Title: An evaluation of sepsis and antimicrobial stewardship in dentistry

Authors:

1. Manas Dave BSc (Hons), BDS (Hons), MJDF RCS (Eng), MFDS RCPS (Glasg), PGCert, FHEA, PGCert. NIHR Academic Clinical Fellow in Oral and Maxillofacial Pathology, University of Manchester, United Kingdom.
manas.dave@postgrad.manchester.ac.uk

2 Siobhan Barry BDS NUI, MFDS RCS Dub, M Paed Dent Glasgow, DClinDent, FDS (Paed Dent), RCPS (Glasg). Senior Lecturer and Honorary Consultant in Paediatric Dentistry, University of Manchester, United Kingdom.
siobhan.barry-2@manchester.ac.uk

3. Paul Coulthard BDS, MDS, PhD, MFGDP(UK), FDSRCS (Eng), FDSRCS(OS), FDSRCPS (Glas), FFDTRCS (Ed). Dean for Dentistry and Institute Director. Professor of Oral and Maxillofacial Surgery. Queen Mary University London, United Kingdom.
p.coulthard@qmul.ac.uk

4. Ron Daniels BEM MbChB
Consultant in Critical Care, Executive director UK Sepsis Trust and Chief Executive of the Global Sepsis Alliance
University Hospitals Birmingham NHS Foundation Trust, United Kingdom
ron@sepsistrust.org

5. Mark Greenwood BDS, MDS, PhD, MB ChB, FDSRCS, FRCS (Eng), FRCS Ed., FRCS(OMFS), FHEA Consultant in Oral and Maxillofacial Surgery and Honorary Professor of Medical Education in Dentistry Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, United Kingdom

mark.greenwood@newcastle.ac.uk

6. Noha Seoudi BDS (Hons), LDS RCS (Eng), MDS, MFDS RCPS (Glasg), PGCAP, DHEA, MInstLM, FRCPath, PhD. Senior Clinical Lecturer in Oral Microbiology. Queen Mary University London, United Kingdom.
n.seoudi@qmul.ac.uk

7. Graham Walton BDS, FDS RCS(Eng), MB, BS, Dip Con Sed
Consultant in Special Care Dentistry, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne
Graham.walton2@nhs.net

8. Neil Patel BDS (Hons), MFDS RCS (Ed), MJDF RCS (Eng), MSc, MOralSurg RCS (Eng), PG Cert, MDTFEd, SFHEA. Senior Lecturer in Oral Surgery, University of Manchester, United Kingdom.
neil.patel@manchester.ac.uk

Keywords

Critical-illness, organ dysfunction, organ failure, sepsis, systemic inflammatory response syndrome, dentistry.

In Brief

- The aim of this paper is to provide a comprehensive overview of sepsis, including its classification, cellular mechanisms and links to clinical signs and management pathways.

- The importance of sepsis in dentistry is discussed along with a literature search of key articles.
- A discussion on antimicrobial stewardship and the importance each practitioner has on judicious antimicrobial use is discussed in relation to sepsis.

Abstract

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. It is a major health concern and causes substantial morbidity and mortality. It is imperative that the signs of sepsis are identified early in both adult and paediatric patients and appropriately escalated to initiate early treatment and improve prognosis. This paper aims to discuss the change in classification from the previous Systemic Inflammatory Response Syndrome (SIRS) criteria to the current definition in adults and also the unchanged definition in children. The hallmark signs of sepsis (both red and amber flags) are discussed in relation to their underlying cellular mechanisms. The rise of antimicrobial resistance is also an increasing global health concern with resistant bacteria from common infections likely to result in greater patient morbidity and worse outcomes. The role of the dental practitioner in antimicrobial stewardship is discussed.

A literature search of reported sepsis cases in dentistry were identified through searches in Ovid Medline and Embase from January 1990 to December 2019. Only primary studies were included with no restrictions on languages. Four articles were identified which reported sepsis associated with tooth extractions, dental abscess and submental/submandibular cellulitis; all studies were low to moderate grades of evidence. Whilst sepsis is uncommon in primary care dentistry, dental healthcare professionals need to be vigilant and understand the specific signs and escalation protocols to ensure patient safety.

Background

Burden of sepsis

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] It causes substantial patient morbidity and mortality and is a major global health concern. In 2017, 48.9 million cases of sepsis and 11 million sepsis related deaths were recorded worldwide.[2] In the United Kingdom, there are over 250,000 cases of sepsis each year resulting in 44,000 deaths.[3] Data from the Office for National Statistics (2019) showed from 2011 to 2017, there had been a 42.5% increase in sepsis identified as the cause of death in England and a 73.4% increase in Wales.[4] The cost to the National Health Service (NHS) has been estimated to be between £1.5-2 billion each year.[5]

NHS England (2015) devised the sepsis action plan that identified strategic areas for improvement including increasing awareness amongst professionals and the public. This is because over 70% of sepsis cases are from the community, with sepsis manifesting as the clinical deterioration of common and preventable infections such as those affecting the respiratory, gastrointestinal and urinary tract systems and skin wounds.[6] Healthcare workers may have variable training in identifying signs of sepsis in community settings and limited access to senior input. This can result in a delay in diagnosis, patient treatment and therefore adversely affecting prognosis. [7] A greater impetus is required for community healthcare professional training to bring to attention sepsis signs and management to improve patient outcomes.

There are a seldom few reports in literature of sepsis from odontogenic infections[8] nonetheless locoregional infections of dental origin have the potential to cause sepsis.[9] Therefore, the aim of this article is to review sepsis from the perspective of dental health professionals.

Terminology and classification

From 2001 to 2016, the diagnosis of sepsis required the presence of two or more systemic inflammatory response syndrome (SIRS) criteria. Many of the parameters included in the criteria such as raised white blood cell count, temperature and heart rate are reflective of an inflammatory response rather than a life threatening, dysregulated immune response.[1] SIRS can be from the result of infection or sepsis. The challenges in distinguishing patients with uncomplicated infection not requiring hospital input from patients with sepsis requiring urgent attention resulted in 1 in 8 patients with severe sepsis being mis-diagnosed.[10] Therefore, there was a requirement to revise the definition of SIRS for sepsis.[1]

In 2016, sepsis was defined as a 'life-threatening organ dysfunction caused by a dysregulated host response to infection', with an organ failure scoring system used to define organ dysfunction.[1, 11] More informative but simplified sepsis diagnostic criteria can help streamline services, clearly identify patients that require urgent intervention and promote antimicrobial stewardship. To clarify terminology, the term sepsis should supersede the use of septicaemia, blood poisoning, sepsis syndrome and severe sepsis. The signs of sepsis are categorised into red and amber flags which are discussed further in this paper.

Septic shock is defined as a subset of sepsis where the underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. This is identified through persistent hypotension requiring vasopressors to maintain mean arterial pressure ≥65 mm Hg and serum lactate levels >2mmol/L despite adequate fluid resuscitation.[1]

Neutropenic sepsis is a life-threatening complication of anticancer and immunosuppressive drug treatment defined as a temperature greater than 38°C or any signs or symptoms of sepsis in patients with a neutrophil count of 0.5 x 10^9/L or lower.[12]

Sepsis in paediatric patients

The change in definition of sepsis from SIRS to organ dysfunction only applies to adults and the paediatric definition of sepsis still remains as SIRS associated with a suspected or proven infection.[13] Severe sepsis in paediatric patients is sepsis with one of the additional complications; cardiovascular organ dysfunction, acute respiratory distress syndrome or two or more organ dysfunctions.[14] The prevalence of paediatric sepsis in developed countries ranges from 6.2-8.2%. However alarmingly, 50% of sepsis related deaths occur within 24 hours of referral.[15] Hospital sepsis-related mortality has been reported at 25%.[13, 16]

The UK Sepsis Trust provides flow diagrams for dental professionals in primary care to follow for children aged under 5 years and those aged 5-11 years. Children of 12 years of age or higher are triaged with the same protocol as for adults. [17]

There has been an increase in the prevalence of adult and paediatric sepsis which may be due to an increasing population with chronic co-morbidities, improved recognition and identification of sepsis in both life and as a cause of death and the rise in drug-resistant microorganisms.[16, 18]

Cellular mechanism and signs of sepsis

The innate immune system is the first line of host defence. Invading pathogens are identified by macrophages and dendritic cells through pattern recognition receptors, following which they are engulfed through phagocytosis and antigens displayed on their cell surface membrane. The activation of the innate immune response also initiates inflammation through the release of pro-inflammatory cytokines (table 1)[19] and the cardinal signs of inflammation (redness, swelling, heat and pain) become apparent.[20] This creates the ideal environment for the adaptive immune response comprising B and T-lymphocytes that should result in pathogen eradication following which there is resolution of the inflammatory response.

Pro-inflammatory cytokines	**Description**
TNF – alpha	Fever, hypotension, activation of neutrophils and endothelial cells.
IL-1	Promotes recruitment of inflammatory cells to site of inflammation, connective tissue breakdown, differentiation of T-helper cells, hypotension and fever.
IL-6	Produces acute phase proteins (such as C-reactive protein, serum amyloid A, fibrinogen etc.) and promotes differentiation of CD4+ and CD8+ T-Cells.
IL-8	Chemotactic agent for neutrophils and T-cells and stimulates angiogenesis.
PGE2	Vasodilation and increased microvascular permeability, initiates pain through action on peripheral sensory neurons.
Anti-inflammatory cytokines	
TGF - beta	Can promote the differentiation of T-helper cells and promote inflammation but also inhibits macrophage activation and suppresses innate immune cells.
IL-10	Supresses IL-1 and macrophage functions.
PGI2	Down-regulation of TNF alpha.
Heat shock proteins	Inhibits TNF alpha and IL-1.
Cortisol	Reduces the production of TNF alpha, IL-1, IL6 and liberates heat shock proteins.
Phosphatases	Deactivation of leukocytes.

Table 1 – Summary of the main pro-inflammatory and anti-inflammatory mediators of inflammation.[21-26] Adapted from Jean-Baptiste (27).

In sepsis, the invading bacteria have several survival mechanisms that confer resistance to the host immune response. These include features such as capsular polysaccharides which decreases the efficacy of antimicrobial agents to penetrate bacterial cell walls and the production of microbial biofilms amongst others. Such bacteria can enter the bloodstream and systemically disseminate along with their bacterial endo and exotoxins. These toxins can directly cause organ dysfunction. Fever or hypothermia may be present however are not reliable indicators of sepsis.[28] Additionally, abundant oxidation from erythrocyte breakdown can lead to intravascular coagulation, hypoxia and organ failure.[29] There are several hallmark signs of sepsis in adults, which will be discussed in relation to their pathophysiological mechanisms (summarised in table 4).

System: Haematological

Signs: Thrombocytopenia, disseminated intravascular coagulation (DIC), petechiae.

Mechanism: Sepsis induces a hypercoagulative state through platelet activation from bacteria and bacterial toxins, as well as endothelial injury from pro-inflammatory cytokines that promote coagulation. Initially, there is thrombocytopenia from the consumption of platelets that can increase susceptibility to bleeding. Additionally, microvascular thrombi and fibrin deposition can cause venous thrombosis and pulmonary emboli. Disseminated Intravascular Coagulation (DIC) is characterised by the action of the coagulation pathways resulting in depletion of platelets and coagulation factors.[30] There is a risk of spontaneous haemorrhage and microcirculation thrombosis causing multiple organ dysfunction syndrome.[31, 32] Micro-bleeding associated with DIC from consumption of platelets also results in petechiae. These are small pinpoint subdermal spot-like lesions, widespread across the skin, which may appear red, brown or purple in colour and don't blanch under pressure.[33]

System: Respiratory

Sign: *Red flags:* Tachypnoea (≥ 25 breaths per minute), need for supplemental oxygen to maintain SpO2 ≥92%

Amber flags: Tachypnoea (≥ 21-24 breaths per minute)

Mechanism: Acute Respiratory Distress Syndrome (ARDS) is characterised by increased permeability of pulmonary capillary endothelial cells and alveolar epithelial cells. This can be caused by inflammatory mediators and results in pulmonary oedema and decreasing lung compliance. The result is impaired gaseous exchange and reduced oxygen uptake and carbon dioxide elimination. The accumulation of carbon dioxide (hypercapnia) causes a reduction in pH and subsequent respiratory acidosis. This is detected through chemoreceptors which increases ventilation causing tachypnoea (rapid and shallow breathing) to decrease the partial pressure of CO_2 to within the normal range. The subsequent inefficient gaseous exchange results in a reduced blood oxygen concentration (hypoxaemia). This is a hallmark feature of sepsis-induced ARDS.[31, 34]

Sepsis has been identified in a high frequency of certain conditions including community-acquired pneumonia (CAP).[35] The 'CRB65' score helps primary care clinicians identify patients with signs of CAP and is a useful tool in predicting both severity and mortality from CAP. The signs of CAP are outlined in table 2.

Acronym	Parameter	Value
C	Confusion	New disorientation to person, place or time
R	Respiratory Rate	≥30 breaths per minute
B	Blood Pressure	DBP ≤60mmHg SBP <90mmHg
65	Age	≥65 years

Table 2 – Signs of Community Acquired Pneumonia from the CRB65 score. DBP – diastolic blood pressure; SBP – systolic blood pressure. Adapted from NICE (36).

System: Cardiovascular

Signs: *Red flags:* Tachycardia (≥130 beats per minute), myocardial depression (reduced left ventricular ejection fraction), hypotension (systolic blood pressure ≤90mmHg or a drop >40mmHg from normal).

Amber flags: Tachycardia (91-130 beats per minute or new dysrhythmia), hypotension (systolic blood pressure 91-100mmHg).

Mechanism: Pro-inflammatory cytokines such as IL-1, IL-8 and TNF-alpha are associated with increased nitric oxide production. Nitric oxide increases oxidative stress of myocardial tissue and myocardial depression and also causes vasodilation. There are a number of pathways including beta-adrenergic signalling, calcium channel alterations and signalling molecules such as cytokines and endothelil-1, which contribute to cardiac dysfunction.[37-39] Cardiac dysfunction is characterised by impaired contractility and reduced cardiac index and ejection fraction as well as diastolic dysfunction. The accumulation of reactive oxygen and nitrogen species can result in tissue hypoxia and contribute to cardiovascular and other organ failure.[31] The overall result is reduced oxygen supply to organs and peripheral tissues, hypotension and compensatory tachycardia.

System: Renal

Signs: *Red flags:* Not passed urine in the last 18 hours.

Amber flags: Not passed urine in the last 12-18 hours.

Mechanism: There are several mechanisms of sepsis induced acute kidney injury including reperfusion injury, direct inflammatory injury and coagulation causing ischaemia and apoptosis. Additionally, the increased nitric oxide production causes systemic vasodilation, reducing blood pressure.[40] This increases sympathetic activity and causes release of angiotensin which causes intrarenal vasoconstriction, retention of water and reduces the glomerular filtration rate which is responsible for the reduction in urine output.[41]

Oliguria (<400ml urine per 24 hours in adults) and anuria (<100ml urine per 24 hours in adults) can also be accompanied by other multi-systemic signs such as polyuria, cloudy urine, haematuria, fever (temperature >38°C), confusion and agitation.[42, 43] Urinary tract infections can be an important pre-renal cause of acute kidney injury (defined in table 3).

Sign	**Time**
An increase in serum creatinine of 26 µmol/L	In 48 hours
An increase in serum creatinine ≥1.5 times above baseline value	In 1 week
A urine output of <0.5 ml/kg/hr	For >6 consecutive hours

Table 3 – Acute kidney injury definition. Adapted from Royal College of Physicians of Edingburgh (44).

System: Neurological:

Signs: *Red flags:* Acute confusional state, responds only to voice or pain/unresponsive.

Amber flags: Relatives concerned about the mental state of the patient.

Mechanism: The disruption of the blood brain barrier through systemic inflammation and endothelial activation results in infiltration of white blood cells and cytokines into the central nervous system. The resulting neurone cell apoptosis and ischaemia can manifest clinically as delirium.[45]

Patients or relatives may show signs of altered mental state (Glasgow Coma Scale<14), or new onset disorientation. If this is accompanied by neck stiffness (nuchal rigidity), a positive Brudzinski's sign and fever (a temperature of >38°C), meningitis may be suspected. Two of the three signs are seen in 95% of patients and all three may be seen together in up to 44% of meningitis cases. [46] Seizure activity, vomiting and non-blanching rashes are also concerning signs for neurological infection.[47]

Cardiovascular	**Respiratory**	**Renal**	**Neurological**	**Haematological**	**Hepatic**
Hypotension	Hypoxaemia	Uraemia	Altered mental state – confusion, disorientation	Thrombocytopenia	Increased bilirubin
Mottled skin (altered microcirculation)	Blue tinged mucosa and grey tinged peripheries	Increase in serum creatinine		Petechiae	Increase in liver enzymes
	Accessory muscle usage	Increase in blood urea nitrogen		Disseminated Intravascular Coagulation	Jaundice
	Intercostal recession	Pruritus scratch marks, skin discolouration			

Table 4 – Summary of the signs of sepsis affecting different organ systems. Adapted from Hotchkiss, Moldawer (31).

The UK Sepsis Trust has published a decision tool for use in primary dental care to assess both children and adults for sepsis.[17] This tool can be applied for patients with a source of orofacial/dental infection (including post-operative infection) and clinical observations outside of normal parameters. The pathway identifies patients with possible red flag sepsis that require urgent blue light transfer to hospital and those patients where sepsis may be likely (amber flags) where additional advice is provided to help practitioners make an informed clinical decision. For either case, accurate record keeping is paramount to ensure patient safety including a brief but clear handover to other dental colleagues within the practice or the ambulatory team. This handover should include patient details, medical history, suspected source of orofacial/dental infection and which red and/or amber flags are present (with documented observations recorded in practice).

Hospital management

The “sepsis six” pathway[48], produced by the UK Sepsis Trust, outlines the necessary intervention required within the first hour of identifying red flag sepsis. This tool is for use in emergency departments/acute medical units and includes administration of oxygen, blood cultures, intravenous antimicrobials (according to Trust protocol with consideration for patient allergies), intravenous fluids and checks for serial lactates and urine output.

Red flags

There are a number of ‘red flags’ which are hallmark signs of sepsis. As sepsis is a time critical condition, identification of any one of these signs should result in dentists in primary care contacting the emergency services (including the local oral and maxillofacial department) for urgent transfer to a hospital. The emergency services telephone operator should be informed that signs of red flag sepsis are present which can be communicated to

paramedics. Sepsis can cause rapid deterioration and is a life-threatening condition; patients having signs of life, being conscious and communicating proficiently should not mitigate the need for delaying urgent medical attention.

Amber flags

These flags may be suggestive of sepsis and therefore clinical judgement is required to assess the level and rate of patient deterioration and possible further investigations such as urine cultures and blood results. Patients in this category in primary care dental settings should be provided with clear verbal and written instructions as part of safety netting if no immediate escalation is deemed necessary. This involves clear instructions given to patients (and their guardians/family members if appropriate) regarding signs that require urgent medical and oral and maxillofacial assessment in a hospital setting. Safety netting will already be performed as part of routine post-operative instructions following certain dental procedures. For example, the importance of attending hospital A&E departments if there is a swelling causing difficulties in breathing following surgical extractions. The same principles are applied to patients demonstrating amber flags of sepsis. Additional factors such as patient understanding of safety netting, communication challenges and if patients are living alone need to be taken into consideration as part of an overall assessment. At any point, if red flag signs are identified, emergency services need to be contacted for urgent transfer to hospital.

The evidence in dentistry and sepsis

Broad search terms of ‘sepsis’ and ‘dental’ were used to search databases from Ovid Medline and Embase for relevant publications from January 1990 to December 2019. Only primary studies which linked sepsis to the oral and maxillofacial regions in both children or

adults were included. The SIRS definition of sepsis was allowable for adults and there were no restrictions on languages. Reviews and other forms of non-primary research were excluded. Evidence was graded using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool by two of the authors independently and results compared (MD and NP). Any discrepancies were resolved through discussion.

The search yielded four studies (summarised in table 5). Tooth extraction[49, 50], dental abscess[51] and bilateral submental/submandibular/sublingual abscess (Ludwig's angina) from suspected carious teeth[8] have been documented as causative factors for sepsis. Evidence was graded to be low to moderate with three case reports and one cross-sectional study.

The studies identified in the searches concur with results from studies undertaking blood cultures following dental interventions. One cross-sectional study reported bacteraemia in 100% patients undergoing dental extractions, 70% of patients with root scaling, 55% of patients with third molar surgery and 20% of patients with endodontic treatment. [52] A paediatric study also reported similar findings, with 50.9% of patients having a positive blood bacterial culture following multiple extractions. Intraligamental injections were the highest, causing identifiable bacteraemia in 96.6% of all patients. There were 365 organisms identified with the most common bacterial aerobic and anaerobic species *Viridans* streptococci and *Streptococcus sanguis* respectively. [53] The presence of bacteria in the blood following dental intervention is considered a transient bacteraemia which does not directly result in sepsis but is nonetheless a causative risk factor in susceptible host and/or if the source of infection was not removed. This highlights the importance of dental professionals having a fundamental understanding of sepsis as part of their routine clinical practice.

Author	Study type	Study aims	Methods	Sepsis definition	Results	Quality of evidence (GRADE)	Commentary
Lee, Hahn (49)	Cross-sectional (with retrospective data collection)	The study aimed to investigate the incidence and risk factors for post-tooth extraction related sepsis.	A national health insurance population-based database was searched in 2005 for all patients with a diagnosis of sepsis who received a tooth extraction	Sepsis was defined as a proven infection with SIRS.	Incidence of post extraction sepsis was 1.48 per 100,000 population. Patients aged 61 and 81 years or over had a significantly higher incidence of post-extraction sepsis in comparison to patients aged 20 years or less.	Moderate	There is uncertainty about the true representation of the patient cohort to the actual population and accuracy of identifying patients with tooth extractions and sepsis.

			within 14 days before the admission were identified.				
Moss, Collier (50)	Case report	To report one patient with sepsis from an odontogenic infection with an unusual reaction to routine treatment.	Not applicable	Implied as a proven infection with SIRS.	A 21 year old man with an unremarkable medical history had a one day history of pain and swelling following a UL8 extraction two days prior. Observations were consistent with SIRS and following administration of intravenous antimicrobials, the patient experienced delirium	Low	This is a single case report which aims to report an unusual reaction to antimicrobials for the treatment of sepsis.

					suspected to be due to a Jarisch-Herxheimer type reaction.		
Carter and Lowis (8)	Case report	To report a case of fatal Ludwig's angina from an odontogenic infection.	Not applicable	Implied as a proven infection with SIRS with confirmed multi system organ failure.	A 67 year old male with chronic lymphocytic leukaemia had an increasing neck swelling and difficulty breathing. There were multiple carious and periodontally involved teeth. His observations were initially consistent with SIRS following which multi system organ failure preceded death.	Low	This is a single case report which aims to report dental disease associated sepsis in the setting of reduced resistance to infection leading to a severe and fatal presentation of Ludwig's angina.

Currie and Ho (51)	Case report	To report a case of an acute dental abscess causing sepsis and Disseminated Intravascular Coagulation related multiple organ failure and death.	Not applicable.	Signs of SIRS with a proven infection and multiple organ failure.	A 31 year old male with an unremarkable medical history complained of toothache for five days before presenting to hospital with spontaneous oral bleeding and signs of SIRS with a facial swelling. Intravenous antimicrobials and extra oral drainage with fluid resuscitation was undertaken however renal function was poor and the patient died from multiple organ failure due	Low	This is a single case report which aims to report death from sepsis caused by an acute dental abscess.

					to Disseminated Intravascular Coagulation secondary to septic shock from an acute dental abscess.		

Table 5 – A summary of the studies identifying sepsis from dental causes.

Antimicrobials

Empirical intravenous antibiotics are administered to patients aged 18 years and over who have confirmed or red flag signs of sepsis with the aim to eradicate the causative bacteria responsible for infection.[54] This should be accompanied with the correct intervention to remove of the source of infection and drainage of the pyogenic material.

The rise of antimicrobial resistance is an increasing global health concern with resistant bacteria from common infections likely to result in greater patient morbidity and worse outcomes. The prolonged sickness and higher costs of treatment will also have wider public health and economic implications.[55] Therefore, inappropriate antimicrobial prescribing is a public health threat and patient safety issues through the increased risk of patients acquiring multidrug-resistant infections.[56]

Antimicrobial stewardship is 'an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness and to achieve the best clinical outcome possible for the patient'.[57] The UK Government has produced a five year action plan to meet several targets including reducing the use of antibiotics by 15% and number of drug-resistant infections by 10%.[58]

The misuse of antimicrobials is well documented in dentistry. It is reported that 10% of all antimicrobial prescriptions globally are from primary dental care however 80% are estimated to be unnecessary.[59] In England, 5% of all antimicrobial prescribing is provided by dentists, and several studies have identified numerous factors including patient expectations, preferences and clinical and time pressures as reasons influencing prescribing behaviour.[60-64] Long and repeated durations of broad spectrum antimicrobials will apply a selective pressure favouring resistant microorganisms, hence careful consideration is required prior to prescription.[65] Preventive measures and r~~R~~emoval of the source of infection early is important to prevent severe odontogenic infections spreading and their complications including sepsis.

The culture of repeated inappropriate prescribing for patients in pain, when it is not clinically justified, reinforces public perception that antibiotics are indicated for their management. The inappropriate use of antimicrobials has also been associated with patient behavioural patterns such as failure to complete the recommended treatment and self-medication that further perpetuates the inappropriate and ineffective use of antimicrobials. [66]

Every healthcare practitioner has a responsibility to promote and deliver good antimicrobial prescribing practice, with the potential of reducing the frequency and severity of sepsis. Dental practitioners in both primary care and hospital settings are encouraged to~~can~~ undertake regular audits to ensure compliance with guidelines and reduce inappropriate prescribing.

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Conflicts of interest

None declared

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