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REVIEW ARTICLE

Multiple organ dysfunction syndrome: what do we know about pain management? A narrative review

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ABSTRACT

Multiple organ dysfunction syndrome (MODS) is observed in 40% of adult patients and 56% of pediatric patients admitted to the intensive care unit (ICU). Mortality in case of MODS can reach 50% and more. Pain management in this population of patients is always a big challenge due to systemic derangements. We give a narrative review of this problem and the recommended lines of action here.

We performed a literaturesearch for a period from 1984 to 2018 in Google Scholar, PubMed, Medline, Embase, and Cochrane. Data from 45 articles devoted to the problems of MODS, severe sepsis, heart, liver and renal failures, coagulation disorders and pain management were accumulated and presented here.First step in the management of any pathology is diagnosis and assessment. Organ dysfunction in adults can be assessed according to Sequential Organ Failure Assessment (SOFA) score, and other Systems in pediatric patients.

Acetaminophen, tramadol and fentanyl is a safe option for analgesia in MODS after dose adjusting according to liver failure or eGFR. Other methods of analgesia can be used in specific types of organ failure, but have limitations or are not well studied, so they are best avoided or used with caution in patients with MODS.

In this article pain management strategies in each particular failure are presented and an algorithm for pain management has been suggested by the authors. Further investigations are required in order to determine the best modalities for pain management in this group of patients.

Key words: Multiple organ dysfunction syndrome;MODS; Narrative review; Mortality; Morbidity; Sequential Organ Failure Assessment score; SOFA; Critical Care; Failure, Heart; Failure, Hepatic; Failure, Renal

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INTRODUCTION

According to the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) multiple organ dysfunction syndrome (MODS) is defined as presence of altered organ function in acutely ill patient such that homeostasis cannot be maintained without intervention.[1] Such structure of the definition was designed for the representation of the different degree of the organ's function violation (dysfunction), which can vary greatly from case to case, and their pathogenetic relation with gradual development and occurrence of multiple symptoms (syndrome). MODS is divided into primary and secondary, which have different underlying pathogenetic mechanisms.

Table 1: SOFA score[18]

SOFA score					
Variables	**0**	**1**	**2**	**3**	**4**
Respiratory PaO_2/FiO_2, mmHg	> 400	≤ 400	≤ 300	≤ 200 (RS)	≤ 100 (RS)
Coagulation Platelets x $10^3/\mu L$	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver Bilirubin, md/dL	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
Cardiovascular Hypotension	No hypotension	Mean arterial pressure < 70 mmHg	Dop ≤ 5 or dob (any dose)	Dop > 5, epi ≤0.1, or norepi ≤0.1	Dop > 15, epi > 0.1 or norepi < 0.1
Central nervous system Glasgow Coma Score	15	13-14	10-12	6-9	< 6
Renal Creatinine (mg/dL) Or urine output (mL/d)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9 Or < 500	> 5.0 or < 200

Dop, dopamine; dob, dobutamine; epi, epinephrine; norepi, norepinephrine; RS, respiratory support.

Table 2: Multiple organ dysfunction (MOD) score.[19]

Organ system	0	1	2	3	4
Respiratory (PO_2/FiO_2 ratio)	> 300	226-300	151-225	76-150	≤75
Renal (serum creatinine) (μmol/L)	≤ 100	101-200	201-350	351-500	> 500
Hepatic (serum bilirubin) (μmol/L)	≤ 20	21-60	61-120	121-240	> 240
Cardiovascular (R/P ratio)	≤ 10.0	10.1-15.0	15.1-20.0	20.1-30.0	> 30.0
Hematologic (platelet count) (10^9/L)	> 120	81-120	51-80	21-50	≤ 20
Neurologic (Glasgow Coma Score)	15	13-14	10-12	7-9	≤ 6

Primary MODS develops after the direct injury of the organ and this damaging factor can be easily defined. Secondary MODS develops as the result of systemic inflammatory response syndrome (SIRS), when the balance of pro-inflammatory and anti-inflammatory factors is greatly impaired.[1] International Sepsis Definition Conference, supported by SCCM, ACCP, European Society of Intensive Care Medicine (ESICM), American Thoracic Society (ATS) and Surgical Infection Society (SIS) have not made any corrections in the definitions of sepsis, severe sepsis and MODS, but have developed criteria for both, because sepsis is a leading cause of MODS. Variables for organ dysfunction are the following:

1. Arterial hypoxemia (PaO_2/FiO_2 < 300);
2. Acute oliguria (urine output < 0.5 mL/kg/h or 45 mmol/L for at least two hours;
3. Creatinine increase > 0.5 mg/dL;
4. Coagulation abnormalities (INR > 1.5 or aPTT > 60 sec);
5. Ileus (absent bowel sounds);
6. Thrombocytopenia (platelet count < 100,000/ μL);
7. Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 mmol/L).[2]

Epidemiology of severe sepsis as of the main cause of MODS varies a lot throughout the world from, 13 to 300 cases per 100,000 population per year for severe sepsis and 11 per 100,000 population for septic shock with the mortality rates of up to 50% in severe sepsis and 80% in septic shock.[3] Incidence of severe sepsis in Europe is 66-114 per 100,000 population per year.[4-6] Prevalence of pediatric severe sepsis in USA in 2005 were 0.89 per 1000 population with the highest incidence in newborns (9.7 per 1000 population).[7] MODS is observed in up to 40% of adult patients admitted to the intensive care unit (ICU)[8,9] and in up to 56% of children admitted to the ICU.[10,11] Mortality on these cases can reach 50% both in pediatric and adult patients.[10,11,12]

Analgesia in such group of patient is very challenging and becomes more complicated with the increase of the number of organ's failure. There is also no clear guidelines for pain management in this group of patients. In this article we will focus on the modalities of analgesia, which can be used in different types of organ failures and try to combine available data into the algorithm, which can be used in MODS

METHODOLOGY

We performed a search of literature from 1984 to 2018 years in Google Scholar, PubMed, Medline, Embase, and Cochrane. Data from 45 articles devoted to the problems of MODS, severe sepsis, heart, liver and renal failures, coagulation disorders and pain management were accumulated and synthesized in the article.

Table 3: Pediatric Logistic Organ Dysfunction (PELOD) System[22]

Variable	Severity Level Score				
	0	1	2	3	4
Age	Systolic blood pressure (mmHg)				
< 1 month ≥ 1 month < 1 year ≥ 1 year < 12 years ≥ 12 years	> 65 > 75 > 85 > 95	55-65 60-75 70-85 80-95	40-54 40-59 55-69 65-79	35-39 35-39 45-54 55-64	35 35 45 55
Glasgow coma score	12-15	7-11	4-6	3	
Serum glutamic oxaloacetic transaminase (IU/l)	≤ 80	81-949	≥ 950		
Prothrombin time % of standard	> 60	20-60	< 20		
White blood cell count (10^9/L)	≥ 4.5	1.5-4.4	< 1.5		
$PaCO_2$ (mmHg)	≤ 90	> 90			
Pupillary reactions	Both reactive	Both fixed			
Heart rate (Beats/min) < 12 years ≥ 12 years	≤ 195 ≤ 150	> 195 > 150			
PaO_2/FiO_2 ratio	> 70	≤ 70			
Mechanical ventilation	No	Yes			
Creatinine (μmol/L)					
< 7 days ≥ 7 days < 1 year ≥ 1 year < 12 years ≥ 12 years	< 140 < 55 < 100 < 140	≥ 140 ≥ 55 ≥ 100 ≥ 140			
Bilirubin (μmol/L)	≤ 85	> 85			
Platelet count (10^9/L)	≥ 35	< 35			

PATHOPHYSIOLOGY

Endothelium occupies a key position in the pathogenesis of sepsis through the regulation of vasomotor tone, cellular trafficking, coagulation, balance of pro- and anti-inflammatory factors.[13] Shapiro et al.[14] demonstrated correlation between the sepsis severity and soluble fms-like tyrosine kinase-1 (sFlt-1), plasminogen activator inhibitor-1 (PAI-1), soluble E-selectin, soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM). Levels of renin-angiotensin system (RAS) mediators increase in sepsis and correlated with organ failure.[15]

Studies in children have defined three pathobiological phenotypes in multiple organ failure (MOF): immune paralysis associated MOF, thrombocytopenia associated MOF, sequential MOF with new hepatobiliary dysfunction. Children with the first phenotype are unable to clear infections. They have decreased TNF response and increased systemic IL-6 and IL-10. Children with the second phenotype have hyperinflammation due to the hyper activation of complement and necrosis due to the thrombosis caused by disseminated intravascular coagulation. Children with the third phenotype fail to clear viral infections or induce apoptosis of activated immune cells. Viral infections in these children cause sFasl-mediated liver injury.[16]

Another study had also defined phenotypic clusters within sepsis-associated MODS. These clusters are shock with renal dysfunction, minimal MODS, shock with hypoxemia and altered mental status, hepatic dysfunction. Associations of these clusters with underlying pathology were not proved. And according to the study's data they represent the clinical course and severity of sepsis.[17]

ASSESSMENT OF MODS SEVERITY AND RISKS

Assessment of MODS and risk of its development is very important for the proper management of MODS itself and underlying pathology. Definition of types of failures present in particular case is of a great importance in the adequate choice of the analgesia methods.

Organ dysfunction in adults can be assessed according to Sequential Organ Failure Assessment (SOFA) score,[18] definitions of Marshal,[19] Logistic Organ Dysfunctions system (LODS)[20] and Denver Post Injury Multiple Organ Failure Score.[21]

LODS use additional parameters for the assessment of each system failure. For renal system it uses additionally serum urea or serum urea nitrogen unlike two other scales represented above. For hematologic system, additional parameter is a white blood cell (WBC). For the assessment of liver function, it also uses prothrombin time.[20] Other parameters are included in other scales.

Pediatric Multiple Organ Dysfunction (PEMOD) and Pediatric Logistic Organ Dysfunction (PELOD) Systems are used for the MODS assessment in pediatric patients.[22]

Risk factors for the MODS development in ICU include resistant pathogen, presence of shock, total parenteral nutrition, APAHCE II score.[23] Risks of the ICU mortality in patients with sepsis: presence of nosocomial infection, 3rd day SOFA score, presence of shock, sedative agent infusion, total parenteral nutrition.[23] MODS risk factors for stroke patients are NIHSS score at admission and infarction in

Table 4: Modified doses of analgesics in patients with renal impairment.[40]

Analgesic drug	GFR > 50	GFR 10-50	GFR < 10
Paracetamol (acetaminophen)	100% of normal dose each 4 h	100% of normal dose each 6 h	100 % of normal dose each 8 h
Aspirin (avoid if possible)	100%	100%	avoid
Tramadol	100%	50%	50% each 12 h
Codeine (avoid if possible)	100% of normal dose each 6 h	75% of normal dose each 8 h	50% of normal dose each 12 h
Fentanyl	100% of normal dose	75% of normal dose	50% of normal dose
Methadone	100%	100%	50-75%
Hydromorphone	100%	75%	50% each 6-8 h
Oxycodone	100%	75%	50%
Morphine (avoid if possible)	100%	75%	50%

multivascular territories.[24]

Mortality risk in the ICU is increasing with the increasing of number organ's failure and starting from 11-14% for patients with 1 failed system and reaching up to 75% for patients with more than 4 systems involved. The highest mortality risk was observed in patients with liver failure. Renal, lung, heart and coagulation failures have similar odds ratios. But cardiovascular and respiratory failures were observed in a bigger number of patients, followed by renal failure, coagulation disorders and liver failure.[25]

PAIN MANAGEMENT IN MODS

As we can conclude from the data above, involvement of different organs is possible in MODS, which can create different combinations of organic failures and dysfunctions in each case. That makes a creation of unified approaches for the pain management in these patients difficult. We will try to accumulate all data available on different types of organic failure and combine them into the simple algorithm.

Pain management in heart failure

Non-steroidal anti-inflammation drugs (NSAIDs) should be avoided or withdrawn according to the American College of Cardiology Foundation/ American Heart Association HF guidelines due to their adverse cardiac effects.[26] Negative cardiac effects of NSAIDs occur due to the retention of sodium and water, increased vascular resistance and worse response to diuretics. Both selective and non-selective cyclooxygenase (COX) inhibitors cause deterioration in HF symptoms, increase risks of hospitalization and cardiovascular events.

Ketamine has negative inotropic effects and stimulates central sympathetic nervous system. Negative inotropic effect is stronger than sympathetic stimulation in patients with decreased LV function, which cause deterioration in cardiac performance. So, use of ketamine is also not recommended in HF.

Pregabalin use was associated with the incidence of peripheral edema, which occurred probably due to the L-type calcium channel block. Data on the effects of pregabalin in patients with HF is limited, nevertheless FDA recommends its cautious use in patients with NYHA class III and IV HF.

Tricyclic antidepressants (TCAs) have peripheral antiadrenergic action, negative inotropic and α-adrenergic blocking effects. They prolong atrioventricular conduction, QRS and QTc intervals. Some case reports linked TCA to cardiomyopathy development, but the long-term data of TCAs use in HF patients is limited.[27] This class of drugs should also be used with caution in patients with HF.

Pain management in liver failure

Acetaminophen is one of the modalities, which can be used in patients with hepatic failure despite its known adverse events. Half-life of acetaminophen is twice longer than in healthy subjects, but no renal or hepatic adverse events were determined in the dose of < 4 g/d of acetaminophen.[28,29] Doses of 2-3 g/d considered to be safe in patients with known liver disease, who are not consuming alcohol.[30] For those who consume alcohol doses of < 2 g is considered to be safe. Still the data on the topic is limited.

NSAIDs: Data on their safety is limited. As NSAIDs are mostly metabolized in the liver by cytochromes P (CYP) and bound with proteins actively, their plasma concentrations will be elevated in patients with severe hepatic failure.[31] Use of NSAIDs in patients with liver failure can be accompanied by the development of hepatorenal syndrome, and gastrointestinal bleeding.[32,33]

Opioid analgesics are metabolized mainly in the liver, so their biotransformation can be greatly impaired in liver disease. Half-life of morphine is doubled in patients with cirrhosis, when compared to healthy controls, and consists 3 to 4 hours.[34] Codeine, hydrocodone, oxycodone are metabolized by the system of cytochromes, so their serum levels can vary a lot in patients with liver disease. Meperidine, methadone and fentanyl bound heavily with proteins,

Table 5: Simple algorithm of pain management in combined organ failures

STEP 1 – MILD PAIN	
No failures	Acetaminophen ≤ 4 g/d NSAIDs standard dosing
Heart failure and/or coagulation disorders	Acetaminophen ≤ 4 g/d
Liver failure and/or renal failure (eGFR: > 50 mL/min/1.73m^2)	Acetaminophen 2-3 g/d
Renal failure, eGFR: 10 - 50 mL/min/1.73m^2 + any failures	Acetaminophen ≤ 2 g/d
Renal failure, eGFR: < 10 mL/min/1.73m^2 + any failures	Acetaminophen ≤ 1.5 g/d
STEP 2 – MODERATE PAIN	
No failures and/or heart failure and/or coagulation disorders and/or renal failure (eGFR: > 50 mL/min/1.73m^2)	Tramadol 50 mg each 6 h
Renal failure, eGFR: 10 - 50 mL/min/1.73m^2 + other failures (except liver failure)	Tramadol 25 mg q 6 h
Liver failure + any failure (except Renal failure, eGFR: < 10 mL/min/1.73m^2)	Tramadol 25 mg q 8 h
Renal failure, eGFR: < 10 mL/min/1.73m^2 + any failure	Tramadol 25 mg q 12 h ± Acetaminophen according to Step 1
STEP 3 – SEVERE PAIN	
No failures and/or heart failure and/or coagulation disorders and/or renal failure (eGFR: > 50 mL/min/1.73m^2)	Fentanyl 2-5 μ/kg/h
Renal failure, eGFR: 10 - 50 mL/min/1.73 m^2 + other failures (except liver failure)	Fentanyl 75 % of normal dose
Renal failure, eGFR: < 10 mL/min/1.73 m^2 + any failure	Fentanyl 50 % of normal dose
Liver failure + any failure	Fentanyl 12.5 μg topically every 72 h ± Acetaminophen according to Step 1

so they require dose adjustment in patients with liver disease.[35] Tramadol is also considered a safer option in patients with liver disease.

TCAs undergo biotransformation in the liver with first-pass effects. These should be carefully up-titrated, because of their possible adverse effects. Nortryptiline and desipramine have less sedative effect, cause less tachycardia and hypotension and should be used as a safer option in patients with liver disease.[36]

Anticonvulsants are used in the treatment of neuropathic pain. Carbamazepine has hepatotoxic effect and should be avoided in patients with liver disease. Gabapentin and pregabalin are not metabolized by liver and have weak bound with proteins and can be used in patients with liver failure.[37]

Treatment algorithm for musculoskeletal or visceral pain in liver disease:
1) Acetaminophen ≤ 2-3 g/d;
2) Tramadol 25 mg q8h;
3) Hydromorphone 1 mg q4h or fentanyl 12.5 μg topically q72 h.

Treatment algorithm for neuropathic pain in liver disease:
1) Nortryptiline 01 mg orally at night or
2) Desipramine 10 mg orally at night or/and
3) Gabapentin 300 mg orally daily or
4) Pregabalin 150 mg orally twice daily and
5) Acetaminophen ≤ 2-3 g/d.[38]

Pain management in renal failure

According to the recent guidelines the use of estimated glomerular filtration rate (eGFR) is preferred in the assessment of renal failure, but it has certain limitations in the presence of edema, low protein levels and acute renal failure.

Opioids: Morphine and codeine (undergoes biotransformation to morphine) have increased risks of adverse events in patients with renal dysfunction. Tramadol is excreted predominantly in the urine and so has a prolonged half-life in renal failure. Fentanyl is eliminated by kidneys, but none of the metabolites have significant pharmacological activity. Methadone is not dependent on kidney excretion. So, recommended opioids for pain management according to recent guidelines are tramadol, methadone and fentanyl.[39,40]

Acetaminophen can be used for pain management with the dose adjustment according to the eGFR.

NSAIDs should be avoided if possible in renal failure.

Anticonvulsants. Gabapentin and pregabalin can be used for the treatment of neuropathic pain in patients with renal failure, but dose adjustment is required according to eGFR. Gabapentin doses for eGFR 50-70 mL/min/1.73 m^2 is 600 mg TID, eGFR 30-49 mL/min/1.73 m^2 – 300 mg TID, eGFR 15-29 mL/min/1.73 m^2 – 300 mg BID, eGFR < 15 mL/min/1.73 m^2 – 300 mg daily. Pregabalin doses for eGFR > 30 mL/min/1.73 m^2 – 150 mg BID, eGFR 15-29 mL/min/1.73 m^2 – 150 mg every other day, < 15 mL/min/1.73 m^2 – 75 mg.[41]

Pain management and coagulation

There is a little data available on analgesia in patients with coagulation disorders in settings of ICU. There is some data available in pain management in patients with hemophilia. As in both cases we are afraid of bleeding, contraindications should be common in coagulation disorders in settings of ICU.

Acetaminophen is preferred first line agent for adults and children with hemophilia and chronic pain.[42] COX-2 selective inhibitors can be used for pain management in settings of hemophilia.[42] Aspirin should not be used in patients with hemophilia.[43]

Opioids. Tramadol can be used as the second step in pain management in such patients.[42] Oxycodone, fentanyl, morphine or hydromorphone.[44]

Simple algorithm of pain management

We suggest an algorithm for pain management in patients with the combination of different organ failures according to the available data. This algorithm includes three steps of pain management represented at WHO pain scale.[45] (Table 5)

SUMMARY

There is no data on pain management in MODS, because MODS can include combinations of failures or dysfunctions of different organs and systems. We covered issues of MODS epidemiology and incidence of different dysfunctions and failures of organs, which can be part of MODS. Highest mortality was associated with the development of liver failure, followed by heart and renal failure, and coagulation disorders. In the article, we covered problems of pain management of each of these failures as a part of MODS and suggested simple algorithm of pain management according to the available resources.

Despite a large number of analgesic agents available, most of them have adverse effects, undesirable or dangerous in different types of failures, which can be a part of MODS. According to the data of different studies, acetaminophen can be considered as a safe drug for the pain management with the proper dose adjustment according to the liver function or eGFR. Acetaminophen can be used in the treatment of mild pain.

Safe option for the treatment of moderate pain is tramadol as there is no data on its negative effects in most organic failures. It can be used in the combination with acetaminophen. Dose adjustment is required both in liver and renal failures.

Fentanyl can be used for the severe pain management. It can be combined with acetaminophen. Doses should be adjusted in renal failure. Topical use is preferred in liver failure.

In authors opinion local anesthesia should be used if applicable, except coagulation disroders.

We accumulated available data and tried to create an algorithm for pain management in patients with MODS, which can be used in patients with different combinations of failures. It needs validation by further investigation performed in different populations and at different centers.

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