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Chapter 20

A Practical Approach to Systemic Inflammatory Conditions in General Practice

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Abstract

Systemic inflammatory conditions encompass a wide range of disorders characterized by dysregulated immune activation resulting in multi-organ involvement. These conditions arise from diverse etiologies, including infectious diseases, autoimmune disorders, malignancies, and drug-induced reactions, and frequently present with non-specific symptoms such as fever, fatigue, and weight loss. This variability poses significant diagnostic challenges in general practice, where early recognition is critical for preventing adverse outcomes.

This chapter outlines a structured, practical approach to the evaluation and management of systemic inflammatory conditions in primary care. It highlights the underlying pathophysiological mechanisms, including the role of innate and adaptive immune responses and cytokine-mediated inflammation. The global burden of these conditions is discussed, emphasizing the dual impact of infectious and non-infectious causes, particularly in low- and middle-income countries.

A stepwise clinical framework is presented, incorporating history taking, physical examination, risk stratification, and targeted investigations, including basic laboratory markers, microbiological studies, autoimmune panels, and advanced imaging modalities. Common clinical scenarios such as acute febrile illness, pyrexia of unknown origin, and chronic inflammatory diseases are addressed to facilitate clinical decision-making. Management strategies focusing on initial stabilization, symptomatic care, etiology-specific treatment, and follow-up are described in alignment with contemporary clinical guidelines.

The chapter underscores the pivotal role of general practitioners in early detection, initial management, coordination of care, and patient education. Emerging advances, including novel biomarkers, point-of-care diagnostics, telemedicine, and artificial intelligence, are also explored, along with public health measures such as vaccination, infection control, and antimicrobial stewardship.

In conclusion, adopting a systematic, evidence-based approach in general practice is essential for improving diagnostic accuracy, optimizing management, and reducing the morbidity and mortality associated with systemic inflammatory conditions.

Keywords: Systemic inflammatory conditions, Primary care; Sepsis, Autoimmune diseases, Diagnostic approach, Acute febrile illness, Inflammatory biomarkers, Clinical management.

1. Introduction

Systemic inflammatory conditions refer to a heterogeneous group of disorders characterized by widespread activation of the immune system leading to inflammation that affects multiple organs. These conditions may arise due to infectious causes such as sepsis, autoimmune diseases, malignancies, or other triggers that induce an exaggerated immune response. The concept overlaps with entities such as systemic inflammatory response syndrome (SIRS), which represents a dysregulated host response to various stressors including infection, trauma, or tissue injury [1].

In general practice, systemic inflammatory conditions are of particular importance because they often present with non-specific symptoms such as fever, fatigue, and malaise. These early manifestations may mimic benign illnesses, making timely diagnosis challenging. General practitioners (GPs) are typically the first point of contact and play a critical role in early recognition, risk stratification, and initiation of management. Prompt identification is especially crucial in conditions like sepsis, where early intervention significantly reduces mortality [2].

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The global burden of systemic inflammatory diseases is substantial. Sepsis alone accounts for approximately 48.9 million cases and 11 million deaths annually, representing nearly 20% of all global deaths [2]. In addition, autoimmune diseases, which are major contributors to chronic systemic inflammation, affect approximately 5–10% of the global population [3,4]. This dual burden of infectious and non-infectious inflammatory conditions is particularly evident in low- and middle-income countries (LMICs), where healthcare resources may be limited.

Given the broad spectrum of etiologies and overlapping clinical features, a structured and systematic clinical approach is essential in general practice. International guidelines from organizations such as the World Health Organization (WHO) and National Institute for Health and Care Excellence (NICE) emphasize early recognition, risk assessment, and timely intervention as key components in improving patient outcomes [2]. Therefore, developing a practical, stepwise approach is fundamental for effective management in primary care settings.

2. Pathophysiology of Systemic Inflammation

Systemic inflammation is driven by a complex interaction between the innate and adaptive immune systems. The innate immune system provides the first line of defense through activation of macrophages, neutrophils, and dendritic cells, which recognize pathogens via pattern recognition receptors such as toll-like receptors. This leads to the rapid release of pro-inflammatory cytokines and chemokines [5].

The adaptive immune system, involving T and B lymphocytes, contributes to a more specific and sustained immune response. While this system is essential for pathogen clearance, dysregulation can lead to autoimmune and chronic inflammatory conditions [5].

A key feature of systemic inflammation is the release of cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These cytokines mediate the acute phase response, resulting in fever, leukocytosis, and increased production of acute-phase proteins such as C-reactive protein (CRP) [6]. Although this response is protective, excessive cytokine release often referred to as a "cytokine storm" can lead to widespread tissue damage.

The progression of systemic inflammation may culminate in systemic inflammatory response syndrome (SIRS), which is characterized by clinical parameters such as fever, tachycardia, tachypnea, and leukocyte abnormalities [1]. If the inflammatory response becomes uncontrolled, it can lead to endothelial dysfunction, capillary leakage, and activation of coagulation pathways, ultimately resulting in multi-organ dysfunction syndrome (MODS).

In conditions such as sepsis, the pathophysiology is further complicated by a biphasic response: an initial hyperinflammatory phase followed by immunosuppression. This dysregulated immune response contributes to both tissue injury and increased susceptibility to secondary infections [6]. Understanding these mechanisms is essential for clinicians in general practice, as it informs both diagnostic reasoning and therapeutic decision-making.

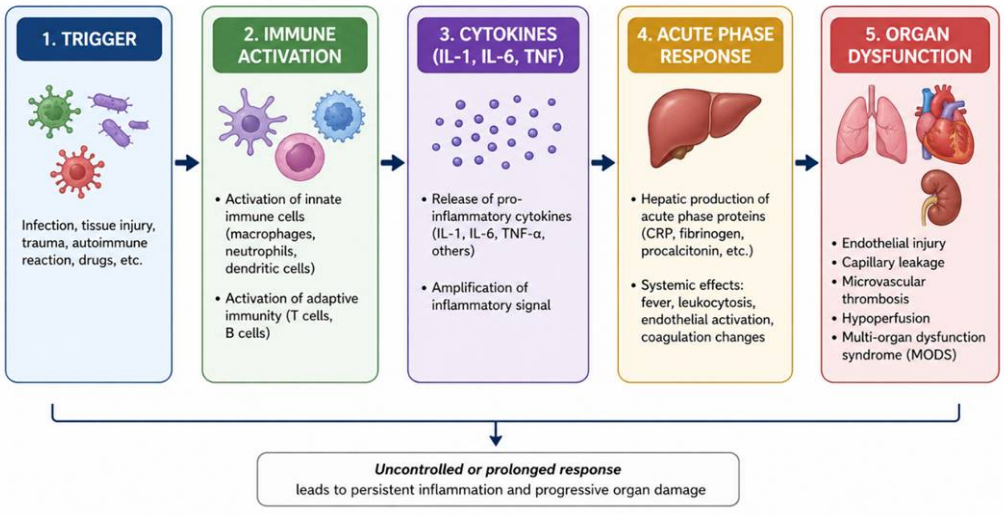

Figure 1: Pathophysiological Cascade of Systemic Inflammation Leading to Organ Dysfunction

3. Epidemiology and Burden

Systemic inflammatory conditions represent a major global health challenge due to their high prevalence, morbidity, and mortality. Among these, sepsis remains one of the leading causes of death worldwide. According to WHO estimates, there are approximately 48.9 million cases of sepsis annually, with 11 million deaths, accounting for nearly one-fifth of all global mortality [2].

The burden is disproportionately higher in low- and middle-income countries (LMICs), where factors such as delayed diagnosis, limited access to healthcare, and high prevalence of infectious diseases contribute to poorer outcomes. In these regions, infectious causes of systemic inflammation including bacterial, viral, and parasitic infections—remain predominant [2].

In contrast, high-income countries are experiencing an increasing burden of non-infectious inflammatory conditions, particularly autoimmune diseases. These conditions affect approximately 7–10% of the global population and are rising due to environmental, genetic, and lifestyle factors [3,4]. Autoimmune diseases not only contribute to chronic morbidity but also increase susceptibility to severe infections, including sepsis, due to immune dysregulation and immunosuppressive therapies [3].

The epidemiological transition observed globally reflects a dual burden:

- Persistent infectious diseases in LMICs
- Increasing chronic inflammatory and autoimmune diseases worldwide

This overlap complicates diagnosis and management, especially in primary care settings. Additionally, systemic inflammatory conditions impose a significant economic burden due to prolonged hospitalizations, intensive care requirements, and long-term disability.

From a public health perspective, these conditions highlight the need for:

- Early detection strategies
- Strengthening primary healthcare systems
- Rational use of antibiotics
- Improved access to diagnostic facilities

Addressing these challenges requires an integrated approach involving clinical care, public health interventions, and health system strengthening to reduce the global burden of systemic inflammatory diseases.

4. Etiology and Classification

Systemic inflammatory conditions arise from a wide spectrum of etiologies that broadly include infectious, immune-mediated, malignant, and iatrogenic causes. A clear understanding of classification helps guide diagnostic evaluation and management in general practice.

4.1. Infectious Causes

Infectious diseases remain the most common cause of systemic inflammation, particularly in low- and middle-income countries. These include bacterial, viral, fungal, and parasitic infections that trigger an exaggerated host immune response.

Bacterial infections such as sepsis are characterized by dysregulated immune activation leading to organ dysfunction. Viral infections including influenza, dengue, and COVID-19 are also important contributors, often associated with cytokine-mediated inflammation. Tuberculosis continues to be a major cause of chronic systemic inflammation in endemic regions [7].

Fungal infections (e.g., candidiasis, aspergillosis) and parasitic diseases (e.g., malaria) can also produce systemic inflammatory responses, particularly in immunocompromised individuals. Early identification of infectious etiology is critical, as prompt antimicrobial therapy significantly improves outcomes [8].

4.2. Autoimmune Disorders

Autoimmune diseases result from an aberrant immune response directed against self-antigens, leading to chronic systemic inflammation. Common examples include rheumatoid arthritis, systemic lupus erythematosus, and systemic vasculitis.

These conditions are characterized by periods of exacerbation and remission, with systemic manifestations such as fever, fatigue, and multi-organ involvement. The pathogenesis involves loss of immune tolerance, production of autoantibodies, and activation of inflammatory pathways [9].

Autoimmune diseases are increasingly recognized worldwide and contribute significantly to the burden of chronic inflammatory disorders, particularly in urban populations [10].

4.3. Autoinflammatory Conditions

Autoinflammatory diseases are distinct from autoimmune disorders in that they primarily involve dysregulation of the innate immune system without autoantibody formation. These conditions are characterized by recurrent episodes of systemic inflammation, often presenting with fever, rash, and serositis.

Examples include adult-onset Still's disease and familial Mediterranean fever. These disorders are associated with abnormal activation of inflammasomes and overproduction of cytokines such as IL-1 [11].

Recognition of these conditions in general practice is challenging due to their rarity and overlapping features with infections and autoimmune diseases.

4.4. Malignancy-Associated Inflammation

Malignancies can induce systemic inflammation through tumor-mediated immune activation or as part of paraneoplastic syndromes. Hematological cancers such as lymphomas and leukemias are particularly associated with systemic inflammatory features, including fever, weight loss, and night sweats.

Solid tumors may also produce inflammatory cytokines, contributing to cachexia and systemic symptoms. Additionally, malignancy-associated inflammation may mimic infectious or autoimmune conditions, complicating diagnosis [12].

4.5. Drug-Induced and Miscellaneous Causes

Certain medications can trigger systemic inflammatory responses, including hypersensitivity reactions, drug-induced lupus, and cytokine release syndromes. Common culprits include antibiotics, anticonvulsants, and biologic agents.

Miscellaneous causes include trauma, burns, pancreatitis, and postoperative states, all of which can activate systemic inflammatory pathways. These non-infectious causes are important considerations in differential diagnosis, especially when infection is not evident [13].

Table 1: Etiology

Cause	Examples	Key Features
Infectious	Sepsis, TB, Dengue	Fever, acute onset
Autoimmune	SLE, RA	Chronic, relapsing
Autoinflammatory	Still's disease	Recurrent fever
Malignancy	Lymphoma	Weight loss, night sweats
Drug-induced	Antibiotics, biologics	Temporal relation

5. Clinical Presentation

Systemic inflammatory conditions often present with non-specific symptoms, making early diagnosis challenging in primary care settings. A high index of suspicion is required, particularly in patients with persistent or unexplained symptoms.

5.1. General Symptoms

Common systemic features include:

- Fever (most frequent presenting symptom)
- Fatigue and malaise
- Unintentional weight loss

Fever may be continuous, intermittent, or remittent, depending on the underlying cause. Constitutional symptoms often reflect cytokine-mediated systemic effects and may precede organ-specific manifestations [14].

5.2. System-Specific Manifestations

Systemic inflammation can involve multiple organ systems:

- **Skin**: Rash, petechiae, purpura, ulcers
- **Joints**: Arthralgia, arthritis, stiffness
- **Respiratory**: Cough, dyspnea, pleuritic pain
- **Gastrointestinal**: Abdominal pain, diarrhea, hepatosplenomegaly
- **Central Nervous System**: Headache, confusion, seizures

The pattern of organ involvement may provide clues to the underlying etiology. For example, rash and arthritis may suggest autoimmune disease, whereas respiratory symptoms may indicate infectious causes [15].

5.3. Red Flag Signs

Certain clinical features indicate severe disease and require urgent evaluation:

- Hypotension or shock
- Evidence of organ dysfunction (renal failure, respiratory distress)
- Altered mental status
- Persistent hypoxia

These signs are suggestive of severe systemic inflammation, including sepsis or cytokine storm, and necessitate immediate referral and aggressive management [16].

Table 2: Red flag signs

Red Flag	Clinical Significance
Hypotension	Shock
Altered sensorium	CNS involvement
Hypoxia	Respiratory failure
Oliguria	Renal failure

6. Initial Assessment in General Practice

A structured approach to assessment is essential for early diagnosis and appropriate management.

6.1. History Taking

A detailed history is critical in identifying the underlying cause:

- Duration and pattern of symptoms
- Travel history and exposure risks

- Drug history
- Occupational and environmental exposures
- Past medical and family history

History helps differentiate between infectious, autoimmune, and other causes of systemic inflammation [17].

6.2. Physical Examination

Comprehensive examination should include:

- Vital signs (temperature, blood pressure, pulse, respiratory rate, oxygen saturation)
- General examination (pallor, lymphadenopathy, edema)
- Systemic examination (respiratory, cardiovascular, abdominal, neurological)

Careful examination may reveal subtle findings such as rash, joint swelling, or organomegaly that guide diagnosis [18].

6.3. Risk Stratification

Risk stratification is essential to identify patients who require urgent intervention.

Clinical scoring systems such as:

- qSOFA (quick Sequential Organ Failure Assessment)
- NEWS (National Early Warning Score)

are recommended by NICE guidelines for early identification of high-risk patients [16].

Patients should be categorized as:

- Low risk $\rightarrow$ outpatient management
- Moderate risk $\rightarrow$ close monitoring
- High risk $\rightarrow$ urgent referral/hospitalization

Early identification of high-risk patients improves outcomes and reduces mortality.

7. Diagnostic Approach

A systematic and stepwise diagnostic approach is essential in evaluating systemic inflammatory conditions, given their broad differential diagnosis and overlapping clinical features. Early and appropriate investigations help identify the underlying etiology, guide treatment, and prevent complications.

7.1. Basic Investigations

Initial laboratory investigations form the cornerstone of evaluation in primary care settings.

- **Complete Blood Count (CBC)**: May reveal leukocytosis in infections, leukopenia in viral illnesses or autoimmune conditions, anemia of chronic disease, or thrombocytopenia in severe systemic illness.
- **Erythrocyte Sedimentation Rate (ESR)**: A non-specific marker of inflammation, often elevated in chronic inflammatory and autoimmune conditions.
- **C-Reactive Protein (CRP)**: A sensitive acute-phase reactant that rises rapidly in response to inflammation and is useful in monitoring disease activity.

These markers are widely recommended for initial assessment of inflammatory states due to their accessibility and clinical utility [19].

7.2. Infection Workup

When an infectious etiology is suspected, targeted investigations are required:

- **Blood cultures**: Should be obtained prior to initiation of antibiotics in suspected sepsis.
- **Urine and other body fluid cultures**: Depending on clinical presentation.
- **Imaging**: Chest X-ray is often the first-line imaging modality for respiratory symptoms, while ultrasound or CT may be required for abdominal or deep-seated infections.

Microbiological confirmation remains the gold standard for diagnosis and helps guide antimicrobial therapy. Early identification of pathogens improves outcomes and supports antimicrobial stewardship [20].

7.3. Autoimmune Panel

In cases where autoimmune disease is suspected, specific immunological tests are indicated:

- **Antinuclear Antibody (ANA)**: Screening test for connective tissue diseases such as systemic lupus erythematosus.
- **Rheumatoid Factor (RF)**: Associated with rheumatoid arthritis but may be present in other conditions.
- **Anti-Cyclic Citrullinated Peptide (Anti-CCP)**: Highly specific for rheumatoid arthritis.

Additional tests such as complement levels and disease-specific antibodies may be required based on clinical suspicion [21].

7.4. Advanced Diagnostics

Advanced investigations are used when initial evaluation is inconclusive or when organ involvement is suspected:

- **Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)**: Provide detailed anatomical assessment and help detect occult infections, malignancies, or inflammatory lesions.
- **Biomarkers**: Procalcitonin is useful in differentiating bacterial infections from non-infectious inflammation, while interleukin-6 (IL-6) levels may reflect severity of systemic inflammation.

These modalities enhance diagnostic accuracy, particularly in complex or atypical cases [22].
Fever → Red flags → Basic labs → Infection vs Autoimmune → Referral.

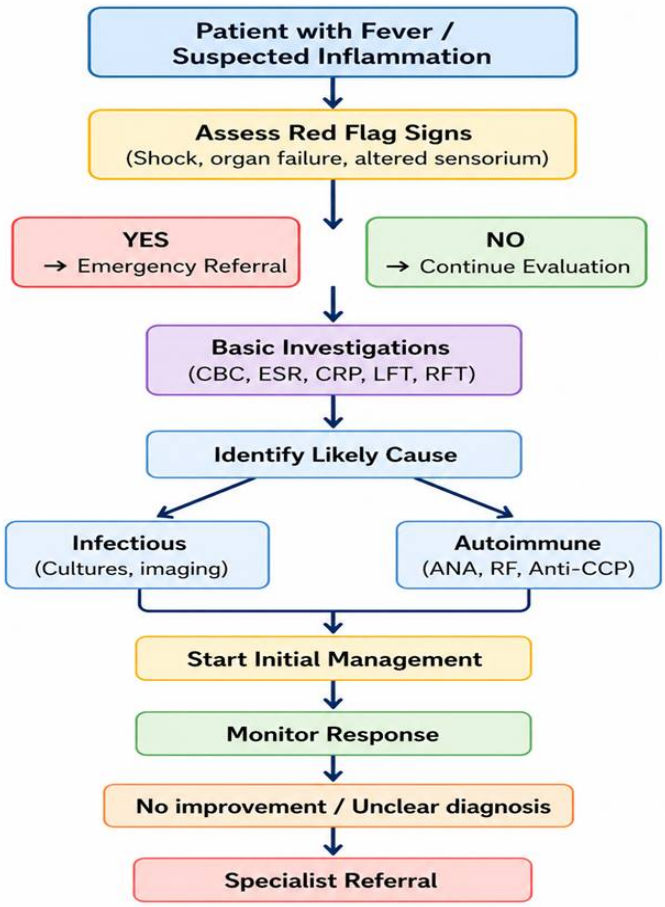

Figure 2: Clinical Algorithm for Evaluation of Systemic Inflammatory Conditions

8. Common Clinical Scenarios

8.1. Acute Febrile Illness

Acute febrile illness is one of the most common presentations in general practice. It is often caused by viral infections but may also indicate early bacterial sepsis or tropical infections.

A systematic approach based on duration, associated symptoms, and epidemiological context is essential. Most cases are self-limiting; however, identifying warning signs of severe disease is critical [23].

8.2. Pyrexia of Unknown Origin (PUO)

PUO is defined as fever lasting more than three weeks with no diagnosis despite appropriate evaluation. The major causes include infections, autoimmune diseases, and malignancies.

A stepwise diagnostic approach is recommended, starting with basic investigations and progressing to advanced imaging and specialized tests. Careful history and repeated clinical evaluation are crucial in establishing the diagnosis [24].

8.3. Chronic Inflammatory Diseases

Chronic inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease present with persistent symptoms and relapsing-remitting patterns.

These conditions require long-term monitoring, multidisciplinary care, and often immunosuppressive therapy. Early diagnosis is important to prevent complications such as joint destruction or organ damage [25].

9. Management Principles

Management of systemic inflammatory conditions is guided by the underlying etiology, severity of illness, and presence of complications.

9.1. Initial Stabilization (ABC Approach)

The first step in management is stabilization of the patient using the Airway, Breathing, Circulation (ABC) approach:

- **Airway**: Ensure patency
- **Breathing**: Provide oxygen support if needed
- **Circulation**: Initiate intravenous fluids for hypotension

Early stabilization is crucial, particularly in patients with sepsis or shock, and is strongly recommended by international guidelines [16].

9.2. Symptomatic Management

Supportive care plays an important role in all patients:

- Antipyretics for fever
- Analgesics for pain
- Adequate hydration and nutritional support

These measures improve patient comfort and help prevent complications [15].

9.3. Etiology-Based Treatment

Definitive treatment depends on the underlying cause:

- **Infections**: Prompt initiation of appropriate antimicrobial therapy
- **Autoimmune diseases**: Immunosuppressive agents such as corticosteroids and disease-modifying drugs
- **Autoinflammatory conditions**: Targeted biologic therapies

Timely initiation of cause-specific treatment is essential to improve outcomes and reduce disease progression [26].

9.4. Monitoring and Follow-Up

Ongoing monitoring is necessary to assess treatment response and detect complications:

- Regular clinical evaluation
- Monitoring laboratory parameters (CRP, ESR, organ function tests)
- Adjusting treatment based on response

Follow-up is particularly important in chronic inflammatory conditions to ensure long-term disease control [27].

10. Role of the General Practitioner

General practitioners play a central role in the management of systemic inflammatory conditions.

Early Recognition

GPs must maintain a high index of suspicion and identify early signs of systemic inflammation, especially in high-risk patients.

Initial Management

They are responsible for initiating basic investigations, providing symptomatic treatment, and stabilizing patients when necessary.

Coordination of Care

GPs act as coordinators between primary care and specialist services, ensuring timely referral and continuity of care.

Patient Education

Educating patients about disease nature, treatment adherence, and warning signs is essential for improving outcomes and preventing complications.

11. Referral Guidelines

Appropriate and timely referral is a critical component in the management of systemic inflammatory conditions. General practitioners must recognize situations requiring urgent escalation versus those suitable for planned specialist evaluation.

11.1. Emergency Referral

Immediate referral to higher centers or emergency services is warranted in patients presenting with:

- Suspected sepsis or septic shock
- Hemodynamic instability (hypotension, tachycardia)
- Acute respiratory distress or hypoxia
- Altered mental status
- Evidence of multi-organ dysfunction

Guidelines recommend early escalation and transfer to facilities with intensive care capabilities in such cases, as delays significantly increase mortality [20].

11.2. Planned Referral

Planned referral to specialists (e.g., rheumatology, infectious diseases, oncology) is indicated in:

- Persistent or unexplained systemic inflammation
- Suspected autoimmune or autoinflammatory diseases
- Chronic inflammatory conditions requiring long-term immunomodulatory therapy
- Diagnostic uncertainty despite initial evaluation

Timely referral ensures appropriate diagnosis, initiation of disease-specific therapy, and prevention of complications [28].

12. Toxicities and Complications

Systemic inflammatory conditions are associated with both disease-related complications and treatment-related adverse effects.

12.1. Disease-Related Complications

Uncontrolled systemic inflammation can lead to:

- Multi-organ dysfunction syndrome (MODS)
- Acute kidney injury
- Acute respiratory distress syndrome (ARDS)
- Disseminated intravascular coagulation (DIC)

These complications are major contributors to morbidity and mortality, particularly in severe infections such as sepsis [8].

12.2. Treatment-Related Adverse Effects

Therapeutic interventions, especially immunosuppressive agents, may result in:

- Increased susceptibility to infections
- Drug toxicity (hepatic, renal, hematologic)
- Gastrointestinal complications
- Hypersensitivity reactions

Long-term use of corticosteroids and biologics is associated with significant adverse effects, necessitating careful monitoring and dose adjustment [25].

13. Treatment Compliance and Challenges

Effective management of systemic inflammatory conditions depends heavily on patient adherence and healthcare system support.

Socioeconomic Barriers

Financial constraints, lack of insurance coverage, and indirect costs (travel, lost wages) can limit access to care and medications, particularly in LMICs [29].

Accessibility Issues

Limited availability of healthcare facilities, diagnostic tools, and specialists can delay diagnosis and treatment, leading to disease progression.

Adherence Challenges

Chronic diseases requiring long-term therapy often face issues of poor adherence due to:

- Side effects of medications
- Complex treatment regimens
- Lack of patient awareness

Improving patient education and follow-up systems is essential to enhance compliance and outcomes [30].

14. Recent Advances

Advancements in diagnostics and healthcare delivery have significantly improved the management of systemic inflammatory conditions.

Biomarkers

Novel biomarkers such as procalcitonin, interleukin-6 (IL-6), and high-sensitivity CRP provide improved diagnostic accuracy and help differentiate infectious from non-infectious causes [31].

Point-of-Care Testing

Rapid bedside tests enable early diagnosis and timely decision-making in primary care settings, especially in resource-limited environments.

Telemedicine

Telehealth services have expanded access to specialist consultation and follow-up care, particularly in remote areas. Telemedicine has proven valuable during pandemics and in chronic disease management [32].

AI in Diagnostics

Artificial intelligence (AI) and machine learning tools are increasingly being used for:

- Early detection of sepsis
- Risk stratification
- Clinical decision support

These technologies have the potential to enhance diagnostic accuracy and improve patient outcomes [33].

15. Public Health and Preventive Strategies

Prevention plays a crucial role in reducing the burden of systemic inflammatory conditions.

Vaccination

Immunization against infectious diseases such as influenza, pneumococcus, and COVID-19 reduces the risk of severe systemic inflammation and complications [34].

Infection Control

Adherence to infection prevention measures including hand hygiene, sanitation, and hospital infection control protocols is essential in reducing disease transmission.

Antibiotic Stewardship

Rational use of antibiotics is critical to prevent antimicrobial resistance, which complicates the management of infections and systemic inflammation [35].

Screening Programs

Early detection of chronic inflammatory and autoimmune diseases through screening programs can prevent complications and improve long-term outcomes.

16. Conclusion

Systemic inflammatory conditions represent a diverse and complex group of disorders that pose significant diagnostic and therapeutic challenges in general practice. Their presentation is often non-specific, ranging from mild constitutional symptoms to life-threatening multi-organ dysfunction. A structured clinical approach beginning with careful history taking, thorough physical examination, and stepwise investigations is essential for accurate diagnosis and effective management.

Early diagnosis plays a pivotal role in improving patient outcomes. Prompt recognition of warning signs, particularly in conditions such as sepsis or severe autoimmune disease, allows for timely intervention and reduces morbidity and mortality. The use of simple, accessible tools such as inflammatory markers and clinical scoring systems further aids in early identification and risk stratification.

Primary care physicians are central to the management of systemic inflammatory conditions. As the first point of contact, they are responsible for early recognition, initiation of basic management, and appropriate referral when necessary. In addition, they play a vital role in long-term follow-up, patient education, and ensuring treatment adherence. Strengthening primary healthcare systems and enhancing clinician awareness are therefore crucial for addressing the growing burden of these conditions.

In conclusion, a comprehensive, evidence-based approach in general practice supported by timely diagnosis, appropriate management, and coordinated care can significantly improve outcomes for patients with systemic inflammatory conditions.

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