Drug-induced Fever versus Infection-induced Fever

Drug-induced fever is a disorder characterized by a febrile response coinciding temporally with the administration of a drug in the absence of underlying conditions that can be responsible for the fever. Fever is a common symptom in day-to-day clinical practice, and a large number of indoor admissions are attributed to patients suffering from fever. Many of these patients are also put on anti-infective agents such as antibiotics, antivirals, antifungals, or antiparasitic drugs, considering infections as the predominant cause of fever. However, drugs initiated for the treatment of underlying diseases can be a cause of fever in such setting. It is a diagnostic dilemma to differentiate between infection-induced fever and drug-induced fever. The following table enlists differences between the two so as to help physician to differentiate between the two to take appropriate decisions. The distinction is especially important with regard to drug discontinuation and decision regarding the initiation of corticosteroid treatment [Table 1].

| Table 1: Drug-induced Fever versus Infection-induced Fever |
|------------------------------------------------------------|
| Definition | Drug-induced fever is a disorder characterized by a febrile response coinciding temporally with the administration of a drug in the absence of underlying conditions that can be responsible for the fever. | Infection-induced fever is a disorder characterized by a febrile response due to infectious agents in the absence of underlying conditions that can be responsible for the fever. |
| Epidemiology | Drug-induced fever contributes to 10%-15% of ADRs. Women and elderly individuals are said to be more susceptible for developing drug-induced fever due to nonantibiotics. | Difficult to estimate as it could be because of various etiologies. |
| Etiology | Antimicrobials, anticonvulsants, antiarrhythmic agents, and other cardiac agents. | Includes pathogens such as bacteria, viruses, fungi, or parasites. In India, malarial fever, typhoid fever, fever due to Gram-negative organisms, tuberculosis, etc., are the common causes of infectious fever. |
| Mechanism of fever | Drug effect on thermoregulation, administration-related reaction, drug’s pharmacological response, idiosyncratic responses, or drug hypersensitivity reaction are the possible mechanisms for drug fever. | Due to the pyrogens secreted by the pathogenic organisms. |
| Onset of fever | Median time for drug fever is 7-10 days after drug initiation. However, it may differ with various drug classes. Latency is more, especially in drug hypersensitivity syndromes. | Varies with different etiological agents (mostly 10-14 days). |
| Temperature | Hyperthermia is always present. | Hyperthermia or hypothermia can be present. |
| Pulse rate | Bradycardia is usually present. | Tachycardia is commonly seen. |
| Cutaneous manifestations | Are present in 18%-19% of cases. Fever can precede or may be present simultaneously at the time of maculopapular rash, SJS, or cutaneous manifestations of drug hypersensitivity syndrome. | Cutaneous manifestations may or may not be seen. Manifestations can precede or follow or may be present at the time of infection. |
| Diagnosis | Diagnosis is usually clinical and requires a high index of suspicion. | Diagnosis is based on clinical features but supported by specific serological or microbiological or histological investigations. |
| Laboratory investigations | Eosinophil count may be elevated in 22% of cases. | Eosinophil count is usually normal. Blood count depends on the nature of underlying infection. Procalcitonin is a useful marker of bacterial sepsis. |
| Treatment | Discontinuation of the offending drug causes prompt relief from fever except in cases of fever due to SJS/TEN or DRESS syndrome. Anti-infective agents will not obviously be helpful. | Initiation of anti-infective agents will help in subsidence of fever. |
| Response to corticosteroids | Dramatic response to oral or parenteral corticosteroids. | No response to oral or parenteral corticosteroids. It will worsen infection. However, long-term or higher dosages of CS may mask fever. |

DRESS: Drug reaction with eosinophilia and systemic symptoms, SJS: Steven–Johnson syndrome, TEN: Toxic epidermal necrolysis, CS: Cyclosporine
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