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Concerns of Infectious and Non-Infectious Fever in Oral and Maxillofacial Surgery:A Clinical Review

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Abstract
Background: *Oral and maxillofacial surgery being a surgery of head and neck region draw the special attention. Postoperative fever (POF) is one of the consequential clinical concerns in maxillofacial surgery***.**
Aims: *The objective of this review is tofocus on the various trends and implications of POF in OMFS, its treatment and management.*
Method: *A comprehensive search of PubMed database, Dental and Oral Sciences Source, Web of Science etc., was done for last 24 years (2000-2023) using appropriate key words.*
Result*: Fever due to OMFS can be of infectious or non-infectious in origin. Hyperpyrexia and hyperthermia are not synonyms. hyperpyrexia is mediated through hypothalamic 'set-point' and exclusively based on the pyrogenic cytokines. Whereas, in hyperthermia the body temperature rise attributed to the hypermetabolic function of skeletal muscles. Most of the POF in OMFS literature are converged on the aetiologies of inflammation and infection. Many of the SISs, sepsis, sever sepsis etc. are of odontogenic in origin. Hyperthermia, irrespective of its aetiology (anaesthetics, neuroleptic, hormonal crisis and or drug reaction) is life threatening.*
Conclusion: *Post operative hyperpyrexia and hyperthermia needevidence-based treatment and hospital base health-hygiene care for early recovery.*
Keywords:*Postoperative fever; oral and maxillofacial surgery; hyperpyrexia; hyperthermia; hospital-based health hygiene; Systematic review*

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I. Introduction

Fever following the surgical intervention of oral and maxillofacial region can be of infectious or non-infectious in origin. Post operative fever (POF) complications of (OMFS) are no way different than that of common surgery but draw the special attention as the surgery site is in the head and neck sector. Reduction, reconstruction, aesthetic and cosmetic interventions of soft and hard anatomical structures in oral and maxillofacial regions are the fundamental persistence of OMFS. Pyrexia is fever and pyroxenes are the factors which induce the on-set of fever. A Roman military physician for the first time could correlated fever with pus formation in wound. Later on, some small proteins were identified and named as pyrogenic cytokines or endogenous pyrogens, which are the peripheral mediators to induce fever.[1,2]Iinterleukins (ILs), tumor necrosis factor (TNF), interferin (INF), granulocyte-macrophage colony stimulating factor (GM-CSF) etc are known as some of the important pyrogenic cytokines.[1,3] Pyrogenic cytokines promote synthesis of prostaglandins at organum vasculosum of the lamina terminalis (OVLT) in brain which is considered as the central mediator for upward shift of hypothalamic thermostatic set point to enhance the body core temperature.[1] Both neural path way and humoral path way of pyrogenic cytokines transmission are established in human model. Certain microbial toxin can also be transmitted directly to the hypothalamus and present fever.[4,5]Surgery causes substantial cellular injury and tissue trauma which disrupt the units of phospholipid from cell membrane and induce the production of pyrogenic cytokines. This also gives scope for microbial infection and inflammation. Thus, cellular injury, inflammation and infection all together promote the production of pyrogenic cytokines.[2] Temperature more than 38C (100.4^{o} F) in a surgical patient can be called as fever or pyrexia. Onset of pyrexia may be recorded during surgical procedure, soon after the surgery, or days after surgery indicating some post operational complicacy. Besides, anaesthetics administration, blood transfusion, specific drug intolerance may also contribute to onset fever during post-surgical period.[2,6,]Concomitant cerebral injury, viral infection, systemic inflammatory response, sepsis, severe sepsis etc. can develop fever during post operative period.[7]However, post operative infection has been established as the principal cause of fever. On set of fever

on the specific day or week may also indicate the different source of infection.[6] Of course fever due to fracture fixation, infection or prosthetic joint infection may appear even weeks after of the surgical intervention[8].Apart of pyrexia, intra operative and post operative hyperthermia arealso found as potential life threatening condition due to hyper body metabolism attributing drug reaction, hormonal strom or crisis and anathetics clinical syndrome.[6,7] The present study is a narrative review on infectious and non-infectious fever after OMFS, conversing on its principle, mechanism and management.

II. Method

A comprehensive search of PubMed database, Dental and Oral Sciences Source, Web of Science, was done for last 24 years (2000-2023) using various key words and their combinations like "Fever", "Hyperthermia", "Pathology-fever", "Post-operative fever," "Fever- maxillofacial surgery" "Fever- dental surgery", "Fever – oral surgery", "Fever-trauma". In addition, search included OMFS, anaesthesia and pain management, dentoalveolar surgery; orthognathic surgery, cleft and cosmetic surgery, reconstruction; temporomandibular disorders; facial trauma; and bone fracture. Literature was also searched manually by library consultation. Mostly critical review, cohort study, case report, management protocols *etc*. were considered for this study.

III. Result

Fever of infectious or non-infectious origin in OMFS are clinically considered as pyrexia, hyperpyrexia and hyperthermia. The review is focused on pyrogens, fever induction pathways, principle of pyrogenic action, clinical manifestation of fever, fever evaluation and management and factors responsible for hyperthermia. These subjects are exclusively discussed with citations of relevant OMFS studies.

Fever related definitions and factors

Pyrexia or fever

Body core temperature is dynamic with metabolic action and diurnal variations. Average normal body temperature set point is unanimously accepted as 37^{o}C (98.6^{o}F). Temperature more than 37.2^{o}C (99^{o}F) during early morning and more than 37.7^{o}C (100^{o}F) at evening is considered as fever. Pyrogens are the substances which can induce the shift of temperature set point at hypothalamic centre more than the normal range. In response to pyrogens body trigger the mechanism to maximize the heat generation and minimize the heat loss so as to reach the new elevated set point. Thus generation of heat and its maintenance at higher set point is known as the fever.[6,9]

Hyperpyrexia

A fever with thermoregulatory set point more than 41.5°C (106.7°F) is known as high fever or hyperpyrexia. Specific viral infection, sepsis, severe sepsis, intracranial haemorrhage etc. are the examples of life-threatening hyperpyrexia. Patient over 43°C (109.4°F) may have serious brain damage, continuous convulsions and shock and cardio-respiratory collapse will likely occur. Post surgical hyperpyrexianeeds immediate attention for the evidence base treatment. [1,9]

Hyperthermia

Hyperthermia is a condition where body temperature increases over the normal set point due to unregulated heat production in the body or heat gain from the environment, more than body dissipates. Heatstroke, neuroleptic malignant syndrome (NMS), malignant hyperthermia(MH) are the examples of some high risk hyperthermic condition of medical emergency. NMS and MH are considered as a severe life-threatening reaction of certain neuroleptic drugs and general anaesthesia respectively in the susceptible patients.[9,10]

Exogenous Pyrogen

Pyrogens art constituents that persuade pyrexia or febrile responses. These constituents are further categorised as exogenous and endogenous elements. Exogenous pyrogens are mostly recognised as microbial in origin. Lipopolysaccharide (LPS) endo-toxin of outer cell membrane in gram negative bacteria and peptidoglycan of the cell wall of gram negative and gram positive bacteria are considered as potential exogenous pyrogens. Killed or live virus and fungal elements are also added to this group. Mostly these exogenous pyrogens cause infectious fever. Non microbial exogenous pyrogenic factors enlist selected antigen, drugs, and steroids as per individual susceptibility.

Endogenous Pyrogen

Endogenous pyrogens are explicit immune regulatory protein, identified as cytokines produced in the host body in response to exogenous pyrogens or some metabolic disorders. Cytokines *viz.* interleukins (ILs), tumour necrosis factor (TNF) and interferon (INF) are considered as the major endogenous pyrogens.[1]

Cytokines

Cytokines are the group of non-structural small proteins with low molecular weights, produced at specific cell site in immune system, play the role of cell signalling. These proteins control inflammatory and haematopoietic processes. Major cytokines are studied under sub categories of pro-inflammatory cytokines, anti-inflammatory cytokines. [1,3]

Pro-inflammatory cytokines

Pro-inflammatory cytokines are the primary mediators that evoke fever through CNS thermoregulation mechanism. Pro-inflammatory cytokines are basically produced and discharged by activated macrophages and promote the inflammatory reactions. Interleukin one beta (IL-1β), Interleukin six (IL-6), and tumour necrosis factor alpha (TNF-α), interferon gama (INF-γ), granulocyte-macrophase colony stimulating factor (GM-CSF) are the distinctive pro-inflammatory cytokines. Other factors viz. IL11, IL12, IL17, IL18, IL8 etc. are less glaringly mediating the inflammatory mechanism. Superfluous synthesis of pro-inflammatory cytokines evokes fever, inflammation and tissue destruction. This factor is induced by infection, trauma, ischemia etc. [1,3].

Anti-inflammatory cytokines

The anti-inflammatory cytokines are the group of immune-regulatory molecules that antagonize the pro-inflammatory cytokine response up to some extent. IL-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11 and IL-13 are some of the potential anti-inflammatory cytokines. Transforming growth factor-β (TGF- β) shows both pro and anti-inflammatory properties. The optimal immune system mechanism may also be affected by surplus production of Anti-inflammatory cytokines.[1,3]

Interleukins

Interleukins (ILs) are a group of cytokines synthesized and released mostly from helper CD4 T lymphocytes, monocytes, macrophages, and endothelial cells. IL-1 and IL-6 are important endogenous pyrogens produced by macrophages and T lymphocytes. Where as IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-14 and TNF are termed as lymphokines (cytokines) secreted by lymphocytes.[1,11]

Tumour Necrosis Factors (TNF)

Generally,monocytes, macrophages and lymphocytescells produce TNF-α and TNF-β factors. Some other cell types *Viz.* type 1 helper (TH1) cells, natural killer cells (NK), neutrophils, mast cells, eosinophils, and glial astrocytes of CNS also produce TNF in response of invasive or injurious stimuli. It is a potent pyrogen that induces fever and inflammation by direct action or by stimulation of interleukin-1 secretion. [1, 12]

Interferon (IFN)

IFNs are a group of cytokines used for protective defences of viral replication in target cells. Three types of interferons such as IFNα, IFNβ and IFNγ found in human cases, differ from each other by their aminoacid sequences and biological activities. Leukocytes, fibroblasts, and macrophages are the site for IFNα and IFNβ synthesis, where as T-lymphocytes produce IFNγ. Symptoms like pyrexia and myalgea are induced by IFNs. INFs boost the antiviral and antitumor activities at high temperature. IFNs also stimulate ß cells to and enhance the antibody production against the viral infections.[1]

Superantigens

Superantigens (Sags) are produced by some viruses and bacteria which can vigorously activate the T-cells and produce huge amount of cytokines mostly Interferon gamma. This IFN-gamma activates the macrophages to producemore cytokines such as IL-1, IL-6 and TNF-alpha.[13]

Acute phase response

In response to cell injury and tissue damage some local inflammatory cells like neutrophil granulocytes and macrophages produce pyrogenic cytokines like interleukins IL1, and IL6, and TNFα. These cytokines promote the febrile conditions and onset fever. During this phase liver synthesize several acute-phase proteins *viz.*C-reactive protein (CRP), serum amyloid-A*etc*. and released into the circulation. CRP helps to arrest and terminatethe microbes by phagocytes and increasing platelet accumulation. Over production of acute phase protein may lead to sepsis[1].

Fever induction path ways

The concept of endogenous pyrogen (peripheral mediator) and its immune signalling to stimulate prostaglandin formation in hypothalamic preoptic area (central mediator) to shift the thermal set point have been successfully demonstrated in different human models. The humoral and neural path ways of endo-toxin and endogenous pyrogens transmission to the thormoregulatorycenters of hypothalamus have already been established. So, it is proved that the immune signalling pyrogens are carried either through vascular system or though peripheral nerve fiber transmission.[9]

Circulating cytokines pathway

Endogenous pyrogens stimulate some of the immune cells such as monocytes/macropages and neutrophils to produce a cascade of cytokines which are released into the circulation. In this cascade initially tumour necrosis factor alpha (TNF-α) is detected in the circulation followed by interleukin- 1ß (IL-1ß), by interleukin- 6 (IL-6), macrophage inflammatory protein-1 (MIP-1) etc in different quantity. However, among these cytokines IL-6 is detected in higher quantity. Similar cascade is also triggered in response to super antigen peptidoglycans or muramyl dipeptides Gram-positive and Gram-negative bacteria. Viral infection or administration of synthetic viral product in adequate dose release the cytokine cascade initiated by interferons. It is revealed that these cascades of pyrogens dominated with interleukin- 6 (IL-6), act as the endogenous humoral signals transported to brain by vascular system to induce fever and related sickness in response to infection and inflammation. OVLT and the subfornical organ (SFO) are the circumventricular organ where specific neurons/ glial cells respond to circulating pyrogens and produce prostaglandin (PG), as the central or secondary mediator in fever path way. Some receptors on endothelial cells also respond the endogenous pyrogen to produce PG. The specific PG *i.e* PGE_2 is seems to be the end player in the fever path way for up shift of thermal set point in the hypothalamus.[4,14]

Afferent neural pathway

Apart from the circulating pathway the stimuli of pro-inflammatory cytokines and endo-toxin can also be transmitted through afferent neural path ways. Attenuation of fever intensity by sub diaphragmatic vagotomy strongly supported the afferent vagus route of transmission of peripheral immune signals to CNS. Other neural pathway of pyrogen communication is thesomatic afferent fibers system. Mechanism of cutaneous sensory nerve for transmission of peripheral immune signals has also been established. LPS administration into a gingival pouch in maxilla elevated temperature which was attenuation by transectioning the trigeminal nerve fibres or use of local anaesthesia. This also elucidate the trigeminal signalling to of pain path way during acute periodontitis.[4,5]

Hypothalamic interpretation of humoral and neural stimuli of fever

The circulating cytokines pass through the blood brain barriers by different means so as to reach into the thermoregulatory canters of hypothalamus. The mode of transportation may be specific active transport and or saturable transport system. In addition, the cytokines also pass through the circum ventricular organs (CVOs) which possesses comparatively less blood brain barriers property. With regards to the sensory nerve pathway, the cytokines or endo-toxin produces the cascade of cytokines in the Kuffer cells and the pyrogenic signals is transmitted to specific hypothalamic area through afferent nerve fibres, brain stem area and nucleus of solitary tract. It is clearly understood that, irrespective of pathways of transmission cytokines induces formation of PGE_2, which act on the thermoregulatory neurons of preoptic hypothalamic area for induction of fever. Synthesis of PGE_2 is a function of cyclooxygenase (COX). COX-1 and COX-2 are isoforms. The latter one induces the formation PGE_2.[1,4,9]

Action point of antipyretic and nonsteroidal inflammatory drugs (NSIDs)

Fever soon after trauma injury or postoperative procedure is commonly caused by the release of endogenous pyrogenic cytokines, primarily interleukin (IL)-1, IL-6, tumour necrosis factor, and interferon-γ. At tissue trauma site these cytokine mediators increase capillary permeability to help the healing process and also act on the anterior hypothalamus to promote the prostaglandin formation.[4] Symptom of the inflammatory response is expressed as fever and pain. Antipyretics like acetaminophen products reduce the production of prostaglandin by inhibit the cyclooxygenase (COX) action in the arachidonic acid metabolism path way which helps to decline the temperature set point at hypothalamus but it cannot reduce the tissue inflammation. It also act on the serotoninergic pathway to reduce pain.Nonsteroidal anti-inflammatory drugs (NSAIDs) are the therapeutics often used for inflammatory conditions of trauma, injury and systemic disorders. Generally, the inflammatory factors at trauma or injury sites trigger vasodilatation, extravagation and protein exudation. It also immediately promotes the nociception. NSAIDs acts on the arachidonic acid pathway to reduce inflammation pain, and fevermostly mediated byCOX inhibition. [4,9,14]

Fever following oral and maxillofacial surgery

The common consensus on post operative fever pathophysiology and fever induction pathway are also applicable for OMFS.[12,15]

Patients of premeditated surgeryhave lesserincidence of postoperative fever than those are subjected to emergent or semi-emergent surgery such as trauma. Emergence of fever on post operative week basis such as immediate, acute, sub-acute and delayed category are described by a school of surgeon. [9,12] However, in the present review the current literature is interpreted under following sub headings.

Intra operative fever

Patient with preoperative sepsis and Ludwig's angina, late presentation of trauma cases with inflammation and pain around the deep wound or bone fracture site can show the temperature spike prior to or during surgical procedure.[12,15]Malignant hyperthermia (MH) is a rare genetic syndrome. People with this syndrome are susceptible to halothane, sevoflurane, desflurane, isoflurane depolarizing muscle relaxant,succinylcholinelikegaseous anaesthetics during intra- operative phase. These anaesthetics may react within first 30 minute of inhalation. In this pharmacogenetic disorder, significant quantity of calcium is instantly discharged from the sarcoplasmic reticulum of the skeletal muscle which promotes the hyper metabolic state. This state not only spike the body temperature but also enhance the carbon dioxide production, metabolic and respiratory acidosis, oxygen consumption rate, activation of the sympathetic nervous system, promotes intravascular coagulation and hyperkalemia.[16,17]

Early post-procedural fever

Onset of fever within 24h of post-operative phase is mostly due to inflammatory pyrogenic cytokinesproduced during the procedure. Fever due to transfusion reaction is also seen during early post operative period. This may be transfusion-related acute lung injury (TRALI) and or transfusion related immunomodulation (TRIM). TRALI is rarely seen, within 6 h of transfusion of blood and blood product. Fever, shortness of breath and hypotension are some of the common indicators for TRALI. TRIM is a complex physiological phenomenon attributed to blood group associated haemolysis reaction and non-haemolytic transfusion reactions. Fever during blood transfusion occurs if donor red cells break in storage phase, if plasma protein is incompatible to donor or due to different types of alloimmunization reaction in the recipient body. These reactions produce pyrogenic cytokines which promote the body temperature.[12,19]

Patient of neuroleptic malignant syndrome react to metoclopramide and promethazine (hypothalamic dopamine receptors antagonist), which may cause muscle rigidity, confusion and hyperthermia.[20]

Atelectasis is a common postoperative respiratory distress may lead to pulmonary collapse and respiratory insufficiency. It may lead to airway obstruction, changed alveolar surface tension, and alveolar compression. Atelectasis implication of early post operative fever is a classical concept.Lack of common consensus on the concept made it still debateable.[9,12] However presentation of low grade fever due to aspiration pneumonia and pulmonary emboli are often found during early post operative days.[21,-23]

Some drugs like (Antimicrobials: Penicillin G , ampicillin, Cephalosporins, Tetracycline; Cardiovascular: Alpha methyldopa, Quinidine, procainamide, hydralazine, CNS: Carbamazepine, phenytoin, Chlorpromazine, Haloperidol, Riamterene) show individual specific immune mediated hypersensitive, may cause mild to severe fever,untoward drug reaction fever is difficult to diagnose unless the drugs are withdrawn phase wise with suitable substitutes.[9,15]

Alcohol withdrawal within 6 hours may cause fever confusion, hallucinations and hyper activity of autonomic nervous system. Such patient may be addressed by benzodiazepines group of drugs [6].

Thyroid storm in susceptible hyperthyroid patients during surgery can cause a temperature rise. Acute adrenal insufficiency may also elevate the temperature. Surgical stress, peri-operative sepsis or suppression of hypothalamo-hypophysial axis by endogenous or exogenous steroids may lead to adrenal insufficiency. Steroid withdrawal in patient can also be considered as one of the important factors for adrenal insufficiency.[24,25]

Acute post-procedural fever

Fever within first few days to few weeks of the procedure is generally considered as acute post operative fever. This may be of routine or nosocomial infections. Aspiration pneumonia,[26] surgical site infection, intravascular catheter infection, urinary tract infection, donor site infection*etc*. result in mild to severe fever for days to weeks.[15] Besides, hospital associated pneumonia (HAP) and ventilator-associated pneumonia (VAP) are caused due to prolong intubationand ventilatorphase respectively.[27,28]

Hyper pyrexia may appear due to some severe soft tissue infections like necrotizing cellulitis, necrotizing fasciitis, and necrotizing myositis *etc*. Culture report substantiate the presence of Group A

hemolytic streptococci, enterococci, coagulase-negative staphylococci. *Staphylococcus aureus* and *clostridial species* as reported by several case studies and reviews.[29,30]

Surgical site infections (SSIs) may develop within 1-2 weeks after procedure, occasionally it developed within 4 weeks of post procedure period. The infections are of polymicrobial in nature. Both aerobic and anaerobic bacteria play role in fever pathogenesis. SSIs initiate as inflammation, erythema and tenderness in surgical sites. The SSIs are classified as superficial (limited to cutaneous and sub-cutaneous tissue), deep (facia and muscles) organ or space infection (involving organs or space deep bellow the surgical site). Fever, fatigue, pain, tender hard edematous affected area, foul-smelling discharge etc. are some of the common symptoms of SSIs.[31-33]

Graft rejection may also develop mild to moderate fiver within first 1-2 weeks of post operative period and need to salvage the prosthetic hardware. Prosthetic materials such as mesh, miniplates, swrews etc. may found as potential source of infection during post operative period from 2-4 weeks or even more. Soft tissue or bone graft infection may reject the grafts.[34]

Non-infectious fever *may* also be seen related to pulmonary emboli,[35,36] DVT,[37,38] inflammation at intravenous device sites, inflammatory response to bone graft, prosthetic hardware (reconstruction plate, mini plate, screw and mess *etc.*).Possibility of fever related to drug effect; endocrine abnormalities are also there as described above.

Sub-acute post-procedural fever

Fever that develops even weeks after the surgical procedure is known as sub-acute post-procedural fever or delayed fever. Deep vein thrombosis (DVT) is one among them. Hospital admitted non-ambulating patient with post operative inflammatory cascade often develop DVT. Consequent upon DVT pulmonary emboli may also cause fever.[35-38] Besides, many other pathological condition like osteomyelitis, osteotomy [39-41], infection in open fracture reduction,[42,43] extended SSIs in graft and implanted hardware also develop fever during this phase.

Fever reducing mechanism

Although fever helps the nonspecific immune response to invade microorganisms, it also leads to certain physiological distress and clinical complications. The drugs which are useful to reduce fever but not to treat thesystemic illness are termed as antipyretics. Paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) *viz.*choline salicylate, magnesium salicylate, and sodium salicylate, are commonly used antipyretics and analgesics.[44,45] Antipyretics like acetaminopheninhibits the enzyme activity of cyclooxygenase and reduces production levels of PGE_2 in the hypothalamus. NSAIDs reduce the pro-inflammatory mediators and trigger the anti-inflammatory property. Unlike NSAIDs, paracetamol has been acclaimed not to reduce tissue inflammation effectively but reduces fever.[12,15]Parenteral administration is more effective than per oral or rectal supposition. Neither acetaminophen products nor NSAIDs are effective for hyperthermia. Phenothiazines group of drugs which acts as vasodilators may help to reduce the body temperature in hyperthermia. Preoperative prophylactic antibiotics are of short half-life and small coverage duration. Specific antibiotics are indicated after proper laboratory report which can narrow down the empiric antibiotics.[46]

Fever evaluation and management

Postoperative core body temperature more than 40^{o} C increases the basal metabolic rate, oxygen demand and heart rate. Proper diagnosis can ascribe causes of fever or hyperthermia. Short duration of fever less than 38^{o}C need no special attention, no laboratory investigation and get subsidised of its own [9,15]. Relative bradycardia or pulse- temperature deficits and fiver spike coincide with the drug administration indicate the drug attributed fever. Sign of lungs consolidation should be correlated with cyanosis oedema and tenderness in extremities to establish the ischemia or DVT related pulmonary thromboembolism. Inspection of peripheral IV catheter site and surgical wound, after day 2 of operation give enough clue for local inflammation and cellulitis if any. Evaluation of quality and quantity of drains also help for diagnosis. Indwelling intravenous and urethral catheters are to be examined regularly and it is wise to remove them as quick as possible after their function application is over. Fomite related transmissionof infectious diseases is to be taken care.[27]

Systemic co-morbidities like glycemic disorder, hypertension, cardiac disease, malignancy, stroke, renal concern etc. of the patient during post operative period are to be revaluated for its change of medication if any.

Application of different physical treatment devices such as ice packs, bed fans, tepid water sponging is essential to reduce the body temperature in hyper pyrexia. The cold-water immersion with a precaution to overcome the over cooling is very much helpful to reduce the hyperthermic conditionof the patient.

Hypovolaemia and hyperpyrexia in cases may be an indicator of septic shock and systemic inflammatory response syndrome (SIRS) bacteraemia. In such cases plasma volume can be maintained by using gelatine or starch solutions added with crystalloid.[47]

IV. Discussion

Pro-inflamatory cytokines play major role for fever and pain development in OMFS. Veleska-Stevkovska[48] and Taher and Bede[49] estimated the level ofIL-1α, IL-6, TNF-α before and after different hours of OMFS procedures. They could correlate the rising level of above cytokines with duration of the procedure and surgical tissue trauma and explain the benefit of minimal invasive surgery. Sattari *et al.*[18] reported a considerable surge of plasma IL-6 at 4 hours oforthognathic surgery and higher levels was correlated to increased duration of surgical procedure.

In a cross-sectional study of cleft surgery, 20% of patient were reported POF within first 24 hours due to inflammation and 71% within next 48 hours due to upper and lower respiratory infection (Liang *et al.* [50]). In case of OMFS infection routs are mostly described as odontogenic, adenogenic, glandgenic, hematogenous, traumatic, and iatrogenic. Infection of sub mandibular area and high fever is recorded in paediatric patients within two days of frenectomy. [51,52]SSI was reported as high 22% in oral cancer by de Melo *et al.*[53]Abscess related high POF was recorded in a facial trauma by *Serra et al.*[54] Instances of sepsis due to odontogenic infection are not uncommon. The sepsis syndrome and related complicatioswith Jarisch–Herxheimer like reaction in OMFS are highlighted in literature.[55,56]A recent retrospective study described severity of fever due to oral & maxillofacial space infections[57]. Tian-Guo *et al.*[58] reported a death case due to sever odontogenic multi space infection such as submandibular space, neck, chest. Lim *et al* [59] in a study of cyst enucleation and bone grafting, reported 16 graft rejection only due to infection of*Streptococcusmitis, Streptococcus anginosus, Staphylococcus aureu, Klebsiella pneumoniae, Prevotellabuccae,* and *Pseudomonas aeruginosa* within 38 days of procedure.Aquino *et al.*[60] reported another rare infection of *Streptococcus pyogens*andStreptococcal toxic shock-like syndrome during post extraction period of third molar.

Numerous published data on nosocomial infection are available after OMFS. Guru *et al.*[28] described 23 % of wound infection and POF in OMFS out of 241 patients with isolation of causative microbes.Major fungal species *i.eCandida albicans, C tropicalis* and *C glabrata* are identified from surgical wounds [15].

In Orthognathic surgery post operative SSI has been reported up to 33% which present moderate to high fever specific to infection severity. [32,33] They suggested a single-dose prophylaxis reduced the severity of SSI. Of course 8% of SSI is seenwith in 15-30 days of the procedure irrespective of prophylactic antibiotic dose.

Postoperative pneumonia is at higher index of nasocomial infection in oral onco surgery. Xu *et al.*[61] while describing the risk factor of free flap reconstruction expressed their concern about 11% cases of pneumonia. In a cohort study of oral oncoresectionsSood *et al.*[62] recorded incidences of infective pneumonia over 5% level. This low incidence as they claim is due to proper management and antibiotic administration. Dexmedetomidine (DEX) is claimed to be protective to post operative pulmonary complication and pneumonia in oral cancer patients[63]. In a case study of ramus osteotomy aspiration pneumonia is identified as the cause of high fever.[64]

Cellulites with gas gangrene is another rapidly-spreading fatal infection after OMFS. A case of sub-mandibular gas gangrene and treatment was reported by Gamoh*et al.* [30]Necrotizing cellulites, necrotizing fasciitis, and necrotizing myositis are interrelated group of severe degenerative soft tissue infections sometimes draw attention of surgeons as SSI after OMFS and often present fever. The fatality rate of necrotizing infection is recorded as high as 30%. Infection mostly attributed as dental origin and spread promptly to face, neck and chest.[29,65] Hechler, and Blakey[66] reported two case of necrotizing soft tissue infection after third molar extraction with common organism as group A *Streptococcu*. Prabhu and Nirmalkumar[67] in their study described 811acute neck fascial space infections of odontogenic origin out of 1034 patients. Necrotizing fasciitis reported after third molar extraction where Streptococcus*milleri*was found as the potential pathogen.[68,69].

Fever presents in the process of fracture reduction and osteotomy.[70] Pathological fractures of the jaw bone consequential to implant placement, tooth extraction, benign and malignant cystic formation, osteomyelitis, osteoradionecrosis, Gorham's disease related fever are also found in literature.[71] A mandibular fracture was reported with fever, malaise and swelling due to acute osteomyelitis after forty-five days of a molar tooth extraction[72]. Studies on acute mandibular osteomiletis following molar, premolar extraction and bilateral sagital split mandibular osteotomy have been focused for effective treatment and management during post operative period.[40,73]

Actinomyces israelii a gram-positive anaerobic bacterium causes actinomycosis. Osteomyelitis due to Actinomycosis in mandible although a rare occurrence could find a place in record.[74] Similarly two case studies ofchronic osteomyelitis of jaw following tooth extraction are also published as the rare findings.[75,76]

The trauma fracture severity of mandibles with fever, pain, and trismus are reported by Gordon *et al.*[77] Sometimes successful treatment may indicate plate salvage.[34]

Sometimes OMFS cases indicate the blood transfusion. Risk factors such as infection, transfusion-related acute lungs injury, hemolytic transfusion reactions, non-hemolytic transfusion reactions etc. may presnt symptoms like fever with or without chills and clear blood-tinged urine.**[19]** In a case study of wide partial maxillectomy. Neswi*et al.*[78] reported delayed hemolytic transfusion reactions with fever with chills.

Ample numbers of review articles and POF case studies of non-infectious types are also found in OMFS discipline. Life risk complicationof obstructive dyspnoea may be seen after OMFS if not addressed properly. Several cross-sectional case studies have been reported in this segment based on upper airway impairment, atelectasis, pneumonia, pneumomediastinum, and pneumothorax time and again. Um *et al.*[21], reported pus obstructive atelectasis. Verstraete *et al.*[22] correlated volutrauma, atelectasis and pneumomediastinum in a post operative bimaxillary surgery. A case study revealed fever followed by maxillary and mandibular osteotomies associated with atelectasis after 24 hours of general anesthesia administration (Aziz *et al.*)[23]. High incidences of atelectasis (37.5%) and fever after maxilla mandibular fixation were also recorded by Aframian-Farnad *et al.*[79]Butthey stated that emergence of fever with atelectasis is not always statistically significant.

Fever incidences of pulmonary embolism (PE) and venous thromboembolism (VTE) are more after oral onco surgery than routine maxillofacial surgery.[35] An outpatient and a short stay patient after tooth extraction and a bimaxillary orthognathic surgery respectively reported VTE and PE.[80] A thromboembolic problem after deep vein thrombosis (DVT) in lower limb on seventh day of orthognathic surgery was recorded by Samieirad*et al.*[38] Two more case reports on lower limb DVT were also recorded during fourth and fifth day of OMFS.[36,37]

Malignant hyperthermia (MH) is a pharmacogenetic disorder. It is uncommonbut life-threatening anaesthetic emergencies during OMFS. Some of the anaesthetics likehalothane, sevoflurane and desflurane may show an abnormally hypermetabolic response in skeletal muscle and generate huge amount of heat. Dantrolene sodium is used as a selected antagonist for the management of MH.[17,81]Reifenstahl and Rowshan[82] suggested some of the dental patient due to excessive pain stress present some symptoms like MH. Some such case study was placed in record by Gibbs *et al.*[83] Patients with neuroleptic malignant syndrome (NMS) react to antipsychotic drugs result in high fever and confusion. A patient with unknown NMS during her post operative mandibular fracture reduction reacted to antiemetic drug followed by an acute hyperthermia.[20] Some case report and reviews on serotonin syndrome are also available as published record.[84] Adrenal insufficiency (AI) is a life-threatening endocrine disorder sometimes caused following sepsis or surgical stress. AI is rare in oral maxillofacial surgery as reported only six cases in a systematic review of 148 articles over 66 years.[85]Thyroid strom or crisis is seldom seen in trauma cases. Weinstock *et al.*[86] recorded a rare case of thyroid crisis in a maxillofacial trauma after two weeks. However recently several literatures deal the subjects in greater depth. [87-89]

V. Conclusion

Many a time fever emerges following any minor or major OMFS. Mild to moderate fever during first 2 days of the procedure may not need specific treatment. Antipyretics can reduce fever but not hyperthermia nor any under laying disease. Oral cavity harbours a few pathogenic microbes that promote POF in OMFS. Post operative hyperpyrexia may be a sign of drug reaction, aggressive infection, sepsis, severs sepsis and SIRS need evidence based treatment and hygiene care. Prophylactic antibiotic does not give complete coverage for all types of infection. Hyperthermia, irrespective of its aetiology (anaesthetics, hormonal crisis and or drug reaction) is life threatening need immediate diagnosis, treatment and care.

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