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Noma (Cancrum Oris)

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Keywords
Noma
Cancrum oris
Orofacial gangrene
Necrotizing stomatitis
Necrotizing gingivitis
Facial reconstruction

Abbreviations
ANG - Acute necrotizing gingivitis
CMV - Cytomegalovirus
FN - Fusobacterium necrophorum
HIV - Human immunodeficiency virus
LIMC - Low-middle-income countries
PEM - Protein energy malnutrition
TMJ - Temporo-mandibular joint
WHO - World Health Organization

Abstract

Noma (also known as cancrum oris, orofacial gangrene of childhood) is a synergistic infection of the oral cavity that causes mutilating necrosis of the orofacial soft tissues and bones. Classical noma, noma-like disease and noma neonatorum are the three clinical variants. Fusobacterium necrophorum, Prevotella intermedia, Peptostreptococcus and Pseudomonas are the key organisms incriminated in the pathogenesis. It usually starts as acute necrotizing gingivitis and progresses to necrotizing periodontitis, necrotizing stomatitis, necrotizing fasciitis and osteo-myonecrosis in that order. Noma is a disease of poverty. Synergistic bacterial infection, immuno-suppressed state and mucosal ulceration form the etiopathogenic triangle. The region extending between Senegal and Ethiopia is known as 'noma belt' due to very high incidence. W.H.O classified noma into 5 clinical stages. Acute noma is managed by giving antibiotics and restoring oral hygiene. The residual deformity of noma offers great technical challenge to the reconstructive surgeon. Facial reconstruction should be individualized based on the nature of tissue defect. With proper treatment the current mortality is less than 10%. In 2023 W.H.O announced noma as a 'neglected tropical disease' and declared that 'noma is more than a disease'.

INTRODUCTION

Noma is a synergistic infection of the oral cavity that causes mutilating necrosis of the orofacial soft tissues and bones.[1-6] It is nicknamed as 'the face of poverty'.[7] It is common in low, middle-income countries (LMIC) among malnourished children of age 1-6 years.[3,5,6,8] It is not clear as to how noma is pathologically different from other necrotizing fasciitis such as Fournier gangrene and Meleney ulcer.[9] Perhaps, destruction of underlying bone is unique of noma. Despite being known for over 1300 years, etiopathogenesis of noma is still elusive.

Acquiring scientific knowledge and reliable statistical data of noma are precluded by several socioeconomic factors.[10] As it is quickly fatal,

several patients die in remote villages even before getting medical help. Social stigma, poverty, poor transport facilities, illiteracy and distrust with allopathic medicine prevent affected children from attending hospitals. Native medicine and witchcraft further worsen the situation. As noma is common among nomadic populations proper enrollment, statistics keeping and long term follow-up are often impractical. Resource limitations in endemic areas preclude sophisticated investigations and advanced surgical corrections.

HISTORY AND ETYMOLOGY

The term *noma* was derived from the Greek word *'numein'*, meaning *'to devour'* or *'to graze'*.[11]. Ancient Greek physicians like Hippocrates (circa 460 - 377 BCE) and Galen (circa 129 – 216 CE) used this term to mean any rapidly progressing disease and they never specifically described orofacial gangrene.[11] Jan Yperman (circa 1260 – 1331 CE), a Flemish surgeon, was the first to mention *'water canker'*, the old Dutch name for noma.[12] The word *'canker'* simply means '*fungating ulcer*' and had been applied to a variety of pathologies including fungal granuloma and neoplasia. In 1595, Carolus Battus gave the first clear description identifying it as a separate entity. In 1649, Arnoldus Boot coined the term *'cancrum oris'*. However, in 1826, Coates criticised the word *'cancrum'* as *"an odd grammatical blunder"* because it uses accusative case *'cancrum'* instead of the proper nominative case *'cancer'*.[13] Unfortunately, until the 18th century, the terms '*canker oris'* and '*cancrum oris'* were confusingly used to mean both oral cancers and orofacial infective necrosis. In 1680, Cornelis van de Voorde was the first to suggest exclusive usage of the term 'noma' to mean orofacial gangrene of childhood.[11]

In 1765 Gabriel Lund recognized the 4 stages of the disease.[7] At the same time, Symmonds elucidated the etiological relationship between noma and measles. In 1781, Leendert Stelwagen was the first surgeon to do successful surgical correction of noma.[7] In 1828 Adolph Richter published the first monograph on noma.[7] In early 19th century Esmarch devised mandibular osteotomy for treating trismus and Estlander described his technique of lip-sharing reconstruction.[7]

With the advent of microbiology as a separate field, Stewart of Leeds, in 1912, isolated a spiral organism (*'Bacillus nomae'*) and concluded noma as a disease of opportunistic infection.[7] This organism was later named as *Borrelia vincentii* and subsequently lost its nominal identity due to frequent taxonomic revisions. During the World War-II, in the concentration camps of Germany and Japan, a noma-like disease (also known as *trench fever* or *Vincent disease*) was described.[14] Subsequently, a distinction between *Vincent disease* and *noma* was drawn for a brief period. Vincent disease (also known as *acute necrotizing gingivitis*) is now once again considered as the prodromal lesion of noma.[14] Interestingly, until the last century the term 'noma' was used to denote genital gangrene in young girls (*noma pudendi*).[7,12]

With the discovery of antibiotics, survival of noma greatly improved. Those who would have died of sepsis, began to live long. This necessitated the shifting of focus from sepsis control to surgical reconstruction of the survivors. Michael Tempest is considered as the founding father of modern noma surgery.[7]

Despite its existence over a millennium, noma has largely been ignored by the western researchers. Finally, World Health Organization (WHO) announced noma as a *'disease of high priority'* in 1994 and as a '*neglected tropical disease'* of great importance in December 2023.[15] WHO slogan is *"Noma is more than a disease"*.[15] GESNOMA (Geneva Study Group on Noma), a humanitarian voluntary association intended to study the pathogenesis of noma, was launched in 2001.[16] In the International Classification of Diseases (ICD-10) noma is coded under '*A69.0: Necrotizing Ulcerative Stomatitis'*.

Box 1: Synonyms of Noma ‡

ANG	Mund krebs
Acute ulcerative gingivitis	Necrotic gingivitis
AUMG	NUS
Aka popo (Zambia)	Orofacial gangrene
Anarchie dentaire	Pagnad Pak Poue (Laos)
Aphthae serpentes	Periodontal gingivitis
Bakin Kare † (Nigeria)	Periodontal stomatitis
Cancer aqauticus sive aquous §	Phagedenic gingivitis
Cancer scorbuticus labii	Plaut-Vincent stomatitis
Cancrum oris infantium	Putrid stomatitis
Canker oris	Putrid mouth sore
Can tan ma (Vietnam)	Schwartzer Krebs
Cheilocace maligna	Scorbutic canker
Ciwon Iska * (Nigeria)	Septic gingivitis
Cone gangreneux	Stomatite charbonnause
Diphtheroid angina	Stomatitis epidemiea
Feldzug stomatitis	Stomatitis gangrenosa
Fetid stomatitis	Stomatitis ulceromembranacea
FS marginal gingivitis	Stomatitis ulcerosa
FS periodontal gingivitis	Stomatocase gangraenosa maligna
Fusospirochetal gangrene	Stomatomalacia putrida
Fusospirochetal gingivitis	Trench mouth / gums
Fusospirochetosis	Todtenwurm
Gangrena oris	Ulcerative gingivitis
Ganrena accutissima caseosa pulpa	Ulcerative stomatitis
Gangraenopsis	Vincent angina
Gangrenous stomatitis	Vincent disease
Gangrenous osteo-gingivitis	Vincent gingivitis
Gilmer's disease	Vincent infection
Mouth canker	Vincent periodontitis
Mund faule	Vincent stomatitis
	Water canker §
	Wasser krebs §

‡ *Compiled from Talma[7], Marck[7], Murayama.[22] This list also contains synonyms of ANG because it is included as Stage-1 Noma in WHO classification.*

* *A Nigerian term meaning 'Disease of the wind'*

† *A neologism meaning 'Dog mouth' coined for the purpose of public awareness by radio announcements in Nigeria.*

§ *These names suggest spread of infection by contaminated water.*

ANG-Acute necrotizing gingivitis; AUMG-Acute ulcero-membraneous gingivitis; FS-Fusospirallary; NUS-Necrotizing ulcerative stomatitis

NOMENCLATURE

Noma is known by a variety of scientific and colloquial names (Box 1).[17] Three distinct clinical forms are recognized: Classical noma, Noma-like lesions and Noma neonatorum.[2] *Classical noma* is due to synergistic infection of aerobic and anaerobic bacteria occurring in malnourished children. Morphologically similar, but pathologically less aggressive lesion occurring in immuno-compromised or debilitated adults and experimental animals is called *'noma-like lesion'*.[18] In 1976 Ghosal introduced the term *'noma neonatorum'* to denote orofacial necrosis due to *Pseudomonas* occurring in edentulous premature neonates.[19,20] It was also suggested that noma neonatorum could be a form of *ecthyma gangrenosum*.[21] Although clinical manifestations are grossly identical between the 3 entities, they significantly differ in pathogenic mechanisms and outcomes. (Table 1)

ETIOPATHOGENESIS

Noma is generally considered to be a synergistic infection of aerobic and anaerobic bacteria.[24,25] Facultative aerobes thriving beneath dental plaques secrete proteolytic enzymes that cause local cell death and ulceration. Dead tissue with reduced oxidative stress facilitates growth of anaerobes. Cytotoxins (hemolysin, endotoxin and leukotoxin) secreted by anaerobes offer immunological protection to aerobes by destroying phagocytic neutrophils. Hemin, an iron containing growth factor essential for aerobes, is also released from hemoglobin by the action of hemolysin.[24] Thus, a synergistic alliance and vicious cycle is established culminating in extensive tissue damage.

Some of the anaerobes are also independently capable of creating their own favorable hypoxic micro-environment by inducing small vessel thrombosis.[26] For example, *Fusobacterium necrophorum* (FN) secretes hemagglutinin and platelet agglutinin that cause vascular thrombosis, dermonecrotic toxin that causes necrosis of the

Table 1: Clinico-pathological differences between the 3 clinical types of noma

	Classical noma	**Noma-like lesion**	**Noma neonatorum**
Nature of infection	Synergistic polymicrobial	Non-specific opportunistic infection	Monomicrobial
Common organisms	*Prevotella* and *Fusobacterium*	Opportunistic bacteria or fungi	*Pseudomonas aeruginosa* (86%)
Source of infection	Community acquired	Community or hospital acquired	Hospital acquired
Origin of infection	Interdental plaques	Hematogenous	Hematogenous
Precursor lesion	Necrotizing gingivitis	None	None
Geographic pathology	Common in LIC	Anywhere including HIC	LMIC
Affected age group	1-6 yrs	Older children, Adults	Newborn
Predisposing condition	Malnutrition, Measles	HIV, Cancer chemotherapy	Prematurity
Metastatic gangrene	Seldom	Never	Genito-perineal involvement in 20%†
Surgical challenge	Huge tissue deficit, malnutrition	Underlying immuno-compromised state	Seldom reach the stage of surgical reconstruction
Clinical course	Rapidly fatal within a few days/weeks	Indolent with survival for several weeks/months	Rapidly fatal within few days
Current Mortality of acute phase	8-15%	54 - 78%	>90%
Recurrence	Extremely rare (only 5 cases reported)*	Common if underlying HIV is not treated *	Seldom survive to have recurrence

** Ref: Calleros[18], Chidzonga[23]; † Ref: Ghosal[20]*

skin[27] and enzymes such as phosphatase-B that causes bone resorption.[24] *FN* provides growth factor necessary for *Prevotella intermedius* which in turn supports FN by secreting enzymes like lipase, di-peptidyl-peptidases and cysteine proteases that causes lipolysis and destruction of IgG.[28-31] For this reason, these two organisms are sometimes referred to as the 'trigger organisms' of noma.[2,24,32,33] Bolivar identified *Prevotella* and *Peptostreptococus* as the sinister trigger.[34]

Acute necrotizing gingivitis (ANG) is generally acknowledged to be the precursor lesion of noma.[35,33] Marginal necrosis of the interdental papilla serves as the entry point of invasive bacteria. Spreading infection progressively affects tooth sockets (*necrotizing periodontitis*), oral mucosa (*necrotizing stomatitis*), soft tissues of cheek and lips (*necrotizing fasciitis*) and bones (*osteo-myonecrosis*) in that order, thereby establishing the classical noma.[25,36] However, noma is also known to occur without preceding ANG.[25]

Pathogenesis of noma is fraught with many riddles. Most importantly, microbes isolated from the noma wounds do not satisfy the Koch's postulates.[2,24] For example, those organisms incriminated in the pathogenesis of ANG and noma are also found in healthy children. (Table 2) These organisms, when inoculation in laboratory animals, did not produce a disease similar to noma.[24,37] Noma, unlike other infectious diseases, is not contagious. It seldom occurs in more than one member of the family although all of them live in the same socio-economic condition.[38] Hence, synergistic infection appears to be just a triggering factor, while antecedent cause must be different. Several such risk factors have been identified.

Table 2: Frequency of organisms isolated from the oral cavity of children

Organism	ANG or Noma	MN *sans* ANG or Noma	Healthy children
Prevotella	85%	61%	13%
Fusobacterium	30%	39%	38%
Peptostreptococcus	30%	-	-
Campylobacter	55%	28%	-
Streptococcus	*45%*	83%	100%
Enteric Gram negative bacilli	*35%*	28%	-

Data from Falkler[24]
ANG-Acute necrotizing gingivitis; MN- Malnutrition

RISK FACTORS

Oral Hygiene: Poor oral hygiene is a predisposing factor of gingivitis. ANG is common in those who use native 'chew stick' rather than toothbrush.[38] Shared drinking vessel and water contaminated with the feces of livestock are associated with noma.[38] Interestingly, ANG is also seen in more than 2% of children with good oral hygiene and only a tiny fraction of those with ANG develop noma.[2] Therefore, there must be other factors responsible for the transformation of ANG into noma.

Malnutrition: Protein-energy malnutrition (PEM) is invariably seen in all noma patients.[6,8,39] In a large series of 250 noma patients, malnutrition was severe in 55%, moderate in 28% and absent in 7%.[40] But its cause-effect relation-ship with noma is not certain. Although children of a poor family share the same type of food, it is perplexing as to why only one of them develop noma. It is hypothesized that malnourished children may have altered pattern of oral micro-flora.[41] Gram negative anaerobes and spirochetes are more common in them, while gram positive cocci are common in healthy children.[2] Protein deficiency is known to compromise immunity by causing atrophy of lymphoid tissue, reduction of lymphocyte count, alteration of CD_4:CD_8 ratio, malfunctioning of neutrophils and impaired synthesis of immunoglobulins (especially IgA that protects epithelial surface and IgG that is responsible for opsonization). High cellular turn-over of oral mucosa requires constant protein supply to maintain its integrity. Thus, malnutrition is known to cause oral ulcers which may act as entry point of infection. On the other hand, trismus of noma precludes proper feeding thereby contributing to malnutrition.[39] Contrary to the foregoing description, among 69 children with noma, albumin and globulin levels were found to be almost normal.[42] In fact, Eckstein found malnutrition only in those who came to hospital very later, thus suggesting it to be an effect of noma.[35] Enwonwu *et al*. advanced the concept of malnutrition to antenatal period and they noted that maternal malnutrition, as indicated by intra-uterine growth retardation, predisposes to noma by affect the developing thymus of the fetus.[5,43]

Vitamin and Trace Element Deficiency: PEM is often accompanied by varying degree of vitamin deficiencies.[8] Vitamin A prevents atrophy of lymphoid tissues and maintains the epithelial integrity. Vitamins B6 and E are essential for antibody synthesis and cell mediated immunity. Vitamin C influence immunity by altering plasma cortisol level and by affecting bactericidal ability of macrophages and neutrophils. It also causes bleeding ulcers of the gums, delays wound healing and reduce collagen synthesis. B1 and B12 deficiency cause oral ulcers. Deficiency of iron impairs antigen response of leukocytes, while zinc deficiency causes atrophy of lymphoid tissues, affects phagocytosis and impair tissue repair.[8] A combined deficiency of these vitamins and elements is thought to weaken body defense thereby predisposing to noma.

Stress and Cortisol: Psychosocial stress and PEM are known to increase plasma cortisol levels.[8,44] It is more pronounced with marasmus than with kwashiorkor. High cortisol reduces cell mediated immunity, epithelial cell-turn over and collagen synthesis. It also increases serum hyaluronidase

which facilitates bone resorption in noma. Salivary cortisol which matches elevated serum levels is also a growth factor for *Prevotella*, the trigger organism of noma.[2] In addition to cortisol, other stress related hormones such as catecholamines, glucagon, and cytokines are also elevated in noma. All these chemicals may play a role in gluco-neogenesis by breaking down of muscle protein thereby contributing to malnutrition. Psychological stress explain the high incidence of ANG in the post-World War-II concentration camps of Germany and Japan.[3]

Measles: Noma virtually vanished from Europe with the advent of measles vaccination. During a German epidemic 33 of 133 children with measles developed noma.[2] In fact, '*noma-like post measles ulceration*' is a well known entity.[45, 46] Hence it was proposed that measles may predispose to noma either by causing mucosal ulcerations or by post-measles malnutrition.[2, 40] Measles virus is known to impair immunity by killing activated T-cells thereby reducing the production of interleukin-12, increasing interleukin-6 and diminishing retinol.[5] However, a vast majority of noma patients do not have preceding measles.

Herpes - Cytomegalovirus*:* Nearly 59% of ANG patients were sero-positive of CMV.[47] CMV is known to alter immunity by destruction of neutrophils. It also increases production of interleukin-1β which promotes bone resorption in noma. *Herpesvirales* infections such as *Herpes simplex,* CMV and Ebstein-Barr virus are well known to cause micro-ulceration of oral mucosa which could be the entry point of noma-triggering organisms.

Human Immunodeficiency Virus (HIV): Spontaneous noma-like lesion is seen in African monkeys with HIV infection.[4] In a Zimbabwean study[48] all the 27 children with noma were HIV-positive, while in Nigeria none had HIV.[25] The incidence of noma among HIV patients is variously reported as 6-31%.[18] A systematic review identified 24 publications reporting 133 HIV patients with noma.[18] But this is a miniscule proportion of the annual incidence of noma.[18] Therefore, HIV infection appears to be coincidental although immunosuppression of HIV may contribute to noma or noma-like disease. Coexistent HIV increases the risk of noma recurrence [48] and mortality.

Malaria: Noma is common in endemic areas of malaria. Eckstein hypothesized that plasmodium infection may contribute to the onset of noma by affecting reticuloendothelial system, especially the spleen.[35] However, Tempest disagreed with this hypothesis and he found no proof of this association.[40]

Debilitating Illnesses: Several infectious diseases such as typhoid fever, typhus fever, tuberculosis, Leishmaniasis, diphtheria, pneumonia, diarrhea, small pox and chicken pox have been incriminated in the pathogenesis of noma.[2] The exact mechanism is not known. Probably, they predispose to noma by causing malnutrition, poor oral hygiene or mucosal ulcerations. The circular shape of noma gangrene prompted an interesting hypothesis that it could be a form of pressure necrosis of cheek, as debilitated children lie down in bed continuously for several days in lateral position.[4] Debilitating illness are also thought to tilt the balance between pro-inflammatory and anti-inflammatory cytokines, thus facilitating invasive infection.[44]

Malignancy: Noma has been reported to complicate a variety of immunosuppressive disorders such as acute myeloid leukemia,[49, 50] cyclic neutropenia, Down syndrome[51] and Burkitt lymphoma.[52] Immunosupression of chemotherapy drugs is said to cause noma-like disease in adults.[53]

From the foregoing it is possible to hypothesize that noma could be the end result of 3 concomitant factors which, perhaps, form an etiological triangle. (Fig. 1) They are: synergistic

infection of FN and *Prevotella,* impaired immunity and mucosal breech. This is supported by animal experiments in which rats inoculated with bacterial isolates never developed oral mucosal necrosis unless subjected to corticosteroid injections and mechanical trauma of gums.[2,54]

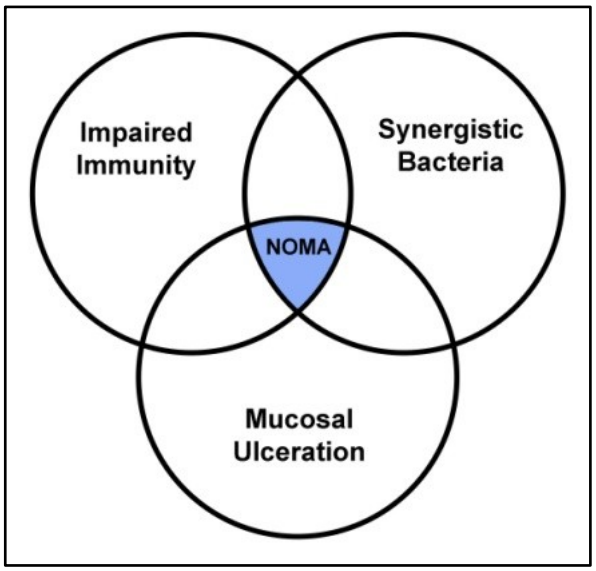

Fig 1. ***Etiological factors of the noma triangle***

DEMOGRAPHY

Exact incidence of noma is not known because many patients with acute disease die in remote villages without getting medical attention.[2,4,55,56] In Nigeria prevalence of ANG is 0.3% and that of noma is 6.4 per 1000 children.[57] Others found 1.6 cases of noma per million population in Nigeria[58] and 4.2 cases per million in Senegal.[59] More interestingly, no new cases of advanced noma were found in the Nigerian survey of 2018.[60] Community prevalence was found to be 3300 per million population in Nigeria.[3] Contrary to these accounts, in 1998, WHO estimated worldwide annual incidence of noma as 140,000 with a prevalence of 770,000 patients.[3,5] This appears to be an overestimate with unknown methodology of calculation [3, 60] A more realistic figure could be 25000 to 40000 new cases per year.[18,61]

Geographic and chronological variation in the incidence of noma is well known. (Fig. 2) In the 1800's noma was frequently reported from Europe and India, in 1900's from Africa and North America and in 2000's from Africa, South America and Asia.[3] Incidence of noma surges following an epidemic of measles.[2] Even within a continent incidence of noma varies from country to country and between rural and urban communities of the same country. The region extending between Senegal and Ethiopia (including Burkina Faso, Mali, Niger and Nigeria), owing to very high incidence of noma, is sometimes referred to as the 'noma belt'.[3, 5, 62] (Fig.2) Incidence of ANG, the precursor of noma, varies between 1-7% in different population.[37, 63]

Several social factors associated with dietary deprivation have been identified as risk factors of noma. They include children raised by grand-mothers,[64] early weaning from breast-milk, absence of chicken at home[2] and families with more than 7 children.[5] *Fusobacterium* is a commensal in the gut of livestock. Feco-oral contamination of animal faeces explains as to why noma is common in dwellers of thatched house, rural communities with unsafe drinking water, barefoot walkers, shared drinking vessels, finger feeding and sleeping on the floor.[38]

Although no age is immune to noma, 80% of patients belong to the age group of 1-6 years.[40] It is seldom seen in edentulous infants and breast feeding babies.[40] William Osler reported high female ratio (M:F - 1:3) from Madagascar, while Durand noted male predominance.[40] Most of the modern series [5, 40] do not find any significant sex predilection. A mild female preponderance may be due to gender discrimination in feeding pattern.

Noma is common in summer months (January-May) when drought and malnutrition are at peak.[5,40] A second smaller peak is seen during winter (July-August) probably due to associated water contamination and malarial epidemics. However some authors deny seasonal variation in the incidence of noma.[40]

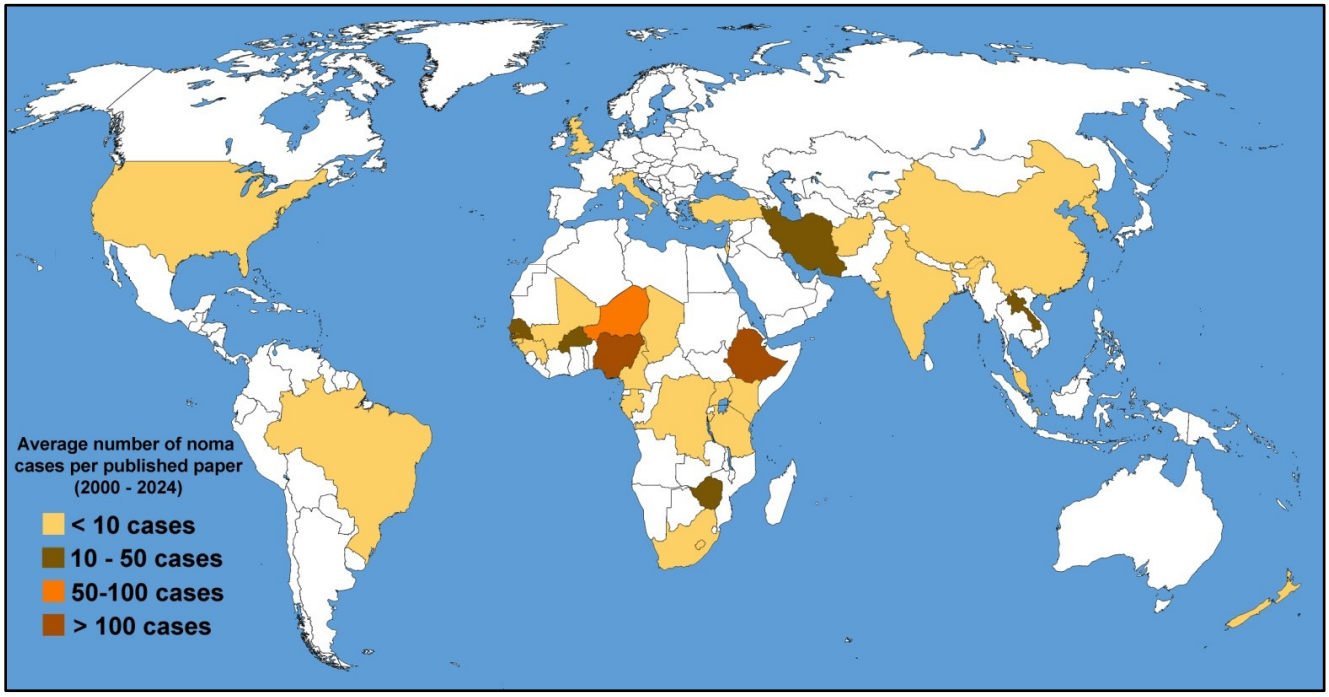

Fig 2. ***Geographic distribution of noma.***

(In the absence of reliable country-wise statistics, the map is constructed based on the number of cases reported from each country as per PubMed records between 2000 and 2024. About 11583 noma patients have been reported in 123 publications in PubMed indexed journals. Country-wise 'case frequency index' was calculated by dividing the number of noma patients reported from a particular country by the number of publications from that geographic location)

PATHOLOGY

Noma usually progresses through a well defined sequence of ANG, necrotizing periodontitis, necrotizing stomatitis, necrotizing fasciitis and osteo-myonecrosis.[36] However, de novo lesions are not unknown.[25]

Noma usually starts at the alveolar margin of pre-molars and mandibular incisors. It is usually uni-lateral; but rarely bilateral. Factors that determine the extent of tissue damage is not known.[25] Although the area of necrosis is not matching with any known pattern of arterial anatomy, noma could still be a vascular phenomenon involving small vessels, capillaries or venous infarction. The necrosed area is in the form of a cone with its apex at skin surface and base at deeper tissues - hence the old name *'cone gangreneux'*.[2] Masticatory muscles and tongue muscles are rarely affected by necrosis but the former are frequently involved in post-gangrene fibrosis.[4]

In very aggressive for of noma, complete destruction of both maxilla and/or mandible occurs.[65] Destruction of bone is perhaps unique of noma differentiating it from other necrotizing fasciitis. Factors incriminated in bone resorption include phosphatase-B secreted by FN, inter-leukin-1β produced by cytomegalovirus and increased serum hyaluronidase in noma. Further, osteonecrosis could also be a vascular event. Involvement of tooth socket may also facilitate onset of early osteomyelitis and bone necrosis.[35] Matrix metalloproteinase an enzyme that is activated by pro-inflammatory cytokines may also contribute to bone resorption.[44,66] Unfortunately, noma affected tissues have not been subjected to proper histopathological studies.[25]

Box 2: Organisms isolated from noma

Gram positive bacilli
Actinomyces israelii [b]
Bacillus cereus [a]
Clostridium beijerinckii [b]
Cutibacterium acnes [1] [b]
Limosilactobacillus fermentum [2] [c]
Lysinibacillus fusiformis [8] [a]
Trueperella pyogenes [3] [c]
Gram negative bacilli
Achromobacter xylosoxidans [a]
Aggregatibacter actinomycetem comitans [c]
Bacteroides fragilis [b]
Brevundimonas diminuta [a]
Brucella anthropi [4] [a]
Cetobacterium [c]
Campylobacter rectus [c]
Capnocytophaga gingivalis [c]
Escherichia coli [c]
Fusobacterium necrophorum * [b]
Fusobacterium nucleatum * [b]
Klebsiella pneumoniae [c]
Mesorhizobium loti [b]
Porphyromonas gingivalis [5] [b]
Prevotella intermedia [6]* [b]
Prevotella melaninogenica [6]* [b]
Prevotella nigrescens * [b]
Pseudomonas aeruginosa * [c]
Selenomonas sp [b]
Stenotrophomonas maltophilia [a]
Tannerella forsythia [b]
Gram positive cocci
Peptostreptococcus micros * [b]
Staphylococcus aureus * [c]
Staphylococcus epidermidis [c]
Streptococcus sp * [c]
Gram negative cocci
Veillonella parvula [b]
Spirochete
Treponema vincentii [7] [c]
Treponema denticola [b]

Former genus name: [1]Propionibacterium, [2]Lactobacillus, [3]Corynebacterium, [4]Ochrobactrum, [5,6]Bacteroides, [7]Borrelia, [8]Bacillus

[a]Aerobe, [b]Anaerobe, [c]Facultative aerobe/anaerobe

** Key pathogenic organisms of noma*

MICROBIOLOGY

Several bacteria have been isolated from noma wounds.(Box-2)[24,67] Molecular studies have shown that only 20-40% of all organisms found in noma lesions could be isolated by conventional bacterial cultures.[2] The principal reason is non availability of anaerobic culture facilities in many resource poor countries where noma is endemic. Paster *et.al.*[68] by molecular studies, isolated 67 different species of microbes from noma wounds. Interestingly, they did not find FN in any of their patients. Large-scale sequencing studies have shown that the identity of isolated organisms are very different from that is reported by conventional techniques.[2]

Bacterial isolates of noma can be classified into primary (causative microbes) and secondary infections (opportunistic commensals invading dead tissue).[8] Clear distinction between the two is often not possible and both of them may contribute to mortality. To exclude secondary pathogens, Eckstein suggested culturing of needle-puncture specimen from tissue adjacent to the margin of necrosis rather than culturing the swab specimens from the gangrenous part.[35] The role of spirochetes in noma is not clear.[24,37,67]

CLASSIFICATION

Noma has two distinct classifications systems: (a) Staging of pathogenesis and (b) Grading of disease severity and extent of tissue damage. Staging is useful in formulating prophylactic and therapeutic strategies, while grading is useful in planning rehabilitative surgery.

Noma Staging

World Health Organisation (W.H.O) originally classified noma into five evolving stages and later added a stage-0. (Box-3)[69] Khammissa *et al.*[36] criticized this classification on several grounds. Although ANG is well accepted to be a precursor of noma, including it in the staging system will inappropriately inflate the statistics of noma. Still

worse is the inclusion of simple gingivitis as the stage-0 which would then mean that one third of the world's population to have noma. According to Khammissa *et al*, this is not only nonsensical but also may potentially distract the scientific understanding of noma as a distinct entity. They also pointed out the inappropriateness of including cheek edema as a stage of noma because it is a non-specific feature seen in several inflammatory disorders. Field workers may mistake edema of other causes for that of noma and vice versa.

Khammissa simplified WHO staging by combining stages 0-1 as 'Noma precursors', stages 2-3 as '*acute noma'* and stages 4-5 as '*arrested noma'*.[36] WHO staging is not without merits, especially in the context of preventive strategies. The statistical and disease-insight concerns of Khammissa *et al*. can be resolved by analyzing stage-specific figures.

From microbiological point-of-view, Falkler[5,8,24] classified noma in to 3 periods: Staging period, Triggering period and Invasive destruction period.

Box 3: Noma staging systems

WHO Staging

Stage 0: Simple gingivitis
Stage 1: Acute Necrotizing Gingivitis
Stage 2: Oedema
Stage 3: Gangrene
Stage 4: Scarring
Stage 5: Sequelae

African Staging

Stage 1: Acute noma
Stage 2: Arrested noma

Noma Grading

There are three popular grading systems of noma: Cariou[4, 70] Montandon[71, 72] and Marck.[73] Cariou classified the resultant defect as simple, extensive and complex. (Box 4) Montandon system is simple and has been adopted by WHO. (Fig. 3) Marck classification is also known as Sokoto or NOITULP classification in which each of the letters stand for a particular anatomical structure: N-nose; O-outer cheek; I-inner cheek; T-trismus; U-upper lip; L-lower lip and P- any other particular problem (e.g. loss of bone or eye). Severity of damage in each of these organs is assessed on a 4 point scale: 0-no loss; 1-loss up to one quarter; 2-loss up to half; 3-loss up to three quarters and 4-near total or complete loss of the anatomical structure. Trismus is assessed on a 4 point scale: T_0 - normal, T_1 - less than 4 cm mouth opening, T_2 - less than 3 cm opening, T_3 - less than 2 cm opening and T_4 - complete trismus. Disease severity of a given patient is then represented by the alphanumeric combination of organ code and severity code (e.g. N_1 O_4 I_4 T_3 U_2 L_1 P-loss of right eye). Obviously, Marck system, albeit accurate, is too complex to follow in clinical practice.

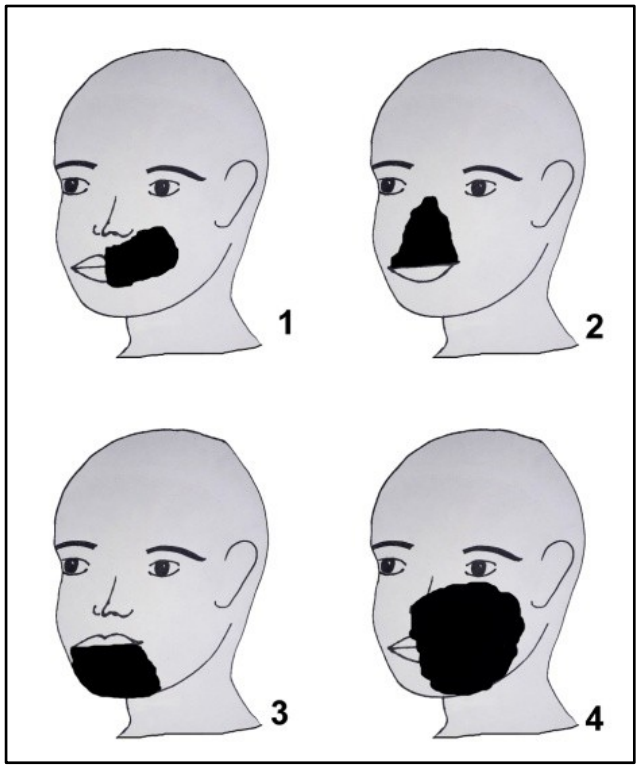

Fig 3. *Montandon (W.H.O) classification*[71]
Type-1 - Defect of lip and cheek involving commissure; Type-2 - Defect of upper lip, maxilla and nose; Type 3 - Defect of lower lip and mandible; Type 4 - Extensive defect of both upper and lower half of face (Art work: Ms. R. Srinidhi)

Box 4: Cariou classification of noma defect[70]

1. **Simple**
   a. Cheek perforation
   b. Commissural destruction
   c. Superior commissuro-labial mutilation
   d. Inferior commissuro-labial mutilation
   e. Supero-medial labial mutilation
   f. Infero-medial labial mutilation
2. **Extensive**
   a. Jugomasseteric mutilation
   b. Labio-mental amputation
   c. Labio-nasal amputation
   d. Labio-maxillo-septo-columellar amputation
3. **Complex**
   a. Lateral hemi-facial lesion
   b. Labio-palatal amputation
   c. Labio-genio-mandibular mutilation

CLINICAL FEATURES

Clinical features of noma differ according to the pathogenic stage of the disease (Table 3 and Fig 4-6).

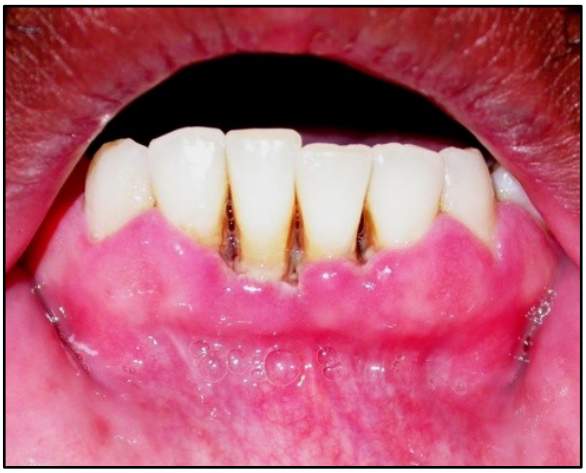

Fig 4. Stage-1 Noma

Acute necrotizing gingivitis with loss of interdental papillae of the mandibular incisors. (Reproduced from Khammissa RAG, et al 2022, Tropical Medicine and Health, under Creative Commons Attribution 4.0 International License. Ref. DOI:10.1186/s41182-022-00431-6)

Fig 5. Stage 3 and 4 gangrenous noma

Clinical appearance before (a) and after (b) the separation of necrotic eschar. (Reproduced from Khammissa RAG, et.al. 2022, Tropical Medicine and Health, under Creative Commons Attribution 4.0 International License. Ref. DOI:10.1186/s41182-022-00431-6)

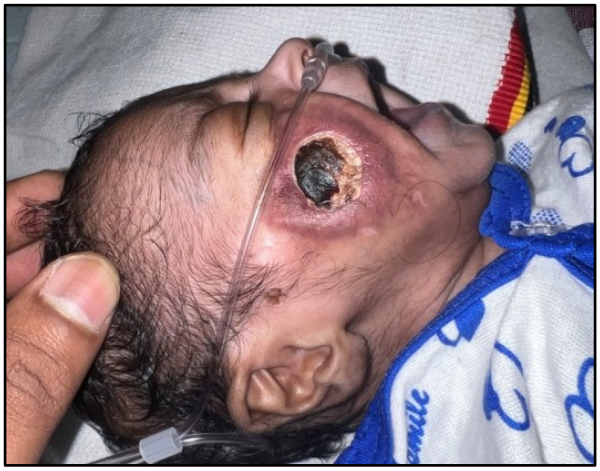

Fig 6. Noma Neonatorum

(Courtesy: Prof. Raveenthiran V. Image not covered under Creative Commons licence. Presented with the permission of parents)

Table 3: Clinical features according to WHO staging of pathogenesis *

WHO Stage	Clinical features
0 (Gingivitis)	Malnutrition, Vitamin deficiency, Anemia, Bleeding, pain, swelling and redness of gums, Listlessness, Apathy
1 (ANG)	Loss of interdental papilla, Halitosis, Excessive salivation, Cervical lymphadenopathy, Pyorrhoea, Fever, Metallic taste
2 (Edema)	Edema of cheek or lips, Acute trismus, Painful mouth opening, Greyish-black ulcers in mucosal aspect of mouth, Leukocytosis
3 (Gangrene)	Black discoloration of perioral skin, Loss or deformity of teeth, Full thickness necrosis of cheek, nose, jaws or lips, Features of systemic sepsis such a fever, tachycardia, lethargy, circulatory shock, tachypnoea, anorexia, fever, dehydration
4 (Scarring)	Established orocutaneous or oronasal fistula, Complete necrosis of cheek, nose, lips and facial bones, Temporo-mandibular ankylosis, Chronic trismus, Feeding difficulties, Malnutrition, impaired articulation of speech
5 (Sequelae)	Regurgitation of feeds, Impaired speech, Cosmetic mutilation of face, Psychological depression, Salivary fistula, Epiphora, Entropion, Exposure keratitis, Corneal ulcers, Loss of lower eyelid, Enophthalmos due to orbital floor necrosis, Deformed permanent teeth, Malocclusion, Anosmia and breathing difficulty due to nasal disfigurement

** Some features of a given stage may overlap with those of preceding and following stages. ANG - Acute necrotizing gingivitis*

DIFFERENTIAL DIAGNOSIS

In pre-gangrene stages constitutional symptoms of noma may be mistaken for febrile illness such as malaria. In *prodromal stages*, noma is indistinguishable from acute herpetic gingivo-stomatitis, acute oral candidiasis and Vincent stomatitis. Facial cellulitis, angioneurotic edema, maxillary rhabdomyosarcoma, Burkitt lymphoma, osteosarcoma and maxillay sinusitis may mimic the *edema stage* of noma. Several necrotic and granulomatous lesions may be mistaken for the mutilating *gangrenous stage* of noma. They include muco-cutaneous Leishmaniasis, chronic lupus erythematosis, syphilis, yaws (gangosa), midline granuloma of Wegener, mucormycosis, oral cancers, lepromatous leprosy, agranulocytic gangrene, clostridium gangrene, lupus vulgaris, ecthyma gangrenosum, Stewart's granuloma, radiation necrosis and sickle cell crisis.[5,6] Grossly deformed face of noma may resemble Romberg disease (progressive facial hemiatrophy) and post-burn contractures. Acute trismus of the noma neonatorum should not be confused with neonatal tetanus.

INVESTIGATIONS

Noma is a clinical diagnosis. However, underlying immuno-suppressive disorders such as HIV, leukemia, anemia and protein malnutrition should be excluded by appropriate lab investigations. Inflammatory markers such as leukocyte count, erythrocyte sedimentation rate, tumor necrotic factor-α, interleukins, and C-reactive protein will be elevated. Although non-specific of noma, they are very useful in monitoring the disease progress during therapy. Very low CD4 count is typical of HIV associated noma.[74] Blood cultures are invaluable in guiding antibiotic treatment. On the other hand, wound swab cultures are not very helpful as they often fail to differentiate primary infection from secondary contaminants. Computed tomography with 3-D reconstruction is essential in planning reconstructive surgery especially when the jaw bones are destroyed.[75]

TREATMENT

Management of Acute Noma

Progression of ANG to gangrenous noma can be arrested by restoring the oral hygiene.[76] This includes using a toothbrush, antiseptic (chlorhexidine) mouthwash and oral antibiotics. Dental scaling, though useful in removing plaques, should be avoided in the presence of active infection, as it may precipitate bacteremia.[22,72] Mobile shaky teeth may be removed. Simultaneously, protein malnutrition, vitamin or trace element deficiencies and anemia should be corrected. Re-feeding syndrome may complicate aggressive nutritional rehabilitation. In moribund patients a brief course of corticosteroids may be helpful.[4] Anecdotal observation suggests that topical phenytoin may be helpful in improving oral health by causing gingival hyperplasia (*Unpublished observation of the senior author - VR)*.

Management of acute noma necessitates hospitalization. In addition to observation of oral hygiene, prompt correction of dehydration, electrolyte imbalance and intravenous administration of broad-spectrum antibiotics are indicated.[25] Severe trismus may necessitate nasogastric tube feeding or supplemental parenteral nutrition. Daily wound cleaning with hydrogen peroxide, povidone-iodine or Eusol is recommended.

Antibiotics are often chosen empirically and rarely on the basis of culture guidance. Chosen combination of antibiotics should cover both aerobic and anaerobic bacteria.[2,22,25,76] Typically the triple combination of a penicillin with clavulanic acid or a third-generation cephalosporin *plus* an aminoglycoside *plus* metronidazole is used. Ciprofloxacin, fluconazole, linezolid and streptomycin are less commonly used. Although clindamycin is very effective against anaerobes, metronidazole is preferred over it to avoid pseudomembranous colitis. Underlying comorbidities such as HIV should also be simultaneously treated by antiretroviral drugs.

Role of Surgery in Acute Phase

Aggressive debridement of gangrenous tissue is generally not advised in the acute stage as it may precipitate fatal bacteremia. Spontaneous, slow separation of eschar is less mutilating than active surgical excision.[4] Occasionally, gentle surgical debridement of eschar and sequestrectomy may be required.[77] After eschar removal, the wound is best allowed to stabilize by secondary healing. No attempt of reconstruction should be done within one year of recovery from acute illness.[25,77] During this waiting period, attention should be diverted towards improving nutrition, treating concomitant immuno-deficiency disorders and preventing temporo-mandibular joint (TMJ) ankylosis. Splinting of the jaws, mouth opening devices and physiotherapy may minimize chronic trismus.[78] Muscle interposition after osteotomy of the mandibular condyloid process may avoid recurrent ankylosis. Psychological rehabilitation should also be started simultaneously.[79]

Anesthetic Considerations

Severe ankylosis of TMJ and poor mouth opening often cause serious problem with endotracheal intubation during anesthesia.[81] This problem is best overcome by fiberoptic bronchoscope aided intubation. Alternatively trans-tracheal induction of anaesthesia, blind nasal intubation, preliminary tracheostomy, excision of coronoid process or osteotomy of the mandibular angle under local anesthesia through a submandibular approach can be done.[4]

Water's technique of endotracheal intubation is an ingenuous method of bypassing severe TMJ ankylosis.[40, 82] In this technique a Tuohy needle with a Huber point is inserted into the trachea through the cricothyroid membrane under local anesthesia. An epidural catheter is then threaded through the needle. The bevel of the needle tip is positioned facing upwards so that the catheter is directed superiorly to pass through the vocal cords into the nasopharynx. The coiled catheter from the nasopharynx is then retrieved by passing

another hooked catheter or endoscopic grasping forceps through nostrils. Keeping the tightly held epidural catheter as guide endotracheal tube is slid into trachea and the guiding catheter removed.

Reconstructive Surgery

Surgical reconstruction of noma defect offers a fertile field for imaginative surgeons. Noma rehabilitation is a team work involving pediatric surgeon, plastic surgeon, maxillofacial surgeon, pedodontist, clinical child psychologist, physio-therapist and community nurse. All the known principles of plastic surgery have to be employed on case-to-case basis and individual tailoring of treatment is the key principle. The order of complex, staged reconstructions include relief of trismus, functional restoration of the oral cavity, reconstruction of bone defect and finally cosmetic fine-tuning.[4,40,77,80]

Lip defects are repaired by Abbe-Eslander flaps or Gillies fan flap.[83] Pedicled forehead flaps and condro-cutaneous flaps from the ear are popular in reconstructing the nose. The full-thickness cheek defects are repaired by a variety of techniques including Dijkstra's platysma flap, Bakamjian's medial based deltopectoral flap,[84] prefabricated scapular flap,[85] supraclavicular flap,[86] lattisimus dorsi myocutaneous flap, tubularized distal pedicle (waltzing) flap[87] and free microvascular flaps.[88] Lattisimus dorsi flaps are preferred over pectoral flaps in females for obvious cosmetic reason. Palatal defects are repaired using galeal or temporal flaps.[4, 40] If simultaneous reconstruction of mandible along with cheek defect is required, forearm osteo-myocutaneous flaps with radial bone is preferred.[89] Lower eyelid contractures may be corrected by Z-plasty or by Gillies bipedicled upper eyelid flap. Severe local scarring often precludes the use of skin expanders in reconstruction.

COMPLICATIONS

Distorted facial growth is a common complication of noma. Metastatic gangrene of the neck, scalp, perineum and genitalia are not uncommon.[4] Malignant transformation of the noma ulcer,[90] maggot infestation,[91] and recurrent parotitis due to distorted salivary duct[92] have rarely been reported.

Following complex facial reconstruction, recurrent trismus due to TMJ ankylosis or scar hypertrophy is known to occur. Facial disfigurement, social isolation and local taboos cause severe psycho-logical depression in one third of the noma survivors.[79,93] Surgery of noma is fraught with all the known complications of reconstructive surgeries such as wound infection, flap necrosis and scar contracture.[94]

PREVENTION

Health education of people, awareness creation among health care professionals, easy access to health care facility, encouraging the usage of toothbrush, mitigation of extreme poverty and malnutrition, segregation of livestock from human inhabitation, provision of safe drinking water and promotion of breast feeding are of paramount importance in preventing noma.[5] Vaccination against measles may reduce the vulnerability of the at-risk population. Noma is non-contagious and hence isolation of affected patients is unnecessary.[3]

OUTCOME

Untreated noma is invariably fatal (80-90%). Most of the children die due to secondary infection, septicemia, malnutrition, aspiration pneumonia and mental depression.[2] Coexistence of HIV increases mortality and it is a risk factor of recurrent noma.[18] With proper treatment, the current mortality of noma is less than 10%.[3]

Recurrent noma is extremely rare.[18,40,77] In a series of 580 children with noma from Zinder,

there were no recurrences.[3] Those who survive acute noma usually live long into adult life, albeit it with severe morbidity.

CONCLUSION

Noma is a preventable opportunistic infection. Maintenance of personal oral hygiene will largely avoid noma. However, other risk factors such as alleviation of poverty and malnutrition, provision of safe drinking water and infrastructural facility to do complex reconstructive surgeries are to be addressed by governments and political will. Therefore, WHO rightly mentioned, *"Noma is more than a disease"*.

Epilogue

Among the published manuscripts on Noma 72% are case reports/series, 10% are retrospective studies, 11% are cross sectional studies, 5% are prospective case control studies.(Farley 2021) [3] *Randomized trials and meta-analysis are not available. Available systematic reviews are descriptive rather than analytical. Hence, opinions expressed herein are of level-4 evidence*.

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