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**Midodrine therapy for vasopressor dependent shock in the intensive care unit: A protocol for a systematic review and meta-analysis**

| Journal: | *BMJ Open* |
| --- | --- |
| Manuscript ID | bmjopen-2022-064060 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 16-May-2022 |
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| Keywords: | INTENSIVE & CRITICAL CARE, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, ORAL MEDICINE |
Midodrine therapy for vasopressor dependent shock in the intensive care unit: A protocol for a systematic review and meta-analysis

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Word Count 2185 Tables 0 Figures 0 Additional Files 1

Keywords: Critical Care; Intensive Care Unit; Midodrine; Vasopressors; Shock
Abstract (218 words):

Introduction: Intensive care unit (ICU) lengths of stay are modified by ongoing need for hemodynamic support in critically ill patients. This is most commonly provided by intravenous (IV) vasopressor therapy. Midodrine has been used as an oral agent for hemodynamic support in patients with orthostatic hypotension or cirrhosis. However, its efficacy in treating shock in the ICU, particularly for patients weaning from IV vasopressors, remains uncertain. The objective of this systematic review is to determine the efficacy of midodrine in vasopressor dependent shock.

Methods and analysis: We will search Ovid MEDLINE, Ovid Embase, CINAHL, and Cochrane Library for observational trials and randomized control trials (RCTs) evaluating midodrine in critically ill patients. We will also review unpublished data and relevant conference abstracts. Outcomes will include ICU length of stay, duration of IV vasopressor support, ICU mortality, hospital mortality, hospital length of stay and rates of ICU readmission. Data will be analyzed in aggregate, where appropriate. We will evaluate risk of bias using the modified Cochrane tool and certainty of evidence using GRADE methodology. We will perform trial sequential analysis for the outcome of ICU length of stay.

Ethics and dissemination: Ethics approval is not required as primary data will not be collected. Findings of this review will be disseminated through peer-related publication and will inform future clinical trials.

Trial Registration: PROSPERO, CRD42021260375
Article Summary

Strengths and Limitations

- Strengths of our review include the inclusion of the MIDAS trial, pre-planned subgroup analysis of different shock etiologies, patients with cirrhosis and AKI, broad inclusion criteria; planned sequential trial analysis and usage of GRADE to assess certainty of evidence.

- Several important limitations remain. First, lack of standardization of midodrine dosing protocols which may not always be in keeping with product monographs and difficulties in aggregate data analysis. We will ensure that we are transparent with reporting drug dosing protocols for our studies and ensure that aggregate study analysis only involves similar dosing protocols.

- Studies have previously included differing etiologies of shock, and this may lead to a heterogeneous patient population. We have addressed by including an a priori subgroups to evaluate the effectiveness of midodrine for shock across subsets of shock and based on pre-existing patient characteristics.

- Finally, while there are many trials that previously evaluated midodrine for IV vasopressor dependent shock, results are conflicting. This has led to uncertainty regarding midodrine use in undifferentiated shock in the ICU. Our sequential trial analysis will provide the necessary methodology for better control of type I and type II errors than traditional meta-analysis and reduce spurious conclusions from previously conducted studies.

Background

Shock is a common reason for ICU admission which often requires IV vasopressor support.[1-3] Vasopressor agents such as norepinephrine, vasopressin and epinephrine are recommended in
However, as patients recover from their critical illness and require less other physiological support, the use of IV vasopressors may be their only indications for ongoing intensive care unit (ICU) admission. This may prolong their ICU length of stay (LoS) and lead to ICU capacity strain. To date, there are no clear guidelines on starting adjuvant oral therapies to help wean off vasopressor therapy in the resolving phases of shock. These resolving phases can include hypotension with no signs of tissue hypoperfusion or end organ damage. Establishing an effective oral adjunctive therapy could reduce need for invasive hemodynamic monitoring in titrating IV vasopressors and could liberate these patients earlier from the ICU.

Midodrine is an oral alpha agonist that is currently indicated in patients with orthostatic hypotension, intradialytic hypotension, and blood pressure management in cirrhosis and hepatorenal syndrome.[7-12] Prior work has assessed midodrine efficacy in critically ill patients with mixed results. Earlier trials have demonstrated reduced duration of IV vasopressor therapy and a decreased ICU length of stay with midodrine therapy.[13, 14] However, this data is not supported by more recent studies.[15] The most recent trial investigating the use of midodrine in critically ill patients, the MIDAS study, found no difference between placebo and midodrine groups in IV vasopressor duration or ICU LoS.[16] However, this study had several important limitations including small size and prolonged recruitment period, which may reflect a participant selection bias and being underpowered to detect a significant difference between groups. While a recently published meta-analysis examining the role of midodrine in resolving shock did not find any difference in IV vasopressor duration, ICU or hospital lengths of stay or mortality, the review did not provide any subgroup analysis or use GRADE recommendations or trial sequential analysis methods.[17] Further, it was conducted prior to the publication of most recent evidence.

Objectives
Accordingly, we aim to conduct a systematic review and meta-analysis on the use of midodrine for IV vasopressor dependent shock in the ICU. We hypothesize that the use of midodrine in critically ill patients will lead to decreased ICU length of stay. We will plan to conduct subgroup analysis on select patient populations that have traditionally benefitted from this therapy, including those patients with cirrhosis and acute kidney injury (AKI), and will perform sequential trial analysis for the outcome of ICU length of stay.

**Methods**

**Patient and public involvement**

No patient or public were involved in this systematic review and meta-analysis.

**Study Design**

We will perform a systematic review of observational and randomized controlled studies. Meta-analysis will be performed on observational and randomized controlled studies separately, as appropriate.

**Study registration**

In accordance with PRIMA-P guidelines, this systematic review is registered with the International Prospective Register of Systematic Reviews (CRD42021260375; July 16, 2021).

**Data source and search methods**

A search strategy was developed in consultation with a research librarian and independently peer-reviewed by a second librarian (Appendix 1).[18] We will search the following electronic databases: Ovid MEDLINE, Ovid Embase, CINAHL, and Cochrane Library (via Wiley) from inception until current date. We will combine search terms related to shock (i.e., hypotension requiring vasopressors), vasopressors (i.e., norepinephrine, epinephrine, vasopressin, phenylephrine), intensive care (i.e., involving any ICU setting) and midodrine.
Additional search sources: we will search unpublished literature through trial registry platforms (ClinicalTrials.gov) and Google Scholar. We will also search for meeting abstracts from the past 2 years, where available, using Conference Proceedings Citation Index (Clarivate Analytics), and by hand-searching published proceedings from the following associations: Society of Critical Care Medicine, European Society of Intensive Care Medicine, International Symposium of Intensive and Emergency Medicine. We will export search results into Covidence (www.covidence.org).

Eligibility criteria

We will include studies if they meet the following eligibility criteria: 1) include patients with vasopressor dependent shock, 2) are performed in the intensive care (i.e., intended to refer to patients admitted to an ICU setting capable of providing vasopressor therapy), 3) evaluate oral midodrine therapy as compared to placebo or usual care and 4) evaluate one of our outcomes of interest. We will include both adult and pediatric studies, all dosing regimens and titration protocols for midodrine, and etiologies of vasopressor dependent hypotension. We will only include observational studies and RCTs; we will review previous systematic reviews, narrative reviews and meta-analyses to ensure we have captured all relevant studies. We will also review relevant conference abstracts and proceedings.

Outcome measures

Outcomes will include: 1) ICU total length of stay; 2) duration of IV vasopressor therapy, 3) hospital length of stay, 4) ICU mortality, 5) hospital mortality, 6) rates and duration of physiological support, 7) rates of ICU readmission, 8) clinically important adverse events. Where possible, this will be determined from decision of ICU discharge and will include total time from ICU admission. Physiological support will include: (a) rate of Invasive mechanical ventilation (IMV), b) duration of IMV, c) Rate of non-invasive ventilation (NIV), d) duration of
NIV, e) rate of renal replacement therapy (RRT), f) duration of RRT). Adverse events will include: (a) bradycardia, b) hypertension, c) cardiac ischemia, d) limb ischemia.

**Screening And Data Extraction**

We will identify eligible studies in a two staged process. In the first phase, at least two investigators will independently review the titles and abstracts of all retrieved citations. Disagreements will be resolved through discussion by the two assessors, then adjudicated by a third author as needed. In the second phase, the same two reviewers will screen full texts for eligibility using a pre-developed tool. We will resolve any disagreements in this second stage using discussion and third-party adjudication if needed. We will capture reasons for exclusion at this second stage and produce a PRISMA flow chart demonstrating the screening process.

We will extract data in duplicate and independently using standardized data abstraction forms. We will extract the following specific variables: patient characteristics, age, sex, type of ICU, etiology of shock, number of patients, study inclusion and exclusion criteria and geographical location. We will also capture the type, dose and duration of IV vasopressors, any co-intervention used (i.e., steroids use; type and amount of intravenous fluids) in either the intervention or comparator groups, and outcome data.

**Risk of Bias assessment**

We will assess risk of bias using the modified Cochrane tool for randomized controlled trials (https://www.evidencepartners.com/resources/methodological-resources/tool-to-assess-risk-of-bias-in-randomized-controlled-trials-distillersr). We will use Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework to evaluate certainty in pooled outcome data based on risk of bias, imprecision, inconsistency, indirectness, and publication bias. Based on these domains, certainty will be assessed between very low, low, moderate and high.
Data analysis

Continuous data will be presented means and standard deviations (SD), or medians and interquartile ranges (IQR), and compared (where appropriate) using a t-test or Wilcoxon rank sum test. Categorical variables and proportions will be compared using the Pearson’s Chi-Square or Fischer’s exact tests as appropriate. We will summarize the eligible studies in terms of point estimates or proportions, with p-values or 95% confidence intervals [CIs], where appropriate. We will perform meta-analyses using RevMan version 5.4 software (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration 2014). Outcomes of interest will include lengths of ICU and hospital stays, ICU and hospital mortality and duration of IV vasopressor use. We will use the method of DerSimonian and Laird to pool effect sizes for each outcome under a random-effects model for all outcomes of interest[19]. Study weights will be calculated using the inverse variance method. We will present the results as relative risk (RR) with 95% confidence intervals (CIs) for dichotomous outcomes[20] and mean difference (MD) for continuous outcomes. We will assess heterogeneity using the I^2 statistic, the χ^2 test for homogeneity (p <0.1 for significance of substantial heterogeneity), and visual inspection of the forest plots. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. We will assess for publication bias using Begg’s funnel plots if there are 10 or more studies per outcome.

Sequential Trial Analysis

We will conduct Trial Sequential Analysis (TSA) using a random effects model for ICU LoS. For the TSA, we will use a statistical significance level of 5%, a power of 80% and a relative risk reduction of 10% to represent a clinically important difference. We will use a model variance-based heterogeneity correction and perform analysis using Trial Sequential Analysis v.0.9.5.10 beta software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigs Hospital, Copenhagen, Denmark)[21].
Subgroup Analyses

Where a sufficient number of trials are available (i.e., greater than 3 studies), we will conduct the following pre-specified subgroup pooled analyses (hypothesized direction of effect in parentheses):

- Septic shock vs. non-septic shock (hypothesis: septic shock would have improved outcomes with midodrine, compared to non-septic shock).
- Surgical vs. non-surgical patients (hypothesis: surgical patients will have improved outcomes with midodrine, compared to non-surgical patients).
- Cirrhotic vs. non-cirrhotic patient shock (hypothesis: cirrhotic would have improved outcomes with midodrine, compared to non-cirrhotic shock).
- AKI vs. non-AKI patients (hypothesis: non-AKI would have improved outcomes with midodrine, compared to AKI patients).
- Age greater or less than 65 years (hypothesis: younger patients will have improved outcomes with midodrine compared to those older than 65 years).

If subgroups effects are credible, we will present the outcomes separately for each subgroup. We will use ICEMAN tool to assess credibility[22].

Discussion

ICU admission is typically required for either monitoring or physiologic support. When hemodynamic support is required, IV vasopressors are the mainstay in treatment of septic and other forms of shock. Norepinephrine has been accepted to be the first choice in treatment of septic shock, according to the latest Surviving Sepsis Campaign[4]. Second line treatments include vasopressin and epinephrine. However, IV vasopressor therapy typically requires central-line insertion and maintenance to minimize complications[23]. Ongoing need of IV vasopressor therapy necessitates ongoing ICU admission, which may be prolonged in slow to recover shock.
Oral agents have been proposed to be an option to shorten duration of IV vasopressor therapy and decrease ICU length of stay. Midodrine is one such agent and has been previously studied[13-17, 24-27].

There have been several previous trials evaluating midodrine as an IV vasopressor sparing agent. While there have been previous reviews of these studies, a major limitation has been the lack of large, prospective, randomized controlled trials evaluating midodrine in critically ill patients.

Recently, the MIDAS trial randomized 136 undifferentiated hypotensive patients to either midodrine or placebo evaluating the median time from study drug initiation until discontinuation of IV vasopressors. The study investigators determined that there was no significant difference between groups. While there exist several methodological concerns with this study (i.e., no change with baseline blood pressure in either group; no details regarding fluid management; only 3 sites from 2 countries; sample size calculation based on only small study data; lack of requirements of other organ supports; and 7-year recruitment period indicating potential selection bias), it is the largest RCT evaluating the effects of midodrine for critically ill patients and will be important to include in any future review (8). Further, previous studies have not included any a priori subgroup analysis and our review will be evaluating the use of midodrine specifically in patients with known cirrhosis as well as with acute kidney injury. Finally, we will be conducting a sequential trial analysis in order to evaluate the evidence of midodrine as it relates to ICU lengths of stay and adjust thresholds for significance if insufficient sample size is reached in our identified RCTs in our meta-analysis.

**Conclusion**

Our systematic review and meta-analysis aim to evaluate the role of midodrine in the treatment of vasopressor dependent shock in the ICU. This, along with our planned subgroup analyses, will inform on the optimal use of midodrine for critically ill patients. We anticipate our systematic
review will inform future RCTs and eventual evidence-based clinical practice guidelines on the
optimal circumstances to initiate midodrine therapy in the ICU.

**Ethics Approval:** This systematic review will only utilize publically accessible documents as
evidence and therefore does not require institutional ethics approval.

**Funding:** Funding is provided by the University of Alberta Hospital Foundation Kaye Fund

**Role of Funders:** The funder had no role in development of the study protocol, drafting of the
manuscript or decision to submit the work for publication.

**Competing interests:** We confirm there are no conflicts of interest associated with this
publication and there has been no significant financial support for this work that could have
influenced its outcome.

**Author contributions:** MK contributed to study protocol development and drafting of the
manuscript, DO, NB, JS, KF, JK, VL, EM, JS, WS and XW contributed to study protocol
development and critical revision of the manuscript, SB and OR conceived the study, developed
the protocol and contributed to development and drafting of the manuscript. All of the authors
approved the final version to be published.

**Data sharing statement:** No additional data available.

**Word count:** 2354 words
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## Appendix 1. Search Strategies

| Database                  | Search Strategy                                                                 |
|---------------------------|---------------------------------------------------------------------------------|
| **MEDLINE**               | 1. midodrine.mp.                                                                |
| Ovid MEDLINE(R) ALL 1946 to February 24, 2022 | 2. exp Shock/                                                                  |
|                           | 3. exp Shock, Septic/                                                           |
|                           | 4. (shock or sepsis).mp.                                                       |
|                           | 5. (hypoperfusion or hypo-perfusion or hypotension or hypo-tensi* or hypotensive or anti-hypotensi* or anti-hypotensi*).mp. |
|                           | 6. exp Catecholamines/ or exp Dobutamine/ or exp Epinephrine/ or exp Felypressin/ or exp Norepinephrine/ or exp Orciprenaline/ or exp Phenylephrine/ or exp Vasopressins/ |
|                           | 7. (adrenaline or argipressin or catecholamine* or desmopressin or dobutamine or dopamine or epinephrine or felypressin or glypressin or lypressin or noradrenaline or norepinephrine or ornipressin or orciprenaline or phenylephrine or terlipressin or vasoconstrictor* or vaso-constrictor* or vasopressin* or vasopressor* or vaso-press* or vasostrict).mp. |
|                           | 8. exp Vasoconstrictor Agents/                                                 |
|                           | 9. or/2-8                                                                       |
|                           | 10. critical care.mp.                                                           |
|                           | 11. critical* ill*.mp.                                                          |
|                           | 12. (intensive care or ICU).mp.                                                |
|                           | 13. Emergency Treatment/ or Emergency Medicine/ or Emergency Medical Services/ or Emergency Service, Hospital/ or Trauma Centers/ or exp Evidence-Based Emergency Medicine/ or exp Emergency Nursing/ or Emergencies/ |
|                           | 14. (emergenic* or casualty department*).mp.                                    |
|                           | 15. ((emergenc* or ED) adj1 (room* or accident or ward or wards or unit or units or department* or physician* or doctor* or nur* or treatment* or visit*)).mp. |
|                           | 16. (trauma adj1 (cent* or care)).mp.                                           |
|                           | 17. or/10-16                                                                   |
|                           | 18. 1 and 9 and 17                                                             |
| **Embase**                | 1. midodrine.mp.                                                                |
| Ovid Embase 1974 to 2022   | 2. exp shock/                                                                  |
|                           | 3. exp septic shock/                                                           |
|                           | 4. (shock or sepsis).mp.                                                       |
|                           | 5. (hypoperfusion or hypo-perfusion or hypotension or hypo-tensi* or hypotensive or anti-hypotensi* or anti-hypotensi*).mp. |
|   |   |
|---|---|
| 6. | exp catecholamine/ or exp dobutamine/ or exp epinephrine/ or exp felypressin/ or exp norepinephrine/ or exp orciprenaline/ or exp phenylephrine/ or exp vasopressin derivative/ |
| 7. | (adrenaline or argipressin or catecholamine* or desmopressin or dobutamine or dopamine or epinephrine or felypressin or glypressin or lypressin or noradrenaline or norepinephrine or ornipressin or orciprenaline or phenylephrine or terlipressin or vasoconstrictor* or vaso-constrictor* or vasopressin* or vasopressor* or vaso-press* or vasostrict).mp. |
| 8. | exp vasoconstrictor agent/ |
| 9. | or/2-8 |
| 10. | critical care.mp. |
| 11. | critical* ill*.mp. |
| 12. | (intensive care or ICU).mp. |
| 13. | emergency treatment/ or emergency medicine/ or emergency health service/ or hospital emergency service/ or exp evidence based emergency medicine/ or exp emergency nursing/ or emergency/ |
| 14. | (emergent* or casualty department*).mp. |
| 15. | (((emergenc* or ED) adj1 (room* or accident or ward or wards or unit or units or department* or physician* or doctor* or nurs* or treatment* or visit*)).mp. |
| 16. | (trauma adj1 (cent* or care)).mp. |
| 17. | or/10-16 |
| 18. | 1 and 9 and 17 |

### CINAHL

- **S1**: midodrine
- **S2**: (MH "Shock+")
- **S3**: (MH "Shock, Septic+")
- **S4**: shock or sepsis
- **S5**: hypoperfusion or hypo-perfusion or hypotension or hypo-tensi* or hypotensive or antihypotensi* or anti-hypotensi*
- **S6**: (MH "Catecholamines+")
- **S7**: (MH "Dobutamine")
- **S8**: (MH "Epinephrine+")
- **S9**: (MH "Norepinephrine")
- **S10**: (MH "Orciprenaline")
- **S11**: (MH "Phenylephrine")
- **S12**: (MH "Vasopressins+")
- **S13**: adrenaline or argipressin or catecholamine* or desmopressin or dobutamine or dopamine or epinephrine or felypressin or glypressin or lypressin or noradrenaline or norepinephrine or ornipressin or orciprenaline or phenylephrine or terlipressin or vasoconstrictor* or vasoconstrictor* or vasopressor* or vasopressor* or vasostrict).mp.
| S14 | (MH "Vasoconstrictor Agents+") |
| S15 | S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 |
| S16 | "critical care" |
| S17 | "critical* ill*" |
| S18 | "intensive care" or ICU |
| S19 | (MH "Emergency Treatment+") |
| S20 | (MH "Emergency Medicine") |
| S21 | (MH "Emergency Medical Services+") |
| S22 | (MH "Emergency Service+") |
| S23 | (MH "Trauma Centers") |
| S24 | (MH "Emergency Nursing+") |
| S25 | (MH "Emergencies+") |
| S26 | emergicent* or "casualty department*" |
| S27 | ((emergenc* or ED) N1 (room* or accident or ward or wards or unit or units or department* or physician* or doctor* or nurs* or treatment* or visit*)) |
| S28 | (trauma N1 (cent* or care)) |
| S29 | S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 |
| S30 | S1 AND S15 AND S29 |

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| Cochrane Library via Wiley |
|---------------------------|
| #1 | midodrine |
| #2 | [mh Shock] |
| #3 | [mh "Shock, Septic"] |
| #4 | shock or sepsis |
| #5 | hypoperfusion or hypo-perfusion or hypotension or hypo-tensi* or hypotensive or anti-hypotensi* or anti-hypotensi* |
| #6 | [mh Catecholamines] or [mh Dobutamine] or [mh Epinephrine] or [mh Felypressin] or [mh Norepinephrine] or [mh Orciprenaline] or [mh Phenylephrine] or [mh Vasopressins] |
| #7 | adrenaline or argipressin or catecholamine* or desmopressin or dobutamine or dopamine or epinephrine or felypressin or glypressin or lypressin or noradrenaline or norepinephrine or ornipressin or orciprenaline or phenylephrine or terlipressin or vasoconstrictor* or vaso-constrictor* or vasopressin* or vasopressor* or vaso-press* or vasostrict |
| #8 | [mh "Vasoconstrictor Agents"] |
| #9 | {OR #2-#8} |
| #10 | "critical care" |
| #11 | critical* NEXT ill* |
| #12 | "intensive care" or ICU |
|-----|------------------------|
| #13 | [mh ^"Emergency Treatment"] or [mh ^"Emergency Medicine"] or [mh ^"Emergency Medical Services"] or [mh ^"Emergency Service, Hospital"] or [mh ^"Trauma Centers"] or [mh "Evidence-Based Emergency Medicine"] or [mh "Emergency Nursing"] or [mh ^"Emergencies"] |
|     | emergicent* or (casualty NEXT department*) |
| #14 | ((emergenc* or ED) NEAR/1 (room* or accident or ward or wards or unit or units or department* or physician* or doctor* or nurs* or treatment* or visit*)) |
| #15 | (trauma NEAR/1 (cent* or care)) |
| #16 | {OR #10-#16} |
| #17 | #1 AND #9 AND #17 |

### Google Scholar

midodrine AND (shock OR sepsis OR hypoperfusion OR hypotension OR hypotensive OR antihypotension) AND ("critical care" OR critical illness OR "emergency department")
## PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA–P) 2015 statement. *Systematic Reviews* 2015 4:1

| Section/topic | # | Checklist item | Information reported | Page number(s) |
|---------------|---|----------------|----------------------|----------------|
| **ADMINISTRATIVE INFORMATION** |  |  | Yes | No | |
| Title |  | Identify the report as a protocol of a systematic review |  |  | 1 |
| Identification | 1a | Identify the report as a protocol of a systematic review, if possible | ☒ | ☐ | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such |  | ☒ | |
| Registration | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract |  | ☒ | 2 |
| Authors |  |  |  |  |  |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author |  |  | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | ☒ | ☐ | 1 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments |  | ☒ | 11 |
| Support |  |  |  |  | |
| Sources | 5a | Indicate sources of financial or other support for the review |  | ☒ | 11 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor |  | ☒ | 11 |
| Role of sponsor/sponsor | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | ☒ | ☐ | 11 |
| **INTRODUCTION** |  |  |  |  |  |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known |  | ☒ | 3, 4 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) |  | ☒ | 5 |

**METHODS**

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
| Section/topic       | #  | Checklist item                                                                                                                                                                                                 | Information reported | Page number(s) |
|--------------------|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|---------------|
| Eligibility criteria | 8  | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | ☒ ☐                  | 6            |
| Information sources | 9  | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | ☒ ☐                  | 5            |
| Search strategy    | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated                                      | ☒ ☐                  | Appendix 1    |
| **STUDY RECORDS**  |    |                                                                                                                                                                                                             |                       |               |
| Data management    | 11a| Describe the mechanism(s) that will be used to manage records and data throughout the review                                                                                                                | ☒ ☐                  | 6            |
| Selection process  | 11b| State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | ☒ ☐                  | 7            |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | ☒ ☐                  | 7            |
| Data items         | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications                                                             | ☒ ☐                  | 6            |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale                                                                              | ☒ ☐                  | 6            |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | ☒ ☐                  | 7            |
| **DATA**           |    |                                                                                                                                                                                                             |                       |               |
| Synthesis          | 15a| Describe criteria under which study data will be quantitatively synthesized                                                                                                                                     | ☒ ☐                  | 7            |
|                    | 15b| If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., \( I^2 \), Kendall’s tau) | ☒ ☐                  | 8            |
|                    | 15c| Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)                                                                                                            | ☒ ☐                  | 9            |
| Meta-bias(es)      | 16 | If quantitative synthesis is not appropriate, describe the type of summary planned                                                                                                                                 | ☒ ☐                  | N/A          |
| Confidence in cumulative evidence | 17 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)                                                                                     | ☒ ☐                  | 8            |
|                    |    | Describe how the strength of the body of evidence will be assessed (e.g., GRADE)                                                                                                                               | ☒ ☐                  | 7            |
# Midodrine therapy for vasopressor dependent shock in the intensive care unit: A protocol for a systematic review and meta-analysis

| Journal:          | BMJ Open                                      |
|-------------------|----------------------------------------------|
| Manuscript ID     | bmjopen-2022-064060.R1                       |
| Article Type:     | Protocol                                     |
| Date Submitted by the Author: | 18-Oct-2022                           |

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**Primary Subject Heading:** Intensive care

**Secondary Subject Heading:** Intensive care, Medical management, Pharmacology and therapeutics

**Keywords:** INTENSIVE & CRITICAL CARE, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, ORAL MEDICINE
Midodrine therapy for vasopressor dependent shock in the intensive care unit: A protocol for a systematic review and meta-analysis

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Word Count 2340 Tables 0 Figures 0 Additional Files 1
Keywords: Critical Care; Intensive Care Unit; Midodrine; Vasopressors; Shock

Abstract (223 words):

Introduction: Intensive care unit (ICU) lengths of stay are modified by ongoing need for hemodynamic support in critically ill patients. This is most commonly provided by intravenous (IV) vasopressor therapy. Midodrine has been used as an oral agent for hemodynamic support in patients with orthostatic hypotension or cirrhosis. However, its efficacy in treating shock in the ICU, particularly for patients weaning from IV vasopressors, remains uncertain. The objective of this systematic review is to determine the efficacy of midodrine in vasopressor dependent shock.

Methods and analysis: We will search Ovid MEDLINE, Ovid Embase, CINAHL, and Cochrane Library for observational trials and randomized control trials (RCTs) evaluating midodrine in critically ill patients from inception to April 21st 2022. We will also review unpublished data and relevant conference abstracts. Outcomes will include ICU length of stay, duration of IV vasopressor support, ICU mortality, hospital mortality, hospital length of stay and rates of ICU readmission. Data will be analyzed in aggregate, where appropriate. We will evaluate risk of bias using the modified Cochrane tool and certainty of evidence using GRADE methodology. We will perform trial sequential analysis for the outcome of ICU length of stay.

Ethics and dissemination: Ethics approval is not required as primary data will not be collected. Findings of this review will be disseminated through peer-related publication and will inform future clinical trials.

Trial Registration: PROSPERO, CRD42021260375
Article Summary

Strengths and Limitations

- Strengths of our review include the inclusion of the MIDAS trial, pre-planned subgroup analysis of different shock etiologies, patients with cirrhosis and AKI, broad inclusion criteria; planned sequential trial analysis and usage of GRADE to assess certainty of evidence.

- Several important limitations remain. First, lack of standardization of midodrine dosing protocols which may not always be in keeping with product monographs and difficulties in aggregate data analysis. We will ensure that we are transparent with reporting drug dosing protocols for our studies and ensure that aggregate study analysis only involves similar dosing protocols.

- Studies have previously included differing etiologies of shock, and this may lead to a heterogenous patient population. We have addressed by including a priori subgroups to evaluate the effectiveness of midodrine for shock across subsets of shock and based on pre-existing patient characteristics.

- Finally, while there are many trials that previously evaluated midodrine for IV vasopressor dependent shock, results are conflicting. This has led to uncertainty regarding midodrine use in undifferentiated shock in the ICU. Our sequential trial analysis will provide the necessary methodology for better control of type I and type II errors than traditional meta-analysis and reduce spurious conclusions from previously conducted studies.
Background

Shock is a common reason for ICU admission which often requires IV vasopressor support.[1-3] Vasopressor agents such as norepinephrine, vasopressin and epinephrine are recommended in septic shock.[4-6] However, as patients recover from their critical illness and require less other physiological support, the use of IV vasopressors may be their only indications for ongoing intensive care unit (ICU) admission. This may prolong their ICU length of stay (LoS) and lead to ICU capacity strain. To date, there are no clear guidelines on starting adjuvant oral therapies for either help managing vasopressor use early in critical illness or to help wean off vasopressor therapy in the resolving phases of shock. These resolving phases can include hypotension with no signs of tissue hypoperfusion or end organ damage. Establishing an effective oral adjunctive therapy could reduce need for invasive hemodynamic monitoring in titrating IV vasopressors and could liberate these patients earlier from the ICU.

Midodrine is an oral alpha agonist that is currently indicated in patients with orthostatic hypotension, intradialytic hypotension, and blood pressure management in cirrhosis and hepatorenal syndrome.[7-12] Prior work has assessed midodrine efficacy in critically ill patients with mixed results. Earlier trials have demonstrated reduced duration of IV vasopressor therapy and a decreased ICU length of stay with midodrine therapy.[13, 14] However, this data is not supported by more recent studies.[15] One of most recent trial investigating the use of midodrine in critically ill patients, the MIDAS study, found no difference between placebo and midodrine groups in IV vasopressor duration or ICU LoS.[16] However, this study had several important limitations including small size and prolonged recruitment period, which may reflect a participant selection bias and being underpowered to detect a significant difference between groups. Further, more recently published RCTs have found results that conflict with the MIDAS trial, further questioning the role of midodrine for vasopressor dependent hypotension.[17-19]
While a recently published meta-analysis examining the role of midodrine in resolving shock did not find any difference in IV vasopressor duration, ICU or hospital lengths of stay or mortality, the review did not provide any subgroup analysis or use GRADE recommendations or trial sequential analysis methods.[20] Further, it was conducted prior to the publication of most recent evidence.

**Objectives**

Accordingly, we aim to conduct a systematic review and meta-analysis on the use of midodrine for IV vasopressor dependent shock in the ICU. We hypothesize that the use of midodrine in critically ill patients will lead to decreased ICU length of stay and decreased duration of IV vasopressors. We will plan to conduct subgroup analysis on select patient populations that have traditionally benefitted from this therapy, including those patients with cirrhosis and acute kidney injury (AKI), and will perform trial sequential analysis for the outcome of ICU length of stay.

**Methods**

**Patient and public involvement**

No patient or public were involved in this systematic review and meta-analysis.

**Study Design**

We will perform a systematic review of observational and randomized controlled studies. Meta-analysis will be performed on observational and randomized controlled studies separately, as appropriate.

**Study registration**

In accordance with PRIMA-P guidelines, this systematic review is registered with the International Prospective Register of Systematic Reviews (CRD42021260375; July 16, 2021).

**Data source and search methods**
A search strategy was developed in consultation with a research librarian and independently peer-reviewed by a second librarian (Appendix 1). We will search the following electronic databases: Ovid MEDLINE, Ovid Embase, CINAHL, and Cochrane Library (via Wiley) from inception until April 21st 2022. We will combine search terms related to shock (i.e., hypotension requiring vasopressors), vasopressors (i.e., norepinephrine, epinephrine, vasopressin, phenylephrine), intensive care (i.e., involving any ICU setting) and midodrine.

Additional search sources: we will search unpublished literature through trial registry platforms (ClinicalTrials.gov) and Google Scholar. We will also search for meeting abstracts from the past 2 years, where available, using Conference Proceedings Citation Index (Clarivate Analytics), and by hand-searching published proceedings from the following associations: Society of Critical Care Medicine, European Society of Intensive Care Medicine, International Symposium of Intensive and Emergency Medicine. We will export search results into Covidence (www.covidence.org).

Eligibility criteria

We will include studies if they meet the following eligibility criteria: 1) include patients with vasopressor dependent shock, 2) are performed in the intensive care (i.e., intended to refer to patients admitted to an ICU setting capable of providing vasopressor therapy), 3) evaluate oral midodrine therapy as compared to placebo or usual care and 4) evaluate one of our outcomes of interest. We will include both adult and pediatric studies, all dosing regimens and titration protocols for midodrine, and etiologies of vasopressor dependent hypotension. We will only include observational studies and RCTs; we will review previous systematic reviews, narrative reviews and meta-analyses to ensure we have captured all relevant studies. We will also review relevant conference abstracts and proceedings.

Outcome measures
Outcomes will include: 1) ICU total length of stay; 2) duration of IV vasopressor therapy, 3) hospital length of stay, 4) ICU mortality, 5) hospital mortality, 6) rates and duration of physiological support, 7) rates of ICU readmission, 8) clinically important adverse events (i.e., bradycardia, uncontrolled hypertension, cardiac ischemia, bowel and limb ischemia.) Where possible, this will be determined from decision of ICU discharge and will include total time from ICU admission. Physiological support will include: (a) rate of invasive mechanical ventilation (IMV), b) duration of IMV, c) rate of non-invasive ventilation (NIV), d) duration of NIV, e) rate of renal replacement therapy (RRT), f) duration of RRT). Adverse events will include: (a) bradycardia, b) hypertension, c) cardiac ischemia, d) bowel and limb ischemia.

Screening And Data Extraction

We will identify eligible studies in a two staged process. In the first phase, at least two investigators will independently review the titles and abstracts of all retrieved citations. Disagreements will be resolved through discussion by the two assessors, then adjudicated by a third author as needed. In the second phase, the same two reviewers will screen full texts for eligibility using a pre-developed tool. We will resolve any disagreements in this second stage using discussion and third-party adjudication if needed. We will capture reasons for exclusion at this second stage and produce a PRISMA flow chart demonstrating the screening process.

We will extract data in duplicate and independently using standardized data abstraction forms. We will extract the following specific variables: patient characteristics, age, sex, type of ICU, etiology of shock, number of patients, study inclusion and exclusion criteria and geographical location. We will also capture the type, dose and duration of IV vasopressors, any co-intervention used (i.e., steroids use; type and amount of intravenous fluids) in either the intervention or comparator groups, and outcome data.

Risk of Bias assessment
We will assess risk of bias using the modified Cochrane tool for randomized controlled trials (https://www.evidencepartners.com/resources/methodological-resources/tool-to-assess-risk-of-bias-in-randomized-controlled-trials-distillersr). We will use Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework to evaluate certainty in pooled outcome data based on risk of bias, imprecision, inconsistency, indirectness, and publication bias. Based on these domains, certainty will be assessed between very low, low, moderate and high.

**Data analysis**

Continuous data will be presented means and standard deviations (SD), or medians and inter-quartile ranges (IQR), and compared (where appropriate) using a t-test or Wilcoxon rank sum test. Categorical variables and proportions will be compared using the Pearson’s Chi-Square or Fischer’s exact tests as appropriate. We will summarize the eligible studies in terms of point estimates or proportions, with p-values or 95% confidence intervals [CIs], where appropriate.

We will perform meta-analyses using RevMan version 5.4 software (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration 2014). Outcomes of interest will include lengths of ICU and hospital stays, ICU and hospital mortality and duration of IV vasopressor use. We will use the method of DerSimonian and Laird to pool effect sizes for each outcome under a random-effects model for all outcomes of interest[22]. Study weights will be calculated using the inverse variance method. We will present the results as relative risk (RR) with 95% confidence intervals (CIs) for dichotomous outcomes[23] and mean difference (MD) for continuous outcomes. We will assess heterogeneity using the I² statistic, the χ² test for homogeneity (p <0.1 for significance of substantial heterogeneity), and visual inspection of the forest plots. We will consider an I² value greater than 50% indicative of substantial heterogeneity. We will assess for publication bias using Begg’s funnel plots if there are 10 or more studies per outcome.
**Trial Sequential Analysis**

We will conduct Trial Sequential Analysis (TSA) using a random effects model for ICU LoS and duration of IV vasopressor therapy. TSA allows for a power calculation to assess whether optimal information size (i.e., events) has been reached which subsequently may inform assessments of precision in pooled point estimates. It is a tool for quantifying the statistical reliability of data in the cumulative meta-analysis adjusting significance levels for sparse data and repetitive testing on accumulating data.[24] For the TSA, we will use a statistical significance level of 5%, a power of 80% and a relative risk reduction of 10% to represent a clinically important difference. We will use a model variance-based heterogeneity correction and perform analysis using Trial Sequential Analysis v.0.9.5.10 beta software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigs Hospitalet, Copenhagen, Denmark)[24].

**Subgroup Analyses**

Where a sufficient number of trials are available (i.e., greater than 3 studies), we will conduct the following pre-specified subgroup pooled analyses (hypothesized direction of effect in parentheses):

- Septic shock vs. non-septic shock (hypothesis: septic shock would have improved outcomes with midodrine, compared to non-septic shock).

- Surgical vs. non-surgical patients (hypothesis: surgical patients will have improved outcomes with midodrine, compared to non-surgical patients).

- Cirrhotic vs. non-cirrhotic patient shock (hypothesis: cirrhotic would have improved outcomes with midodrine, compared to non-cirrhotic shock)

- AKI vs. non-AKI patients (hypothesis: non-AKI would have improved outcomes with midodrine, compared to AKI patients)
• Age greater or less than 65 years (hypothesis: younger patients will have improved outcomes with midodrine compared to those older than 65 years)

If subgroups effects are credible, we will present the outcomes separately for each subgroup. We will use ICEMAN tool to assess credibility[25].

Discussion

ICU admission is typically required for either monitoring or physiologic support. When hemodynamic support is required, IV vasopressors are the mainstay in treatment of septic and other forms of shock. Norepinephrine has been accepted to be the first choice in treatment of septic shock, according to the latest Surviving Sepsis Campaign[4]. Second line treatments include vasopressin and epinephrine. However, IV vasopressor therapy typically requires central-line insertion and maintenance to minimize complications[26]. Ongoing need of IV vasopressor therapy necessitates ongoing ICU admission, which may be prolonged in slow to recover shock.

Oral agents have been proposed to be an option to shorten duration of IV vasopressor therapy and decrease ICU length of stay. Midodrine is one such agent and has been previously studied[13-16, 20, 27-30]. There have been several previous trials evaluating midodrine as an IV vasopressor sparing agent. While there have been previous reviews of these studies, a major limitation has been the lack of large, prospective, randomized controlled trials evaluating midodrine in critically ill patients.

Recently, there have been several RCTs that have evaluated the use of midodrine as an adjunctive therapy to IV vasopressor dependent hypotension.[16-19] The MIDAS trial randomized 136 undifferentiated hypotensive patients to either midodrine or placebo evaluating the median time from study drug initiation until discontinuation of IV vasopressors. The study investigators determined that there was no significant difference between groups. While there exist several methodological concerns with this study (i.e., no change with baseline blood
pressure in either group; no details regarding fluid management; only 3 sites from 2 countries; sample size calculation based on only small study data; lack of requirements of other organ supports; and 7-year recruitment period indicating potential selection bias), it is the largest RCT evaluating the effects of midodrine for critically ill patients and will be important to include in any future review (8). More recently, there have been smaller published RCTs that have shown conflicting results.[17-19] Adly et al. evaluated the use of midodrine in 60 patients with septic shock and clinical stability on low-dose IV vasopressors for at least 24 hours and determined that midodrine was associated with significantly shortened duration of IV vasopressor support and significant decreased mortality. However, this study was not blinded and was small in size, thus limiting its validity.[17] Ahmed et al. evaluated midodrine specifically for the use of blood pressure support in 90 patients with neurogenic shock and also determined that the use of midodrine was associated with decreased duration of IV vasopressor support and decreased ICU length of stay. Again, however, this study was unblinded and of small sample size, which also limits its validity.[18] Finally, the MAVERIC study, a pilot open-label RCT of 62 patients on low-dose IV vasopressor therapy, determined that adjunctive midodrine, while safe to use, was not associated with any physiological or clinical efficacy.[19] While previous systematic reviews have included the MIDAS study, there has been no review or meta-analysis conducted to date that has included the most recently published RCTs. Further, previous studies have not included any a priori subgroup analysis and our review will be evaluating the use of midodrine specifically in patients with known cirrhosis as well as with acute kidney injury. We do appreciate that while many potential subgroup analyses have been pre-determined, these may not all be possible to conduct due to limited sufficient trials and patient numbers. Finally, we will be conducting a sequential trial analysis in order to evaluate the evidence of midodrine as it relates
to ICU lengths of stay and adjust thresholds for significance if insufficient sample size is reached in our identified RCTs in our meta-analysis.

Our systematic review and meta-analysis aim to evaluate the role of midodrine in the treatment of vasopressor dependent shock in the ICU. This, along with our planned subgroup analyses, will inform on the optimal use of midodrine for critically ill patients. We anticipate our systematic review will inform future RCTs and eventual evidence-based clinical practice guidelines on the optimal circumstances to initiate midodrine therapy in the ICU.

**Ethics Approval:** This systematic review will only utilize publicly accessible documents as evidence and therefore does not require institutional ethics approval.

**Funding:** Funding is provided by the University of Alberta Hospital Foundation Kaye Fund

**Role of Funders:** The funder had no role in development of the study protocol, drafting of the manuscript or decision to submit the work for publication.

**Competing interests:** We confirm there are no conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

**Author contributions:** MK and SK contributed to study protocol development and drafting of the manuscript, DO, JS, KF, CK, JK, VL, EM, BR, JS, WS and XW contributed to study protocol development and critical revision of the manuscript, SB and OR conceived the study, developed the protocol and contributed to development and drafting of the manuscript. All of the authors approved the final version to be published.

**Data sharing statement:** No additional data available.

**Word count:** 2340 words
References:

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Appendix 1. Search Strategies

| Database        | Search Strategy                                                                 |
|-----------------|----------------------------------------------------------------------------------|
| **MEDLINE**     | 1. midodrine.mp.                                                                  |
| Ovid MEDLINE(R) | 2. exp Shock/                                                                     |
| ALL 1946 to     | 3. exp Shock, Septic/                                                             |
| February 24, 2022| 4. (shock or sepsis).mp.                                                          |
|                 | 5. (hypoperfusion or hypo-perfusion or hypotension or hypo-tensi* or             |
|                 | hypotensive or antihypotensi* or anti-hypotensi*).mp.                            |
|                 | 6. exp Catecholamines/ or exp Dobutamine/ or exp Epinephrine/ or exp            |
|                 | Felypressin/ or exp Norepinephrine/ or exp Orciprenaline/ or exp                 |
|                 | Phenylephrine/ or exp Vasopressins/                                              |
|                 | 7. (adrenaline or argipressin or catecholamine* or desmopressin or              |
|                 | dobutamine or dopamine or epinephrine or felypressin or glypressin or          |
|                 | lypressin or noradrenaline or norepinephrine or ornipressin or                  |
|                 | orciprenaline or phenylephrine or terlipressin or vasoconstrictor* or          |
|                 | vaso-constrictor* or vasopressin* or vasopressor* or vaso-press* or            |
|                 | vasostrict).mp.                                                                  |
|                 | 8. exp Vasoconstrictor Agents/                                                   |
|                 | 9. or/2-8                                                                        |
|                 | 10. critical care.mp.                                                            |
|                 | 11. critical* ill*.mp.                                                           |
|                 | 12. (intensive care or ICU).mp.                                                  |
|                 | 13. Emergency Treatment/ or Emergency Medicine/ or Emergency Medical             |
|                 | Services/ or Emergency Service, Hospital/ or Trauma Centers/ or exp             |
|                 | Evidence-Based Emergency Medicine/ or exp Emergency Nursing/ or                 |
|                 | Emergencies/                                                                    |
|                 | 14. (emergenic* or casualty department*).mp.                                     |
|                 | 15. ((emergenc* or ED) adj1 (room* or accident or ward or wards or unit or      |
|                 | units or department* or physician* or doctor* or nurs* or treatment* or        |
|                 | visit*).mp.                                                                     |
|                 | 16. (trauma adj1 (cent* or care)).mp.                                            |
|                 | 17. or/10-16                                                                    |
|                 | 18. 1 and 9 and 17                                                              |

| **Embase**      | 1. midodrine.mp.                                                                  |
| Ovid Embase     | 2. exp shock/                                                                     |
| 1974 to 2022    | 3. exp septic shock/                                                              |
| February 24     | 4. (shock or sepsis).mp.                                                          |
|                 | 5. (hypoperfusion or hypo-perfusion or hypotension or hypo-tensi* or             |
|                 | hypotensive or antihypotensi* or anti-hypotensi*).mp.                            |
6. exp catecholamine/ or exp dobutamine/ or exp epinephrine/ or exp felypressin/ or exp norepinephrine/ or exp orciprenaline/ or exp phenylephrine/ or exp vasopressin derivative/
7. (adrenaline or argipressin or catecholamine* or desmopressin or dobutamine or dopamine or epinephrine or felypressin or glypressin or lypressin or noradrenaline or norepinephrine or ornipressin or orciprenaline or phenylephrine or terlipressin or vasoconstrictor* or vaso-constrictor* or vasopressin* or vasopressor* or vaso-press* or vasostrict).mp.
8. exp vasoconstrictor agent/
9. or/2-8
10. critical care.mp.
11. critical* ill*.mp.
12. (intensive care or ICU).mp.
13. emergency treatment/ or emergency medicine/ or emergency health service/ or hospital emergency service/ or exp evidence based emergency medicine/ or exp emergency nursing/ or emergency/
14. (emergenc* or casualty department*).mp.
15. ((emergenc* or ED) adj1 (room* or accident or ward or wards or unit or units or department* or physician* or doctor* or nurs* or treatment* or visit*)).mp.
16. (trauma adj1 (cent* or care)).mp.
17. or/10-16
18. 1 and 9 and 1

CINAHL

S1 midodrine
S2 (MH "Shock+")
S3 (MH "Shock, Septic+")
S4 shock or sepsis
S5 hypoperfusion or hypo-perfusion or hypotension or hypo-tensi* or hypotensive or antihypotensi* or anti-hypotensi*
S6 (MH "Catecholamines+")
S7 (MH "Dobutamine")
S8 (MH "Epinephrine+")
S9 (MH "Norepinephrine")
S10 (MH "Orciprenaline")
S11 (MH "Phenylephrine")
S12 (MH "Vasopressins+")
S13 adrenaline or argipressin or catecholamine* or desmopressin or dobutamine or dopamine or epinephrine or felypressin or glypressin or lypressin or noradrenaline or norepinephrine or ornipressin or orciprenaline or phenylephrine or terlipressin or vasoconstrictor* or
| Vasoconstrictor* or vasopressin* or vasopressor* or vaso-press* or vasostrict |
|---|
| S14 (MH "Vasoconstrictor Agents") |
| S15 S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 |
| S16 "critical care" |
| S17 "critical* ill*" |
| S18 "intensive care" or ICU |
| S19 (MH "Emergency Treatment") |
| S20 (MH "Emergency Medicine") |
| S21 (MH "Emergency Medical Services") |
| S22 (MH "Emergency Service") |
| S23 (MH "Trauma Centers") |
| S24 (MH "Emergency Nursing") |
| S25 (MH "Emergencies") |
| S26 emergicent* or "casualty department" |
| S27 ((emergenc* or ED) N1 (room* or accident or ward or wards or unit or units or department* or physician* or doctor* or nur* or treatment* or visit*)) |
| S28 (trauma N1 (cent* or care)) |
| S29 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 |
| S30 S1 AND S15 AND S29 |

### Cochrane Library via Wiley

| #1 midodrine |
| #2 [mh Shock] |
| #3 [mh "Shock, Septic"] |
| #4 shock or sepsis |
| #5 hypoperfusion or hypo-perfusion or hypotension or hypo-tensi* or hypotensive or antihypotensi* or anti-hypotensi* |
| #6 [mh Catecholamines] or [mh Dobutamine] or [mh Epinephrine] or [mh Felypressin] or [mh Norepinephrine] or [mh Orciprenaline] or [mh Phenylephrine] or [mh Vasopressins] |
| #7 adrenaline or argipressin or catecholamine* or desmopressin or dobutamine or dopamine or epinephrine or felypressin or glypressin or lypressin or noradrenaline or norepinephrine or ornipressin or orciprenaline or phenylephrine or terlipressin or vasoconstrictor* or vaso-constrictor* or vasopressin* or vasopressor* or vaso-press* or vasostrict |
| #8 [mh "Vasoconstrictor Agents"] |
| #9 {OR #2-#8} |
| #10 "critical care" |
| #11 critical* NEXT ill* |
| #   | Query                                                                                       |
|-----|---------------------------------------------------------------------------------------------|
| #12 | "intensive care" or ICU                                                                    |
| #13 | [mh ^"Emergency Treatment"] or [mh ^"Emergency Medicine"] or [mh ^"Emergency Medical Services"] or [mh ^"Emergency Service, Hospital"] or [mh ^"Trauma Centers"] or [mh "Evidence-Based Emergency Medicine"] or [mh "Emergency Nursing"] or [mh ^"Emergencies"] |
| #14 | emergicent* or (casualty NEXT department*)                                                   |
| #15 | ((emergenc* or ED) NEAR/1 (room* or accident or ward or wards or unit or units or department* or physician* or doctor* or nurs* or treatment* or visit*)) |
| #16 | (trauma NEAR/1 (cent* or care))                                                             |
| #17 | {OR #10-#16}                                                                               |
| #18 | #1 AND #9 AND #17                                                                          |

**Google Scholar**

midodrine AND (shock OR sepsis OR hypoperfusion OR hypotension OR hypotensive OR antihypotension) AND ("critical care" OR critical illness OR "emergency department")
# PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

| Section/topic | # | Checklist item | Information reported | Page number(s) |
|---------------|---|----------------|----------------------|----------------|
| **ADMINISTRATIVE INFORMATION** | | | Yes | No | |
| Title | | | ☒ | ☐ | 1 |
| Identification | 1a | Identify the report as a protocol of a systematic review | ☒ | ☐ | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | ☐ | ☒ | |
| Registration | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | ☒ | ☐ | 2 |
| Authors | | | ☒ | ☐ | 1 |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | ☒ | ☐ | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | ☒ | ☐ | 11 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | ☒ | ☐ | 11 |
| Support | | | ☒ | ☐ | 11 |
| Sources | 5a | Indicate sources of financial or other support for the review | ☒ | ☐ | 11 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | ☐ | ☒ | 11 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | ☒ | ☐ | 11 |
| **INTRODUCTION** | | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | ☒ | ☐ | 3,4 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | ☒ | ☐ | 5 |
| **METHODS** | | | | |
| Section/topic | # | Checklist item                                                                                                                                                                                                                                                                                                                                 | Information reported | Page number(s) |
|---------------|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------|
| Eligibility criteria | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review                                                                                                                                   | ✗ | 6 |
| Information sources | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage                                                                                                                                  | ✗ | 5 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated                                                                                                     | ✗ | Appendix 1 |
| STUDY RECORDS | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review                                                                                                                                                                                                                                  | ✗ | 6 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)                                                                                                                     | ✗ | 7 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators                                                                                                    | ✗ | 7 |
| Data items | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications                                                                                                                                                           | ✗ | 6 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale                                                                                                                                                                         | ✗ | 6 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis                                                                                                 | ✗ | 7 |
| DATA | 15a | Describe criteria under which study data will be quantitatively synthesized                                                                                                                                                                                                                                                      | ✗ | 7 |
| Synthesis | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I², Kendall’s tau)                                                                 | ✗ | 8 |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)                                                                                                                                                                                                                           | ✗ | 9 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned                                                                                                                                                                                                                                            | ✗ | N/A |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)                                                                                                                                                                                                | ✗ | 8 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE)                                                                                                                                                                                                                                                   | ✗ | 7 |