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# Iatrogenic meningitis

## Meningites iatrogênicas

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**ABSTRACT**

Iatrogenic meningitis can be caused by a number of mechanisms. The recent case reports of fungal meningitis after application of epidural methylprednisolone caused warning in the medical community. Cases were caused by contaminated lots of methylprednisolone from a single compounding pharmacy. Several medications can cause meninigitis by probable hypersensitivity mechanism. Neurologists should be alert to the recent description of the use of lamotrigine and development of aseptic meningitis.

**Keywords:** iatrogenesis, meningitis, methylprednisolone, lamotrigine.

**RESUMO**

As meningites iatrogênicas podem ser provocadas por uma série de mecanismos. Os recentes relatos de casos de meningite por fungos após a aplicação de injeção epidural de metilprednisolona causou alerta na comunidade médica. Os casos foram causados por lotes contaminados de metilprednisolona produzidos por uma única farmácia de produção. Diversos medicamentos podem causar meningite por provável mecanismo de hipersensibilidade. Neurologistas devem ficar alerta para a recente descrição do uso de lamotrigina e o desenvolvimento de meningite asséptica.

**Palavras-Chave:** meningite, iatrogenia, metilprednisolona, lamotrigina.

Iatrogenic meningitis is an inflammatory process of the meninges caused by: (a) injection of contaminated pharmacologic agent in the epidural compartment; (b) complication of diagnostic and therapeutic lumbar puncture; or (c) undesirable side effect of systemic drugs (the term "aseptic meninigitis" is more common, although it is broader and also include non-drug causes).

Iatrogenic meningitis gained the attention of the scientific community and in particular the Center for Disease Control (CDC) (Atlanta) last year, after a report of epidemic cases of fungal meningitis triggered by the epidural injection of contaminated methylprednisolone. Several states reported cases, although the highest concentration has been reported in Michigan and Tennessee.

Sixty-six patients were studied in an article published on November 6, 2012, in the *New England Journal of Medicine*, although at least 158 cases have been related to the same mechanism, the injection of epidural contaminated methylprednisolone. The investigation began after the isolated report case of *A. fumigatus* meningitis in an immunocompetent patient who had received epidural methylprednisolone in the state of Tennessee on September 18, 2012. Local health authorities (Tennessee Health Department) initiated an epidemiologic investigation immediately and detected two other cases of fungal meningitis in immunocompetent patients who had undergone the same procedure. The CDC was notified and, thereafter, it was discovered that the reported cases throughout the U.S. were caused by specific lots of contaminated methylprednisolone produced by the New England Compounding Center, Framingham, MA.

Although the index case was caused by *A. fumigatus*, the majority of other cases were caused by fungus *Exserohilum rostratum*. The main clinical manifestations were: meningitis (73%), cauda equina syndrome or epidural abscess (17%) and posterior circulations stroke with or without meningitis (12%). Patients with meningitis and altered cerebrospinal fluid results (N=59) showed: white-cell count median 534 cells/mm$^3$ (range: 4-10,140); granulocytes median 76% (range: 0-97); protein median 114 mg/dl (range: 29-440); glucose median 45 mg/dl (range: 12-121). Table 1 shows the main clinical features of the 66 published cases.

The drug-induced aseptic meningitis may be caused by a number of pharmacological agents used in clinical practice and administered systemically or intrathecally. The correlation between drug application in epidural space and the appearance of meningeal symptoms is, in most cases, obvious and will not be discussed here.

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**Table 1.** Clinical and Demographic Features of the Patients with Fungal Iatrogenic Meningitis after Epidural Contaminated Methylprednisolone.

| Variable | N | % |
|---|---|---|
| Age (years) | | |
| Median | 69 | |
| Range | 23-91 | |
| Gender | | |
| Female | 47 | 71 |
| Signs and symptoms | | |
| Fever | 23 | 35 |
| Headache | 48 | 73 |
| Nausea/vomiting | 42 | 63 |
| Stiff neck | 19 | 29 |
| Cervical pain | 12 | 18 |
| Back pain | 33 | 50 |

**Table 2.** Drugs potentially related to the appearance of aseptic meningitis.

| |
|---|
| Non-steroidal anti-inflammatory drugs (ibuprofen, in particular) |
| Trimethoprim/sulfamethoxazole |
| Lamotrigine |
| Amoxicilin |
| Ciprofloxacin |
| Allopurinol |
| Immunoglobulin (IV) |
| OKT3 |
| Isoniazid |
| Valacyclovir |
| Metronidazole |

The medications most commonly charged with the appearance of signs and symptoms of meningeal irritation are listed in Table 2, although any medication has the potential to cause the frame. The diagnosis depends on clinical suspicion. It may be stressed that this is a diagnosis of exclusion. In general, the signs and symptoms begin within 24 hours from the medication, although it can take more days. Neurologists should be alert to the recent and consistent description of aseptic meningitis induced by lamotrigine.

The pathophysiological mechanism is not completely understood, although it must involve an acute hypersensitivity reaction, since repeated exposure to the triggering agent induce increasingly early appearance of meningitis. There is a particular association between NSAID (non-steroidal anti-inflammatory drugs) use and the onset of signs and symptoms of meningitis in patients diagnosed with systemic lupus erythematosus and other collagen diseases. The association should not be fortuitous and possibly involves the occurrence of the phenomenon of hypersensitivity mediated by deposition of immune complexes (type III hypersensitivity reaction).

Cerebrospinal fluid study shows pleocytosis of polymorphonuclear predominance, although there are reports of eosinophilic or lymphocytic predominance. Glucose concentrations are usually normal or slightly decreased; proteins are commonly elevated. Cultures (bacteria, fungi and viruses), by definition, are always negative.

Management is primarily symptomatic and the drug needs to be discontinued. Symptoms usually disappear 24 to 48 hours after drug withdrawal.

## References


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