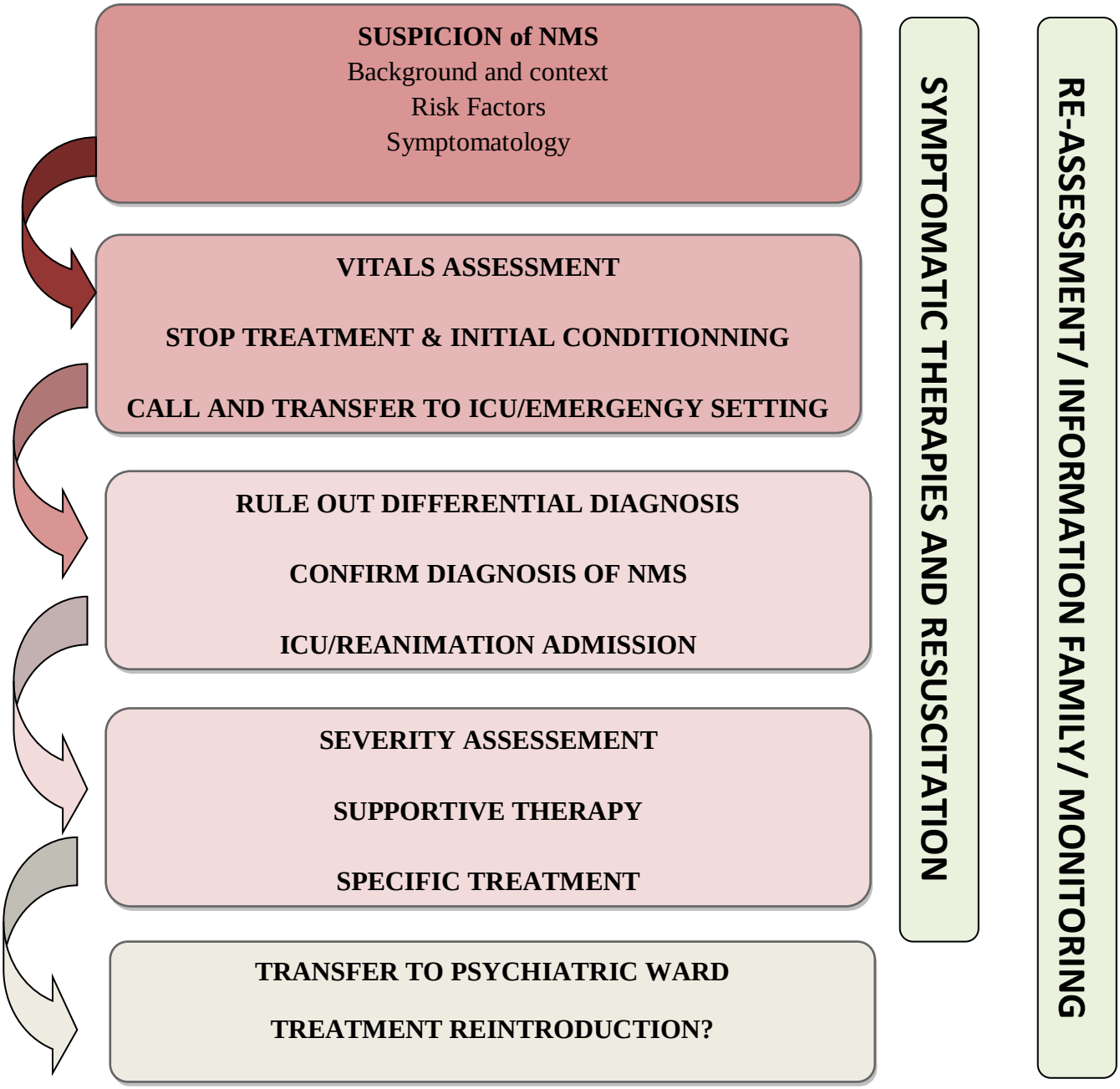
Simplified protocol for the management of Neuroleptic Malignant Syndrome

Protocol for the management of Neuroleptic Malignant Syndrome (English Version)

Neuroleptic Malignant Syndrome (NMS) management requires **multidisciplinarity** (emergency physicians, anesthesists/intensivists, psychiatrists, neurologists, radiologists…) and implementation of standardized and **customized local procedures**.



FLOWCHART OF THE MANAGEMENT OF NEUROLEPTIC MALIGNANT SYNDROME

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SUSPICION OF NMS

➔ **CHECK FOR RISK FACTORS?**

RISK FACTORS	
PHARMACOLOGICAL TREATMENT	Initial stages of treatment Changing doses High doses of NL Parenteral route (IV or IM) Poly medication Antipsychotic treatment Combinations of Molecules
ENVIRONEMENTAL	Physical contention Dehydration High room temperature
DEMOGRAPHICS	Age Co morbidities
GENETICS	Personal history of NMS Familial history of catatonia

➔ **WHAT TREATMENTS ARE INVOLVED?** (NON-EXHAUSTIVE LISTS)

- First generation anti-psychotics: chlorpromazine, fluphenazine, haloperidol, paliperidone, perphenazine, thioridazine....
- Second generation anti-psychotics: aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone....
- Any drug that interferes with dopaminergic transmission: antiemetics (domperidone, metoclopramide....).....
- Abrupt discontinuation of dopaminergic agonists (L-Dopa...)

➔ **IS CLINICAL PRESENTATION SUGGESTIVE ?**

- Hyperthermia
- Muscular rigidity
- Dysautonomia
- Mental status impairment

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INITIAL MANAGEMENT BEFORE TRANSFER TO ICU/EMERGENCY SETTING

➔ MANGEMENT OF SUSPECTED TREATMENT

- ✓ Immediate discontinuation of psychotropic drugs or any medication at risk.
- ✓ Restart dopaminergic agonists if abruptly stopped.

➔ VITALS ASSESSMENT following to ABCDE procedures:

A- Airway with C-spine protection	Airway liberation and protection Respect of the head-neck-trunk axis
B- Breathing	Respiratory support
C- Circulation	Hemodynamic support
D- Disability	Neurologic Function
E- Exposure, Environment	**Glycemia,** cooling, overall assessment, trauma?

➔ INITIAL CONDITIONING AND MANAGEMENT

- ✓ Half-seated or lateral safety position depending on the situation.
- ✓ Guedel cannula, oxygen therapy on mask, ± naso-gastric tube.
- ✓ Peripheral venous catheter 18 or 16 G.
- ✓ Saline 0.9% 500 ml.

➔ REGULATED TRANSFER (Through Emergency Call Service) to a specialized facility with written records of:

- ✓ Patient identification
- ✓ Co-morbidities
- ✓ Treatments (Molecules, doses, routes of administration, duration)
- ✓ Time of suspected treatment discontinuation and initial management
- ✓ Family Contact
- ✓ Contact details of the attending psychiatrist

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NMS DIAGNOSIS CONFIRMATION

1. CHECK DMS-5 DIAGNOSTIC CRITERIA FOR NMS

➔ **Exposure to a dopaminergic antagonist, or dopaminergic agonist withdrawal, within the last 72 hours;**

➔ **A suggestive symptomatology (No specific criteria)**

- ✓ Hyperthermia > 38°C at least twice;
- ✓ Muscular rigidity, « lead-pipe » rigidity in generalized presentations;
- ✓ Mental status alteration : delirium or altered consciousness ranging from stupor to coma ;
- ✓ Creatine phosphokinases (CPK) elevation, at least 4 times normal;
- ✓ Autonomic dysfunction (lability and hypermetabolism) :
  - Tachycardia, at least 25% over the baseline value;
  - Diaphoresis ;
  - Increasing systolic or diastolic blood pressure by at least 25% from baseline or blood pressure fluctuation (by at least 20 mm Hg for diastolic or 25 mm Hg for systolic in the last 24 hours);
  - Increase in respiratory rate of at least 50% over baseline value;
  - Urinary incontinence …..

➔ **Negative examination for infectious, toxic, metabolic and neurologic causes.**

2. REQUEST TESTS FOR POSITIVE, DIFFERENTIAL AND COMPLICATION DIAGNOSIS? (According to context)

To request	Why ?
Blood glucose	
Infection check-up Blood count, C-reactive protein, blood cultures, urine and cerebrospinal fluid analysis	To exclude infection
Toxicological testing = Blood and urine screening	To exclude acute poisoning
Radiological assessment Brain CT scan ± MRI	To exclude a neurological cause (infection, trauma, vascular, tumor…)
CPK and CPK-MB Myoglobinemia et myoglobinuria	To support NMS diagnosis
Urea, creatinine	Check for kidney failure
Blood electrolytes : Ca, Na, K, Mg, Ph	Check for electrolyte disorders
Arterial blood gas : pH, $HCO3^-$, paCO2, BE, paO2 Lactates	Check for respiratory failure and/or metabolic acidosis
Liver tests + Hemostasis : Prothrombin, INR, TCA, Platelets, AST, ALT, Factor V, Albuminemia	Check for liver failure and disseminated vascular coagulation

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SEVERITY ASSESSMENT OF NMS (Should be dynamic)

A. IN PSYCHIATRY AND/OR EMERGENCY SETTINGS

➔ **QUICK-SOFA**

Systolic Blood Pressure ≤ 100 mmHg	**1 point**
Respiratory Rate ≥ 22 breaths/min	**1 point**
Glasgow Coma Scale ≤ 14	**1 point**

➔ **ACCORDING TO NMS STAGES OF SEVERITY**

Severity stages	Clinical presentation
I : Drug-induced Parkinsonism	Rigidity, tremor
II : Drug-induced Catatonia	Rigidity, mutism, stupor
III : Mild and early NMS	Mild rigidity, catatonia or confusion, Temperature ≤ 38°C, Heart Rate ≤100 beats/min.
IV : Moderate NMS	Moderate rigidity, catatonia or confusion. Temperature 38 - 40° Heart rate : 100 - 120 batt/min
V : Severe NMS	Severe rigidity Catatonia or coma Temperature ≥ 40°C Heart rate ≥ 120 batt/min

B. IN ICU

➔ SOFA

SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE					
Variables/Score	0	1	2	3	4
PaO_2/FiO_2 (mmHg)	> 400	≤ 400	≤ 300	≤ 200	≤ 100
Platelets ($\times 10^3/mm^3$)	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Bilirubin (mg/l)	< 12	12 - 19	20 - 59	60 - 119	> 120
Cardiovascular (µg/kg/min)	No hypotension	MAP < 70 mmHg	Dopa ≤ 5 or Dobu (any dose)	Dopa > 5 or norepi ≤ 0,1	Dopa> 15 or norepi > 0,1
Glasgow Coma Scale	15	13 - 14	10 - 12	6 - 9	< 6
Creatinine (mg/l) or urine output	< 12	12 - 19	20 - 34	35 – 49 or < 500 ml/day	> 50 or < 200 ml/day
MAP : Mean Arterial Pressure, Dopa :Dopamine, Dobu: Dobutamine, Norepi : Norepinephrine					

➔ **SACHDEV RATING SCALE**

Name & Surname : _____**Date :**_____
Patient Index : _____

Physician : _____**Time :**_____

Evaluation performed: for the whole day / at a given time

Categories / Items	Rating*							Sub-total	Score Category
I/ Oral Temperature	0	1	2	3	4	5	6	____	____
II/ Extrapyramidal syndrome									
Rigidity	0	1	2	3				____	____
Dysphagia	0	1						____	
Resting tremor	0	1	2					____	
III/ Dysautonomie									
Systolic Blood Pressure	0	1						____	____
Diastolic Blood Pressure	0	1						____	
Tachycardia	0	1						____	
Hypersudation	0	1						____	
Incontinence	0	1						____	
Tachypnea	0	1						____	
IV/ Impairment of consciousness	0	1	2	3	4	5	6	____	____
V/ Catatonia / movement disorder									
Posture	0	1						____	____
Poor speech	0	1						____	
Mutism	0	1	2					____	
Choreiform movements	0	1						____	
Dystonia	0	1						____	
VI/ Laboratory tests									
CPK Levels	0	1	2	3	4			____	____
WBC count	0	1	2					____	
Total									**____/36**

A total score > 8 and score ≥ 2 in 3 categories supports diagnosis

Sachdev Scale Rating System

Category I: Oral Temperature

Highest temperature over 24 hours: 0 (< 37°C); 1 (37.0 - 37.4°C); 2 (37.5 - 37.9°C); 3 (38 - 38.9°C); 4 (39 - 39.9°C); 5 (40 - 41.9°C); and 6 (≥ 42°C).

Category II: Extrapyramidal Syndrome

- **Rigidity** assessed at the flexor muscles of the wrist and elbow and at passive rotation of the neck:
  - 0 : absent
  - 1: light (Tight jaw)
  - 2: moderate without limitation of passive movement
  - 3: severe with limitation of passive movement
- **Dysphagia :**
  - 0 : absent
  - 1 : present (or indirect sign: hyper salivation)
- **Resting tremor** : assessed in a subject seated with the arms resting on the chair arms or on the knees:
  - 0 : No tremor
  - 1 : Intermittent and/or unilateral tremor
  - 2 : Predominant bilateral tremors at rest

Catégorie III : Dysautonomia

Item Absent 0 or Present 1, at any time within 24 hours.

Systolic Blood Pressure Increase = 30 mm above baseline or = 150 mm if baseline reference not available.

Diastolic Blood Pressure Increase = 20 mm above baseline or = 100 mm if baseline reference not available.

Tachycardia: Heart rate = 30 beats/min above baseline, or = 100 if baseline not available.

Hypersudation: Excessive transpiration not related to room temperature or other etiology.

Incontinence: Fecal or urinary incontinence not related to altered consciousness or catatonic state.

Tachypnea: respiration rate = 15 / min above baseline or = 40 / min if baseline reference not available.

Category IV : Impairment of consciousness

- 0 : If no altered consciousness or alteration due to any other cause

- 1 : Obvious perplexity but patient completely oriented
- 2 : Mild disorientation in time or space
- 3 : Fluctuating level of consciousness with periods of normality
- 4 : Prolonged delirium clinically evident or abnormal EEG
- 5 : Stuporous patient responding to painful stimuli
- 6 : Comatose patient, totally non-responsive ➔ GCS

Category V : Catatonia / movement disorder

- 0 : Absent or present before use of the suspected agent
- 1 : Present

Posture = unexplained maintenance of an abnormal posture for an extended period of time.

Poor speech = reduction of spontaneous speech and response to questions.

Mutism = unexplained lack of intermittent :1 or continuous speech: 2.

Patients may develop **choreiform movements** or **dystonia** such as retrocollis, opisthotonus, trismus or oculogyric seizures.

Category VI : Laboratory tests

CPK Levels (UI/l):

- 0 : < 200
- 1 : 200-400 (0 if intramuscular injection within the previous 24 hours)
- 2 : 400-200 (1 if intramuscular injection within the previous 24 hours)
- 3 : 1000-10000
- 4 : 10000

WBC count :

- 0 : < 15000
- 1 : 15000- 30000
- 2 : > 30000

SUPPORTIVE THERAPIES

CONDITIONING AND MONITORING	▪ Half-seated position, head at 45°. ▪ Standard monitoring: heart rate and rhythm, blood pressure, oxygen saturation, temperature, urinary output. ▪ 2 peripheral venous lines 18 - 16 Gauge ± central venous line. ▪ Biology: blood count + platelets, liver function, kidney function, haemostasis, electrolytes (kalaemia, calcaemia, phosphatemia, magnesia), glycaemia, C-Reactive protein, arterial blood gases, lactates, urinary pH, procalcitonin. ▪ Nasogastric tube if: swallowing disorder, hyper-salivation, consciousness alteration. ▪ Standard chest x-ray.
FLUID RESCUCITATION AND RENAL SUPPORT	▪ Cristalloids: Saline 0.9%, Lactate Ringer ▪ 3 to 6 liters / 24 hours or more + monitoring ▪ Renal objectives: Urinary output 2 - 3 ml/kg/h and urinary pH > 6.5. ▪ STOP Vascular filling if oliguria and optimized volemia because of risk of overload. ▪ AVOID NEPHROTOXICS ▪ Colloids PROSCRIBED ▪ Bicarbonates on a case-by-case basis ▪ Dialysis
COOLING	▪ Ambient temperature around 23º C. ▪ Cooling blankets and ice blocks.
RESPIRATORY SUPPORT	▪ Chest position elevated at 45° from bed level. ▪ Oxygen therapy. ▪ Respiratory kinesitherapy: postural measures, incentive spirometry and drainage of bronchial secretions. ▪ Tracheal intubation and mechanical ventilation.

AGITATION CONTROL	▪ Avoid restraint as much as possible. ▪ Benzodiazepines (lorazepam or midazolam): 1-2 mg intravenously every 4-6 hours; Maximum 8 mg / day.
ANTIARRHYTHMIC AND ANTIHYPERTENSIVE TREATMENT	▪ Correction of hydroelectrolytic disorders ▪ Anti arrhythmia therapies ▪ Calcium Inhibitors (Do not combine with Dantrolene)
PREVENTION OF COMPLICATIONS RELATED TO ICU STAY	▪ Stress Ulcer prevention. ▪ Pharmacologic and/or mechanic thromboembolic prophylaxis. ▪ Prevention of decubitus complications: Regular position changes; anti-bedsore mattress; motor kinesitherapy and early mobilization. ▪ Prevention of metabolic complications : Energy intake based on 5% glucose serum with electrolytes + Nutritional management: enteral (oral or by naso-gastric tube) and/or parenteral.
SPECIFIC THERAPIES	▪ Bromocriptine 2.5 - 5 mg every 8 hours (Oral or nasogastric tube), or Amantadine: 100 mg/8h (Oral or nasogastric tube) ▪ Dantrolene: 1 mg/kg every 4 - 6 hours intravenously for 48 hours (Maximum 10mg/kg/day). ▪ Electroconvulsivotherapy as seconf line therapy.

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SPECIFIC THERAPY ACCORDING TO SEVRITY

Severity	Therapies
I : Drug-induced parkinsonism	Reduce doses or change the psychotropic drug
II : Drug-induced catatonia	Psychotropic discontinuation, reduction or change Lorazepam (Maximum 8 mg / day)
III : Mild and early NMS	Psychotropic discontinuation Lorazepam: 1-2 mg/ 4-6 h and Maximum 8 mg / day
IV : Moderate NMS	Psychotropic discontinuation Intensive Care Unit Lorazepam: 1-2 mg/ 4-6 h and Maximum 8 mg / day Bromocriptine 2.5 - 5 mg every 8 hours (Oral or NG tube) if available, or Amantadine: 100 mg/8h (Oral or NG tube) if available Electroconvulsive therapy (ECT) in 2nd line
V : Severe NMS	Psychotropic discontinuation Intensive Care Unit **Dantrolene IV: 1 mg/kg every 4 - 6 hours for 48 hours (Maximum 10mg/kg/d) if available** Bromocriptine 2.5 - 5 mg every 8 hours (Oral or NG tube) if available, or Amantadine: 100 mg/8h (Oral or NG tube) if available Electroconvulsive therapy (ECT) in 2nd line

Requirements for ECT	▪ Preanaesthetic evaluation ▪ Anesthetic technical platform set-up (Monitoring, Oxygen, guedel cannula .....) ▪ Anesthesiologist-Operator communication ▪ Avoid Succinylcholine

TREATMENT REINTRODUCTION ?

If reintroduction of psychotic treatment is being considered, it is recommended:

- ➔ To wait at least two weeks before re-starting treatment or more if residual symptoms are present.
- ➔ Avoid the use of the same drug involved.
- ➔ Use less powerful agents.
- ➔ Start at low doses with slower titration schedules.
- ➔ Avoid the parenteral route.
- ➔ Avoid lithium.
- ➔ Prevent and quickly correct dehydration.
- ➔ Close monitoring for early detection of recurrence of NMS.