited to those retrievable by a MEDLINE search, with noma, cancrum oris, or both as the key words. Reviews by Tempest[1] and Marck[2] were guides to historical descriptions of noma in earlier centuries. Only reports published in English, French, or German were reviewed.

Figure 2: **A malnourished boy aged 2·2 years with a noma lesion involving the orofacial tissues, lips, and nose, and extending to the infraorbital margin**

Global burden of noma

Nomawas not always restricted to tropical or African countries.[2,10] It was common in Europe until the end of the 19th century.[1,2] Noma disappeared from more developed countries in the 20th century, except for cases reported in the concentration camps of Bergen-Belsen and Auschwitz[18,19] and, more recently, in association with intense immunosuppressive therapy[20] in patients with HIV infection or AIDS,[8,9] as well as in native American children with severe combined immunodeficiency syndrome.[21] The disease almost disappeared in more developed countries with improvements in the standard of living, even before the discovery of penicillin.[2,3,13] By contrast, noma has remained an important health problem of deprived children in sub-Saharan Africa.[10,22,23] Most of the cases in Africa occur in a belt stretching across western and central Africa towards Sudan.[10,12,14] Several countries in this hot, arid zone are characterised by mass poverty and frequent famines. In Nigeria[1,3,24] and Senegal,[23] for example, a few specific regions account for most of the cases of noma in those countries. WHO has prepared a global map of reported cases during the period before 1980 and up to 2000 (figure 3), showing that although most of the countries affected are in Africa, Asia and Latin America are also involved.[2,10]

There is a severe lack of global data on acute noma in children. The major obstacles have been extensively documented.[10,13,23] In 1998, WHO estimated that worldwide 140 000 children contract noma each year, and 79% of them die from the disease and associated complications.[25] In 2003, Fieger and colleagues[26] estimated an annual incidence of 6·4 cases per 1000 children in north-west Nigeria and, by extrapolation, an incidence of 25 600 for the countries bordering the Sahara. In specific African countries such as Senegal,[23] Gambia,[27] and Niger,[10] the annual incidences derived from hospital records are 0·28–0·84, 1·9, and 0·7–1·4 per 1000 children, respectively. These rates

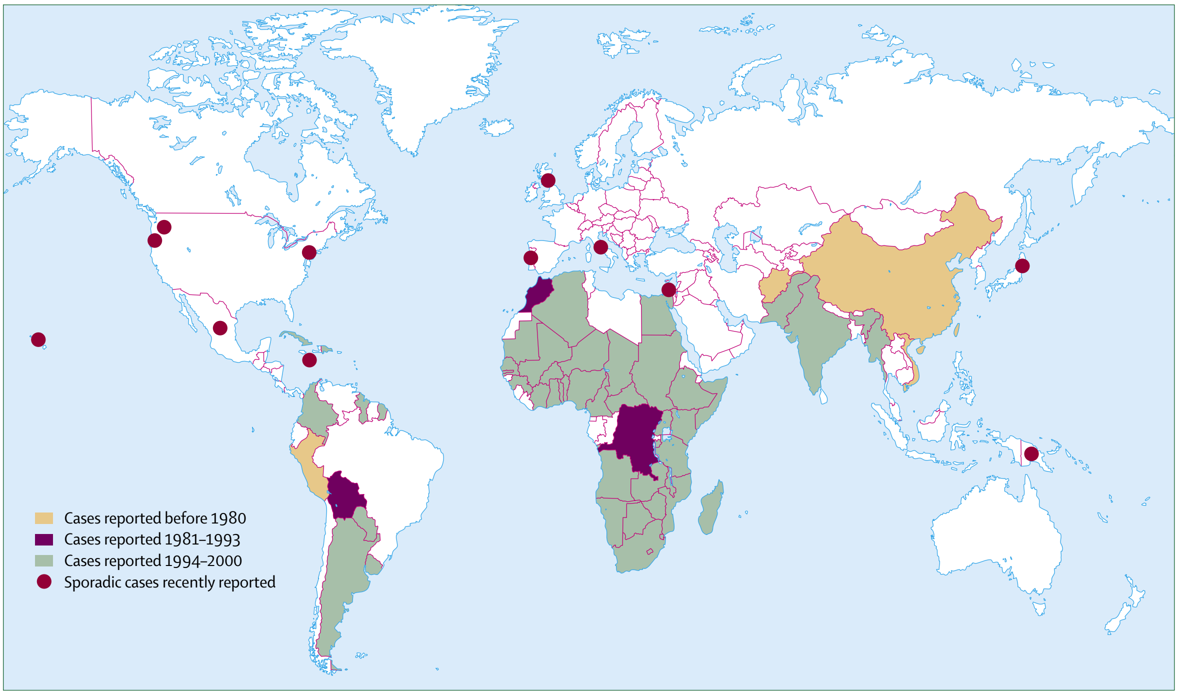

Figure 3: **Worldwide distribution of reported cases of noma**
Adapted from WHO. Before 1980, many less developed countries, particularly in sub-Saharan Africa, had poor noma reporting systems. Since the 1990s, awareness of noma has increased in these countries, and some have established control plans.

represent the tip of the iceberg, because no more than 10% of affected children seek medical care during the acute stage.[7,16]

Over the years, acute noma was known as a disease of deprived children **[A: since we explain in the next sentence that the disease has now appeared in HIV-positive children, we think the part of the sentence about non-immunocompromised was superfluous and potentially confusing.]**.[1,3,11,24] More recently, there have been sporadic reports of acute noma-like disease occurring in HIV-positive individuals.[8,9,28,29] Between 1989 and 1993, the HIV status of 26 of the 45 children younger than 3 years admitted to the University of Zambia Hospital for treatment of noma was ascertained; nine (35% **[A: we round percentages up or down if the denominator is less than 100 and especially when talking about people]**) were seropositive.[9] Noma is not listed among the clinical syndromes associated with HIV/AIDS in children.[30,31] Costini and colleagues[32] expressed concern that the AIDS epidemic could increase the number of noma cases. There are large subregional differences in the prevalence of HIV infection in sub-Saharan Africa; southern and eastern Africa have much higher rates than western Africa.[33] Nonetheless, the reported incidence of noma is higher in western Africa.[2,4,34,35]

Clinical presentation, progression, and sequelae

Many patients with acute noma present with a range of features reflecting pre-existing, debilitating health conditions. They include fever (temperature 38·3–40·5°C), tachycardia, high respiratory rate, and anorexia. The medical history generally shows recurrent fevers, diarrhoea, infections with parasites (eg, malaria) and viruses (eg, measles, herpes) in the recent past.[1,2,3,5] Severe anaemia, with haemoglobin concentrations as low as 50–60 g/L, white-blood-cell counts of 20–30×10^9 per L **[A: we give cell counts per litre; please check conversions]**, and hypoalbuminaemia are common.[3,24,36,37] Serum concentrations of antioxidant micronutrients are very low, consistent with severe malnutrition and presence of infections.[3,37] Studies in Nigeria have shown that serum concentrations of the proinflammatory and anti-inflammatory cytokines are higher in children with acute noma than in healthy urban children of similar age, but there is less difference between affected children and their malnourished neighbourhood counterparts without noma.[37] The most prominent feature of children with acute noma is growth retardation (table 1), and many are severely or critically affected.[11,38]

Orofacial features

The orofacial lesion can occur unilaterally or bilaterally, but it is unilateral in many cases. Descriptions of the initial stages are inconsistent because the disease is generally well established before the victim seeks medical help.[1,2,16] The early features include soreness of the mouth, pronounced halitosis, foetid taste, tenderness of the lip or cheek, cervical lymphadenopathy, a foul-smelling purulent oral discharge, and a blue-black discoloration of the skin in the affected area.[1,3,5,7] The face on the affected side is swollen in most cases (figure 4). There is general consensus that noma starts as gingivitis, most commonly in the premolar to molar and mandibular incisor regions, extends to the labiogingival fold and on to the mucosal surface of the cheek and lip.[1,3,14,23] Necrotising ulcerative gingivitis, a painful inflammation of the marginal interdental papillae, has long been thought to be the precursor of noma,[3,39–41] but this view is now disputed.[4,22,28] This disorder predominantly affects deprived African children, and has a peak age incidence corresponding to that of acute noma.[3,41,42] Emslie[40] stated that noma is an extension of necrotising ulcerative gingivitis; to

	Neighbourhood village children (n=55)	Noma group (n=58)	p
Mean (SD) age, years	2·40 (1·28)	2·58 (1·02)	
Height for age Z score			
Mean (SD)	–1·43 (2·22)	–3·82 (2·16)	<0·001
Number (%) –2·0 SD or more	20 (37%)	53 (91%)	<0·001
Number (%) –3·0 SD or more	7 (13%)	41 (70%)	<0·001
Number (%) –4·0 SD or more	4 (8%)	25 (43%)	<0·001
Weight for age Z score			
Mean (SD)	–1·87 (1·67)	–3·65 (1·82)	<0·001
Number (%) –2·0 SD or more	26 (47%)	51 (88%)	<0·001
Number (%) –3·0 SD or more	12 (21%)	47 (81%)	<0·005
Number (%) –4·0 SD or more	5 (10%)	27 (47%)	<0·05

Adapted from Enwonwu and colleagues[11] with permission. The neighbourhood village children without noma include siblings of those with noma.

Table 1: **Anthropometric data for Nigerian children** [A: we prefer to give exact p values rather than <0·??; please can you give these? Also, we like to give actual numbers with percentages; please check.]

Figure 4: **A 2-year-old deprived girl of 5 kg in weight and 73 cm in height**
The child presented with facial swelling, anaemia, angular cheilosis, skin lesions particularly around the nose, and prominent malodorous breath. Intraoral examination revealed necrotising ulcerative gingivitis involving the posterior right quadrant of the maxilla

Figure 5: **A Nigerian child with necrotising ulcerative gingivitis involving the maxillary right quadrant with simultaneous ulceration of the adjacent cheek**
Reprinted with permission from Enwonwu.[3]

Figure 6: **Small orofacial noma destruction involving the mandible in a malnourished child aged 2·5 years**
Courtesy Noma Children Hospital, Sokoto, Nigeria.

Figure 7: **A 2-year-old child after removal of tissue slough and bone sequestration, showing extensive intraoral destruction**

differentiate between the two, he chose alveolar bone exposure as the transition point, a view shared by others.[43,44] However, infection with the measles virus[1,3,36] and other viruses might initiate noma.[8,45] Postmeasles necrotic lesions of the mouth occur in malnourished children.[36,39,46] When the inflammation simultaneously involves the gingivae and the mucosal surface of the adjacent cheek (figure 5), further progression leading to perforation of the cheek is rapid, in a matter of days in many cases.[1,3,5,7] Generally, the external tissue loss is not closely related to the more extensive intraoral destruction.[7,9] Sequestration of the exposed bone and teeth occurs spontaneously after separation of the soft-tissue slough. In some cases, debridement of the wound is necessary to prevent secondary infection and promote the healing process.[9] The loss of orofacial tissues is diverse, varying from a small area (figure 6) to more extensive destruction (figure 7) of the nose, upper lip, and premaxilla, and the infraorbital margin.[2,9]

The sequelae of acute noma depend largely on the sites affected, the extent and severity of tissue destruction, and the stage of development of the orofacial complex before the onset.[1,7] They can include displacement of the teeth, disfiguring, intense scarring, bony fusion between the maxilla and mandible, trismus, defective speech, and nasal regurgitation if the maxilla is lost. Thus, survivors of the acute phase have the two-fold problems of disfigurement and functional impairment, as well as the attendant psychological trauma. Details of these and their surgical management are described elsewhere.[2,14,17]

Differential diagnosis of noma

The disorder known as noma neonatorum affects newborn and preterm infants and clinically resembles noma in children.[47–49] The necrotic lesion, generally in the oronasal region, develops during the first month of life; in most cases, there is evidence of infection with *Pseudomonas aeruginosa*, *Escherichia coli*, klebsiella, or staphylococci.[47,48] Except for one case in a preterm baby in the USA,[50] virtually all the reported cases hav been in infants born in India, China, Lebanon, or Israel.[51–53] Preterm birth and severe intrauterine growth retardation (IUGR) are important predisposing factors.[48] Other ulcerative lesions to be considered in the differential diagnosis of noma include leishmaniasis, agranulocytic angina, malignant oral lesions, midline granuloma of the face, and syphilis, but most of these are rare in children aged 2–5 years.[1] Skin lesions associated with ecthyma gangrenosum occur predominantly in the perineal area and the limbs, with rare facial involvement.[54] Extensive and disfiguring destruction of the mucous membranes of the nose, mouth, and throat can occur in mucocutaneous leishmaniasis, but 90% of cases occur in Bolivia, Brazil, and Peru.[64] **[A: reference numbering goes from 54 to 64; please indicate where references 55 to 63 should be cited. Some of them are cited later, but the order is incorrect if those are the first citations.]** Buruli ulcer resulting from infection with *Mycobacterium ulcerans*, preferentially affects the limbs, particularly the legs.[65] Necrotising diseases of the periodontium associated with HIV infection[66] can resemble the early intraoral signs of noma. Serological testing for HIV infection should be done in these patients. In the diagnosis of the early stages of noma, history of a recent exanthematous fever or debilitating disease, oral mucosal ulcer with bone exposure, excessive salivation, malodorous breath, and severe stunting or wasting in a deprived child are important warning signs. Diagnosis of a well-established case of noma in children is not difficult.[1,3]

	Isolates/number of patients sampled
Fusobacterium necrophorum	7/8
Prevotella intermedia	6/8
α streptococci	4/8
Actinomyces spp	3/8
Peptostreptococcus micros	1/8
Veillonella parvula	1/8
Pseudomonas spp	1/8
Staphylococcus aureus	1/8

Details of the sampling and culture procedures are given in Falkler and colleagues.[65]

Table 2: **Microorganisms recovered from noma lesions in Nigerian children**

Microbiology

The earliest bacteriological studies of noma were described by Weaver and Tunnicliff in 1907.[57] An important major microscopic observation is the presence of large numbers of fusiform bacilli and spirochaetes.[1,16,57] Hicken and Eldredge[58] suggested that a symbiotic association of fusiform bacilli with a non-haemolytic streptococcus and *Staphylococcus aureus* was needed to produce noma. Emslie[40] observed that these organisms were predominant in smears from patients with acute noma but also reported presence of other organisms. Macdonald[59] studied cultures from patients with noma in Nigeria and reported that *Bacteroides melaninogenicus* might be an important associated microorganism in mixed infections of mucous membranes.

Early studies of necrotising ulcerative gingivitis, a putative precursor of noma,[3,40,41] incriminated spirochaetes, fusiform bacteria and *Prevotella intermedia* as potential causative agents.[60,61] Some reports have associated necrotising ulcerative gingivitis, noma, or both with human cytomegalovirus,[62] measles virus,[3,40] herpes simplex virus,[40,46] and other unspecified viruses. PCR studies of herpesviruses in 22 Nigerian children with necrotising ulcerative gingivitis showed that 15 (68%) had viral infection and eight (36%) had viral coinfection **[A: please check calculations of absolute numbers.]**.[45] Human cytomegalovirus infection (59%) was the most common. The findings suggested that this virus and possibly other herpesviruses contribute to the onset or progression of necrotising ulcerative gingivitis in malnourished Nigerian children. Microbiological samples from the same children were cultured anaerobically on selective media.[63] The predominant bacteria isolated were *Prevotella intermedia, Fusobacterium nucleatum*, *Peptostreptococcus micros*, campylobacter, streptococci, and enteric gram-negative rods; these findings did not differ from those in the healthy sites of malnourished children without necrotising ulcerative gingivitis. More anaerobes, particularly *Prevotella intermedia*, were present in the mouths of the malnourished than of the healthy children. These findings suggested that malnourished children have a different flora from healthy children, as previously reported by Sawyer and colleagues.[64] The presence of similar organisms in malnourished children with or without necrotising ulcerative gingivitis also suggested that some other organisms or factors might lead to the development of noma from this putative precursor lesion.

Table 2 summarises the microorganisms recovered from the active sites of noma lesions in Nigerian children; *Fusobacterium necrophorum* was the most commonly isolated.[65] **[A: no need to repeat data from table; the percentages aren't really necessary with a denominator of 8.]** Actinomyces, veillonella, and α-streptococci are normal oral flora. Most of the other microorganisms (staphylococci, pseudomonas) isolated from one or a few cases have previously been associated with noma lesions.[40] *Prevotella intermedia* is involved in periodontal diseases[66,67] and has also been identified as a putative pathogen in necrotising ulcerative gingivitis in young adults.[61] This microorganism promotes tissue destruction through its ability to degrade lipids[66] and the production of proteolytic enzymes.[68]

The association of *F necrophorum* with necrobacilliosis in wallabies,[22,69] and the similarity of this disease to noma in people resulted in the proposal that the organism is involved in the aetiology of human noma.[22] *F necrophorum* did not seem to be part of the normal flora in malnourished Nigerian children without noma living in agricultural and herding villages.[70] In that study,[70] *F nucleatum* was recovered from all 30 children sampled and *F necrophorum* from only one child. These findings in children at risk of noma suggest that *F necrophorum* is a trigger organism for the disease and that it gains a foothold only when certain staging conditions, such as lowered host resistance or oral lesions, are present.[65,70] Although a predominantly animal pathogen, *F necrophorum* has been isolated from people with Lemierre's syndrome[71] and other infectious diseases.[72] The infections in animals associated with *F necrophorum* include liver abscesses and diphtheria in cattle, foot rot in domestic animals, and necrotic lesions in the oral cavity.[73] These diseases are typified by necrosis of the tissues involved, abscess formation, and a characteristic putrid odour. The organism is a commensal in the gut of herbivores, and infection arises from faecal contamination of damaged mucous membranes or skin.[74] Virulence factors of *F necrophorum* have been summarised elsewhere;[13,65] they include various toxins and a growth-stimulating factor for *Prevotella intermedia*. More studies are needed to identify the role of this microorganism in the causation of noma.

In an attempt to explore the bacterial diversity in noma lesions by culture-independent molecular methods, 16S ribosomal RNA genes of bacteria isolated from advanced noma lesions of four Nigerian children were PCR amplified with universally conserved primers and spirochaetal selective primers and cloned into *Escherichia coli*.[75] 67 bacterial species or phylotypes were detected, of which 25 have not yet been grown in vitro.[75] Since advanced noma lesions are infections open to the environment, detection of species not commonly associated with the oral cavity (eg, from the soil) was not surprising.

Risk factors for noma

Noma has not been reported in healthy, privileged African children.[13,22] Poverty is the key risk factor in Africa[2,3,22] and elsewhere.[43,44] A retrospective study of 173 cases at a hospital in Nigeria showed that 98% were from very poor homes with a mean of seven children per family.[76] The global dimensions of poverty and its health implications, particularly malnutrition, are well documented.[77] Chronic malnutrition is a major predisposing factor in all countries reporting noma.[2,3,13,16] The global distribution pattern of the disease[10] reflects the worldwide distribution of malnutrition, particularly deficiencies of vitamin A and other micronutrients in children younger than 5 years.[10,78] These associations, the occurrence of noma in the wartime concentration camps,[18,19] and the absence of cases in well-nourished African children[22] strongly support the role of malnutrition in its development. Most of the reported cases of noma in African countries occur during the dry season, when food is scarce[1,3,39] and the incidence of severe measles is highest.[1,79]

Noma is common in environments with unsafe drinking water, scanty sanitation, poor oral health, limited access to good health-care services, close proximity to neglected livestock, nomadic lifestyle, and a high prevalence of diseases such as measles, malaria, and diarrhoea.[11,13,80] The rate of low birthweight in these communities is as high as 20%,[81] and it is attributable mainly to IUGR rather than to prematurity.[82] Exclusive breastfeeding in the first 3 months of life is rare in communities at risk of noma;[83] the reported rate of exclusive breastfeeding in Nigerian villages, for example, varies from less than 2%[84] to about 12%.[85] Foods given to infants are of poor quality and are prepared under conditions of poor hygiene. The infant mortality rate is as high as 114 per 1000 live births in some communities.[11]

Virtually all patients with noma report histories of previous recent debilitating infections, measles and malaria being the most frequent.[1,3,36,80] The potential contribution of several viruses, especially in relation to their role in the causation of necrotising ulcerative gingivitis, has been discussed.[8,28,45] Studies in Nigeria suggest an increasing frequency of necrotising ulcerative gingivitis among poor rural children.[24,45] During the past two decades, there has also been an increase worldwide in the prevalence of necrotising ulcerative gingivitis associated with HIV/AIDS.[29,32] Nonetheless, in both HIV-positive and HIV-negative children in Africa, only a small proportion of cases of necrotising ulcerative gingivitis or other oral ulcers evolve into noma.

Panel 1: Recommendations for the management of acute noma

- Correction of dehydration and electrolyte imbalance
- Nutritional rehabilitation
- Treatment of predisposing diseases—eg, malaria, measles, tuberculosis
- Antibiotics (penicillin and metronidazole are generally effective)
- Local wound care (irrigation of the wound with appropriate antiseptic)
- Physiotherapy to reduce fibrous scarring
- Removal of any remaining tissue slough and sequestra; generally, necrotectomy is not done until acute stage is controlled
- Serological test for HIV infection and appropriate referral if positive

Interventions

Treatment of acute noma

The key points of management during the acute phase of noma (panel 1) are prompt admission to hospital, correction of dehydration and electrolyte imbalance, nutritional rehabilitation to correct energy deficit and deficiencies of proteins and micronutrients, treatment with antibiotics, daily dressing of the lesion with gauze soaked in oral antiseptic, and treatment of associated systemic diseases.[2,16,86] Some researchers[16] recommend the use of a broad-spectrum antibiotic, whereas others[86] believe that metronidazole (20 mg/kg daily) is adequate since noma is associated with predominantly anaerobic microorganisms. Except for control of secondary haemorrhage and removal of any loose teeth, invasive intraoral procedures are contraindicated Oral hygiene measures are indicated when local conditions permit.[16] Patients should rinse their mouths daily with a solution of chlorhexidine digluconate (0·12–0·20%).[86] Marck[2] emphasised that oral feeding, although the best option, may not be possible owing to pain or incipient trismus, thus necessitating enteral nutrition with a tube. Parenteral nutrition is mandatory if the patient is very sick. A high-protein diet, enriched with energy source and essential micronutrients, is recommended. At the Noma Children Hospital, Sokoto, Nigeria, a highly enriched nutrition formula (Enfortal; ??????????, Netherlands **[A: please give name of manufacturer and the city where it is based]**) has given good results.[2] The patient's weight should be monitored daily.

Physiotherapy should be initiated during the healing phase and continued after surgery to prevent stricture of the mouth resulting from fibrous scarring.[87] Wooden spatulas can help to keep the mouth open in the absence of qualified physiotherapists, but the Therabite (**[A: please give name of manufacturer and the city and country where it is based]**) is preferable.[86]

Surgical repair

There have been several reviews on this subject.[2,9,16] The modalities used depend largely on extent and location of the lesions, available technical facilities, and the competence of the surgical team.[88] Since the reconstructive surgery is complex in many cases, a careful preoperative classification of the tissue defects based on extent and severity of the lesion is necessary. Several classifications have been reported.[2,88,89] Various flap techniques, ranging from simple flaps and autoplasty to complex procedures involving microsurgery, have been described for repair.[1,2,88,89] Even in the most advanced medical environments, the results of surgical repair are less than perfect.[90] Treated cases must be followed up, therefore, and efforts made to reintegrate them into society.

Prevention and early detection of noma

Noma is encountered mainly in underprivileged, illiterate, remote communities. It becomes established very rapidly, leaving patients little time to seek medical assistance. Parents, and even many health personnel, know little about the disease. Information campaigns are therefore needed at national, regional, and village levels. All health personnel, including physicians and dentists, should routinely screen at-risk children for early signs of noma (panel 2), and suspected cases should be promptly referred to appropriate facilities.[2,16,22] Training of public-health personnel on recognition of early lesions is essential. All oral mucosal ulcers in deprived, stunted children should be viewed with suspicion. Factors to prevent noma are listed in panel 3. At the governmental level, eradication of poverty should be a top priority.

Panel 2: Early detection of acute noma

- Routine mouth examination
- Severe growth failure in first 6 months of life
- Evidence of severe malnutrition and poor dietary habits; persistent diarrhoea
- Oral mucosal ulcers (eg, necrotising ulcerative gingivitis, measles, herpes, cytomegalovirus)
- Prominent malodorous breath

Panel 3: Prevention of noma

- Information campaign/national awareness about noma
- Eradication of poverty
- Improved living conditions, with particular attention to environmental sanitation
- Segregation of livestock from human living quarters
- Proper oral-hygiene practices
- Adequate nutrition, with particular emphasis on exclusive breastfeeding in the first 3–6 months of life
- Clean drinking water
- Timely immunisations against common childhood diseases, particularly measles
- Increased awareness of the nutritional and health needs of women, particularly during pregnancy and lactation

Proposed pathogenesis of noma

There is a three-way relation between malnutrition, immune dysfunctions in the host, and increased susceptibility to infections.[91–95] As shown in figure 8 under the broad umbrella of poverty, this relation tends to be synergistic[91,94] and results in impaired oral mucosal immunity. In African communities at risk of noma, the adverse consequences of IUGR, which include impaired development of immune function, especially cell-mediated immunity,[96,97] become apparent in early postnatal life, and continue into adulthood in terms of increased risk to disease.[77,96] Programming of the endocrine axes, which occurs during crucial phases of fetal development, is adversely affected by IUGR.[98]

The coincidence of the peak age incidence of acute noma[11,42,76] and the timing of linear growth retardation in impoverished African children[83,85] may not be fortuitous. Growth faltering in deprived African infants becomes noticeable at age 3–4 months with discontinuation of exclusive breastfeeding[84,85] and continues until about 36 months.[85,99] The importance of exclusive breastfeeding in preventing infections of the host via mucosal membranes has been reported.[100,101] The infancy-childhood-puberty model divides human growth into three additive, partly superimposed phases; the infancy phase starts in the middle of gestation and ends at about 3–4 years of life.[102,103] Malnutrition and a continuous burden of immunostimulation by environmental antigens explain the occurrence of linear growth retardation in deprived children.[104–106] Since stunting in infants is a process that might start in utero,[102,107] the contribution of prenatal events to the severe growth failure seen in children with acute noma (table 1) needs to be explored.

Amounts of secretory IgA, a major component of the mucosal immune system,[108] are lower than normal in malnutrition.[92] Plasma concentrations of C-reactive protein and the proinflammatory cytokines are higher in malnourished African children than in their healthy counterparts; in both groups, infections intensify the high concentrations.[109] As AIDS does,[110] the two most commonly reported infections preceding noma, malaria[111] and measles,[112,1,3] promote a shift from a proinflammatory to an anti-inflammatory cytokine profile. Studies of malnourished Nigerian children (younger than 5 years) with acute measles show severe depletion of plasma interleukin 12, an increase in interleukin 6, diminished

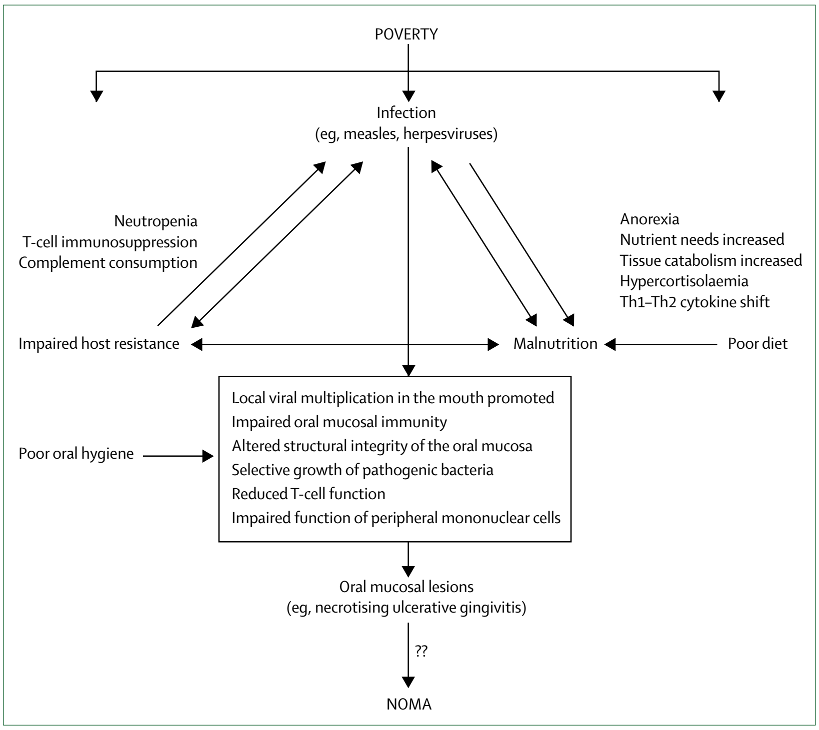

***Figure 8*: Suggested scheme for the pathogenesis of noma in deprived African children**
Adapted from Enwonwu and colleagues.[77] **[A: which reference please; there are two in 1999]**

circulating retinol, and increased plasma cortisol compared with measles-free, neighbourhood children of the same age.[112] By impairing T-cell function, measles seems to increase further the vulnerability of immunologically compromised malnourished children to infection with the microorganisms that cause noma.[112,113]

No more than 20% of the variability in inflammatory periodontal disease expression is thought to be attributable to local causative factors, so there must be a substantial contribution from the host's responses.[114] The rapid destruction of orofacial tissues in acute noma[3,5] suggests an immunopathological reaction to microbial factors. Plasma concentrations of proinflammatory and anti-inflammatory/regulatory cytokines are higher in children with necrotising ulcerative gingivitis than in healthy control children.[115] In response to bacterial products, oral epithelial cells and other resident cells secrete several proinflammatory cytokines and chemokines.[116,117] The proinflammatory cytokines stimulate expression of the matrix metalloproteinases[118] and also have a role in pathological bone loss.[119]

Despite the high prevalence of necrotising ulcerative gingivitis and other oral mucosal ulcers[120,121] in deprived African children, only a small proportion of cases progress to noma. The reason for the transition from these ulcers to noma is not clear (figure 8). While still searching for the missing link, one of us (COE) speculates that acute noma occurs in a small subset of deprived children whose prenatal development is compromised by maternal malnutrition and infection.[122,123] According to this hypothesis, because IUGR and exclusive breastfeeding promote normal thymic function, T-cell differentiation, and other features of immune development,[124,125] the vulnerability of such infants to infections becomes even more profound with early discontinuation of exclusive breastfeeding. Unlike preterm low-birthweight infants who recover immunologically much earlier (2–3 months of age), most low-birthweight infants who are small for gestational age show long-lasting impairment of cell-mediated immunity up to age 12 years.[92,126] Perhaps there is no pathogenetic difference between noma in children and the histopathologically similar noma neonatorum in preterm infants, since the consequences of prenatally impaired immune function can manifest at various postnatal stages of life.[77,96,97]

Noma robs many children of their future. There is urgent need for countries where noma is still prevalent to set up control plans that emphasise prevention and early detection of the disease, while addressing poverty, environmental hygiene, perinatal health care, maternal and infant nutrition, and timely immunisation of children against endemic diseases, particularly measles.

Conflict of interest statement
We declare that we have no conflict of interest.

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