MANAGEMENTUL REACȚIILOR ADVERSE NEUROLOGICE INDUSE DE ANTIBIOTERAPIE

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https://www.cdc.gov/medicationsafety/parents_childrenadversedrugevents.html

EFECTE ADVERSE INDUSE DE ANTIBIOTERAPIE

- Tulburari gastro-intestinale (greturi, varsaturi, diaree)
- Infectii fungice, cu perturbarea florei bucale şi vaginale (candidoze)
- Fotosensibilitate
- Modificari ale dentitiei si structurii osoase
- Tulburari neurologice (parestezii, sindroame confuzionale, crize comitiale)
- Modificari hematologice

Marie F. Grill, Rama K. Maganti, British Journal of Clinical Pharmacology – Neurotoxic effects associated with antibiotic use- 2011

EFECTE ADVERSE GRAVE INDUSE DE ANTIBIOTERAPIE

- Anafilaxie
- MDR - Rezistenta multidrog
- Infecția cu Clostridium difficile
- Insuficienta renala
- Sepsis indus prin eliberare de endotoxine (meningita, urosepsis)

Marie F. Grill, Rama K. Maganti, British Journal of Clinical Pharmacology – Neurotoxic effects associated with antibiotic use- 2011.
Holzheimer RG, Antibiotic induced endotoxin release and clinical sepsis: a review, J Chemother. 2001 Nov;13 Spec No 1(1):159-72.

Table 2. Rates of 30-Day Antibiotic-Associated Adverse Drug Events in 1488 Hospitalized Patients Receiving Antibiotics per 10 000 Person-days (PD)[a]

Antibiotic Agent	No. of Patients Receiving Agent	Cardiac		Gastrointestinal[b]		Hematologic		Hepatobiliary		Renal		Neurologic		Other Events[c]	
		No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)
β-Lactam[d]	1187	0	...	59	17.4 (13.5-22.4)	27	8.7 (5.3-11.3)	6	3.4 (3.1-7.9)	17	6.9 (3.1-12.9)	10	3.8 (1.5-5.3)	2	0.6 (0.1-2.2)
Ampicillin	63	0	...	2	11.6 (2.9-46.2)	1	5.6 (0.8-39.6)	0	...	1	5.6 (0.8-39.6)	0	...	0	...
Amoxicillin-clavulanate	102	0	...	3	12.6 (4.5-25.2)	0	...	0	...	0	...	0	...	0	...
Ampicillin-sulbactam	52	0	...	1	7.2 (1.0-51.2)	0	...	0	...	2	14.2 (13.9-49.6)	0	...	0	...
Oxacillin	33	0	...	4	37.1 (12.0-105.0)	1	10.8 (1.5-76.4)	2	21.6 (5.4-86.6)	0	...	0	...	0	...
Piperacillin-tazobactam	315	0	...	16	14.8 (13.1-23.0)	4	4.3 (1.6-11.4)	1	1.1 (0.2-7.9)	1	1.1 (0.2-7.9)	1	1.1 (0.2-7.9)	1	1.1 (0.2-7.9)
Cefazolin	79	0	...	0	...	1	4.4 (0.6-31.4)	0	...	2	8.2 (1.6-24.8)	0	...	0	...
Ceftriaxone	607	0	...	14	8.0 (4.7-13.5)	11	6.2 (3.4-11.3)	3	2.1 (1.4-12.3)	5	2.8 (1.2-6.8)	1	0.6 (0.1-3.9)	0	...
Cefpodoxime	89	0	...	2	7.7 (1.9-30.9)	0	...	0	...	0	...	0	...	0	...
Cefepime	414	0	...	10	8.5 (4.6-15.8)	6	5.0 (2.2-11.1)	0	...	6	5.0 (2.2-11.1)	7	6.7 (2.7-12.0)	1	0.8 (0.1-5.8)
Ertapenem	85	0	...	3	12.1 (3.9-37.6)	0	...	0	...	0	...	0	...	0	...
Meropenem	80	0	...	4	18.0 (6.8-48.0)	3	12.9 (4.2-40.1)	0	...	0	...	1	4.4 (0.8-29.4)	0	...
Non-β-lactams															
Aminoglycosides	32	0	...	0	...	0	...	0	...	2	21.2 (12.5-66.0)	0	...	0	...
Azithromycin	400	1	0.8 (0.1-5.9)	1	0.8 (0.1-5.9)	0	...	4	3.4 (1.3-9.0)	0	...	0	...	0	...
Clindamycin	193	0	...	3	5.4 (1.8-16.8)	0	...	0	...	0	...	0	...	0	...
Daptomycin	8	0	...	0	...	0	...	0	...	0	...	0	...	1	44.8 (6.3-318.3)
Doxycycline	57	0	...	2	12.4 (3.1-49.7)	0	...	0	...	0	...	0	...	0	...
Fluoroquinolones	394	1	0.9 (0.1-6.2)	5	4.4 (1.8-10.6)	1	0.9 (0.1-6.2)	3	2.6 (0.8-8.0)	1	0.9 (0.1-6.2)	1	0.9 (0.1-6.2)	1	0.9 (0.1-6.2)
Linezolid	23	0	...	0	...	0	...	0	...	0	...	1	15.8 (2.2-112.3)	0	...
Metronidazole	175	0	...	1	2.0 (0.3-14.2)	0	...	0	...	0	...	1	2.0 (0.3-14.2)	0	...
Trimethoprim-sulfamethoxazole	155	0	...	5	11.2 (4.7-26.9)	0	...	0	...	6	13.2 (5.9-29.3)	0	...	1	2.1 (0.3-15.1)
Intravenous vancomycin	544	0	...	2	1.3 (0.3-5.2)	0	...	0	...	19	12.1 (7.7-19.0)	0	...	2	1.3 (0.3-5.2)
Overall rates	1488[e]	2	0.4 (0.1-1.8)	78	18.2 (14.6-22.8)	28	6.4 (4.4-9.2)	13	2.9 (1.7-5.0)	45	10.6 (7.9-14.2)	13	2.9 (1.7-5.0)	7	1.6 (0.8-3.3)

[a] The following regimens are included in the overall rates and resulted in no 30-d adverse drug events: penicillin (21), amoxicillin (47), dicloxacillin (1), cephalexin (44), second-generation cephalosporins (38), ceftazidime (6), ceftaroline (8), aztreonam (22), fosfomycin (10), nitrofurantoin (26), tigecycline (3), oral vancomycin (84).

[b] Includes nausea, emesis, non–*Clostridium difficile*–associated diarrhea.

[c] Other adverse drug events include cefepime-associated anaphylaxis (1), piperacillin-tazobactam–associated drug fever (1), ciprofloxacin-associated tendinitis (1), daptomycin-associated myositis (1), trimethoprim-sulfamethoxazole–associated pancreatitis (1), vancomycin-associated hives (1), and trimethoprim-sulfamethoxazole-related nonhives rash (1).

[d] Some patients received more than 1 β-lactam antibiotic.

[e] Most patients (1176 [79%]) received more than 1 antibiotic.

Pranita D. Tamma, Association of Adverse Events With Antibiotic Use in Hospitalized Patients, JAMA Intern Med. 2017

EVALUAREA EFECTELOR ADVERSE ALE ANTIBIOTICELOR

- Efectele adverse posibile se vor analiza in functie de:
  - Varsta pacientului
  - Statusul pacientului
  - Comorbiditati
  - Asocierea cu alte medicamente
  - Durata si tipul antibioterapiei

Marie F. Grill, Rama K. Maganti, British Journal of Clinical Pharmacology – Neurotoxic effects associated with antibiotic use- 2011

INTERACȚIUNI ALE ANTIBIOTICELOR CU ALTE MEDICAMENTE

- anticoagulante
- antiparkinsoniene
- antidiabetice
- antihistaminice
- **antiacide**
- **multivitamine**
- contraceptive
- hipocolesterolemiante, inclusiv statine
- antidepresive triciclice
- **medicamente antiinflamatoare nesteroidiene**
- medicatie pentru psoriazis
- medicatie pentru artrita reumatoida
- steroizi

Tammie Lee Demler, Drug-induced neurologic conditions, US Pharmacist, Neurology 2014

EFECTELE NEUROTOXICE ALE ANTIBIOTICELOR

- Manifestari neurologice centrale
  - sindroame confuzionale
  - crize de epilepsie
  - coree
  - atetoza
  - coma
- prin actiune asupra transmisiei GABA

- Manifestari neurologice periferice :
  - Neuropatie periferica – de tip axonal senzitiv
  - Afectarea jonctiunii neuro-musculare prin blocarea eliberarii cuantelor de acetilcolina sau a receptorilor de acetilcolina

Sindromul cerebelos poate fi cauzat de antibiotice aminoglicozide – disfunctii in coordonare si echilibru

Marie F. Grill, Rama K. Maganti, British Journal of Clinical Pharmacology – Neurotoxic effects associated with antibiotic use- 2011,
Tammie Lee Demler, Drug-induced neurologic conditions, US Pharmacist, Neurology 2014

EFECTELE NEUROTOXICE ALE PENICILINELOR

- manifestari de tip central: sindroame confuzionale, crize epileptice
- Factori de risc: afectiuni SNC preexistente (epilepsie)
  insuficienta renala
  cresterea permeabilitatii barierei hemato-encefalice

Cele mai frecvent implicate peniciline – benzylpenicilina, Penicilina G, Piperacilina, Ticarcilina, Ampicilina, Amoxicilina, Oxacilina

- Dintre toate penicilinele, benzylpenicilina are cel mai mare potential epileptogenic, independent de concentratia in LCR.

Marie F. Grill, Rama K. Maganti, British Journal of Clinical Pharmacology – Neurotoxic effects associated with antibiotic use- 2011,
Samuel Deshayes, Pub Med – Neurological Adverse Effects Attributable to B-Lactam Antibiotics – 2017

EFECTELE NEUROTOXICE ALE CEFALOSPORINELOR

- manifestari de tip central: crize epileptiforme, encefalopatie cu modificari EEG – unde trifazice, mioclonii
- Factori de risc: varsta
    - afectiune renala,
    - afectiune preexistenta SNC
    - supradozaj
- Cefalosporine cu potential mare de a determina neurotoxicitate:
- Cefazolin, Cefesolis, Ceftazidime, Cefoperazone, Cefepime
- Managementul crizelor: se vor administra antiepileptice de tip benzodiazepine, fenitoina, acid valproic temporar

Marie F. Grill, Rama K. Maganti, British Journal of Clinical Pharmacology – Neurotoxic effects associated with antibiotic use- 2011,
Samuel Deshayes, Pub Med – Neurological Adverse Effects Attributable to B-Lactam Antibiotics – 2017

EFECTELE NEUROTOXICE ALE CARBAPENEMELOR

- Carbapeneme – manifestari de tip central si periferic (polineuropatii)
  - Facori de risc – insuficienta renala
    - Afectiuni preexistente SNC (inclusive istoric de crize comitiale)
    - Varsta
    - Greutatea corporala scazuta
- Cel mai frecvent au fost descrise crize comitiale tonico-clonice generalizate

Marie F. Grill, Rama K. Maganti, British Journal of Clinical Pharmacology – Neurotoxic effects associated with antibiotic use- 2011,
Samuel Deshayes, Pub Med – Neurological Adverse Effects Attributable to B-Lactam Antibiotics – 2017

EFECTELE NEUROTOXICE ALE AMINOGLICOZIDELOR

- Aminoglicozide – ototoxicitate (effect de clasa), neuropatie periferica, afectarea transmisiei neuromusculare (efect de clasa)
  - Factori de risc –crestera permeabilitatii hematoencefalice
    - Administrare intratecala
    - Supradozaj
- Administrarea intratecala a gentamicinei a generat leziuni trunchi cerebral (punte si mezencefal) la o serie de cazuri .
- Amikacina, tobramicina, neomicina, gentamicina si kanamicina sunt aminoglicozidele care au determinat cel mai frecvent blocarea transmisiei neuro-musculare. Acest efect advers are implicatii in cazul pacientilor cu mistenia gravis si sindrom Lambert –Eaton – cazuri in care este contraindicate administrarea

Marie F. Grill, Rama K. Maganti, British Journal of Clinical Pharmacology – Neurotoxic effects associated with antibiotic use- 2011

EFECTELE NEUROTOXICE ALE QUINOLONELOR

- Quinolone – manifestari la nivelul sistemului nervos central (inclusiv sindrom Tourette, delirium, psihoza toxica, sindrom extrapiramidal)
  - Factori de risc: - afectiune SNC preexistenta
    - Cresterea permeabilitatii membranei hematoencefalice
    - Supradozaj medicamentos

- Nu exista o corelatie intre concentratia quinolonelor in LCR si riscul de dezvoltare de crize epileptice.

Marie F. Grill, Rama K. Maganti, British Journal of Clinical Pharmacology – Neurotoxic effects associated with antibiotic use- 2011

EFECTELE NEUROTOXICE ALE MACROLIDELOR

- Macrolide/azalide – manifestari din partea SNC (delirium, psihoze, confuzie), ototoxicitate si accentuarea unei miastenii preexistente
  - Factori de risc: - tulburari psihice preexistente
    - Insuficienta renala
    - Supradozaj

- Foarte frecvent au fost identificate EA de tip ototoxic prin afectarea cohleei ceea ce determina , pe langa tulburari de auz si tulburari de echilibru.
- **Identificarea rapida a acestui EA este esentiala pentru a minimalize riscurile ulterioare de afectare permanenta a sistemului vestibulo-cohlear.**

Marie F. Grill, Rama K. Maganti, British Journal of Clinical Pharmacology – Neurotoxic effects associated with antibiotic use- 2011

Intensive Care Med. 2002 Jul;28(7):824-33. Epub 2002 May 30.

Clinical implications of antibiotic-induced endotoxin release in septic shock.

Lepper PM[1], Held TK, Schneider EM, Bölke E, Gerlach H, Trautmann M.

Antibiotic-induced release of bacterial cell wall components can have immediate adverse effects for the patient. This article reviews the data on endotoxin release after initiation of antibiotic therapy and its role in the pathogenesis of sepsis and septic shock. Antibiotics differ in their potential to liberate endotoxins from bacterial cell walls. When used for treatment of systemic Gram-negative infection, some classes of beta-lactam antibiotics lead to markedly increased levels of free endotoxins while treatment with carbapenems and aminoglycosides produces relatively low amounts of endotoxins. Antibiotics that induce the formation of long, aberrant bacterial cells before effectively killing the microorganisms show the highest degree of endotoxin liberation. There is increasing evidence from animal models and clinical studies of sepsis that the antibiotic-mediated release of biologically active cell wall components derived from Gram-positive, Gram-negative or fungal organisms is associated with a rapid clinical deterioration.

Bhattacharyya S, Darby RR, Raibagkar P, Gonzalez Castro LN, Berkowitz AL, Antibiotic-associated encephalopathy, Neurology. 2016 Mar 8;86(10):963-71. doi: 10.1212/WNL.0000000000002455. Epub 2016 Feb 17.

- Delirium is a common and costly complication of hospitalization. Although medications are a known cause of delirium, antibiotics are an underrecognized class of medications associated with delirium. In this article, we comprehensively review the clinical, radiologic, and electrophysiologic features of **antibiotic-associated encephalopathy (AAE).**
- AAE can be divided into 3 unique clinical phenotypes:
- encephalopathy commonly accompanied by seizures or myoclonus arising within days after antibiotic administration (caused by cephalosporins and penicillin);
- encephalopathy characterized by psychosis arising within days of antibiotic administration (caused by quinolones, macrolides, and procaine penicillin);
- encephalopathy accompanied by cerebellar signs and MRI abnormalities emerging weeks after initiation of antibiotics (caused by metronidazole).
- These 3 clinical phenotypes are correlated with underlying pathophysiologic mechanisms of antibiotic neurotoxicity. Familiarity with these types of antibiotic toxicity can improve timely diagnosis of AAE and prompt antibiotic discontinuation, reducing the time patients spend in the delirious state.

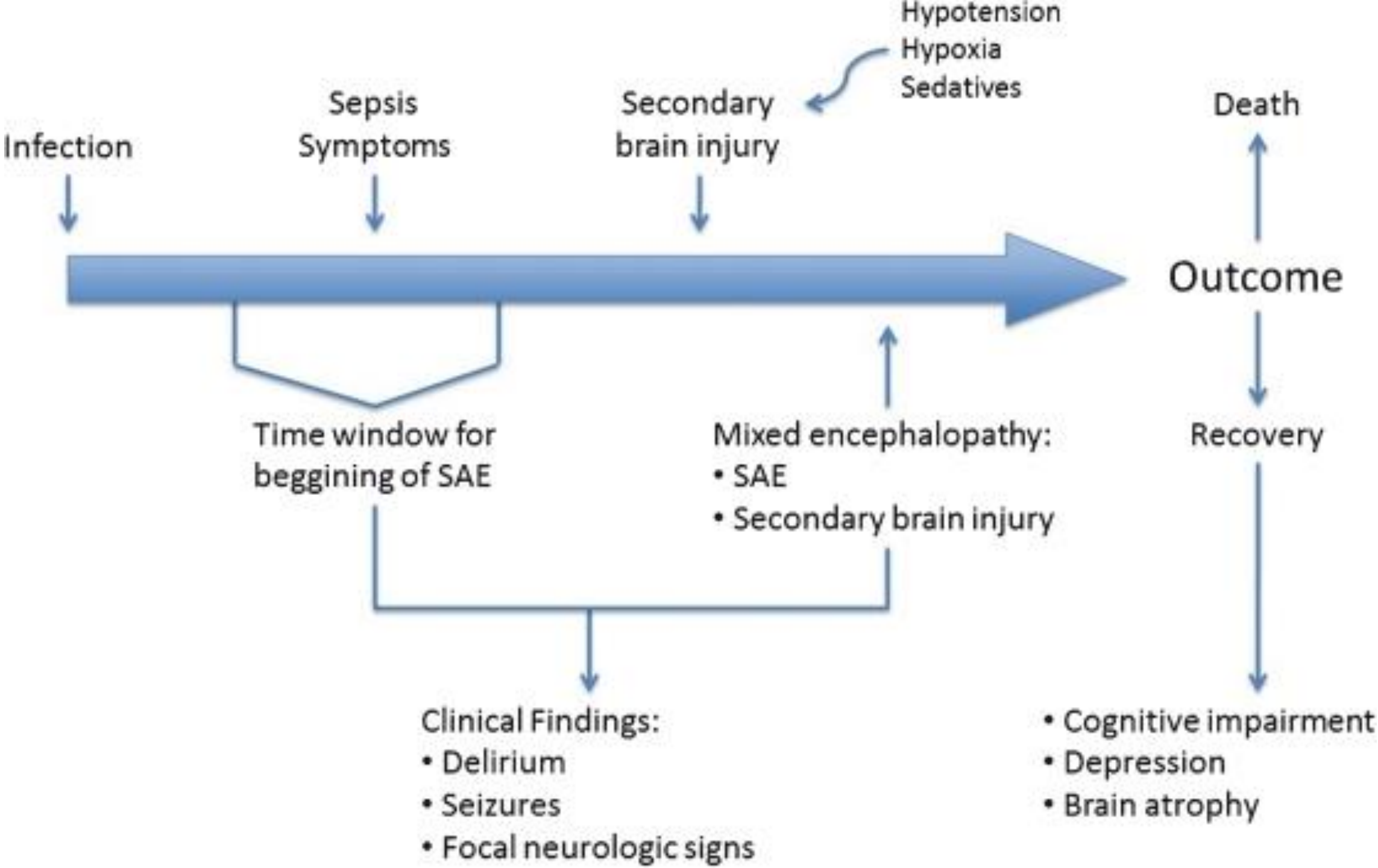
Neera Chaudhry, Ashish Kumar Duggal, Sepsis Associated Encephalopathy, Adv Med. 2014; 2014: 762320. Published online 2014 Sep 30. doi: 10.1155/2014/762320

- **A critical point in evaluation of patients with suspected SAE is a proper evaluation of the drugs that the patient is receiving. It should be noted that besides the obvious culprits such as benzodiazepines, opiates, anticonvulsants and anticholinergics, several other classes of drugs including antibiotics (particularly penicillins, cephalosporins, carbapenems, and quinolones), antiarrhythmics, steroids, and nonsteroidal anti-inflammatory drugs may be associated with brain dysfunction in critically ill patients**

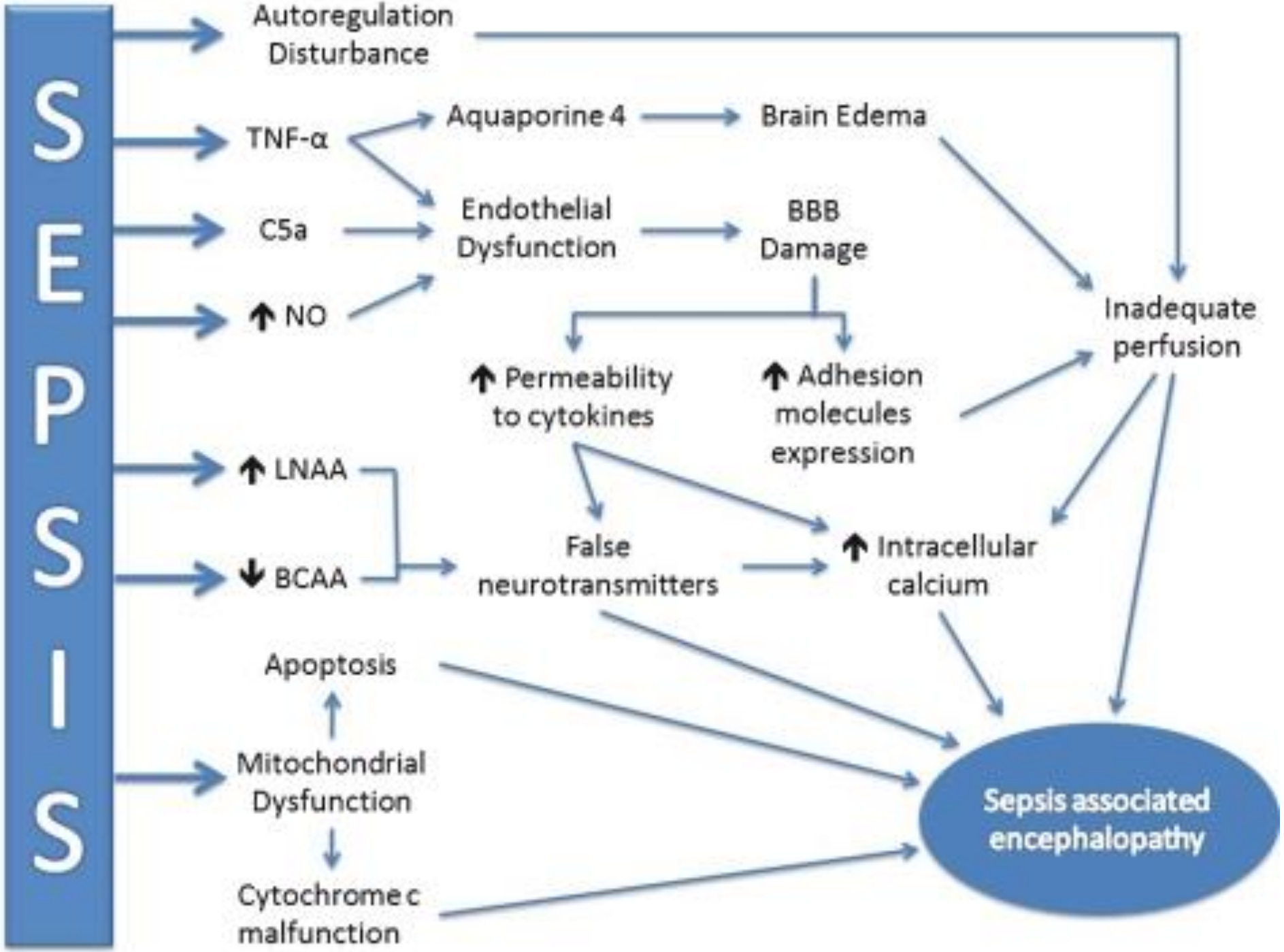
Romain Sonneville et al, Understanding brain dysfunction in sepsis, Ann Intensive Care. 2013; 3: 15. Published online 2013 May 29. doi: 10.1186/2110-5820-3-15

Medications associated with brain dysfunction in the intensive care unit

Agent	Mechanism of action
Antibiotics	Inhibition of GABA-A receptors
Penicillins, cephalosporins, carbapenems, Quinolones	

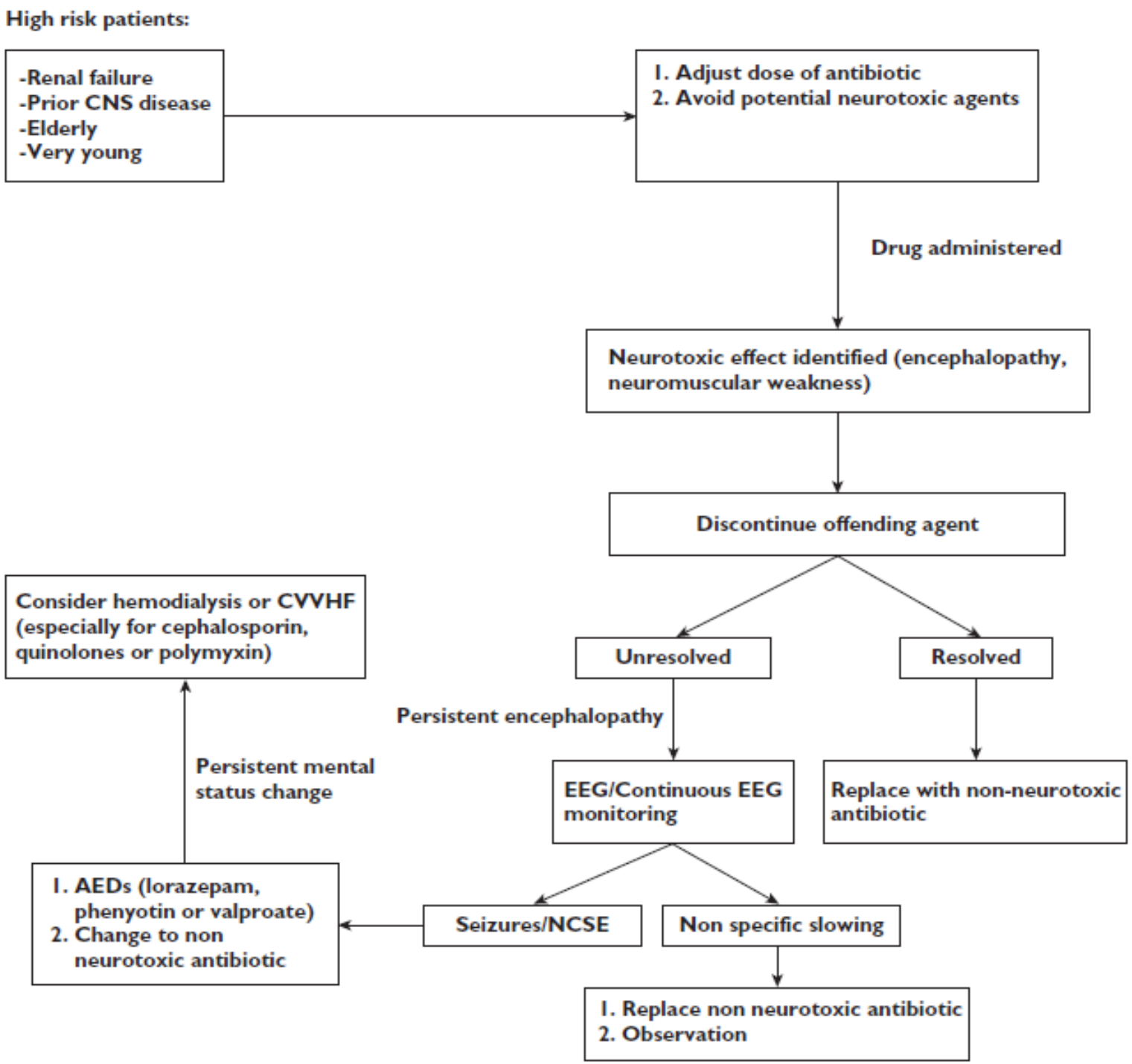


Fernando G. Zampieri, Marcelo Park, Fábio Santana Machado, Luciano Cesar Pontes Azevedo, Sepsis-associated encephalopathy: not just delirium, Published in Clinics 2011



Fernando G. Zampieri, Marcelo Park, Fábio Santana Machado, Luciano Cesar Pontes Azevedo, Sepsis-associated encephalopathy: not just delirium, Published in Clinics 2011

Managementul neurotoxicitatii induse de antibioterapie



Marie F. Grill, Rama K. Maganti, British Journal of Clinical Pharmacology – Neurotoxic effects associated with antibiotic use- 2011

CONCLUZII

1. Evaluarea clinica riguroasa a cazului, anterior introducerii medicatiei antibiotice
2. Analiza raportului risc/beneficiu in functie de comorbiditati
3. Evaluarea corecta a statusului functional, a comorbiditatilor si a medicatiei concomitente
4. Monitorizarea si identificarea precoce a reactiilor adverse dupa initierea antibioterapiei
5. Stabilirea corecta a

- dozelor
- tipului de antibiotic
- asocierii de antibiotice
- căii de administrare
- duratei de tratament

PE PRIMUL LOC TREBUIE SĂ FIE SIGURANȚA PACIENTULUI